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Local corticosteroid injection versus placebo for carpal tunnel syndrome (Review)

Ashworth NL, Bland JDP, Chapman KM, Tardif G, Albarqouni L, Nagendran A

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TABLE OF CONTENTS

ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
SUMMARY OF FINDINGS 4
BACKGROUND 7
OBJECTIVES 8
METHODS 8
RESULTS 11
Figure 1. 13
Figure 2. 15
DISCUSSION 20
AUTHORS' CONCLUSIONS 21
ACKNOWLEDGEMENTS 21
REFERENCES 23
CHARACTERISTICS OF STUDIES 30
DATA AND ANALYSES 65
Analysis 1.1. Comparison 1: Local corticosteroid injection (LCI) versus control: improvement in symptoms, Outcome 1: Symptoms ≤ 3 months 68
Analysis 1.2. Comparison 1: Local corticosteroid injection (LCI) versus control: improvement in symptoms, Outcome 2: Symptoms > 3 months 68
Analysis 1.3. Comparison 1: Local corticosteroid injection (LCI) versus control: improvement in symptoms, Outcome 3: Symptoms ≤ 3 months by local anaesthetic (LA) use 69
Analysis 1.4. Comparison 1: Local corticosteroid injection (LCI) versus control: improvement in symptoms, Outcome 4: Symptoms > 3 months by LA use 70
Analysis 1.5. Comparison 1: Local corticosteroid injection (LCI) versus control: improvement in symptoms, Outcome 5: Symptoms ≤ 3 months by corticosteroid dose 71
Analysis 1.6. Comparison 1: Local corticosteroid injection (LCI) versus control: improvement in symptoms, Outcome 6: Symptoms > 3 months by corticosteroid dose 72
Analysis 1.7. Comparison 1: Local corticosteroid injection (LCI) versus control: improvement in symptoms, Outcome 7: Symptoms ≤ 3 months by duration of action of corticosteroid 72
Analysis 1.8. Comparison 1: Local corticosteroid injection (LCI) versus control: improvement in symptoms, Outcome 8: Symptoms ≤ 3 months by type corticosteroid 73
Analysis 1.9. Comparison 1: Local corticosteroid injection (LCI) versus control: improvement in symptoms, Outcome 9: Boston Carpal Tunnel Questionnaire (Symptom Severity Scale) ≤ 3 months 73
Analysis 1.10. Comparison 1: Local corticosteroid injection (LCI) versus control: improvement in symptoms, Outcome 10: Boston Carpal Tunnel Questionnaire (Symptom Severity Scale) > 3 months 74
Analysis 2.1. Comparison 2: Local corticosteroid injection (LCI) versus control: improvement in function, Outcome 1: Function ≤ 3 months 77
Analysis 2.2. Comparison 2: Local corticosteroid injection (LCI) versus control: improvement in function, Outcome 2: Function > 3 months 77
Analysis 2.3. Comparison 2: Local corticosteroid injection (LCI) versus control: improvement in function, Outcome 3: Function ≤ 3 months by local anaesthetic (LA) use 78
Analysis 2.4. Comparison 2: Local corticosteroid injection (LCI) versus control: improvement in function, Outcome 4: Function > 3 months by LA use 79
Analysis 2.5. Comparison 2: Local corticosteroid injection (LCI) versus control: improvement in function, Outcome 5: Function ≤ 3 months by dose of corticosteroid 80
Analysis 2.6. Comparison 2: Local corticosteroid injection (LCI) versus control: improvement in function, Outcome 6: Function > 3 months by dose of corticosteroid 80
Analysis 2.7. Comparison 2: Local corticosteroid injection (LCI) versus control: improvement in function, Outcome 7: Function ≤ 3 months by duration of action of corticosteroid 81
Analysis 2.8. Comparison 2: Local corticosteroid injection (LCI) versus control: improvement in function, Outcome 8: Function ≤ 3 months by type of corticosteroid 81
Analysis 2.9. Comparison 2: Local corticosteroid injection (LCI) versus control: improvement in function, Outcome 9: Boston Carpal Tunnel Questionnaire (Functional Status Scale) ≤ 3 months 82

Analysis 2.10. Comparison 2: Local corticosteroid injection (LCI) versus control: improvement in function, Outcome 10: Boston Carpal Tunnel Questionnaire (Functional Status Scale) > 3 months 82
Analysis 3.1. Comparison 3: Local corticosteroid injection (LCI) versus control: improvement in neurophysiological parameters, Outcome 1: Median nerve distal motor latency (DML) ≤ 3 months 85
Analysis 3.2. Comparison 3: Local corticosteroid injection (LCI) versus control: improvement in neurophysiological parameters, Outcome 2: Median nerve DML > 3 months 85
Analysis 3.3. Comparison 3: Local corticosteroid injection (LCI) versus control: improvement in neurophysiological parameters, Outcome 3: Median nerve DML ≤ 3 months by local anaesthetic (LA) use 86
Analysis 3.4. Comparison 3: Local corticosteroid injection (LCI) versus control: improvement in neurophysiological parameters, Outcome 4: Median nerve DML ≤ 3 months by dose of corticosteroid 87
Analysis 3.5. Comparison 3: Local corticosteroid injection (LCI) versus control: improvement in neurophysiological parameters, Outcome 5: Median nerve DML > 3 months by dose of corticosteroid 87
Analysis 3.6. Comparison 3: Local corticosteroid injection (LCI) versus control: improvement in neurophysiological parameters, Outcome 6: Median nerve DML ≤ 3 months by duration of action of corticosteroid 88
Analysis 3.7. Comparison 3: Local corticosteroid injection (LCI) versus control: improvement in neurophysiological parameters, Outcome 7: Median nerve DML ≤ 3 months by type of corticosteroid 88
Analysis 3.8. Comparison 3: Local corticosteroid injection (LCI) versus control: improvement in neurophysiological parameters, Outcome 8: Median nerve sensory nerve conduction velocity (SNCV) ≤ 3 months 89
Analysis 3.9. Comparison 3: Local corticosteroid injection (LCI) versus control: improvement in neurophysiological parameters, Outcome 9: Median nerve SNCV > 3 months 89
Analysis 4.1. Comparison 4: Local corticosteroid injection (LCI) versus control: other outcomes, Outcome 1: Requirement for surgery 90
Analysis 4.2. Comparison 4: Local corticosteroid injection (LCI) versus control: other outcomes, Outcome 2: Change in quality of life (Short-Form Six-Dimension Instrument) 90
APPENDICES 90
CONTRIBUTIONS OF AUTHORS 92
DECLARATIONS OF INTEREST 92
SOURCES OF SUPPORT 93
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 93
NOTES 93
INDEX TERMS 93

[Intervention Review]

Local corticosteroid injection versus placebo for carpal tunnel syndrome

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ABSTRACT

Background

Carpal tunnel syndrome (CTS) is a very common clinical syndrome manifested by signs and symptoms of irritation of the median nerve at the carpal tunnel in the wrist. Direct and indirect costs of CTS are substantial, with estimated costs of two billion US dollars for CTS surgery in the USA in 1995 alone. Local corticosteroid injection has been used as a non-surgical treatment for CTS many years, but its effectiveness is still debated.

Objectives

To evaluate the benefits and harms of corticosteroids injected in or around the carpal tunnel for the treatment of carpal tunnel syndrome compared to no treatment or a placebo injection.

Search methods

We used standard, extensive Cochrane search Methods. The searches were 7 June 2020 and 26 May 2022.

Selection criteria

We included randomised controlled trials (RCTs) or quasi-randomised trials of adults with CTS that included at least one comparison group of local injection of corticosteroid (LCI) into the wrist and one group that received a placebo or no treatment.

Data collection and analysis

We used standard Cochrane methods. Our primary outcome was 1. improvement in symptoms at up to three months of follow-up. Our secondary outcomes were 2. functional improvement, 3. improvement in symptoms at greater than three months of follow-up, 4. improvement in neurophysiological parameters, 5. improvement in imaging parameters, 6. requirement for carpal tunnel surgery, 7. improvement in quality of life and 8. adverse events. We used GRADE to assess the certainty of evidence for each outcome.

Main results

We included 14 trials with 994 participants/hands with CTS. Only nine studies (639 participants/hands) had useable data quantitatively and in general, these studies were at low risk of bias except for one quite high-risk study. The trials were conducted in hospital-based clinics across North America, Europe, Asia and the Middle East. All trials used participant-reported outcome measures for symptoms, function and quality of life.

There is probably an improvement in symptoms measured at up to three months of follow-up favouring LCI (standardised mean difference (SMD) −0.77, 95% confidence interval (CI) −0.94 to −0.59; 8 RCTs, 579 participants; moderate-certainty evidence). Up to six months this was still evident favouring LCI (SMD −0.58, 95% CI −0.89 to −0.28; 4 RCTs, 234 participants/hands; moderate-certainty evidence).

There is probably an improvement in function measured at up to three months favouring LCI (SMD −0.62, 95% CI −0.87 to −0.38; 7 RCTs, 499 participants; moderate-certainty evidence). We are uncertain if there is a difference in median nerve DML at up to three months of follow-up (mean difference (MD) −0.37 ms, 95% CI −0.75 to 0.02; 6 RCTs, 359 participants/hands; very low-certainty evidence). The requirement for surgery probably reduces slightly in the LCI group at one year (risk ratio 0.84, 95% CI 0.72 to 0.98; 1 RCT, 111 participants, moderate-certainty evidence). Quality of life, measured at up to three months of follow-up using the Short-Form 6 Dimensions questionnaire (scale from 0.29 to 1.0; higher is better) probably improved slightly in the LCI group (MD 0.07, 95% CI 0.02 to 0.12; 1 RCT, 111 participants; moderate-certainty evidence). Adverse events were uncommon (low-certainty evidence). One study reported 2/364 injections resulted in severe pain which resolved over "several weeks" and 1/364 injections caused a "sympathetic reaction" with a cool, pale hand that completely resolved in 20 minutes. One study (111 participants) reported no serious adverse events, but 65% of LCI-injected and 16% of the placebo-injected participants experienced mild-to-moderate pain lasting less than two weeks. About 9% of participants experienced localised swelling lasting less than two weeks. Four studies (229 participants) reported that they experienced no adverse events in their studies. Three studies (220 participants) did not specifically report adverse events.

Authors' conclusions

Local corticosteroid injection is effective for the treatment of mild and moderate CTS with benefits lasting up to six months and a reduced need for surgery up to 12 months. Where serious adverse events were reported, they were rare.

PLAIN LANGUAGE SUMMARY

Local steroid injection for carpal tunnel syndrome

Key messages

Corticosteroid injection into the wrist probably improves symptoms of carpal tunnel syndrome (compression of a nerve in the wrist) and function of the hand for up to six months. Quality of life assessments, and tests of nerve conduction measured up to three months after injection, may also improve. Corticosteroid injection may reduce the need for surgery, assessed at one-year follow-up. Side effects appear to be rare. However, spontaneous improvement without treatment can occur in up to a third of people.

What is carpal tunnel syndrome?

Carpal tunnel syndrome is very common worldwide, affects people's quality of life and has significant financial costs for health systems. Symptoms occur when the median nerve in the wrist becomes 'irritated', which causes pain, tingling, numbness, and sometimes weakness and loss of function, mainly in the hand and fingers.

How is carpal tunnel syndrome treated?

Corticosteroids are medicines that reduce inflammation and swelling. Corticosteroid injections into the carpal tunnel (a narrow passageway surrounded by bones and ligaments on the palm side of the hand) tends to be used for mild or moderate symptoms and is much cheaper than surgery, but its effectiveness and how long any effects last are disputed.

What did we want to do?

We wanted to find out if local corticosteroid ('steroid') injection into the carpal tunnel at the wrist benefits people with carpal tunnel syndrome. The review authors collected and analysed all relevant studies to answer this question and found 14.

What did we do?

We searched medical databases for studies assessing the effects of local corticosteroid injections on symptoms and function of the hands and on improvements in electrical tests for nerve damage (called nerve conduction studies) up to six months after injection. We also looked at requirement for surgery, quality of life and side effects for up to 12 months.

What did we find?

We found nine studies involving 639 people conducted in hospital-based clinics across North America, Europe, and the Middle East. The studies excluded people with underlying conditions that often occur with carpal tunnel syndrome, such as arthritis and diabetes, and all participants had 'mild' or 'moderate' disease at the carpal tunnel.

Local corticosteroid injection probably improves symptoms and function of the hand at up to three months. Local corticosteroid injection probably improves nerve conduction. Quality of life at up to three months may improve and there may be a reduced need for surgery at one year. Serious complication rates were very low but only 66% of the studies reported them.

What are the limitations of the evidence?

Corticosteroid injections might work better or worse in people with more severe disease or with other conditions such as diabetes. We cannot say because those people typically were not included in the studies.

How up to date is this review?

The review authors searched for studies that had been published up to 26 May 2022.

SUMMARY OF FINDINGS

Summary of findings 1. Local corticosteroid injection (LCI) compared to saline no treatment or placebo for carpal tunnel syndrome

Local corticosteroid injection (LCI) compared to sham saline or local anaesthetic injections, or no treatment for carpal tunnel syndrome

Patient or population: people with carpal tunnel syndrome

Setting: hospital outpatients

Intervention: LCI

Comparison: sham saline or local anaesthetic injections, or no treatment

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with sham saline or local anaesthetic injections, or no treatment	Risk difference with LCI
Improvement in symptoms at ≤ 3 months assessed with: BCTQ or VAS Follow-up: range 1–13 weeks	579 (8 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	—	—	**SMD 0.77 SD more**[b] (0.59 more to 0.94 more)
Improvement in function at ≤ 3 months assessed with: BCTQ or DASH Follow-up: range 1–13 weeks	499 (7 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	—	—	[b]**SMD 0.62 SD more** (0.38 more to 0.87 more)
Improvement in symptoms at > 3 months assessed with: BCTQ or VAS Follow-up: mean 6 months	234 (3 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	—	—	**SMD 0.58 SD more**[b] (0.28 more to 0.89 more)
Improvement in neurophysiological parameters at ≤ 3 months assessed with: median nerve DML (ms)	359 (6 RCTs)	⊕⊖⊖⊖ **Very low**[b,c,d]	—	—	**MD 0.37 ms more** (0.02 less to 0.75 more)

Follow-up: mean 13 weeks					
Requirement for carpal tunnel surgery assessed with: rate of surgery Follow-up: mean 1 year	111 (1 RCT)	⊕⊕⊕⊖ **Moderate**[e]	**RR 0.84** (0.72 to 0.98)	919 per 1000	**147 fewer per 1000** (257 fewer to 18 fewer)
Improvement in quality of life assessed with: SF6D Scale: 0.29–1.0 (higher score indicates better quality of life) Follow-up: mean 10 weeks	111 (1 RCT)	⊕⊕⊕⊖ **Moderate**[e]	—	The mean quality of life improvement was 0 points	**MD 0.07 points more** (0.02 more to 0.12 more)
Adverse events Follow-up: range 2 weeks to 6 months	639 (9 RCTs)	⊕⊕⊖⊖ **Low**[a,f]	Adverse events were uncommon. 1 study reported 2/364 injections resulted in severe pain which resolved over "several weeks" and 1/364 injections caused a "sympathetic reaction" with a cool, pale hand that completely resolved in 20 minutes. 1 study (111 participants) reported no serious adverse events but 65% of LCI-injected and 16% of placebo-injected participants experienced mild-to-moderate pain lasting < 2 weeks. About 9% of participants experienced localised swelling lasting < 2 weeks. 4 studies (229 participants) reported that they experienced no adverse events. 3 studies (220 participants) did not report adverse events.		

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect#.

Moderate certainty: 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 certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

*The **risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

BCTQ: Boston Carpal Tunnel Questionnaire;**CI:** confidence interval; **DASH:** Disabilities of the Arm, Shoulder and Hand; **LCI:** local corticosteroid injection; **MD:** mean difference; **RCT:** randomised controlled trial; **RR:** risk ratio; **SF6D:** Short-Form Six-Dimension Instrument; **SMD:** standardised mean difference; **VAS:** visual analogue scale.

[a]Downgraded one level for imprecision: included studies that used 'hands' as the unit of analysis.
[b]Typically an SMD of 0.2 would tend to represent a small effect, 0.5 a moderate effect and 0.8 a large effect (Cohen1988).
[c]Downgraded one level for inconsistency: heterogeneity.
[d]Downgraded one level for imprecision: CIs included zero.

[e]Downgraded one level for imprecision: wide CIs.
[f]Downgraded one level for inconsistency: 3/9 trials did not report adverse events. There was wide variation in definition of adverse events.

BACKGROUND

Description of the condition

Carpal tunnel syndrome (CTS) is a clinical syndrome manifested by symptoms and signs of irritation or impairment, or both, of the median nerve at the level of the wrist. The median nerve runs from the axilla (armpit), through the forearm and into the palm of the hand. CTS was first described in the 1880s as so-called "thoracic outlet syndrome", and was erroneously attributed to a brachial plexopathy (damage to the large plexus of nerves on the side of the neck) (Pfeffer 1988). With the advent of electrodiagnostic studies in the 1950s and 1960s, CTS was recognised as an entrapment at the level of the transverse ligament of the wrist (i.e. in the carpal tunnel) (Simpson 1956). The following description of the clinical presentation of CTS from a BMJ editorial in 1966 remains the best to this day.

- "The patient is usually a middle-aged woman, but adults of both sexes and all ages may be affected. The complaint is of tingling, numbness, and burning pain in the hand and fingers, often associated with pain spreading proximally along the outer aspect of the arm to the elbow or even to the shoulder. In the hand the symptoms are usually confined to the thumb and first three fingers, but patients often say that all fingers seem to be affected during a severe attack. The little and ring [fourth] fingers are never the main site of complaint. Symptoms are worse after unusual use of the hand or wrist, such as after a long period of decorating, polishing, or driving; characteristically they wake the patient in the early hours of the morning, forcing her to hang her hand out of the bedclothes or walk about the room to obtain relief" (BMJ Editors 1966).

CTS is very common worldwide. One Swedish study determined the prevalence of clinically certain CTS in the general population to be 3.8% in 1997 (Atroshi 1999). CTS is two to five times more common in women than in men. For example, Bland and Rudolfer found a rate of 61.5 to 120.5 cases per 100,000 women, and 35 to 60 cases per 100,000 men, in the UK in 1991 to 2001 (Bland 2003). Meanwhile, Petit and colleagues using data from 2007 to 2010 reported odds of symptomatic CTS in a French working population of 2.9 women to one man (Petit 2015). A third study identified an even higher annual incidence rate in the Italian general population of 139 cases per 100,000 men and 506 cases per 100,000 women over 1991 to 1998 (Mondelli 2002).

The natural history of CTS has not been thoroughly investigated. In one study, up to one-third of participants had spontaneous improvement of their symptoms without any formal medical treatment (Futami 1992). Similarly, Padua and colleagues confirmed that a number of people with CTS improve spontaneously without treatment, and a short duration of symptoms is a positive prognostic indicator (Padua 2001). In this prospective study, for those participants who did not have surgical treatment, 34% experienced symptom improvement and 45% had symptoms that remained the same over one year. Likewise, Ortiz-Corredor and colleagues found that approximately one-third of untreated people with CTS recovered, one-third remained the same and one-third got worse clinically and electrophysiologically over a two-year follow-up (Ortiz-Corredor 2008). Most of the participants in these studies would be in the 'mild' or 'moderate' category of disease.

There are many proposed 'treatments' for CTS, ranging from surgical release of the transverse ligament through to acupuncture. Most interventions have little or no evidence of efficacy. Corticosteroid injections have been used for many diseases (such as arthritis or tendinitis), typically to manage inflammation and pain, with varying degrees of success. They have been used as a treatment for CTS for more than 50 years.

CTS can incur high costs to health systems and to society as even in 1995 an estimated 500,000 surgeries for CTS were being performed each year at a cost of more than USD 2 billion (more than GBP 1.6 billion) in the USA alone (Milone 2017). These costs are projected to double in the next decade as rates of obesity and diabetes — which are both associated with CTS — increase (Bebbington 2015). Given that local corticosteroid injection (LCI) is considerably cheaper than surgery, it is critical to determine not only whether LCI is an effective treatment for CTS but also how long that effect will last and ultimately how will this impact patients' quality of life (Milone 2017).

Description of the intervention

The treatment of CTS falls into two broad categories, surgical or non-surgical. Surgical treatment is generally preferred in 'severe' cases of CTS, whilst non-surgical treatment is usually initiated for 'mild' to 'moderate' CTS (Keith 2010; Verdugo 2008). However, it is worth noting that there is no widely accepted definition of what constitutes 'mild', 'moderate' or 'severe' CTS. Examples of non-surgical treatments that are typically in use include wrist splints, oral non-steroidal anti-inflammatory drugs and LCI into the carpal tunnel (O'Connor 2003; O'Connor 2012; Page 2012a; Page 2012b; Page 2013; Rankin 2017; Scholten 2007; Vasiliadis 2014). This review focused on LCI compared to no treatment or a placebo.

How the intervention might work

The pathophysiology of CTS is not well understood. Early theories — for example, that people with CTS have smaller carpal tunnels, or larger, chronically inflamed flexor tendons — have mostly not stood up to more detailed study and cannot account for many of the features of CTS. Imaging studies show that the cross-sectional area of the median nerve significantly increases in CTS for reasons that are unclear.

We can postulate that people with CTS are in some way genetically at increased risk of developing the syndrome, given its strong familial link. It also seems likely that one of the initial triggers for CTS is increased pressure in the carpal tunnel that results in some local ischaemia in the tissues of the wrist. It is possible that people with CTS experience an exaggerated response to ischaemia by upregulating and releasing larger than normal amounts of a variety of compounds. Interleukins (interleukin-6), vascular endothelial growth factor and prostaglandins (prostaglandin E_2) have all been found in higher concentrations in the flexor tenosynovium in people with CTS (Ettema 2004; Freeland 2002; Talmor 2003). Circumstantial evidence suggests the incidence of CTS is influenced by oestrogen and progesterone, and likely also by genetic factors. Corticosteroids are known to dramatically suppress many of the compounds that seem to be upregulated in CTS, and, therefore, this may represent their main mode of action. We do know that there is a reduction in the swelling of the median nerve after corticosteroid injection, as well as a decrease in vascularity (Cartwright 2011).

Peripheral nerves are typically highly mobile structures and do not tolerate stretch or compression. Median nerve mobility seems to be restricted in CTS. It has been suggested that the injection of fluid into the tunnel (i.e. hydrodissection) may break down adhesions between the nerve and surrounding tissues, independent of any pharmacological effect of the injectate (Evers 2017).

Why it is important to do this review

Corticosteroid injection into the carpal tunnel has been the subject of many studies. However, most are either retrospective in design or prospective but non-randomised. There are two important, and possibly unrelated, questions that need to be answered. First, what is the initial effectiveness of corticosteroid injection and second, how long is it effective (i.e. what is the remission rate)? The effectiveness of corticosteroids is unclear and recurrence rates of symptoms have varied from 8% to 100% (Girlanda 1993; Kulick 1986; van der Bracht 1958). In addition, little is known about the duration of effect for corticosteroid injection. This variation in the reported effectiveness of corticosteroids could be due to several reasons, such as different outcome measures, trial design and patient population, as well as differences in the dose or type of corticosteroid and differences in the natural history of CTS. Since the prevalence of mild-to-moderate CTS is high, the impact of this conservative intervention could be significant for managing the syndrome. Also, since a significant proportion of CTS cases resolve spontaneously, only controlled trials will provide evidence for the true effectiveness of this intervention. Adverse events following LCI have been reported as 'rare' (less than 0.1%) in retrospective epidemiological studies (Kaile 2018), but it will be important to clarify this with data from prospective randomised trials.

This systematic review evaluated the effectiveness of corticosteroids compared to placebo for relieving symptoms in the hand and wrist and improving overall function in the arm. The last version of the full review was published in 2007 (Marshall 2007) with a protocol published in 1999 (Marshall 1999). We decided to revise the protocol (Ashworth 2020) and review in order to define the review questions and bring the methods in line with current standards (Higgins 2019a), before updating the review with new evidence.

OBJECTIVES

To evaluate the benefits and harms of corticosteroids injected in or around the carpal tunnel for the treatment of carpal tunnel syndrome compared to no treatment or a placebo injection.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) and quasi-RCTs. Quasi-RCTs are studies that allocate participants to groups using methods that are partly systematic, for example by alternation, or use of a case record number. We included studies reported as full text and those published as an abstract only. There were no language or publication status restrictions. We included cluster-RCTs and cross-over RCTs of non-surgical treatments, given that these may be feasible designs for certain comparisons.

Types of participants

We included studies of adults (aged 18 years and above) with a diagnosis of CTS.

Study participants had CTS diagnosed in one or both hands according to standard predefined criteria, preferably following the consensus criteria for the classification of CTS in epidemiological study guidelines (see below); however, similar author-defined criteria were also usually acceptable. We included studies evaluating treatment for people with idiopathic CTS and studies that were specifically targeted at subgroups of interest, such as CTS in people with diabetes, rheumatoid arthritis or hypothyroidism, or pregnant women.

Rempel criteria

According to Rempel 1998, diagnosis of CTS requires classic/probable or possible symptoms (see below) and positive electrodiagnostic criteria. If no electrodiagnostic studies are available then diagnosis requires classic/probable symptoms and positive physical examination findings (see below) or night-time symptoms (or both).

- CTS symptoms
  - Classic/probable: numbness, tingling, burning or pain in at least two of digits 1, 2, or 3 (where digit 1 is the "thumb"). Palm pain, wrist pain, or radiation proximal to the wrist is allowed.
  - Possible: tingling, numbness, burning, or pain in at least one of digits 1, 2, or 3.
  - Unlikely: no symptoms in digits 1, 2, and 3.
- Physical examination
  - Positive Tinel's sign, Phalen's test, two-point discrimination or carpal compression test.
  - Tinel's sign: the test is positive if the person perceives paraesthesia during manual percussion on the palmar face of the wrist at the level of the median nerve.
  - Phalen's test: the test is positive if, during maximum active flexion of the wrist for one minute (elbow extended), paraesthesia appears in the area of the median nerve. The time taken for the symptoms to appear (in seconds) is noted (Chammas 2014).

Types of interventions

The treatment intervention was local corticosteroid injection (LCI), with or without the addition of a local anaesthetic (LA), into or near the carpal tunnel. We included any type or dose of corticosteroid.

Eligible comparisons included no treatment, a placebo injection or sham injection. Within these comparisons, we presented subgroup analyses where possible for the following: injection of different corticosteroid doses, and types of corticosteroid, with or without LA, different injection techniques (e.g. with or without imaging guidance), and single or multiple injections. However, when this was not possible (due to low numbers of papers or wrong comparators), we specifically created separate comparisons to look at the effect of these subgroups independent of the intervention.

We considered LCI in combination with other co-interventions provided that all intervention groups received the same co-intervention. We included studies where more than one injection

was administered, provided that the criteria for the decision to administer a second or subsequent injection were clearly specified in advance.

Types of outcome measures

The following outcomes were of interest in the review; we included studies regardless of whether they measured these outcomes. If more than one outcome time point was available within three months, we used the longest.

Primary outcomes

- **Improvement in symptoms** at up to three months of follow-up. Preferably this was demonstrated through a validated participant-reported outcome measure for CTS (in order of preference: Boston Carpal Tunnel Questionnaire (BCTQ; Levine 1993)), Global Symptom Score (GSS; Herskovitz 1995), Disabilities of the Arm, Shoulder and Hand (DASH/QUICKDASH; Hudak 1996). If a study used more than one of the preferred measures, we used the measure that was highest in the hierarchy.

Secondary outcomes

- **Improvement in function** at up to three months of follow-up and greater than three months of follow-up. Preferably this was demonstrated through a validated participant-reported outcome measure for CTS (in order of preference: BCTQ, DASH/QUICKDASH).
- **Improvement in symptoms** at greater than three months of follow-up. Preferably this was demonstrated through a validated participant-reported outcome measure for CTS (in order of preference: BCTQ, GSS, DASH/QUICKDASH).
- **Improvement in neurophysiological parameters** at up to three months and greater than three months of follow-up. Preferably this was measured as the change in median distal motor latency (DML), or median sensory conduction velocity if the DML was unavailable.
- **Improvement in imaging parameters** at up to three months and greater than three months of follow-up. Preferably this was measured as the change in cross-sectional area of the median nerve, as assessed by ultrasound.
- **Requirement for carpal tunnel surgery**
- **Improvement in quality of life** at up to three months and greater than three months of follow-up. Preferably this was demonstrated through a validated measure such as the EuroQol 5 dimensions (EQ-5D) (EuroQol 1990), World Health Organization Quality of Life (WHOQOL; WHO 1997), or 12- or 36-item Short Form Health Survey (Ware 1992; Ware 1996).
- **Adverse events**, reported as the number of participants experiencing any adverse event.

Search methods for identification of studies

Electronic searches

On 7 June 2020 and 26 May 2022, the Cochrane Neuromuscular Information Specialist searched for trials from the following resources, using the search strategies listed in the appendices. All databases were searched from their inception, and we imposed no restriction on the language of publication.

- Cochrane Neuromuscular Specialised Register via CRS Web (Appendix 1).
- Cochrane Central Register of Controlled Trials (CENTRAL) via Cochrane Register of Studies (CRS-Web; Appendix 2).
- MEDLINE via OvidSP (1946 to 25 May 2022) (Appendix 3).
- Embase via OvidSP (1974 to 25 May 2022) (Appendix 4).
- Cumulative Index to Nursing and Allied Health Literature (CINAHL Plus with Full Text) via EBSCOhost (1937 to 25 May 2022; Appendix 5).
- US National Institutes for Health Clinical Trials Registry, ClinicalTrials.gov (clinicaltrials.gov; Appendix 6).
- World Health Organization International Clinical Trials Registry Portal (ICTRP) (apps.who.int/trialsearch/; Appendix 7).

We ran searches for four related Cochrane Review titles with a shared protocol (Ashworth 2020), and selected trials for each review based on interventions and comparisons.

Searching other resources

We searched reference lists of all primary studies and review articles for additional references. We searched relevant manufacturers' websites for trial information. We searched for errata or retractions of included studies.

Data collection and analysis

Selection of studies

Three pairs of review authors (NA, GT, KC, JB, LA, AN) independently selected and reviewed the titles and abstracts of all the potential studies identified by the search using Covidence (Covidence). The review authors were not blinded to trial authors, institution or journal.

We retrieved the full-text study reports/publications of potentially relevant studies and two review authors (NA, JB) independently screened the full-text and identified studies for inclusion. They also identified and recorded any reasons for exclusion of ineligible studies. We resolved any disagreements through discussion and consensus. We identified and excluded duplicates and collated multiple reports of the same study so that each study rather than each report was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Moher 2009).

Data extraction and management

We extracted study characteristics and outcome data and piloted the extraction process on at least one study in the review. We used Covidence to manage study selection, risk of bias assessment and data extraction (Covidence). At least two review authors (GT, KC, JB, LA, AN, NA) extracted study characteristics from included studies. We extracted the following study characteristics: study design and setting, characteristics of participants (e.g. disease severity and age), whether hands or participants were randomised/treated, eligibility criteria, intervention details, outcomes assessed, source(s) of study funding and any conflicts of interest amongst investigators.

At least two review authors (GT, KC, JB, LA, AN, NA) independently extracted outcome data from included studies. We noted in the Characteristics of included studies table if outcome data were not reported in a usable way. We resolved disagreements by consensus

or by involving a third review author. One review author (JB or NA) transferred data into Review Manager Web (RevMan Web 2022). A second different review author (JB or NA) checked the outcome data entries. Another review author (LA, GT, AN, KC) spot-checked study characteristics for accuracy against the trial report.

When reports required translation, the translator extracted data directly using a data extraction form, or the review authors extracted data from the translation provided. Where possible, a review author checked numerical data in the translation against the study report.

Assessment of risk of bias in included studies

Two or more review authors (GT, KC, JB, LA, AN, NA) independently assessed the risk of bias for each study using the Cochrane RoB 1 tool and criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion to reach a consensus. We assessed the risk of bias according to the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Selective outcome reporting.
- Incomplete outcome data (attrition).
- Other sources of bias (e.g. bias associated with cluster-RCTs (e.g. recruitment bias) or cross-over RCTs (e.g. availability of only first-period data, or the presence of carry-over effects)).

We judged each study at high, low or unclear risk of bias for each domain. We provided a quote from the study report, together with a justification for our judgement, in the risk of bias table. We summarised the risk of bias judgements across different studies for each of the domains listed. Where information on the risk of bias related to unpublished data or correspondence with a trialist, we noted this in the risk of bias tables.

When considering treatment effects, we considered the risk of bias for the studies that contributed to that outcome. We made summary assessments of the risk of bias for each important outcome (across domains) within and across studies (Higgins 2011).

Measures of treatment effect

We analysed dichotomous data (requirement for surgery, adverse events) as risk ratios (RRs). We analysed continuous data (all other outcomes) as mean difference, or standardised mean difference (SMD) for results across studies with outcomes that were conceptually the same but measured in different ways (e.g. visual analogue scale (VAS) and the BCTQ for sensory symptoms). We reported corresponding 95% confidence intervals (CIs). We entered data presented as a scale with a consistent direction of effect. If trial authors had dichotomised a continuous measure and continuous data were unavailable, we analysed the outcomes according to the methods for dichotomous data (see above).

Wherever possible we performed our own analysis of the original data and compared the change in outcome value (pre- and postintervention) between treatment and control groups. We calculated the standard deviations (SDs) of the change in means according to Cochrane methodology (Deeks 2019). We reported non-parametric measures of central tendency and dispersion (e.g. median and ranges) narratively.

Unit of analysis issues

We checked included studies for unit-of-analysis errors, which are common in the CTS literature as many authors include both hands of one participant with bilateral CTS as independent 'participants'. This can theoretically result in an overestimation of the statistical significance of the results by not accounting for the clustering of pairs of hands belonging to the same participant in the data (Ukoumunne 1999), but has not been specifically demonstrated to occur in people with CTS. For any measures with unit-of-analysis errors that could not be reanalysed, we presented numbers for people and hands in the forest plots separately. Where there was no difference, we pooled the two subgroups and reported the combined results.

Where a single trial reported multiple trial groups, we included only the interventions and comparators relevant to the review topic. If two comparisons from the same trial (e.g. low dose and high dose versus placebo) were suitable for inclusion in a meta-analysis, we followed the guidance in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* to avoid a situation where the same participants appeared twice in the same meta-analysis (Higgins 2019b). For instance, if clinically appropriate, we combined the different doses to create a single pair-wise comparison.

Where appropriate, we reported effect estimates and their standard errors (SEs) from correctly analysed cross-over and cluster-RCTs and included them in analyses using the generic inverse-variance method in Review Manager Web (RevMan Web 2022). If a cross-over study did not report an SE, we attempted to calculate it from the CIs, a paired t-statistic, or P value from a paired t-test. For a missing SD, we used the SD of the difference from other studies that use the same scale. We performed a sensitivity analysis to determine the effect of any imputed data. For cross-over trials, if there was an insufficient wash-out period between the first and second period to prevent carry-over effects, we only included the first period of the trial, and we analysed the trial as a single, parallel-group design, recognising the potential for bias in this approach.

If reported analyses of cluster-RCTs were not appropriate, we attempted to extract data as described in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* and perform an approximate analysis (Higgins 2019b). We performed a sensitivity analysis to determine the effect of any cluster-RCTs on the results.

Dealing with missing data

We contacted investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study was available as an abstract only).

Where the trials reported continuous outcomes as end-of-follow-up data rather than change-from-baseline, we calculated the change in mean from baseline, and estimated the SD for the change using the methods described in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019c). We used an assumed value of 0.8 for the correlation coefficient between baseline and end of follow-up, which seemed the most reasonable

choice (Higgins 2019c). Studies in CTS tend to have small sample sizes and their quality can be variable, which means even a calculated correlation coefficient from the original data is unlikely to be accurate.

We transformed data presented purely in graphical form (and also unobtainable from the original authors) using Plotdigitizer (Plotdigitizer 2015).

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity amongst the trials in each analysis (Higgins 2003). If we identified substantial unexplained heterogeneity, we reported it and explored possible causes by prespecified subgroup analysis. We used the guide to interpretation outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*, as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

We avoided the use of absolute cut-off values but interpreted the I^2 statistic in relation to the size and direction of effects and strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or CI for the I^2 statistic) (Deeks 2019).

Assessment of reporting biases

We assessed in-trial reporting bias as part of our risk of bias assessment by assessing whether outcomes reported in the Types of outcome measures section were reported in the results for the included studies. We would have created and examined a funnel plot to explore possible small-study biases if we had been able to pool more than 10 studies. If our searches identified trial protocols, clinical trial registrations or abstracts indicating the existence of unpublished studies, we attempted to determine the status of any unpublished studies by contacting the investigators.

Data synthesis

We combined the results of studies with similar characteristics (participants, interventions, outcome measures and timing of outcome measurement) to provide estimates of the efficacy of corticosteroid injection for treating CTS. We undertook meta-analysis on pooled results using a random-effects model (because we thought it likely that significant heterogeneity exists in the literature). We discussed the findings based on the direction, magnitude, certainty and clinical importance of the result.

Where data could not be combined, we presented a narrative synthesis of results according to the Synthesis Without Meta-analysis (SWiM) guidelines (Campbell 2020). In brief, we described any deviations from the protocol data analysis plan with reasons for any changes.

Subgroup analysis and investigation of heterogeneity

We carried out subgroup analyses for the following factors (on both the primary and secondary outcomes where possible): corticosteroid doses; types of corticosteroid; whether LA was used or not; different injection techniques (with or without imaging guidance); and single or multiple injections. We used the formal test for subgroup interactions in Review Manager Web (RevMan Web 2022).

Sensitivity analysis

We carried out sensitivity analyses in which we repeated the analysis whilst excluding the following types of study.

- Unpublished studies
- Studies at high risk of bias in any domain
- Cluster-RCTs and cross-over RCTs

Summary of findings and assessment of the certainty of the evidence

After we entered data into Review Manager Web and completed the risk of bias assessments (RevMan Web 2022), we created a summary of findings table using GRADEpro GDT software. Note that where outcomes were expressed as SMDs we used Cohen's effect sizes (where 0.2 represents a small effect, 0.5 a moderate effect and 0.8 a large effect; Cohen1988) for interpretation.

We presented the following outcomes, as defined in greater detail in Types of outcome measures.

- Improvement in symptoms at up to three months of follow-up
- Improvement in function at up to three months of follow-up
- Improvement in symptoms at greater than three months of follow-up
- Improvement in neurophysiological parameters at up to three months of follow-up
- Requirement for carpal tunnel surgery
- Improvement in quality of life
- Adverse events

Two review authors (KC, GT, AN, LA, NA or JB) independently used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of the evidence (studies that contributed data for the specified outcomes). We used methods and recommendations described in Chapters 14 and 15 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2019a; Schünemann 2019b). We resolved any disagreements by discussion or by involving another review author. We assessed the certainty of evidence according to the GRADE criteria. We considered RCTs as providing high-certainty evidence if the five factors above were not present to any serious degree could downgrade the certainty to moderate, low or very low. We downgraded the certainty of evidence once if a GRADE consideration was of serious concern and twice if it was of very serious concern. We justified all decisions to downgrade the certainty of evidence using footnotes, and we made comments to aid readers' understanding of the review where necessary in the summary of findings table.

RESULTS

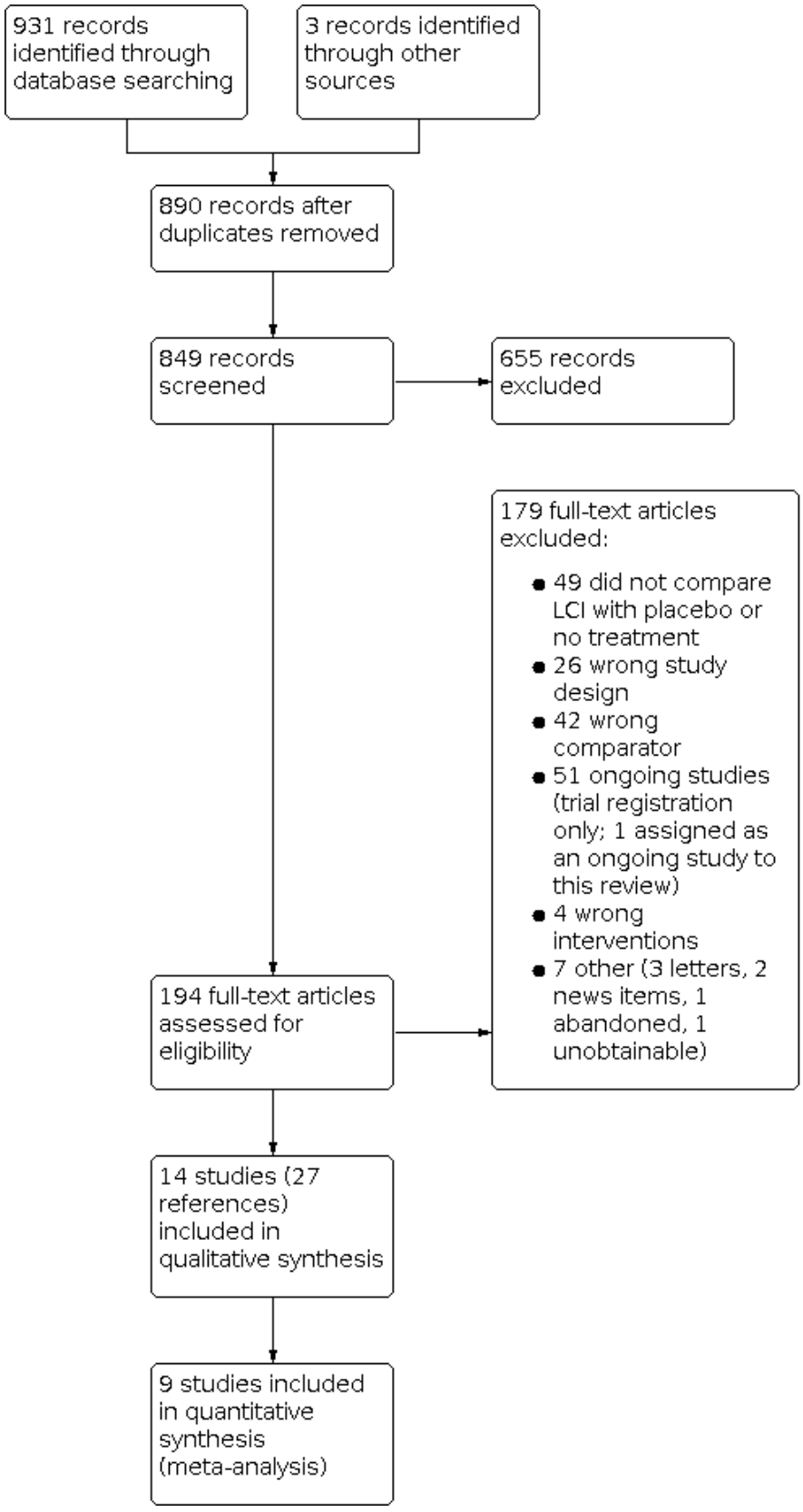
Description of studies

Results of the search

We ran a single search for four related Cochrane Reviews with a shared protocol (Ashworth 2020). We allocated studies to each review after full-text review.

The search strategy identified 931 references and the review authors found three more from their own sources missed by the search (total of 934 references) (see Figure 1). There remained 890 records after removing duplicates. We excluded 655 records after screening the titles and abstracts. We assessed 194 full-text articles for eligibility and excluded 174 of them. We reported a subset of key excluded studies in the Characteristics of excluded studies table.

Figure 1. PRISMA flow diagram.



We included 14 studies (described in 27 references) that compared LCI with either saline injection (six studies), no treatment (one study), LA injection (two studies) or compared LCI plus splinting with splinting (five studies). Nine studies had data that were usable in the quantitative analysis in some way and we reported qualitatively on only five studies.

Included studies

We included 14 studies (reported in 27 references) that were all parallel-group RCTs in this review. All included a group that received an active LCI in or near to the carpal tunnel. A total of 994 participants/hands were enroled from hospital-based outpatient clinics across North America, Europe and the Middle East. All studies were investigator led and none were industry funded. All trials used participant-reported outcome measures for symptoms, function and quality of life. Nine studies had data that were usable in a quantitative way and we reported the results of the remaining five qualitatively (Dammers 1999; Dehghani 2012; Elbaz 1994; Girlanda 1993; O'Gradaigh 2000).

Six studies used sham saline injections as a comparison in the control group (Armstrong 2004; Atroshi 2013; Girlanda 1993; Karadaş 2012; Peters-Veluthamaningal 2010; Salman Roghani 2018). Three of these also used LA in the LCI and control group (Armstrong 2004; Atroshi 2013; Salman Roghani 2018), and two used sham LA injections (Dammers 1999; Karadaş 2011). Four studies identically splinted participants (Dehghani 2012; Khosrawi 2016; Ucan 2006; Wu 1991), and, in addition, were randomised to either LCI or 'no [further] treatment'. One study compared LCI plus splinting with saline injection plus splinting (Elbaz 1994). One study compared LCI with "no treatment" (O'Gradaigh 2000).

Five studies used hands as the unit of analysis (Elbaz 1994; Girlanda 1993; Karadaş 2011; Karadaş 2012; Wu 1991). Overall, 83/239 (35%) participants had bilateral CTS. Two studies were unclear on whether they used hands or participants (Dehghani 2012; Ucan 2006), but ultimately we considered it most likely that Ucan 2006 used hands (no response was obtained from the study authors). We were unable to use any of the data from Dehghani 2012 in any case.

Nine studies followed participants for three months or less (Armstrong 2004; Atroshi 2013; Dammers 1999; Dehghani 2012; Elbaz 1994; Girlanda 1993; Khosrawi 2016; Peters-Veluthamaningal 2010; Wu 1991). Note that in one study (Atroshi 2013), which followed participants for up to one year (and in a later paper up to five years (Hofer 2021)), we were only able to use outcomes other than requirement for carpal tunnel surgery for up to three months of follow-up because of the very high rates of surgery performed in each comparison group after this time.

See Characteristics of included studies table for details.

Excluded studies

We excluded 179 references after full-text review (49 did not compare with placebo or no treatment, 26 were not RCTs or quasi-RCTs, 42 were the wrong comparator (where it was not possible to calculate the effect of LCI versus placebo or no treatment due to the design of the comparator groups), 51 were ongoing studies (trial registration only), four were wrong interventions, three were letters, two were news items, one had been abandoned and one was unobtainable despite extensive efforts to locate it).

See Characteristics of excluded studies table for details of a subset of key excluded studies.

Studies awaiting classification

No studies are awaiting classification.

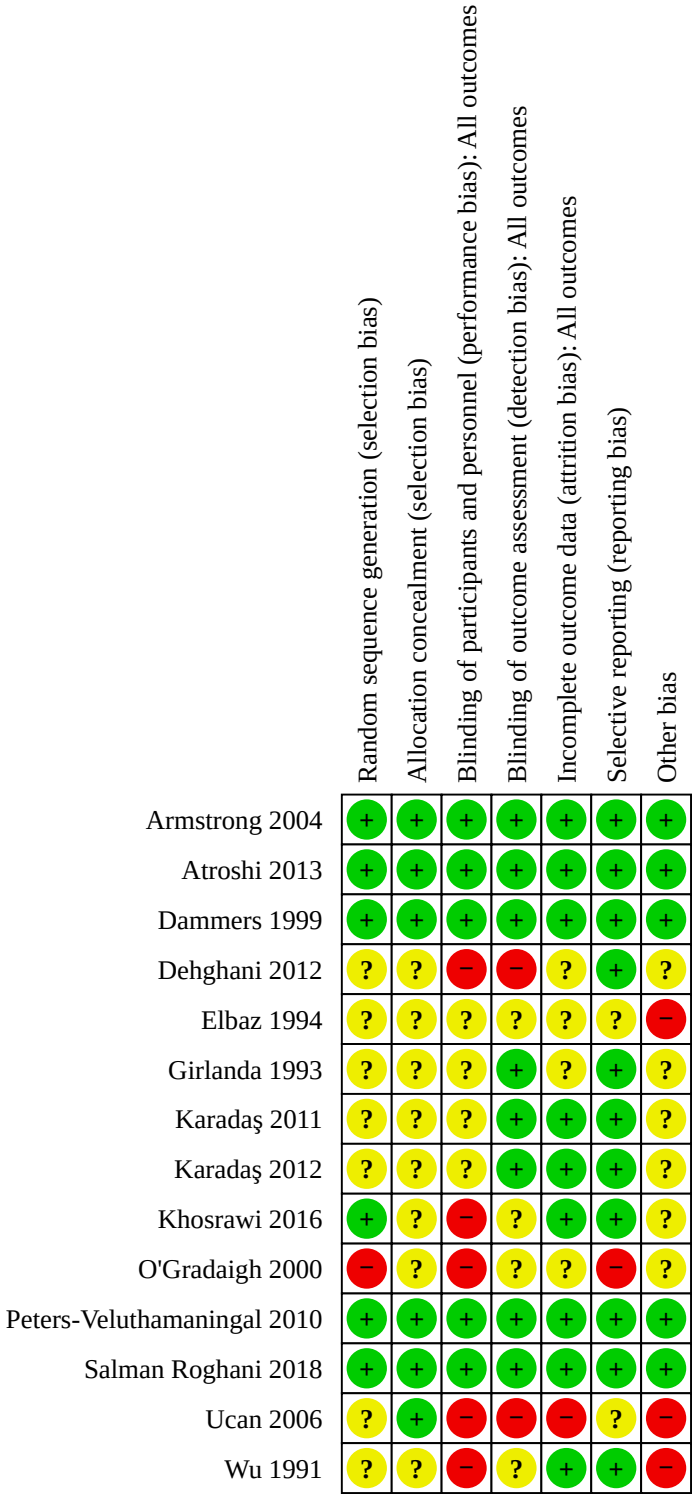
Ongoing studies

One study relevant to this review is ongoing (CTRI201812016604). See Characteristics of ongoing studies table for details.

Risk of bias in included studies

Eight studies used in the quantitative analyses were mostly at low or unclear risk of bias (Armstrong 2004; Atroshi 2013; Karadaş 2011; Karadaş 2012; Khosrawi 2016; Peters-Veluthamaningal 2010; Salman Roghani 2018; Wu 1991). The ninth study was high risk in four domains (Ucan 2006). Two studies had at least one high-risk judgement (Khosrawi 2016; Wu 1991). In the additional five studies that are mentioned qualitatively, one had a low risk of bias (Dammers 1999), but the other four were at unclear high risk (Dehghani 2012; Elbaz 1994; Girlanda 1993; O'Gradaigh 2000). See Figure 2 for a summary of authors' judgements for each study across domains, and the Characteristics of included studies table for details.

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



Allocation

Six studies were at low risk of bias for random sequence generation (Armstrong 2004; Atroshi 2013; Dammers 1999; Khosrawi 2016; Peters-Veluthamaningal 2010; Salman Roghani 2018), seven were unclear (Dehghani 2012; Elbaz 1994; Girlanda 1993; Karadaş 2011; Karadaş 2012; Ucan 2006; Wu 1991), and one was high risk (O'Gradaigh 2000). We considered O'Gradaigh 2000 to be high risk in part because the randomisation method was not described and because for inexplicable reasons, participants with positive findings on electrodiagnostic studies were "randomized separately" to those who did not have findings on electrodiagnostic studies.

Six studies were at low risk of bias for allocation concealment (Armstrong 2004; Atroshi 2013; Dammers 1999; Peters-Veluthamaningal 2010; Salman Roghani 2018; Ucan 2006), and eight were unclear (Dehghani 2012; Elbaz 1994; Girlanda 1993; Karadaş 2011; Karadaş 2012; Khosrawi 2016; O'Gradaigh 2000; Wu 1991).

Blinding

Five studies were at low risk of bias for both blinding domains (Armstrong 2004; Atroshi 2013; Dammers 1999; Peters-Veluthamaningal 2010; Salman Roghani 2018). Although blinding in Atroshi 2013 was broken when the last participant had completed one-year follow-up, all CTS surgeries were performed while participants, investigators and surgeons were still blinded to group allocation, therefore the bias profile at five-year follow-up (Hofer 2021), was no different from the original study.

Four studies were at unclear risk of bias for blinding of participants and personnel (Elbaz 1994; Girlanda 1993; Karadaş 2011; Karadaş 2012) and five were at high risk (Dehghani 2012; Khosrawi 2016; O'Gradaigh 2000; Ucan 2006; Wu 1991). These five studies were high risk because we judged that the design of the study meant that it would be impossible to blind participants or clinicians to the procedures (all participants either received a LCI or no further treatment). Two of these four studies were also at high risk of bias for blinding of outcome assessment, in part because the studies measured patient-reported outcome measures (PROM) (Dehghani 2012; Ucan 2006). See Characteristics of included studies table for further details.

Incomplete outcome data

Nine studies were at low risk of attrition bias (Armstrong 2004; Atroshi 2013; Dammers 1999; Karadaş 2011; Karadaş 2012; Khosrawi 2016; Peters-Veluthamaningal 2010; Salman Roghani 2018; Wu 1991). We considered four at unclear risk (Dehghani 2012; Elbaz 1994; Girlanda 1993; O'Gradaigh 2000). We considered one study at high risk because there was a high rate of dropouts but we were unable to determine from which group and the percentage who completed the study was not provided (Ucan 2006).

Selective reporting

Eleven studies were at low risk of bias. Two were at unclear risk (Elbaz 1994; Ucan 2006). One was at high risk (O'Gradaigh 2000). We deemed O'Gradaigh 2000 high risk because only median DML was reported from the nerve conduction study outcome, and only P values were reported for symptom outcomes.

Other potential sources of bias

Five studies were at low risk from other potential sources of bias (Armstrong 2004; Atroshi 2013; Dammers 1999; Peters-Veluthamaningal 2010; Salman Roghani 2018), six were at unclear risk (Dehghani 2012; Girlanda 1993; Karadaş 2011; Karadaş 2012; Khosrawi 2016; O'Gradaigh 2000), and three were at high risk (Elbaz 1994; Ucan 2006; Wu 1991). All three used 'hands' as the unit of analysis and, in addition, Elbaz 1994 was an abstract that was never published in full in a peer-reviewed journal (the authors did not respond to our requests for more information). Wu 1991 did not state the dose of corticosteroid used and no baseline data were reported, and Ucan 2006 did not state a primary outcome and had very asymmetric group sizes with high dropout rates. See Characteristics of included studies table for further details.

Effects of interventions

See: **Summary of findings 1** Local corticosteroid injection (LCI) compared to saline no treatment or placebo for carpal tunnel syndrome

See Summary of findings 1.

Primary outcome

Improvement in symptoms at up to three months of follow-up

Eleven studies measured symptom improvement at up to three months of follow-up, but we could only report quantitatively on eight. We described findings from three studies qualitatively below (Elbaz 1994; Girlanda 1993; O'Gradaigh 2000).

Quantitative assessments

We included eight trials in the meta-analysis (Armstrong 2004; Atroshi 2013; Karadaş 2011; Karadaş 2012; Khosrawi 2016; Peters-Veluthamaningal 2010; Salman Roghani 2018; Ucan 2006). There is probably an improvement in symptoms measured at up to three months of follow-up favouring LCI (SMD −0.77, 95% CI −0.94 to −0.59; 579 participants; moderate-certainty evidence; Analysis 1.1). An effect size of 0.8 is large, based on Cohen's effect sizes (Cohen1988). We downgraded the evidence because we included studies with 'hands' as the unit of analysis. There was no heterogeneity ($I^2 = 0$; Chi^2 test P = 0.47).

There was no apparent difference between trials that used hands as the unit of analysis (i.e. Karadaş 2011; Karadaş 2012; Ucan 2006), and those that used participants (SMD favouring LCI of −0.60, 95% CI −0.89 to −0.30 for 'hands' versus SMD favouring LCI of −0.86, 95% CI −1.07 to −0.64 for 'participants'); hence, we continued to pool results. It is important to realise that we do not have enough studies in this subgroup analysis to confidently say whether using 'hands' as the unit of analysis makes a true difference to the outcomes or not. Using 'hands' certainly violates the assumption of independence for statistical testing and this may well lead to overestimates of effect size and erroneously narrow CIs. It would be a much better design to use 'individuals' as the unit of analysis. We had stated a priori that we would analyse 'hands' in a subgroup analysis and combine the results if we found no subgroup difference. We also performed an analysis that only included studies using the BCTQ measure (Armstrong 2004; Atroshi 2013; Karadaş 2012; Khosrawi 2016; Peters-Veluthamaningal 2010; Salman Roghani 2018; Ucan 2006), which would be easier to interpret, but this had substantial heterogeneity ($I^2 = 70\%$; Chi^2 test

P = 0.002). The fixed-effect and random-effects models reported similar results in favour of LCI (random-effects model: MD −0.41, 95% CI −0.58 to −0.25; Analysis 1.9). The minimal clinically important difference (MCID) for the sensory component of the BCTQ scale has a wide range from 0.16 to 1.45 in the literature. One of the more recent, higher-quality studies of 180 participants with CTS before and after surgery found an MCID of 0.46 (Kleermaeker 2018).

Subgroup analyses

We performed a subgroup analysis based on LA injection use (Analysis 1.3). There were six different combinations: LCI versus saline (Karadaş 2012; Peters-Veluthamaningal 2010), LCI versus LA (Karadaş 2011; Karadaş 2012), LCI versus no treatment (Khosrawi 2016), LCI+LA versus saline+LA (Armstrong 2004; Atroshi 2013; Salman Roghani 2018), LCI+LA versus LA (Karadaş 2011), and LCI +LA+splints versus splints (Ucan 2006). There were differences between subgroups but the designs of the studies made it very difficult to determine if the use (or non-use) of LA had any effect on outcomes.

We performed a subgroup analysis of the dose of corticosteroid used (Analysis 1.5). Three groupings of corticosteroid dose were naturally formed: low dose corresponding to approximately 20 mg equivalent of methylprednisolone (Peters-Veluthamaningal 2010; Ucan 2006), medium dose corresponding to approximately 40 mg equivalent of methylprednisolone (Armstrong 2004; Atroshi 2013; Karadaş 2011; Karadaş 2012; Khosrawi 2016; Salman Roghani 2018), and high dose corresponding to approximately 80 mg equivalent of methylprednisolone (Atroshi 2013; Salman Roghani 2018). There was no evidence of a difference between the three dosage groups, although it was notable that the low-dose group CIs included the possibility of no effect compared to the medium- and high-dose groups that did not.

We performed a subgroup analysis of the duration of corticosteroid action (Analysis 1.7). Two groupings were possible: intermediate-acting LCI lasting 12 to 36 hours (Atroshi 2013; Karadaş 2011; Karadaş 2012; Khosrawi 2016; Peters-Veluthamaningal 2010; Salman Roghani 2018; Ucan 2006), and long-acting LCI lasting more than 48 hours (Armstrong 2004). There was no evidence of a difference between subgroups.

We performed a subgroup analysis of the type of corticosteroid used in terms of its relative mineralocorticoid activity (Analysis 1.8). Two groupings were possible: mineralocorticoid-acting LCI (Atroshi 2013; Khosrawi 2016), and non-mineralocorticoid-acting LCI (Armstrong 2004; Karadaş 2011; Karadaş 2012; Peters-Veluthamaningal 2010; Salman Roghani 2018; Ucan 2006). There was no evidence of a difference between subgroups.

Qualitative assessments

We could only report on O'Gradaigh 2000 qualitatively. They compared three treatments (hydrocortisone 25 mg, hydrocortisone 100 mg and triamcinolone 30 mg injections) with 'no treatment'. They asked participants to rate the changes in symptoms at six weeks or six months of follow-up on a 5-point Likert-type scale they created. At six weeks, 63% to 73% of participants reported being "better" or "much better" compared to only 5% of the "no treatment" group (P < 0.05). The authors did not respond to our requests for further information.

We reported on Girlanda 1993 qualitatively because the trial authors presented the results as P values and there was no response to our request for further information. They compared two injections of methylprednisolone 15 mg with normal saline injections at up to two months and found that compared to baseline the placebo group improved from 9 to 8 and the LCI group improved from 8 to 2 at two months in the composite 'symptoms' score they created. However, they did not compare improvements between groups.

We reported on Elbaz 1994 qualitatively as this was published as an abstract with very limited information and no useable data. The study was never published in full and there was no response from the authors. They compared betamethasone 3 mg injection plus splinting with saline injection plus splinting and found (quote) "no statistically significant differences … for most clinical and electrophysiological parameters" at six weeks.

We reported on Dehghani 2012 qualitatively because the data were unusable. The investigators compared a group who received methylprednisolone 40 mg injection plus splints for two weeks with a group who received only splints for two weeks. They measured "pain" on a VAS (and Phalen's and Tinel's signs) at one, three and six months of follow-up. They recruited 88 participants but it was unclear how many were in each group (or whether they used hands as the unit of analysis). They reported that outcomes were better in the LCI group at three months and greater. The authors did not respond to our requests for further information.

Secondary outcomes

Functional improvement at up to three months and greater than three months of follow-up

Quantitative assessments

Seven trials reported functional improvement at up to three months of follow-up (Armstrong 2004; Atroshi 2013; Karadaş 2012; Khosrawi 2016; Peters-Veluthamaningal 2010; Salman Roghani 2018; Ucan 2006). There is probably an improvement in function measured at up to three months favouring LCI (SMD −0.62, 95% CI −0.87 to −0.38; 499 participants/hands; moderate-certainty evidence; Analysis 2.1). We downgraded the certainty because we included studies with 'hands' as the unit of analysis. There was some heterogeneity (I^2 = 41%; Chi^2 test P = 0.12) and with almost identical results from the fixed-effect model, which likely means this was not important. This SMD represents a moderate-to-large effect size.

There was a difference between the two trials that used hands as the unit of analysis (i.e. Karadaş 2012; Ucan 2006) and those that used participants. The two trials that used hands both found no clear advantage to the LCI group (and both were the highest risk of bias studies), whereas the five trials that used participants all showed benefit (SMD −0.14, 95% CI −0.52 to 0.24 for 'hands' versus SMD −0.78, 95% CI −0.99 to −0.56 for 'participants'). Given there were only two studies, we chose to continue to pool the results as this also was the most conservative option. We performed an analysis that only included studies using the BCTQ measure as a way of providing easier interpretation. At up to three months, this analysis included six of the seven studies (Armstrong 2004; Karadaş 2012; Khosrawi 2016; Peters-Veluthamaningal 2010; Salman Roghani 2018; Ucan 2006). There was an improvement in the BCTQ functional status score favouring LCI (−0.33 points more,

95% CI −0.51 to −0.14; 388 participants/hands; Analysis 2.9). There was little difference between the two trials that used hands as the unit of analysis (i.e. Karadaş 2012; Ucan 2006), and those that used participants, hence we continued to pool results. The MCID for the functional component of the BCTQ scale has a wide range from 0.28 to 1.7 in the literature. One of the more recent, higher-quality studies of 180 participants before and after surgery found an MCID of 0.28 (Kleermaeker 2018). Note that for one study, which followed participants for up to one year (and in a later paper up to five years (Hofer 2021)), we could only use outcomes for up to three months of follow-up because of the very high rates of surgery performed in each comparison group after this time (72% to 93%) (Atroshi 2013).

For functional improvement measured at greater than three months of follow-up, the meta-analysis included three trials (Karadaş 2012; Salman Roghani 2018; Ucan 2006). There was no evidence of a difference between groups, and the result was very imprecise (SMD 0.01, 95% CI −0.43 to 0.46; 200 participants/hands; Analysis 2.2). There was no important heterogeneity (I^2 = 56%).

Subgroup analyses

We performed a subgroup analysis based on LA injection use (Analysis 2.3). At up to three months of follow-up, there were five different combinations: LCI versus saline (Karadaş 2012; Peters-Veluthamaningal 2010), LCI versus LA (Karadaş 2012), LCI versus no treatment (Khosrawi 2016), LCI+LA versus saline+LA (Armstrong 2004; Atroshi 2013; Salman Roghani 2018), and LCI+LA +splints versus splints (Ucan 2006). There were differences between subgroups but the designs of the studies made it very difficult to determine if the use (or non-use) of LA had any effect on outcomes. At follow-up of greater than three months, there was no difference between the four subgroups identified (Analysis 2.4).

We performed a subgroup analysis of the dose of corticosteroid used (Analysis 2.5). At up to three months of follow-up, three groupings of corticosteroid dose were naturally formed: low dose, corresponding to approximately 20 mg equivalent of methylprednisolone (Peters-Veluthamaningal 2010; Ucan 2006), medium dose, corresponding to approximately 40 mg equivalent of methylprednisolone (Atroshi 2013; Karadaş 2012; Khosrawi 2016; Salman Roghani 2018), and high dose, corresponding to approximately 80 mg equivalent of methylprednisolone (Atroshi 2013; Salman Roghani 2018). There was no difference observed between the three dosage groups although it was notable that the 95% CI of the low-dose group included the possibility of no effect, unlike the medium- and high-dose groups, which did not. However, at follow-up greater than three months, there was a difference between groups. The improvement in the LCI group for the single study of high-dose methylprednisolone was better than the two medium-dose studies, which were better than the single low-dose study (Analysis 2.6), with a follow-up time of six months for all groups.

We performed a subgroup analysis of the duration of corticosteroid action (Analysis 2.7). Two groupings were possible: intermediate-acting LCI lasting 12 to 36 hours (Atroshi 2013; Karadaş 2012; Khosrawi 2016; Peters-Veluthamaningal 2010; Salman Roghani 2018; Ucan 2006), and long-acting LCI lasting more than 48 hours (Armstrong 2004). There was no evidence of a difference between subgroups at up to three months of follow-up.

We performed a subgroup analysis of the type of corticosteroid used in terms of its relative mineralocorticoid activity (Analysis 2.8). Two groupings were possible: mineralocorticoid acting LCI (Atroshi 2013; Khosrawi 2016), and non-mineralocorticoid-acting (Armstrong 2004; Karadaş 2012; Peters-Veluthamaningal 2010; Salman Roghani 2018; Ucan 2006). There was no evidence of a difference between subgroups at up to three months of follow-up.

Improvement in symptoms at greater than three months of follow-up

Quantitative assessments

We included three trials in the meta-analysis (Karadaş 2011; Karadaş 2012; Salman Roghani 2018). There is probably an improvement in symptoms measured at greater than three months favouring LCI (SMD −0.58, 95% CI −0.89 to −0.28; 234 participants; moderate-certainty evidence; Analysis 1.2). We downgraded the certainty of evidence because we included studies with 'hands' as the unit of analysis. There was no important heterogeneity (I^2 = 20%; Chi^2 test P = 0.29). This represents a moderate to large effect size. The three studies included in the analysis all had a follow-up of six months. There was no difference between trials that used hands as the unit of analysis (i.e. Karadaş 2011; Karadaş 2012), and those that used participants (SMD favouring LCI of −0.44, 95% CI −0.77 to −0.10 for 'hands' versus SMD favouring LCI of −0.84, 95% CI −1.30 to −0.39 for 'participants'); therefore, we were able to pool results. We originally attempted to include the six-month data from Ucan 2006 in this meta-analysis; however, the heterogeneity became considerable (I^2 = 86%; Chi^2 test P = 0.0007). This trial had very significant issues with a high risk of bias compared to the other trials; in addition, the comparator groups were more complex in that they compared LCI plus splinting versus splinting, which we considered were the likely reasons for the heterogeneity. We also performed a further analysis that only included studies using the BCTQ measure as a way of providing easier interpretation (Analysis 1.10). This analysis included three studies (Karadaş 2012; Salman Roghani 2018; Ucan 2006). There was a mean improvement in the BCTQ symptom severity score favouring LCI of −0.24 points (95% CI −0.395 to −0.09). Note that for one study (Atroshi 2013), which followed participants for up to one year (and in a later paper (Hofer 2021) up to five years), we were only able to use outcomes for up to three months of follow-up because of the very high rates of surgery performed in each comparison group after this time (72% to 93%).

Subgroup analyses

We performed a subgroup analysis based on LA use (Analysis 1.4). We identified five different combinations: LCI versus saline (Karadaş 2012), LCI versus LA (Karadaş 2011; Karadaş 2012), LCI +LA versus saline+LA (Karadaş 2012; Salman Roghani 2018), LCI+LA versus LA (Karadaş 2011), and LCI+LA+splints versus splints (Ucan 2006). There were differences between subgroups but the designs of the studies made it difficult to determine if the use (or non-use) of LA had any effect on outcomes.

We performed a subgroup analysis of the dose of corticosteroid used (Analysis 1.6). Three groupings of corticosteroid dose were naturally formed: low dose, corresponding to approximately 20 mg equivalent of methylprednisolone (Ucan 2006), medium dose corresponding to approximately 40 mg equivalent of methylprednisolone (Karadaş 2011; Karadaş 2012; Salman Roghani 2018), and high dose corresponding to approximately 80 mg equivalent of methylprednisolone (Salman Roghani 2018). There

was a difference between the three dosage groups. The improvement in the LCI group for the single study of high-dose methylprednisolone was better than the three medium-dose studies, which were better than the single low-dose study (Analysis 1.6), with a follow-up time of six months for all groups.

Qualitative assessments

We reported on O'Gradaigh 2000 qualitatively. The trial authors compared three treatments (hydrocortisone 25 mg, hydrocortisone 100 mg and triamcinolone 100 mg injections) with 'no treatment'. They asked participants to rate the changes in symptoms at six weeks or six months of follow-up on a 5-point Likert type scale they created. At six months, 50% to 66% of participants reported being "better" or "much better". However, they did not follow up the "no treatment" group after six weeks, hence essentially the study was no longer controlled. The authors did not respond to our requests for further information.

Improvement in neurophysiological parameters at up to three months and greater than three months of follow-up

Quantitative assessments

At up to three months of follow-up, six trials reported change in median nerve DML (Armstrong 2004; Karadaş 2012; Khosrawi 2016; Salman Roghani 2018; Ucan 2006; Wu 1991). There was no difference between the three trials that used hands as the unit of analysis (i.e. Karadaş 2012; Ucan 2006; Wu 1991) and those that used participants. We are uncertain if there is a difference in median nerve DML at up to three months of follow-up (MD −0.37 ms, 95% CI −0.75 to 0.02; 359 participants; very low-certainty evidence; Analysis 3.1). The certainty of the evidence was downgraded because of considerable unexplained heterogeneity (I^2 = 97%), the CIs included zero, and we included studies with 'hands' as the unit of analysis.

At greater than three months of follow-up, three studies reported median nerve DML (Karadaş 2012; Salman Roghani 2018; Ucan 2006). The meta-analysis indicated a point estimate in favour of LCI, but the CI included the possibility that the control group was superior (MD −0.11 ms, 95% CI −0.32 to 0.09; 200 participants; Analysis 3.2). There was no difference between the two trials that used hands as the unit of analysis (i.e. Karadaş 2012; Ucan 2006) and those that used participants (SMD −0.35, 95% CI −0.83 to 0.13 for 'hands' versus SMD −0.44, 95% CI −1.06 to 0.18 for 'participants'); hence, we were able to pool results.

Subgroup analyses

We performed a subgroup analysis based on LA injection use (Analysis 3.3). We identified five different combinations: LCI versus saline (Karadaş 2012), LCI versus LA (Karadaş 2012), LCI versus no treatment (Khosrawi 2016), LCI+LA versus saline+LA (Armstrong 2004; Salman Roghani 2018), and LCI +LA+splints versus splints (Ucan 2006; Wu 1991). There were differences between subgroups but the designs of the studies made it very difficult to determine if the use (or non-use) of LA had any effect on outcomes.

We performed a subgroup analysis of the dose of corticosteroid used (Analysis 3.4; Analysis 3.5). The three groupings of corticosteroid dose were: low dose, corresponding to approximately 20 mg equivalent of methylprednisolone (Ucan 2006), medium dose corresponding to approximately 40 mg equivalent of methylprednisolone (Armstrong 2004; Karadaş 2012; Khosrawi 2016; Salman Roghani 2018), and high dose corresponding to approximately 80 mg equivalent of methylprednisolone (Salman Roghani 2018). Note that we were unable to determine the dose used in one study (Wu 1991). There was no evidence of a difference between the three dosage groups at up to three months or greater than three months.

We performed a subgroup analysis of the duration of corticosteroid action (Analysis 3.6). Two groupings were possible: intermediate-acting LCI lasting 12 to 36 hours (Karadaş 2012; Khosrawi 2016; Salman Roghani 2018; Ucan 2006), and long-acting LCI lasting more than 48 hours (Armstrong 2004; Wu 1991). There was no difference between these two subgroups.

We performed a subgroup analysis of the type of corticosteroid used in terms of its relative mineralocorticoid activity (Analysis 3.7). Two groupings were possible: mineralocorticoid-acting LCI (Khosrawi 2016) and non-mineralocorticoid-acting LCI (Armstrong 2004; Karadaş 2012; Salman Roghani 2018; Ucan 2006; Wu 1991). There was a difference in favour of the mineralocorticoid-acting corticosteroid (MD for mineralocorticoid-acting −0.95 ms, 95% CI −1.08 to −0.82 compared with MD non-mineralocorticoid-acting −0.24 ms, 95% CI −0.43 to −0.05).

Qualitative assessments

We reported on O'Gradaigh 2000 qualitatively. The trial investigators compared three treatments (hydrocortisone 25 mg, hydrocortisone 100 mg and triamcinolone 30 mg injections) with 'no treatment'. They reported median nerve DML results "before treatment" and "after treatment"; however, it was not possible to determine whether the "after treatment" was at six weeks or six months of follow-up. The paper reported no difference in the change in median motor DMLs between any of the groups. The authors did not respond to our requests for further information.

We reported on Girlanda 1993 qualitatively because the report presented the results as P values and the trial authors did not respond to a request for further information. They compared two injections of methylprednisolone 15 mg with normal saline injections at up to two months and found that compared to baseline both groups had improvements in median DML. However, they did not compare improvements between groups.

We reported on Elbaz 1994 qualitatively as it was only published as an abstract with very limited information and no useable data. The study was never published in full and the authors did not respond to our enquiry. The trial compared betamethasone 3 mg injection plus splinting with saline injection plus splinting and found (quote) "no statistically significant differences … for most clinical and electrophysiological parameters" at six weeks.

Improvement in imaging parameters at up to three months and greater than three months of follow-up

None of the included studies measured imaging-related outcomes.

Requirement for carpal tunnel surgery

Quantitative assessments

One study reported the requirement for surgery at one year of follow-up (Atroshi 2013). The requirement for surgery probably reduces slightly in the LCI group at one year (RR 0.84, 95% CI 0.72 to 0.98; 111 participants; moderate-certainty evidence; Analysis 4.1).

This would translate to about 147 fewer surgeries per 1000 people with CTS. At five years of follow-up of the same participants, only an additional four in each dosage group (methylprednisolone 40 mg and 80 mg) and an additional two in the placebo group had undergone surgery (all within 16 months of the injection), hence there was effectively little change in effect (RR 0.90, 95% CI 0.82 to 1.0; 111 participants; Analysis 4.1) (reported in Hofer 2021).

Qualitative assessments

We reported on Dammers 1999 qualitatively because of the type of outcome measured and the open design of the trial after one month. Dammers 1999 found that 50% of participants who received LCI required further treatment by one year compared to 93% of participants in the control group who initially received an LA injection and were then offered either LCI or surgery as required.

Improvement in quality of life at up to three months and greater than three months of follow-up

One study reported quality of life measures. Atroshi 2013 found that the SF6D (scale from 0.29 to 1.0; higher is better) measured at up to three months of follow-up improved more in the LCI group (MD 0.07 points, 95% CI 0.02 to 0.12; 111 participants; moderate-certainty evidence; Analysis 4.2). Note that for one study, which followed participants for up to five years, we could only use outcome data for up to three months of follow-up because of the very high rates of surgery performed in each comparison group after this time (72% to 93%) (Atroshi 2013).

Adverse events

Seven studies (520 participants) provided information on adverse events (Armstrong 2004; Atroshi 2013; Girlanda 1993; Karadaş 2011; Karadaş 2012; Khosrawi 2016; Ucan 2006). Seven studies (397 participants) did not mention adverse events (Dammers 1999; Dehghani 2012; Elbaz 1994; O'Gradaigh 2000; Peters-Veluthamaningal 2010; Salman Roghani 2018; Wu 1991).

Armstrong 2004 reported that 2/364 injections resulted in severe pain, which resolved over "several weeks," and 1/364 injections caused a "sympathetic reaction" with a cool, pale hand that completely resolved in 20 minutes. Atroshi 2013 (111 participants) reported no serious adverse events, but 65% of LCI and 16% of the placebo-injected participants experienced mild-to-moderate pain lasting less than two weeks. About 9% of participants experienced localised swelling lasting less than two weeks. Karadaş 2011, Karadaş 2012, Khosrawi 2016, and Ucan 2006 (229 participants) reported that participants experienced no adverse events in their studies. Girlanda 1993 reported that, "No complications occurred in either group". See Summary of findings 1.

DISCUSSION

Summary of main results

This review included 14 studies involving 994 participants/hands with CTS, although it was only possible to use nine studies (639 participants/hands) in the quantitative analyses. Moderate-certainty evidence indicates that LCI probably improves symptoms and function in the hands at up to three months after a single treatment, in comparison to placebo or no treatment. Moderate-certainty evidence from three trials indicates superior symptom relief with LCI over placebo at up to six months. These findings are partially corroborated by very low-certainty evidence for improvement in median nerve DML at three months or less. None of the studies reported any radiological outcomes. There is moderate-certainty evidence of a probable reduction in the need for surgery at 12 months in the LCI group. Quality of life probably improved in the LCI group at up to three months of follow-up; this evidence was also moderate certainty. Serious adverse events were rare.

The planned subgroup analyses showed no real difference between different doses of corticosteroid given at up to three months; however, at up to six months there did seem to be a dosage effect with high doses (approximately 80 mg equivalent of methylprednisolone) superior to medium (approximately 40 mg equivalent of methylprednisolone) which were superior to low doses (approximately 20 mg equivalent of methylprednisolone).

There did not seem to be any differences between types of corticosteroids or duration of effect. We could not determine if the coadministration of LA made any difference in outcome or not.

Overall completeness and applicability of evidence

The included studies all directly addressed the main study question and provided partially satisfactory answers to the supplementary questions, apart from the effect of LCI on imaging abnormalities. All participants were drawn from North American, European and Middle Eastern populations and the applicability of the findings in other populations may be limited. All the studies excluded people with many forms of chronic pathology that commonly occur concurrently with CTS, such as osteoarthritis, diabetes and tenosynovitis, so the effectiveness of LCI in people with multiple hand pathology remains uncertain. In addition, all studies selected participants with 'mild-to-moderate' CTS, although exact definitions of severity varied. We found no studies evaluating LCI in severe CTS and the finding of this review cannot be applied to people with thenar atrophy and severe nerve conduction abnormalities. The included studies observed several variations on the basic procedure of LCI, including the use of different doses and types of corticosteroid and the addition of LA to the injectate. We did find evidence in the subgroup analyses that higher doses may have a longer-term effect than lower doses, this could be a reason why there is variation in the findings from different studies. Only about half of the studies reported on adverse events.

Quality of the evidence

For the most part, the nine studies included in the quantitative analyses were high-quality, placebo-controlled randomised trials at low risk of bias. We consider the evidence to be broadly of low to moderate certainty. We downgraded the certainty of the evidence for the main findings relating to symptom and functional improvement to moderate because the meta-analysis included studies that used 'hands' as their unit of analysis. Other outcomes were additionally affected by heterogeneity, imprecision, or both. The certainty of the evidence for adverse events was low, as three of nine trials did not report on adverse events and there was a wide variation in definitions.

Potential biases in the review process

The complexity of this review means that it can never be fully up to date. New publications relating to CTS are frequent and the most recent, appearing during the time in which we were analysing the results of the last search, may have been missed.

Using 'hands' as the unit of analysis (which occurred in five studies) violates the independence assumption in statistical testing and may result in overestimates of treatment effect so ideally 'participants' should be used. However, we did not have enough studies to say confidently whether using 'hands' makes any significant difference. In addition, the overall percentage of participants with bilateral CTS (35%) was low, which may have mitigated any potential effects.

When calculating missing SDs using the suggested formula, we assumed the correlation between pre- and post-data was 0.8, but cannot be sure this is correct without the original data from the study (which we were unable to obtain).

Agreements and disagreements with other studies or reviews

This review builds upon the previous version (Marshall 2007), and, with the inclusion of new evidence, both confirms the short-term benefit of corticosteroids over placebo shown in that review and extends the period for which there is strong evidence of benefit from six weeks to three months. We are aware of no other directly comparable reviews.

In a Bayesian Network meta-analysis of corticosteroid injection for CTS (Chen 2015), one of the subanalyses compared symptom relief from injection with that from placebo at any follow-up interval and showed results clearly in favour of injection.

Two reviews have recently compared surgical decompression of the carpal tunnel with conservative treatment regimens (Klokkari 2018; Shi 2020). In Shi 2020, seven of the 10 included studies used a corticosteroid injection, either alone or as part of combination therapy, as the comparator. The change in symptoms at three months was comparable to that achieved by surgery, but with considerable heterogeneity (I^2 = 96%), and there was no subgroup analysis for the studies using corticosteroids alone. In Klokkari 2018, in which six of 15 included studies involved corticosteroid injection, the authors reported no difference between surgery and conservative management at three months, but somewhat greater benefit for surgery than conservative management at six months. Again, heterogeneity was high, and there were no subgroup analyses for particular types of non-surgical intervention. The fact that a group of studies, most of which included corticosteroid injection, produced similar symptomatic benefit at three months to a treatment which is widely considered to be 'definitive' (surgery), provides circumstantial evidence in support of our conclusions.

One review carried out for the American Association of Orthopaedic Surgeons concluded that corticosteroids were more effective than non-steroidal anti-inflammatory drugs and diuretics, but that more work was required on duration of effect and use of repeated injections (Ono 2010).

AUTHORS' CONCLUSIONS

Implications for practice

Local corticosteroid injection (LCI) is effective for the treatment of mild and moderate carpal tunnel syndrome (CTS) with benefits lasting up to six months and possibly a reduced need for surgery up to 12 months. The dosage of corticosteroid may not be important at up to three months; however, after three months, higher dose groups (approximately 80 mg equivalent of methylprednisolone) seem to have superior symptom and functional outcomes than moderate dose groups (approximately 40 mg equivalent of methylprednisolone) who have superior outcomes compared to low dose (approximately 20 mg equivalent of methylprednisolone) groups. Serious complication rates in the included studies were rare, where reported at all. We could not determine if the inclusion of local anaesthetic makes any difference to the outcomes.

Implications for research

Despite the strength of the primary conclusion in this review, considerable uncertainties remain around the use of LCI for CTS. We require better long-term (more than three-month) outcome studies, especially studies addressing the questions of whether LCI reduces the requirement for surgery, or whether repeated injections become less or more successful over time, result in increased injection complications, or adversely affect the outcomes from subsequent surgery. It remains unclear whether a long-term strategy of repeated injection as necessary is superior or inferior to early surgery, or surgery on relapse after a single injection. Designs of future studies should use 'participants' (and not 'hands') as the unit of analysis.

In the course of this review it has also become apparent that corticosteroid injection at the wrist is a complex intervention with many variations in the way it is performed. Significant variables may include the:

- type of corticosteroid injected;
- dose of corticosteroid injected;
- total volume of injectate;
- addition of an LA to the injectate;
- exact site of injection (into the tunnel or proximal or distal to it);
- use of ultrasound guidance;
- use of 'hydrodissection' – an attempt to hydraulically separate the median nerve from surrounding structures with the injectate under ultrasound guidance, a procedure which has often been performed with an injectate containing a large dose of corticosteroid.

Independent therapeutic effects in CTS have been claimed for hydrodissection (Wu 2019), LAs (Karadaş 2012), and the injection of an apparently neutral fluid such as 5% dextrose (Aghaee 2018; Wu 2018a). Future studies should attempt to eliminate as many of these confounding factors as possible from their designs unless they are the variables of interest. Limited evidence indicates that methylprednisolone 80 mg injections may be more effective than methylprednisolone 40 mg in reducing the need for surgery but, conversely, smaller doses have also been found to be effective. Further high-quality studies to establish the optimum dose of corticosteroid, with follow-up periods of at least one year should be the priority.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Armstrong 2004

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel group **Unit of analysis (hands or participants):** participants (explicitly stated) **Country:** USA **Setting:** hospital **Dates:** recruitment between November 1998 and January 2000
Participants	**Baseline characteristics** Local corticosteroid injection • *Age (mean)*: 51.9 years • *Sex (% female)*: 35% • *BCTQ (SSS)*: 2.5 • *BCTQ (FSS)*: 2.3 • *Median DML*: 5.6 • *Median SCV*: not reported • *Number of hands randomised*: 43 • *Number of participants randomised*: 43 Placebo injection • *Age (mean)*: 51.2 years • *Sex (% female)*: 28% • *BCTQ (SSS)*: 2.6 • *BCTQ (FSS)*: 2.5 • *Median DML*: 5.7 • *Median SCV*: not reported • *Number of hands randomised*: 38 • *Number of participants randomised*: 38 Overall • *Age (mean)*: not reported • *Sex (% female)*: not reported • *BCTQ (SSS)*: not reported • *BCTQ (FSS)*: not reported • *Median DML*: not reported

Armstrong 2004 *(Continued)*

- *Median SCV*: not reported
- *Number of hands randomised*: 81
- *Number of participants randomised*: 81

Inclusion criteria: aged 18–80 years with typical symptoms of CTS (nocturnal, postural or usage-associated paraesthesias in the median nerve distribution, with or without pain), with symptoms refractory to activity modification and use of a night splint for ≥ 6 weeks' duration. Daytime splint usage, treatment with NSAIDs, or non-traditional treatments were permitted but not required for inclusion in the trial.

Exclusion criteria: CTR on the symptomatic side; previous corticosteroid injection in either carpal tunnel; treatment with systemic (injected or oral) corticosteroids during previous 6 months; current use of warfarin; pregnancy; serious illness; inability to complete an 18-month study; allergy to lidocaine or corticosteroid medications; fracture in the affected wrist or hand in previous 12 months; or current participation in another study.

Pretreatment: none that were different at baseline

Interventions	**Intervention characteristics** Local corticosteroid injection • *Dosage*: (1 mL) 6 mg • *Type of corticosteroid*: betamethasone • *Location of injection*: wrist • *LA (or not)*: 1 mL 1% lidocaine Placebo injection • *Dosage*: 1 mL • *Type of corticosteroid*: none (saline) • *Location of injection*: wrist • *LA (or not)*: 1 mL 1% lidocaine
Outcomes	*BCTQ (SSS)* • **Outcome type:** continuous *BCTQ (FSS)* • **Outcome type:** continuous *Median DML* • **Outcome type:** continuous *Adverse events* • **Outcome type:** dichotomous *Median sensory latency change* • **Outcome type:** continuous • **Reporting:** fully reported • **Range:** 0 to 20 • **Unit of measure:** ms • **Direction:** lower is better • **Data value:** change from baseline
Identification	**Sponsorship source:** Southern California Kaiser Permanente Department of Research and Evaluation provided the funding

Armstrong 2004 *(Continued)*

	Conflicts of interest: not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Treatment was determined by a computer-generated randomization schedule." Computer-generated randomisation table, read by nurse who prepared and wrapped syringes.
Allocation concealment (selection bias)	Low risk	Nurse who read the randomisation list and prepared the syringes was not otherwise involved in the study.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Contents of syringes were concealed from injector and participant. Both injections contained lidocaine so would have felt similar. All follow-up assessments were blind to allocation at 2 weeks.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All outcome assessors were blind to treatment allocation at 2 weeks – the treatments were indistinguishable.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 dropouts, all data remained fully reported except for the baseline SCV.
Selective reporting (reporting bias)	Low risk	No prior published protocol available for this trial but all outcomes described in the methods were presented in the results.
Other bias	Low risk	Quote: "For patients receiving bilateral injections, the more symptomatic side was considered the study hand for purposes of outcome analysis. If the symptoms were equal on the two sides, the dominant hand was taken as the study hand. The patient was instructed to consider only the study hand when answering questions concerning outcome of injections."

Atroshi 2013

Study characteristics

Methods	**Study design:** RCT **Study grouping:** parallel group **Unit of analysis (hands or participants):** participants **Country:** Sweden **Setting:** hospital **Dates:** enrolment started in November 2008, and follow-up was completed in March 2012.
Participants	**Baseline characteristics** Local corticosteroid injection

Atroshi 2013 *(Continued)*

- *Age (mean)*: 45.5 years
- *Sex (% female)*: 71.5%
- *BCTQ (SSS)*: 3.03
- *QUICKDASH*: 40.35
- *Median/ulnar sensory latency difference*: 1.55
- *Quality of life (SF6D)*: 0.70
- *Number of hands randomised*: 74
- *Number of participants randomised*: 74

High-dose corticosteroid injection

- *Age (mean)*: 47 years
- *Sex (% female)*: 70%
- *BCTQ (SSS)*: 2.93
- *QUICKDASH*: 39.9
- *Median/ulnar sensory latency difference*: 1.7
- *Quality of life (SF6D)*: 0.71
- *Number of hands randomised*: 37
- *Number of participants randomised*: 37

Placebo injection

- *Age (mean)*: 49 years
- *Sex (% female)*: 76%
- *BCTQ (SSS)*: 3.18
- *QUICKDASH*: 44.0
- *Median/ulnar sensory latency difference*: 1.5
- *Quality of life (SF6D)*: 0.71
- *Number of hands randomised*: 37
- *Number of participants randomised*: 37

Medium-dose corticosteroid injection

- *Age (mean)*: 44 years
- *Sex (% female)*: 73%
- *BCTQ (SSS)*: 3.13
- *QUICKDASH*: 40.8
- *Median/ulnar sensory latency difference*: 1.4
- *Quality of life (SF6D)*: 0.69
- *Number of hands randomised*: 37
- *Number of participants randomised*: 37

Overall

- *Age (mean)*: not reported
- *Sex (% female)*: not reported
- *BCTQ (SSS)*: not reported
- *QUICKDASH*: not reported
- *Median/ulnar sensory latency difference*: not reported
- *Quality of life (SF6D)*: not reported
- *Number of hands randomised*: 111
- *Number of participants randomised*: 111

Inclusion criteria: people referred by primary care physicians to 1 orthopaedic department for evaluation were examined by trial investigators (orthopaedic surgeons) and screened; primary idiopathic CTS, aged 18–70 years, symptoms of classic or probable CTS (numbness or tingling in ≥ 2 of the 4 radi-

Atroshi 2013 *(Continued)*

	al fingers) according to the Katz diagnostic criteria, unsuccessful 2-month treatment with wrist splinting, symptom severity that warranted referral for consideration for surgery, nerve conduction test results that showed median neuropathy at the wrist. If nerve conduction test results were normal, 2 orthopaedic surgeons independently diagnosed the person with CTS. **Exclusion criteria:** previous corticosteroid injection, thenar muscle atrophy, sensory loss (2-point discrimination 8 mm), diabetes mellitus, thyroid disorder, inflammatory disease, polyneuropathy, current pregnancy, previous CTR, surgery on the contralateral hand in past 2 months, inability to respond to questionnaires, severe illness and drug or alcohol abuse
Interventions	**Intervention characteristics** Local corticosteroid injection • *Dosage*: half of combined group received 40 mg and the other half received 80 mg • *Type of corticosteroid*: methylprednisolone • *Location of injection*: 1 cm proximal to the wrist crease, ulnar to the midline, and advanced in a 45° to 60° angle to the forearm • *LA (or not)*: 1 mL lidocaine High-dose corticosteroid injection • *Dosage*: 80 mg • *Type of corticosteroid*: methylprednisolone • *Location of injection*: 1 cm proximal to the wrist crease, ulnar to the midline, and advanced in a 45° to 60° angle to the forearm • *LA (or not)*: 1 mL lidocaine Placebo injection • *Dosage*: 2 mL • *Type of corticosteroid*: none (saline) • *Location of injection*: 1 cm proximal to the wrist crease, ulnar to the midline, and advanced in a 45° to 60° angle to the forearm • *LA (or not)*: 1 mL lidocaine Medium-dose corticosteroid injection • *Dosage*: 40 mg • *Type of corticosteroid*: methylprednisolone • *Location of injection*: 1 cm proximal to the wrist crease, ulnar to the midline, and advanced in a 45° to 60° angle to the forearm • *LA (or not)*: 1 mL lidocaine
Outcomes	*Change in BCTQ (SSS)* • **Outcome type:** continuous *Change in QUICKDASH* • **Outcome type:** continuous *Requirement for surgery* • **Outcome type:** dichotomous *Change in quality of life* • **Outcome type:** continuous • **Scale:** SF6D • **Unit of measure:** units

Atroshi 2013 *(Continued)*

- **Direction:** higher is better
- **Data value:** change from baseline

Adverse events

- **Outcome type:** dichotomous

Identification	**Sponsorship source:** grant support: by the Region of Scania Research and Development Foundation and Hassleholm Hospital Organization to Isam Atroshi **Conflicts of interest:** none
Notes	Very high rates of surgery in all comparison groups after 12 weeks (73–92% at 1 year) means that outcomes (other than rate of surgery) beyond 3 months could not be used. See Hofer 2021 for 5-year follow-up.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "statistician made a computer-generated randomization list (3 groups; 1:1:1 ratio) in varying blocks. Sequentially numbered, opaque, concealed envelopes containing group assignments were prepared."
Allocation concealment (selection bias)	Low risk	Quote: "plus 1 mL of lidocaine. Randomization was done by the study nurse, who opened the envelope containing the group assignment. In bilateral symptoms, the most symptomatic hand (identified by the patient as the main source of symptoms and activity limitations) was treated." Quote: "The nurse prepared the injection in a covered syringe to mask the orthopedic surgeon and patient immediately after randomization." Quote: "Sequentially numbered, opaque, concealed envelopes containing group assignments were prepared."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The nurse prepared the injection in a covered syringe to mask the orthopedic surgeon and patient immediately after randomization." Although blinding was broken when the last participant had completed one-year follow-up, all CTS surgeries were performed while participants, investigators and surgeons were still blinded to group allocation. Therefore, the bias profile for the requirement for surgery outcome at 5-year follow-up, reported in Hofer 2021, remained low risk.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: patients (who were both participants and assessors as PROMs were used) were kept unaware of test results to avoid possible in fluency on PROMs. Surgeons who conducted the telephone interviews were blind to allocation. At later follow-up visits, the scar area was concealed with a dressing to hide whether surgery had been performed. Although blinding was broken when the last participant had completed 1-year follow-up, all CTS surgeries were performed while participants, investigators and surgeons were still blinded to group allocation. Therefore, the bias profile for the requirement for surgery outcome at 5-year follow-up, reported in Hofer 2021, was no different from the original study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Three patients had missing 10-week data. All patients had 1-year data."

Atroshi 2013 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: trial protocol was published in advance and all planned outcome measures were fully reported in the final paper.
Other bias	Low risk	Comment: 1 hand per participant correctly included (subjectively most severe), and analysed by participant.

Dammers 1999

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel group **Unit of analysis (hands or participants):** participants **Country:** the Netherlands **Setting:** hospital **Dates:** not stated
Participants	**Baseline characteristics** Local corticosteroid injection • *Age (mean)*: 53 years • *Sex (% female)*: 80% • *Number of hands randomised*: 30 • *Number of participants randomised*: 30 Placebo injection • *Age (mean)*: 51 years • *Sex (% female)*: 87% • *Number of hands randomised*: 30 • *Number of participants randomised*: 30 Overall • *Number of hands randomised*: 60 • *Number of participants randomised*: 60 **Inclusion criteria:** people referred to the Medical Centre Alkmaar with signs and symptoms of CTS of > 3 months' duration confirmed by electrophysiological tests. In those with bilateral symptoms, the arm with the most severe symptoms was chosen, and treatment of this arm was randomised. **Exclusion criteria:** aged < 18 years or those who had already been treated for symptoms of CTS.
Interventions	**Intervention characteristics** Local corticosteroid injection • *Dosage*: 40 mg • *Type of corticosteroid*: methylprednisolone • *Location of injection*: at the volar side of the forearm 4 cm proximal to the wrist crease between the tendons of the radial flexor muscle and the long palmar muscle • *LA (or not)*: lignocaine 10 mg

Dammers 1999 *(Continued)*

	Placebo injection • *Dosage*: • *Type of corticosteroid*: none (placebo) • *Location of injection*: at the volar side of the forearm 4 cm proximal to the wrist crease between the tendons of the radial flexor muscle and the long palmar muscle • *LA (or not)*: lidocaine 10 mg
Outcomes	*Requirement for surgery or LCI* • **Outcome type:** dichotomous *Requirement for further treatment* • **Outcome type:** dichotomous • **Reporting:** fully reported • **Direction:** lower is better • **Data value:** change from baseline
Identification	**Sponsorship source:** none **Conflicts of interest:** none declared **Comments:** blinding broken early or at 1 month if more treatment needed.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Using a random number table, the hospital pharmacist prepared the trial drug in blocks of 20."
Allocation concealment (selection bias)	Low risk	Quote: "The syringes for injection were sent from the pharmacy to the outpatient department, where it was impossible to distinguish the syringes containing methylprednisolone plus lignocaine [lidocaine] from those containing lignocaine as paper was glued around the syringes."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "To further ensure blinding, the assessments were carried out by another neurologist (MMV). Neither the doctor nor the participant, therefore, knew what treatment was given. The doctors and participants remained blind to treatment during the assessments at follow up."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All present.
Selective reporting (reporting bias)	Low risk	All reported.
Other bias	Low risk	No other sources of bias identified.

Dehghani 2012

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel group **Unit of analysis (hands or participants):** unclear **Country:** Iran **Setting:** hospital **Dates:** no information
Participants	**Baseline characteristics** Local corticosteroid injection • *Age (mean)*: not reported • *Sex (% female)*: not reported • *VAS (symptoms)*: not reported • *Number of hands randomised*: not reported • *Number of participants randomised*: not reported Hyaluronidase injection • *Age (mean)*: not reported • *Sex (% female)*: not reported • *VAS (symptoms)*: not reported • *Number of hands randomised*: not reported • *Number of participants randomised*: not reported Overall • *Age (mean)*: not reported • *Sex (% female)*: not reported • *VAS (symptoms)*: not reported • *Number of hands randomised*: unsure • *Number of participants randomised*: 88 **Inclusion criteria:** mild and moderate CTS based on clinical and electrodiagnostic studies. Age < 50 years and symptoms < 3 months **Exclusion criteria:** radiculopathies or polyneuropathies **Pretreatment:** not reported
Interventions	**Intervention characteristics** Local corticosteroid injection + splints • *Dosage*: 40 mg • *Type of corticosteroid*: methylprednisolone • *Location of injection*: region of the carpal tunnel • *LA (or not)*: none • *Splinting protocol*: ≥ 2 weeks neutral wrist splint *Splints*

Dehghani 2012 *(Continued)*

	• *Splinting protocol*: ≥ 2 weeks neutral wrist splint
Outcomes	VAS (symptoms) • continuous
Identification	**Sponsorship source:** none **Conflicts of interest:** no information **Comments:** translated from Farsi
Notes	Translated from Farsi – no usable data. Authors did not respond.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as randomised but not described.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported but would be impossible given design.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported but given outcomes were mostly PROM then not possible.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not detailed enough data
Selective reporting (reporting bias)	Low risk	No evidence that they missed anything but limited information.
Other bias	Unclear risk	Not sure if used hands or participants.

Elbaz 1994

Study characteristics	
Methods	**Study design:** prospective, randomised, double-blind study **Unit of analysis (hands or participants):** hands **Country:** Canada **Setting:** hospital **Dates:** not reported
Participants	People with 'mild' CTS

Elbaz 1994 *(Continued)*

	Number of hands randomised: 54 *Number of participants randomised*: 37
Interventions	Betamethasone 3 mg + splinting 6 weeks Normal saline 1 mL + splinting 6 weeks
Outcomes	"Clinical and electrophysiological" outcomes measured at baseline and 6 weeks (not reported) No differences reported between groups
Identification	**Sponsorship source:** not reported **Conflicts of interest:** not reported
Notes	Abstract only – authors did not respond to request for further information. Canadian

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated "randomized" but not described.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated "double blind" but unclear methods.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Inadequately described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	This was an abstract only and the authors did not respond to requests for further information. It is unclear what 'clinical parameters' means, neither is the electrophysiology described and no numbers are presented.
Selective reporting (reporting bias)	Unclear risk	Unable to comment.
Other bias	High risk	This was an abstract only and the authors did not respond to requests for further information. The study was not apparently ever fully published in a peer-reviewed journal. Used 'hands' as unit of analysis.

Girlanda 1993

Study characteristics

Methods	**Study design:** RCT

Girlanda 1993 *(Continued)*

Study grouping: parallel group

Unit of analysis (hands or participants): hands

Country: Italy

Setting: hospital

Country: Iran

Setting: hospital

Dates: no information

Participants	**Baseline characteristics** Local corticosteroid injection • *Age (mean)*: 44 years • *Sex (% female)*: 87% • Symptoms: median composite score 8/16 • *Median DML*: 5.76 ms • *Number of hands randomised*: 26 • *Number of participants randomised*: 16 Saline injection • *Age (mean)*: 47 years • *Sex (% female)*: 75% • Symptoms: median composite score 9/16 • *Median DML*: 6.07 ms • *Number of hands randomised*: 27 • *Number of participants randomised*: 16 Overall • *Age (mean)*: not reported • *Sex (% female)*: not reported • Symptoms: not reported • *Median DML*: not reported • *Number of hands randomised*: 53 • *Number of participants randomised*: 32 **Inclusion criteria:** with clinical and electrophysiological evidence of idiopathic CTS based on usual symptoms and signs. The electrophysiological investigations for diagnosis consisted of electromyographic examination of abductor pollicis brevis, abductor digiti minimi and flexor carpi radialis muscles, motor and antidromic sensory conduction velocities of median and ulnar nerves. **Exclusion criteria:** known causes of entrapment neuropathies or systemic diseases were excluded by means of extensive laboratory investigations; previously received any treatment for CTS. **Pretreatment:** none look significantly different at baseline
Interventions	**Intervention characteristics** Local corticosteroid injection • *Dosage*: 15 mg × 2 (2nd given 1 week later) • *Type of corticosteroid*: methylprednisolone • *Location of injection*: wrist • *LA (or not)*: none

Girlanda 1993 *(Continued)*

	Placebo injection • *Dosage*: "same volume as steroid" (2nd given 1 week later) • *Type of corticosteroid*: none (saline) • *Location of injection*: wrist • *LA (or not)*: none
Outcomes	Symptom score based on scoring 4 types of symptoms (paraesthesias, nocturnal acroparaesthesias, pain and motor deficit) from 0 = absent; 1 = very mild; 2 = mild; 3 = moderate; 4 = marked and adding total score • **Outcome type:** ordinal Clinical signs score based on scoring 3 types of signs (weakness, atrophy and hypaesthesia) from 0 = absent; 1 = very mild; 2 = mild; 3 = moderate; 4 = marked and adding total score • **Outcome type:** ordinal Median sensory latency • **Outcome type:** continuous *Median DML* • **Outcome type:** continuous *Adverse events* • **Outcome type:** dichotomous
Identification	**Sponsorship source:** Institute of Neurological and Neurosurgical Sciences, University of Messina. Sicily, Italy **Conflicts of interest:** not reported
Notes	Outcomes only reported as P values hence unusable. No response from authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly assigned to one of two groups."
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Clinical and electrophysiological findings were evaluated, double blind, at regular intervals."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts were not mentioned. Mostly only P values were reported.

Girlanda 1993 *(Continued)*

Selective reporting (reporting bias)	Low risk	All reported.
Other bias	Unclear risk	Used 'hands' as unit of analysis.

Karadaş 2011

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel group **Unit of analysis (hands or participants):** hands **Country:** Turkey **Setting:** hospital **Dates:** not reported
Participants	**Baseline characteristics** Local corticosteroid injection • *Age (mean)*: 48.02 years • *Sex (% female)*: 85% • *VAS (symptoms)*: 5.65 • *Median DML*: 3.99 • *Median SCV*: 42.59 • *Number of hands randomised*: 40 • *Number of participants randomised*: 34 Procaine injection • *Age (mean)*: 46.75 years • *Sex (% female)*: 87% • *VAS (symptoms)*: 5.92 • *Median DML*: 3.89 • *Median SCV*: 42.03 • *Number of hands randomised*: 40 • *Number of participants randomised*: 32 Procaine injection + LCI • *Age (mean)*: 46.35 years • *Sex (% female)*: 88% • *VAS (symptoms)*: 5.87 • *Median DML*: 4.06 • *Median SCV*: 41.26 • *Number of hands randomised*: 40 • *Number of participants randomised*: 33 Overall • *Age (mean)*: not reported • *Sex (% female)*: not reported

Karadaş 2011 *(Continued)*

- *VAS (symptoms)*: not reported
- *Median DML*: not reported
- *Median SCV*: not reported
- *Number of hands randomised*: 120
- *Number of participants randomised*: 99

Inclusion criteria: symptoms of CTS, including nocturnal paraesthesia, pain in the median nerve distribution during activity, or numbness in the median nerve distribution, and positive electrophysiology study results; aged > 18 years; with symptoms for < 1 year

Exclusion criteria: evidence of inflammatory arthritis, hypothyroidism, previous wrist trauma, or pregnancy; previously been injected with corticosteroids or LAs into the carpal tunnel, splinted, or operated on at the carpel tunnel; people with fibrillation potentials, positive sharp waves or chronic neuropathic changes (decreased recruitment pattern, long duration or high amplitude of motor unit potentials) during needle electromyography and people with both normal motor and sensory conduction values

Interventions	**Intervention characteristics** Local corticosteroid injection • *Dosage*: 40 mg • *Type of corticosteroid*: triamcinolone acetonide • *Location of injection*: 1 cm proximal to the distal wrist-flexion crease, between palmaris longus and flexor carpi radialis tendons • *LA (or not)*: none Procaine injection • *Dosage*: 40 mg in 4 mL • *Type of corticosteroid*: none (procaine) • *Location of injection*: 1 cm proximal to the distal wrist-flexion crease, between palmaris longus and flexor carpi radialis tendons • *LA (or not)*: procaine is the 'active treatment' Procaine injection + LCI • *Dosage*: 40 mg • *Type of corticosteroid*: triamcinolone acetonide • *Location of injection*: 1 cm proximal to the distal wrist-flexion crease, between palmaris longus and flexor carpi radialis tendons • *LA (or not)*: 40 mg procaine in 4 mL
Outcomes	*VAS (symptoms)* • **Outcome type:** continuous *Median DML* • **Outcome type:** continuous *Median SCV* • **Outcome type:** continuous *Adverse events* • **Outcome type:** dichotomous
Identification	**Sponsorship source:** not stated

Karadaş 2011 *(Continued)*

	Conflicts of interest: (quote) "no conflicts of interest have been reported by the authors or by any individuals in control of the content of this article."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details of sequence generation in paper.
Allocation concealment (selection bias)	Unclear risk	No description in paper.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Separate investigator, unaware of treatment group performed nerve conduction studies. Did not specifically state that participants were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Most outcomes were blinded, although possibly not VAS, given that it was participant reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts declared.
Selective reporting (reporting bias)	Low risk	All planned outcomes appeared to be reported.
Other bias	Unclear risk	Unit of analysis was by hand with no adjustment in statistical analysis.

Karadaş 2012

Study characteristics

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Unit of analysis (hands or participants):** hands **Country:** Turkey **Setting:** hospital **Dates:** not reported
Participants	**Baseline characteristics** Local corticosteroid injection • *Age (mean)*: 46.4 years • *Sex (% female)*: 85% • *BCTQ (SSS)*: 2.73 • *VAS (symptoms)*: 6.01

Karadaş 2012 *(Continued)*

- *BCTQ (FSS)*: 2.77
- *Median DML*: 4.11
- *Median SCV*: 41.45
- *Number of hands randomised*: 30
- *Number of participants randomised*: 20

Placebo injection

- *Age (mean)*: 48.4 years
- *Sex (% female)*: 89%
- *BCTQ (SSS)*: 2.72
- *VAS (symptoms)*: 6.11
- *BCTQ (FSS)*: 2.82
- *Median DML*: 4.24
- *Median SCV*: 40.76
- *Number of hands randomised*: 30
- *Number of participants randomised*: 19

Procaine injection

- *Age (mean)*: 46.8 years
- *Sex (% female)*: 89%
- *BCTQ (SSS)*: 2.63
- *VAS (symptoms)*: 5.90
- *BCTQ (FSS)*: 2.79
- *Median DML*: 4.08
- *Median SCV*: 41.67
- *Number of hands randomised*: 30
- *Number of participants randomised*: 18

Overall

- *Age (mean)*: not reported
- *Sex (% female)*: not reported
- *BCTQ (SSS)*: not reported
- *VAS (symptoms)*: not reported
- *BCTQ (FSS)*: not reported
- *Median DML*: not reported
- *Median SCV*: not reported
- *Number of hands randomised*: 90
- *Number of participants randomised*: 57

Inclusion criteria: people with clinically suspected primary CTS referred to hospital electromyography laboratory with symptoms of CTS, including nocturnal paraesthesia, pain in the median nerve distribution during activity or numbness in the median nerve distribution, and positive electrophysiology study results; aged > 18 years and symptoms for < 1 year. Among the participants with bilateral symptoms and positive electrophysiology findings, both hands were included in the study.

Exclusion criteria: inflammatory arthritis, hypothyroidism, previous wrist trauma, or pregnancy, previous injection with corticosteroids or LAs into the carpal tunnel, splinted, or operated on the carpal tunnel. People with fibrillation potentials, positive sharp waves or chronic neuropathic changes (decreased recruitment pattern, long duration or high amplitude of motor unit potentials) during needle electromyography, and people in whom both motor and sensory conduction values were normal were excluded.

Pretreatment: no apparent difference between groups

Karadaş 2012 *(Continued)*

Interventions	**Intervention characteristics** Local corticosteroid injection • *Dosage*: 40 mg • *Type of corticosteroid*: triamcinolone acetonide • *Location of injection*: 25 G needle was inserted 1 cm proximal to the distal wrist-flexion crease, between the palmaris longus and the flexor carpi radialis tendons. The needle was introduced slowly and the injection was stopped if the participant experienced pain or the sensation of pins and needles in the median nerve distribution. Following appropriate needle placement, the injections were administered. Each participant was injected only once. • *LA (or not)*: no Placebo injection • *Dosage*: 1 mL • *Type of corticosteroid*: none (0.09% saline) • *Location of injection*: 25 G needle was inserted 1 cm proximal to the distal wrist-flexion crease, between the palmaris longus and the flexor carpi radialis tendons. The needle was introduced slowly and the injection was stopped if the patient experienced pain or the sensation of pins and needles in the median nerve distribution. Following appropriate needle placement, the injections were administered. Each participant was injected only once. • *LA (or not)*: no Topical anaesthetic • *Dosage*: 4 mL 1% procaine • *Location of injection*: 25 G needle was inserted 1 cm proximal to the distal wrist-flexion crease, between the palmaris longus and the flexor carpi radialis tendons. The needle was introduced slowly and the injection was stopped if the patient experienced pain or the sensation of pins and needles in the median nerve distribution. Following appropriate needle placement, the injections were administered. Each participant was injected only once. • *LA (or not)*: 1% procaine
Outcomes	*BCTQ (SSS)* • **Outcome type:** continuous *VAS (symptoms)* • **Outcome type:** continuous *BCTQ (FSS)* • **Outcome type:** continuous *Median DML* • **Outcome type:** continuous *Median SCV* • **Outcome type:** continuous *Adverse events* • **Outcome type:** dichotomous
Identification	**Sponsorship source:** not reported **Conflicts of interest:** not reported

Karadaş 2012 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study participants were randomly assigned to 1 of 3 groups.
Allocation concealment (selection bias)	Unclear risk	No detailed reporting to allow judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The same investigator (unaware of the electrophysiological findings and clinical data) performed all the injections. However, the report does not state if this investigator was blind to allocation nor whether participants were blinded. Trial authors reported that personnel and participants were blinded – but unclear how.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All the nerve conduction studies were performed by the same investigator, who was unaware of the treatment groups. All the patients completed the BCTQ and visual analogue scale (VAS) of pain. BCTQ has two components to assess symptom severity and functional disability."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All present.
Selective reporting (reporting bias)	Low risk	All reported.
Other bias	Unclear risk	The unit of analysis was the hand and no adjustment was made in the statistical analysis.

Khosrawi 2016

Study characteristics

Methods

Study design: randomised controlled trial

Study grouping: parallel group

Unit of analysis (hands or participants): participants (probably)

Country: Iran

Setting: outpatient clinics affiliated to Isfahan University of Medical Sciences

Dates: participants enroled from September 2013 to March 2015

Participants

Baseline characteristics

Local corticosteroid injection (plus splinting)

- *Age (mean)*: 51.86 (SD 11.86) years
- *Sex (% female)*: 90%
- *BCTQ (SSS)*: 2.59
- *BCTQ (FSS)*: 2.15

Khosrawi 2016 *(Continued)*

- *Median DML*: 6.55 (SD 1.8)
- *Median SCV*: 15.38 (SD 7.1)
- *Number of hands randomised*: 21
- *Number of participants randomised*: 21

No treatment (splinting)

- *Age (mean)*: 50.91 (SD 10.41) years
- *Sex (% female)*: 82%
- *BCTQ (SSS)*: 2.5
- *BCTQ (FSS)*: 1.7
- *Median DML*: 5.76 (SD 0.69)
- *Median SCV*: 17.26 (SD 7.19)
- *Number of hands randomised*: 22
- *Number of participants randomised*: 22

Overall

- *Age (mean)*: not reported
- *Sex (% female)*: not reported
- *BCTQ (SSS)*: not reported
- *BCTQ (FSS)*: not reported
- *Median DML*: not reported
- *Median SCV*: not reported
- *Number of hands randomised*: 23
- *Number of participants randomised*: 23

Inclusion criteria: diagnosis of severe CTS, based on the clinical signs and symptoms of CTS including pain, paraesthesia, hypoaesthesia, numbness, tingling, positive Tinel's test (≥ 2 symptoms, or 1 sign plus 1 symptom) and electrodiagnostic evidence of severe CTS (severe: median nerve distal sensory latency (MNDSL) > 3.6 ms and median nerve DML > 4.2 ms with an absent sensory nerve action potential amplitude, or absent thenar compound muscle action potential or decreased thenar compound muscle action potential height).

Exclusion criteria: people with severe CTS who have thenar muscle atrophy and people with a history of inflammatory arthritis, hypothyroidism, diabetes, coexisting serious illness, malignancy, distal radius fracture, fibromyalgia, CTS related to systemic diseases and pregnancy, cervical disc herniation, previous wrist trauma, and history of corticosteroid injection, splint or operation of the carpal tunnel

Pretreatment: no differences

Interventions	**Intervention characteristics** All participants were splinted with a wrist splint (cock-up) that immobilised the wrist in neutral. The splint was prescribed for full-time (24-hour) use. Local corticosteroid injection (plus splinting) • *Dosage*: 40 mg • *Type of corticosteroid*: methylprednisolone • *Location of injection*: 25 G needle was inserted to the `wrist-flexion` crease, just ulnar to the palmaris longus tendon. • *LA (or not)*: none No treatment (splinting) • *Dosage*: none • *Type of corticosteroid*: none • *Location of injection*: none

Khosrawi 2016 *(Continued)*

	• *LA (or not)*: none
Outcomes	*BCTQ (SSS)* • **Outcome type:** continuous *BCTQ (FSS)* • **Outcome type:** continuous *Median DML* • **Outcome type:** continuous *Median SCV* • **Outcome type:** continuous *Adverse events* • **Outcome type:** dichotomous
Identification	**Sponsorship source:** none **Conflicts of interest:** none
Notes	All participants were splinted in the same way hence we judged this to be a comparison of LCI versus 'no treatment.'

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Selected patients with CTS were randomly allocated in two intervention groups using random allocation software." Exact software not reported.
Allocation concealment (selection bias)	Unclear risk	Randomisation and allocation processes not well enough described to determine whether allocation was adequately concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	No attempt was made at blinding because of the nature of the interventions.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Different risk of bias for different outcomes. Could be high risk for PROM.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Trial protocol available and all the planned outcomes were reported.
Other bias	Unclear risk	No mention of how bilateral disease was handled.

O'Gradaigh 2000

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Unit of analysis (hands or participants):** participants (explicitly stated) **Country:** USA **Setting:** hospital **Dates:** recruitment between November 1998 and January 2000
Participants	**Baseline characteristics** Very low dose local corticosteroid injection (hydrocortisone 25 mg) • *Age (mean)*: not reported • *Sex (% female)*: not reported • *Median DML*: 4.8 • *Median SCV*: not reported • *Number of hands randomised*: 32 • *Number of participants randomised*: 32 Low dose local corticosteroid injection (hydrocortisone 100 mg) × 2 groups • *Age (mean)*: not reported • *Sex (% female)*: not reported • *Median DML*: 4.55 • *Median SCV*: not reported • *Number of hands randomised*: 32 + 21 • *Number of participants randomised*: 32 + 21 Low dose local corticosteroid injection (triamcinolone 30 mg) • *Age (mean)*: not reported • *Sex (% female)*: not reported • *Median DML*: 4.7 • *Median SCV*: not reported • *Number of hands randomised*: 18 • *Number of participants randomised*: 18 Local corticosteroid injection (4 groups combined) • *Age (mean)*: not reported • *Sex (% female)*: not reported • *Median DML*: 4.7 • *Median SCV*: not reported • *Number of hands randomised*: 103 • *Number of participants randomised*: 103 No treatment • *Age (mean)*: not reported • *Sex (% female)*: not reported • *Median DML*: 4.3 • *Median SCV*: not reported • *Number of hands randomised*: 20

O'Gradaigh 2000 *(Continued)*

- *Number of participants randomised*: 20

Overall

- *Age (mean)*: not reported
- *Sex (% female)*: not reported
- *BCTQ (SSS)*: not reported
- *BCTQ (FSS)*: not reported
- *Median DML*: not reported
- *Median SCV*: not reported
- *Number of hands randomised*: 123
- *Number of participants randomised*: 123

Inclusion criteria: people attending or newly referred to the rheumatology department with a suspected diagnosis of CTS were invited to participate. Each participant recorded the distribution of symptoms on a hand diagram. Phalen's and Tinel's tests were carried out in the standard manner. Nerve conduction studies compared the ulnar and median nerves, examining the symptomatic and normal hands when applicable (normal values: median nerve latency > 3.7 ms, sensory amplitude > 10 µV, motor velocity > 50 ms^{-1}). Inclusion for randomisation required either positive (i.e. abnormal) nerve conduction studies, or a positive Phalen's and Tinel's test together with a classic distribution of symptoms. Patients with positive and negative nerve conduction studies were randomised separately.

Exclusion criteria: history and examination identified causes of secondary CTS; these patients were excluded from the study. Other exclusion criteria were previous surgical treatment of CTS or corticosteroid injection for CTS within the previous 6 months.

Interventions	**Intervention characteristics** Local corticosteroid injection • *Dosage*: variable • *Type of corticosteroid*: hydrocortisone 25 mg, hydrocortisone 100 mg or triamcinolone 30 mg • *Location of injection*: wrist • *LA (or not)*: none No treatment • Untreated group received nothing
Outcomes	*Subjective change in symptoms* • **Outcome type:** ordinal (5-point Likert) *Subjective change in Tinel's test or Phalen's test* • **Outcome type:** dichotomous (negative or positive) *Nerve conduction study parameters* *Only the medial DML was reported* *Median DML* • **Outcome type:** continuous
Identification	**Sponsorship source:** Southern California Kaiser Permanente Department of Research and Evaluation provided the funding **Conflicts of interest:** not reported
Notes	Data were unusable as we are unable to determine whether the nerve conduction data were from the 6-week or 6-month time point. Plus the outcome of 'symptomatic improvement' just involved asking

O'Gradaigh 2000 *(Continued)*

participants whether they were symptomatically improved or not. Electrodiagnostic outcomes were reported as P values.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Stated "random" but unclear method. Also, participants with positive and negative electrodiagnostic studies were "randomized separately"?
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Stated "blinded" but unclear who and how? The design of the study (injections versus 'no treatment') means it is impossible to blind participants and clinicians.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated but the design of the study will mean that this is likely high risk of bias for the PROM and unclear for the nerve conduction data (used in Cochrane).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not completely reported in paper – unsure if electrodiagnostic outcomes were for 6 weeks or 6 months of follow-up.
Selective reporting (reporting bias)	High risk	Only median DML was reported for electrodiagnostic studies. Key baseline data were missing. Only P values were reported for symptom outcomes.
Other bias	Unclear risk	Study was performed in "two stages" and not entirely clear how the stages were linked. Possible these were 2 completely separate studies or even same participants used in second stage? Also, unclear about how 'bilateral' disease was handled.

Peters-Veluthamaningal 2010

Study characteristics

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Unit of analysis (hands or participants):** participants **Country:** the Netherlands **Setting:** primary care **Dates:** recruitment February 2003 to October 2005, follow-up finished in October 2006
Participants	**Baseline characteristics** Local corticosteroid injection • *Age (mean)*: 56.5 years • *Sex (% female)*: 75% • *BCTQ (SSS)*: 2.89 • *BCTQ (FSS)*: 2.48

Peters-Veluthamaningal 2010 *(Continued)*

- *Number of hands randomised*: 36
- *Number of participants randomised*: 36

Placebo injection

- *Age (mean)*: 57.6 years
- *Sex (% female)*: 79%
- *BCTQ (SSS)*: 2.82
- *BCTQ (FSS)*: 2.35
- *Number of hands randomised*: 33
- *Number of participants randomised*: 33

Overall

- *Age (mean)*: not reported
- *Sex (% female)*: not reported
- *BCTQ (SSS)*: not reported
- *BCTQ (FSS)*: not reported
- *Number of hands randomised*: 69
- *Number of participants randomised*: 69

Inclusion criteria: people presenting to the participating general practitioners with symptoms and signs suggestive of CTS. In participants with bilateral symptoms, general practitioners were instructed to include the hand with the most severe complaints.

Exclusion criteria: thenar atrophy, being less than [missing from paper] years of age, contraindications for corticosteroid injection (hypersensitivity to corticosteroids, local skin infection), prior treatment for CTS in the last 6 months with corticosteroid injection or surgery, traumatic or neoplastic origin of symptoms, inability to fill in follow-up forms, or absence of self-determination in the participant

Pretreatment: none significant

Interventions	**Intervention characteristics** Local corticosteroid injection • *Dosage*: 11 participants received 1 injection (10 mg) and 24 participants received 2 injections (20 mg total) (1 person refused to participate in trial before intervention) • *Type of corticosteroid*: triamcinolone • *Location of injection*: wrist • *LA (or not)*: no Placebo injection • *Dosage*: 1 mL • *Type of corticosteroid*: none (saline) • *Location of injection*: wrist • *LA (or not)*: no
Outcomes	*BCTQ (SSS)* • **Outcome type:** continuous *BCTQ (FSS)* • **Outcome type:** continuous
Identification	**Sponsorship source:** not reported in paper **Conflicts of interest:** (quote) "The authors declare that they have no competing interests."

Peters-Veluthamaningal 2010 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "For the randomisation procedure an electronic online randomization tool developed by G. Urbaniak (www.randomizer.org, accessed on 22.12.2002) was used. Block randomisation was realised by creating 7 sets of blocks of 10 random numbers. Even numbers corresponded with active trial medication and uneven numbers with placebo to ensure equal numbers of allocation to active and placebo treatment. Treatment allocation was written on a paper and enclosed."
Allocation concealment (selection bias)	Low risk	Treatment allocation envelopes were drawn by an independent pharmacist not otherwise involved in the trial who sent the trial medication to the injecting general practitioner.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Because a placebo look-alike of the triamcinolonacetonide injection suspension could not be manufactured, blinding was realised by applying the injection while the participant was blindfolded." A second general practitioner not involved in recruitment or follow-up injected the trial medication; blinding was broken at 2 weeks.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcomes here were the SSS and FSS, which are PROMs; therefore, participant blinding was the important concern and this seemed to have been well done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 losses to follow-up, 1 in corticosteroid group and 2 in placebo groups – otherwise complete outcome data.
Selective reporting (reporting bias)	Low risk	All the declared outcomes in the methods were reported but no published trial protocol identified.
Other bias	Low risk	Quote: "in participants with bilateral symptoms general practitioners were instructed to include the hand with the most severe complaints" – analysis is therefore by participant – 1 hand per participant.

Salman Roghani 2018

Study characteristics

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Unit of analysis (hands or participants):** participants **Country:** Iran **Setting:** hospital **Dates:** participants referred between 2014 and 2016
Participants	**Baseline characteristics**

Salman Roghani 2018 *(Continued)*

Medium-dose corticosteroid injection

- *Age (mean)*: 66 years
- *Sex (% female)*: 87.5%
- *VAS (symptoms)*: 6.22
- *Median DML*: 5.15
- *Median CSA*: 12.23
- *Number of hands randomised*: 35
- *Number of participants randomised*: 35

High-dose corticosteroid injection

- *Age (mean)*: 66.1 years
- *Sex (% female)*: 68.75%
- *VAS (symptoms)*: 7.29
- *Median DML*: 5.08
- *Median CSA*: 11.73
- *Number of hands randomised*: 34
- *Number of participants randomised*: 34

Placebo injection

- *Age (mean)*: 63.4 years
- *Sex (% female)*: 90%
- *VAS (symptoms)*: 5.8
- *Median DML*: 4.69
- *Median CSA*: 12.09
- *Number of hands randomised*: 33
- *Number of participants randomised*: 33

Local corticosteroid injection

- *Age (mean)*: 66 years
- *Sex (% female)*: 78.5%
- *VAS (symptoms)*: 6.76
- *Median DML*: 5.12
- *Median CSA*: 11.98
- *Number of hands randomised*: 69
- *Number of participants randomised*: 69

Overall

- *Age (mean)*: not reported
- *Sex (% female)*: not reported
- *VAS (symptoms)*: not reported
- *Median DML*: not reported
- *Median CSA*: not reported
- *Number of hands randomised*: 102
- *Number of participants randomised*: not reported 102

Inclusion criteria: clinical diagnosis of CTS and electrodiagnostic confirmation of moderate CTS: for clinical diagnosis, our physician examined all patients based on the American Academy of Orthopaedic Surgeons Clinical Practice Guideline recommendations. The examiner included a detailed history, personal characteristics, pace activities, and comorbidities of the patients. Accordingly, he conducted a standard sensory examination, manual muscle testing of the upper extremity, and provocative tests, e.g. Phalen's and compression test and discriminatory tests such as Spurling test for alternative diagnoses. In the electrodiagnostic part, nerve conduction studies were performed by just 1 physician with

Salman Roghani 2018 *(Continued)*

	10 years of experience, based on the guidelines of the American Association of Neuromuscular and Electrodiagnostic Medicine for suspected CTS. The reference values of CTS outlined by Dumitru 2002 were used. Only the dominant hand in patients with bilateral CTS was chosen, in order to optimise patients' function. **Exclusion criteria:** severe weakness, requiring carpal tunnel release; history of CTS treatment or injection; corticosteroid or triamcinolone allergy or contraindication; diabetes mellitus, rheumatoid arthritis, thyroid dysfunction, or any severe heart disease, including life-threatening arrhythmia; neurological disorders such as polyneuropathy, proximal median or ulnar neuropathy, plexopathy, mononeuritis multiplex, and cervical radiculopathy, applying electrodiagnostic tests.
Interventions	**Intervention characteristics** Medium-dose corticosteroid injection • *Dosage*: 40 mg (1 mL) • *Type of corticosteroid*: triamcinolone • *Location of injection*: wrist • *LA (or not)*: 1 mL of 2% lidocaine • *Saline*: 1 mL High-dose corticosteroid injection • *Dosage*: 80 mg (2 mL) • *Type of corticosteroid*: triamcinolone • *Location of injection*: wrist • *LA (or not)*: 1 mL of 2% lidocaine • *Saline*: 1 mL Placebo injection • *Dosage*: 0 • *Type of corticosteroid*: none (saline) • *Location of injection*: wrist • *LA (or not)*: 1 mL of 2% lidocaine • *Saline*: 1 mL
Outcomes	*BCTQ (SSS)* • **Outcome type:** continuous *VAS (symptoms)* • **Outcome type:** continuous *BCTQ (FSS)* • **Outcome type:** continuous *Median DML* • **Outcome type:** continuous *Median CSA* • **Outcome type:** continuous
Identification	**Sponsorship source:** University of Social Welfare and Rehabilitation Sciences (USWR), Tehran, Iran **Conflicts of interest:** (quote): "The authors report no conflicts of interest in this work."

Salman Roghani 2018 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Recruited subjects who met inclusion and exclusion criteria were randomized to one of three groups using a computer-generalized randomization list." Computer-generated randomisation list.
Allocation concealment (selection bias)	Low risk	Quote: "A study nurse was the only investigator aware of the code, and she prepared the study injection medication out of the sight of the injector and patient in an opaque syringe (covered with white opaque paper) based on the group allocation, immediately before the injection procedure."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Each patient received a unique code, indicating their assigned group. A study nurse was the only investigator aware of the code, and she prepared the study injection medication out of the sight of the injector and patient in an opaque syringe (covered with white opaque paper) based on the group allocation, immediately before the injection procedure."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "prospective, triple-blind, randomized."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts fairly similar between groups.
Selective reporting (reporting bias)	Low risk	All reported. However, trial authors combined BCTQ symptoms and function, which made the data unusable in the review.
Other bias	Low risk	None. Only the dominant hand in people with bilateral CTS was chosen.

Ucan 2006

Study characteristics

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Unit of analysis (hands or participants):** hands. However, the authors use "hands" and "participants" interchangeably in paper. **Country:** Turkey **Setting:** hospital **Dates:** recruitment over a period of 6 months, dates not specified
Participants	**Baseline characteristics** Splinting • *Age (mean)*: 44.5 years

Ucan 2006 *(Continued)*

- *Sex (% female)*: 95.7%
- *BCTQ (SSS)*: 2.66
- *BCTQ (FSS)*: 2.47
- *Median DML*: 4.14
- *Median SCV*: 35.36
- *Number of hands randomised*: 23

Local corticosteroid injection and splinting

- *Age (mean)*: 44.46 years
- *Sex (% female)*: 91.3%
- *BCTQ (SSS)*: 2.79
- *BCTQ (FSS)*: 2.19
- *Median DML*: 4.13
- *Median SCV*: 34.13
- *Number of hands randomised*: 23

Surgical carpal tunnel decompression (any method)

- *Age (mean)*: 45.27 years
- *Sex (% female)*: 90.9%
- *BCTQ (SSS)*: 3.09
- *BCTQ (FSS)*: 2.7
- *Median DML*: 4.49
- *Median SCV*: 33.47
- *Number of hands randomised*: 11

Overall

- *Age (mean)*: not reported
- *Sex (% female)*: not reported
- *BCTQ (SSS)*: not reported
- *BCTQ (FSS)*: not reported
- *Median DML*: not reported
- *Median SCV*: not reported
- *Number of hands randomised*: 57
- *Number of participants randomised*: not reported

Inclusion criteria: study group generated from referrals to Ankara Numune Education and Research Hospital Physical Medicine and Rehabilitation Outpatient Clinic with symptoms and signs of suspected CTS over 6 months; diagnosis confirmed with nerve conduction studies and the patients were classified as mild, moderate or advanced CTS according to the American Association of Electrodiagnostic Medicine guidelines

Exclusion criteria: people with advanced CTS or thenar atrophy, or with underlying aetiologies, i.e. metabolic disorders such as diabetes mellitus, thyroid, kidney diseases, connective tissue disorders, malignancy, distal radius fracture, and pregnancy, or conditions that could affect the management response, such as cervical disc herniation, fibromyalgia and previous CTS treatment

Interventions	**Intervention characteristics** Splinting • *Splinting protocol*: the hands were splinted in neutral position with a standard cotton–polyester splint. Participants were encouraged to use the splints at night-time and daytime whenever possible for 3 months Local corticosteroid injection and splinting

Ucan 2006 *(Continued)*

- *Dosage*: 20 mg
- *Type of corticosteroid*: triamcinolone
- *Location of injection*: the penetration point of the needle was just ulnar to the palmaris longus tendon with an angle of 60°
- *LA (or not)*: lidocaine 20 mg
- S*plinting protocol*: nocturnal + encouraged daytime

Surgical carpal tunnel decompression (any method)

- *Surgery type*: flexor retinaculum was sectioned completely with a short incision.

Outcomes	*BCTQ (SSS)* • **Outcome type:** continuous *BCTQ (FSS)* • **Outcome type:** continuous *Median DML* • **Outcome type:** continuous *Median SCV* • **Outcome type:** continuous *Adverse events* • **Outcome type:** dichotomous
Identification	**Sponsorship source:** not stated **Conflicts of interest:** not reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly enumerated." Note the design was intended to produce 3 equal-sized groups.
Allocation concealment (selection bias)	Low risk	Quote: "closed envelopes which contained the three treatment methods were given consecutively to each patient."
Blinding of participants and personnel (performance bias) All outcomes	High risk	None of the participants or personnel were blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Very little blinding possible with this design especially for PROM.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Four patients who did not accept operation after joining the study, five patients who could not be reached for assessments in the third or sixth month, and 1 patient who was diagnosed with rheumatoid arthritis after the study were excluded."

Ucan 2006 *(Continued)*

		All components appeared to have been reported, but the dropouts in the surgical group make this particular comparison suspect. Splint versus splint + injection less subject to bias. The number of participants who completed the study was not provided. 4 out of the surgery group refused surgery – likely high percentage given only 11 hands completed study (≥ 27%). 5 other dropouts plus 1 participant who developed rheumatoid arthritis; we are unsure which group.
Selective reporting (reporting bias)	Unclear risk	Particularly in respect to adverse events, which were not defined appropriately.
Other bias	High risk	Unclear if the study used hands or participants as unit of analysis. Very asymmetrical group sizes (because of very high (> 50%) surgical dropout rate). No primary outcome stated. Multiple statistical tests without correction group size for the surgical group much smaller.

Wu 1991

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Unit of analysis (hands or participants):** hands **Country:** China **Setting:** hospital **Dates:** not reported
Participants	**Baseline characteristics** Local corticosteroid injection plus splinting • *Age (mean)*: not reported • *Sex (% female)*: not reported • *Median DML*: 5.3 • *Median SCV*: 54 • *Number of hands randomised*: 18 • *Number of participants randomised*: 16 Splinting • *Age (mean)*: not reported • *Sex (% female)*: not reported • *Median DML*: 5.2 • *Median SCV*: 52 • *Number of hands randomised*: 19 • *Number of participants randomised*: 17 Overall • *Age (mean)*: not reported • *Sex (% female)*: not reported • *Number of hands randomised*: 37 • *Number of participants randomised*: 33

Wu 1991 *(Continued)*

	Inclusion criteria: clinical and electrodiagnostic criteria. 3 months of symptoms and electrodiagnostic findings (motor DML > 4 ms, sensory < 32 m/s) **Exclusion criteria:** "severe CTS" and no other diagnoses **Pretreatment:** only have electrodiagnostic findings to compare, which seemed similar.
Interventions	**Intervention characteristics** Local corticosteroid injection • *Dosage*: not reported (1 mL for up to 3 injections but unknown dose) • *Type of corticosteroid*: dexamethasone • *Location of injection*: wrist • *LA (or not)*: 1 mL 1% lidocaine • Also given splints: 24 hours/day for 2 weeks then just night-time for remaining 2 months. Neutral to 30° Splinting • *Splinting protocol*: 24 hours/day for 2 weeks then just night-time for remaining 2 months. Neutral to 30°
Outcomes	Measured at 1 and 2 months *Median DML* • **Outcome type:** continuous outcome *Median SCV* • **Outcome type:** continuous outcome
Identification	**Sponsorship source:** not stated **Conflicts of interest:** not stated
Notes	Translated from Mandarin. Included 5 different comparison groups: vitamins B_6/B_{12}, corticosteroid injection, splints, vitamins B_6/B_{12} + splints, corticosteroids + splints.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reports "randomized" but unclear how.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported but unlikely to be able to blind in this design. Probably unblinded given the nature of the interventions.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported, but it is possible they were blinded given the outcomes were nerve conduction study findings.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Apparently no dropouts.

Wu 1991 *(Continued)*

Selective reporting (reporting bias)	Low risk	They seemed to have reported everything they set out to.
Other bias	High risk	No baseline comparison of key demographic or other data so unsure if randomisation was effective. Used hands as unit of analysis.

BCTQ: Boston Carpal Tunnel Questionnaire; CTR: carpal tunnel release; CTS: carpal tunnel syndrome; DML: distal motor latency; FSS: Functional Status Scale; QUICKDASH: Disabilities of the Arm, Shoulder and Hand (abbreviated version); NSAID: non-steroidal anti-inflammatory drug; PROMS: participant-reported outcome measures; SCV: sensory conduction velocity; SD: standard deviation; SF6D: Short-Form Six-Dimension health index; SSS: Symptom Severity Scale; VAS: visual analogue scale.

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

Study	Reason for exclusion
Aygul 2005	Wrong comparison
Bardak 2009	Wrong comparator
Basu 2019	Wrong comparison
Bilgici 2010	Wrong comparison
Boyer 2008	Wrong study design
Celik 2016	Wrong study design
Dammers 2006	Wrong comparison
De Entrambasaguas 2006	Wrong comparison
Dernek 2017	Not randomised
Elbaz 1992	Unobtainable
Ginanneschi 2012	Wrong comparison
Gökoğlu 2005	Wrong comparison
Habib 2006	Wrong study design
Hong 2015	Wrong study design
Hsu 2018	Wrong study design
Kirschner 2011	No usable data
Kocaoglu 2017	Wrong comparison
Kotb 2014	Wrong comparator
Lampl 2009	Wrong comparator
Makhlouf 2014	Wrong comparison

Study	Reason for exclusion
Manz 1974	Wrong study design
Moghtaderi 2009	Wrong comparison
Monov 2017	Not randomised
Mottaghi 2019	Wrong intervention
Nair 2020	Wrong comparator
Nalamachu 2006	Wrong comparison
Ozdogan 1984	Wrong comparison
Rayegani 2019	Wrong comparison
Santoso 2020	Wrong study design
Schuchmann 1971	Wrong study design
Seror 1989	Wrong study design
Sevim 2004	Wrong comparator
Taspinar 2007	Wrong comparison
Ustun 2013	Wrong comparison
Uzun 2017	Wrong study design
Vahdatpour 2019	Wrong comparison
Wong 2005	Wrong comparison
Wu 2018b	Wrong comparison

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

CTRI201812016604

Study name	A clinical trial to compare three ultrasound guided therapies for management of patients with carpal tunnel syndrome
Methods	Randomised controlled trial
Participants	People with CTS aged ≥ 18 years having nerve conduction studies for confirmed CTS with persistent symptoms and not resolving with medications or splinting
Interventions	Intervention 1: normal saline: 5–10 mL normal saline (hydrodissection fluid) Intervention 2: corticosteroid + normal saline: 7–10 mL of hydrodissection fluid comprising 2 mL injectate (1 mL triamcinolone 40 mg + 1 mL 1% lidocaine) and the remainder normal saline

CTRI201812016604 *(Continued)*	Control intervention 1: corticosteroid injection: 2 mL of injectate comprising 1 mL triamcinolone 40 mg and 1 mL of 1% lidocaine
Outcomes	Primary outcome: change from baseline of: severity of symptoms and functional status using BCTQ; pain using VAS; cross-sectional area of the median nerve using ultrasound; conduction velocity and amplitude of median nerve as and when applicable Time points: 4, 12 and 24 weeks (when feasible) postprocedure No secondary outcomes
Starting date	2018
Contact information	Anupama Tandon; anupamatandon@hotmail.com; University College of Medical Sciences and GTB Hospital, Delhi, India
Notes	Supported by University College of Medical Sciences and Guru Teg Bahadur Hospital, Dilshad Garden, Delhi 110095, India

BCTQ: Boston Carpal Tunnel Questionnaire; CTS: carpal tunnel syndrome; VAS: visual analogue scale.

DATA AND ANALYSES

Comparison 1. Local corticosteroid injection (LCI) versus control: improvement in symptoms

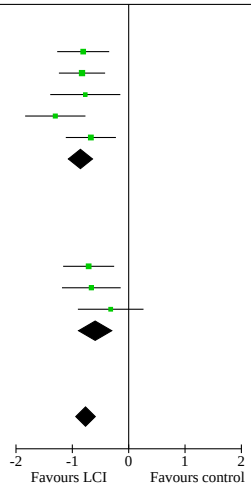
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Symptoms ≤ 3 months	8	579	Std. Mean Difference (IV, Random, 95% CI)	-0.77 [-0.94, -0.59]
1.1.1 LCI versus control	5	393	Std. Mean Difference (IV, Random, 95% CI)	-0.86 [-1.07, -0.64]
1.1.2 LCI versus control (hands as unit of analysis)	3	186	Std. Mean Difference (IV, Random, 95% CI)	-0.60 [-0.89, -0.30]
1.2 Symptoms > 3 months	3	234	Std. Mean Difference (IV, Random, 95% CI)	-0.58 [-0.89, -0.28]
1.2.1 LCI versus control	1	94	Std. Mean Difference (IV, Random, 95% CI)	-0.84 [-1.30, -0.39]
1.2.2 LCI versus control (hands as unit of analysis)	2	140	Std. Mean Difference (IV, Random, 95% CI)	-0.44 [-0.77, -0.10]
1.3 Symptoms ≤ 3 months by local anaesthetic (LA) use	8		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.3.1 LCI versus saline	2	111	Std. Mean Difference (IV, Random, 95% CI)	-1.02 [-1.62, -0.41]
1.3.2 LCI versus LA	2	105	Std. Mean Difference (IV, Random, 95% CI)	-0.50 [-0.92, -0.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3.3 LCI versus no treatment	1	43	Std. Mean Difference (IV, Random, 95% CI)	-0.77 [-1.39, -0.15]
1.3.4 LCI+LA versus saline+LA	3	284	Std. Mean Difference (IV, Random, 95% CI)	-0.77 [-1.02, -0.52]
1.3.5 LCI+LA versus LA	1	60	Std. Mean Difference (IV, Random, 95% CI)	-1.74 [-2.37, -1.12]
1.3.6 LCI+LA+splints versus splints	1	46	Std. Mean Difference (IV, Random, 95% CI)	-0.32 [-0.90, 0.26]
1.4 Symptoms > 3 months by LA use	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.4.1 LCI versus saline	1	45	Std. Mean Difference (IV, Random, 95% CI)	-0.60 [-1.23, 0.04]
1.4.2 LCI versus LA	2	105	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-0.69, 0.13]
1.4.3 LCI+LA versus saline+LA	2	154	Std. Mean Difference (IV, Random, 95% CI)	-0.73 [-1.07, -0.39]
1.4.4 LCI+LA versus LA	1	60	Std. Mean Difference (IV, Random, 95% CI)	-1.98 [-2.63, -1.33]
1.4.5 LCI+LA+splints versus splints	1	46	Std. Mean Difference (IV, Random, 95% CI)	0.89 [0.28, 1.50]
1.5 Symptoms ≤ 3 months by corticosteroid dose	8		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.5.1 Low-dose (approx 20 mg equivalent methylprednisolone) LCI versus control	2	112	Std. Mean Difference (IV, Random, 95% CI)	-0.82 [-1.78, 0.15]
1.5.2 Medium-dose (approx 40 mg equivalent methylprednisolone) LCI versus control	6	345	Std. Mean Difference (IV, Random, 95% CI)	-0.60 [-0.88, -0.31]
1.5.3 High-dose (approx 80 mg equivalent methylprednisolone) LCI versus control	2	103	Std. Mean Difference (IV, Random, 95% CI)	-0.93 [-1.51, -0.35]
1.6 Symptoms > 3 months by corticosteroid dose	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.6.1 Low-dose (approx 20 mg equivalent methylprednisolone) LCI versus control	1	46	Std. Mean Difference (IV, Random, 95% CI)	0.89 [0.28, 1.50]
1.6.2 Medium-dose (approx 40 mg equivalent methylprednisolone) LCI versus control	3	187	Std. Mean Difference (IV, Random, 95% CI)	-0.25 [-0.54, 0.04]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.6.3 High-dose (approx 80 mg equivalent methylprednisolone) LCI versus control	1	47	Std. Mean Difference (IV, Random, 95% CI)	-1.47 [-2.16, -0.78]
1.7 Symptoms ≤ 3 months by duration of action of corticosteroid	8		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.7.1 Intermediate-acting (12–36 hours) LCI versus control	7	500	Std. Mean Difference (IV, Random, 95% CI)	-0.76 [-0.96, -0.56]
1.7.2 Long-acting (> 48 hours) LCI versus control	1	79	Std. Mean Difference (IV, Random, 95% CI)	-0.81 [-1.27, -0.35]
1.8 Symptoms ≤ 3 months by type corticosteroid	8		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.8.1 Mineralocorticoid-acting LCI versus control	2	154	Std. Mean Difference (IV, Random, 95% CI)	-0.81 [-1.15, -0.47]
1.8.2 Non-mineralocorticoid-acting LCI versus control	6	425	Std. Mean Difference (IV, Random, 95% CI)	-0.75 [-0.98, -0.52]
1.9 Boston Carpal Tunnel Questionnaire (Symptom Severity Scale) ≤ 3 months	7	499	Mean Difference (IV, Random, 95% CI)	-0.41 [-0.58, -0.25]
1.9.1 LCI versus saline	5	410	Mean Difference (IV, Random, 95% CI)	-0.48 [-0.67, -0.30]
1.9.2 LCI versus no treatment	2	89	Mean Difference (IV, Random, 95% CI)	-0.23 [-0.51, 0.05]
1.10 Boston Carpal Tunnel Questionnaire (Symptom Severity Scale) > 3 months	3	200	Mean Difference (IV, Random, 95% CI)	-0.24 [-0.39, -0.09]
1.10.1 LCI versus saline	2	154	Mean Difference (IV, Random, 95% CI)	-0.31 [-0.45, -0.16]
1.10.2 LCI versus no treatment	1	46	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.31, 0.09]

Analysis 1.1. Comparison 1: Local corticosteroid injection (LCI) versus control: improvement in symptoms, Outcome 1: Symptoms ≤ 3 months

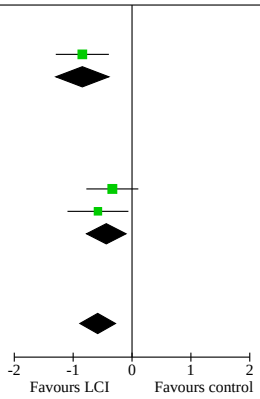
Study or Subgroup	LCI Mean	LCI SD	LCI Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
1.1.1 LCI versus control									
Armstrong 2004	-0.78	0.8	43	-0.19	0.62	36	14.1%	-0.81 [-1.27 , -0.35]	+ + + + + + +
Atroshi 2013	-1.04	0.98	74	-0.3	0.66	37	17.9%	-0.83 [-1.24 , -0.42]	+ + + + + + +
Khosrawi 2016	-1.21	0.52	21	-0.81	0.5	22	7.8%	-0.77 [-1.39 , -0.15]	+ ? − ? + + ?
Peters-Veluthamaningal 2010	-0.924	0.45	35	-0.286	0.52	31	10.5%	-1.30 [-1.84 , -0.77]	+ + + + + + +
Salman Roghani 2018	-0.51	0.44	64	-0.21	0.45	30	15.2%	-0.67 [-1.12 , -0.23]	+ + + + + + +
Subtotal (95% CI)			**237**			**156**	**65.4%**	**-0.86 [-1.07 , -0.64]**	
Heterogeneity: Tau² = 0.00; Chi² = 3.47, df = 4 (P = 0.48); I² = 0%									
Test for overall effect: Z = 7.84 (P < 0.00001)									
1.1.2 LCI versus control (hands as unit of analysis)									
Karadaş 2011	-1.65	1.11	40	-0.95	0.82	40	14.7%	-0.71 [-1.16 , -0.26]	? ? ? + + + ?
Karadaş 2012	-0.3	0.44	30	-0.03	0.36	30	11.1%	-0.66 [-1.18 , -0.14]	? ? ? + + + ?
Ucan 2006	-1.38	0.42	23	-1.27	0.23	23	8.9%	-0.32 [-0.90 , 0.26]	? + − − − ? −
Subtotal (95% CI)			**93**			**93**	**34.6%**	**-0.60 [-0.89 , -0.30]**	
Heterogeneity: Tau² = 0.00; Chi² = 1.18, df = 2 (P = 0.56); I² = 0%									
Test for overall effect: Z = 3.96 (P < 0.0001)									
Total (95% CI)			**330**			**249**	**100.0%**	**-0.77 [-0.94 , -0.59]**	
Heterogeneity: Tau² = 0.00; Chi² = 6.63, df = 7 (P = 0.47); I² = 0%									
Test for overall effect: Z = 8.67 (P < 0.00001)									
Test for subgroup differences: Chi² = 1.98, df = 1 (P = 0.16), I² = 49.5%									



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.2. Comparison 1: Local corticosteroid injection (LCI) versus control: improvement in symptoms, Outcome 2: Symptoms > 3 months

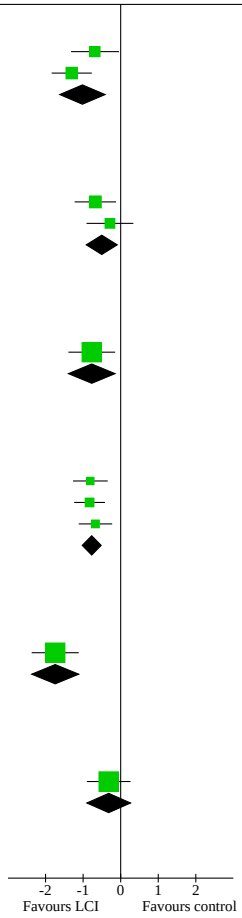
Study or Subgroup	LCI Mean	LCI SD	LCI Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
1.2.1 LCI versus control									
Salman Roghani 2018	-0.8	0.44	64	-0.42	0.46	30	35.3%	-0.84 [-1.30 , -0.39]	+ + + + + + +
Subtotal (95% CI)			**64**			**30**	**35.3%**	**-0.84 [-1.30 , -0.39]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 3.67 (P = 0.0002)									
1.2.2 LCI versus control (hands as unit of analysis)									
Karadaş 2011	-0.75	1.05	40	-0.45	0.69	40	36.5%	-0.33 [-0.78 , 0.11]	? ? ? + + + ?
Karadaş 2012	-0.27	0.43	30	-0.04	0.35	30	28.3%	-0.58 [-1.10 , -0.06]	? ? ? + + + ?
Subtotal (95% CI)			**70**			**70**	**64.7%**	**-0.44 [-0.77 , -0.10]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 1 (P = 0.48); I² = 0%									
Test for overall effect: Z = 2.55 (P = 0.01)									
Total (95% CI)			**134**			**100**	**100.0%**	**-0.58 [-0.89 , -0.28]**	
Heterogeneity: Tau² = 0.01; Chi² = 2.51, df = 2 (P = 0.29); I² = 20%									
Test for overall effect: Z = 3.78 (P = 0.0002)									
Test for subgroup differences: Chi² = 2.01, df = 1 (P = 0.16), I² = 50.3%									

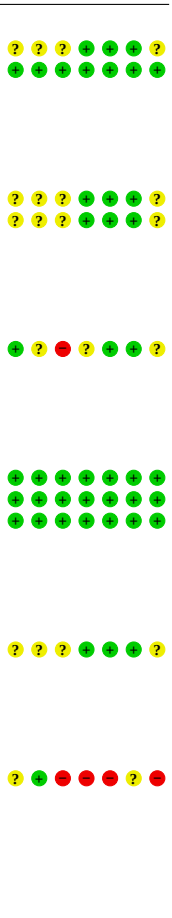


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.3. Comparison 1: Local corticosteroid injection (LCI) versus control: improvement in symptoms, Outcome 3: Symptoms ≤ 3 months by local anaesthetic (LA) use

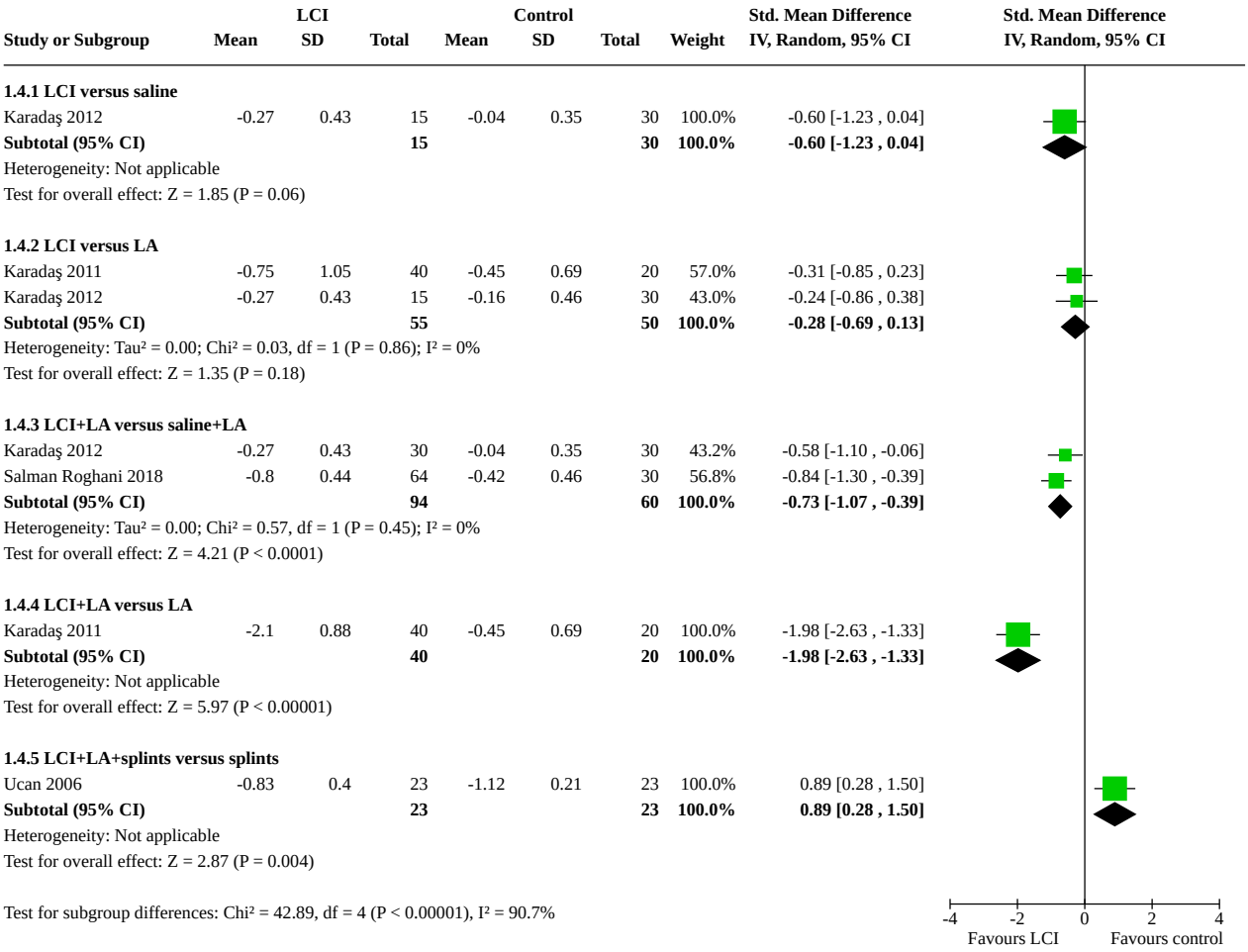
Study or Subgroup	LCI Mean	LCI SD	LCI Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.3.1 LCI versus saline								
Karadaş 2012	-0.3	0.44	15	-0.03	0.36	30	45.9%	-0.68 [-1.32 , -0.05]
Peters-Veluthamaningal 2010	-0.924	0.45	35	-0.286	0.52	31	54.1%	-1.30 [-1.84 , -0.77]
Subtotal (95% CI)			**50**			**61**	**100.0%**	**-1.02 [-1.62 , -0.41]**
Heterogeneity: Tau² = 0.10; Chi² = 2.12, df = 1 (P = 0.15); I² = 53%								
Test for overall effect: Z = 3.30 (P = 0.0010)								
1.3.2 LCI versus LA								
Karadaş 2011	-1.65	1.11	40	-0.95	0.82	20	56.1%	-0.67 [-1.23 , -0.12]
Karadaş 2012	-0.3	0.44	15	-0.17	0.45	30	43.9%	-0.29 [-0.91 , 0.34]
Subtotal (95% CI)			**55**			**50**	**100.0%**	**-0.50 [-0.92 , -0.09]**
Heterogeneity: Tau² = 0.00; Chi² = 0.84, df = 1 (P = 0.36); I² = 0%								
Test for overall effect: Z = 2.39 (P = 0.02)								
1.3.3 LCI versus no treatment								
Khosrawi 2016	-1.21	0.52	21	-0.81	0.5	22	100.0%	-0.77 [-1.39 , -0.15]
Subtotal (95% CI)			**21**			**22**	**100.0%**	**-0.77 [-1.39 , -0.15]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.43 (P = 0.02)								
1.3.4 LCI+LA versus saline+LA								
Armstrong 2004	-0.78	0.8	43	-0.19	0.62	36	29.9%	-0.81 [-1.27 , -0.35]
Atroshi 2013	-1.04	0.98	74	-0.3	0.66	37	37.9%	-0.83 [-1.24 , -0.42]
Salman Roghani 2018	-0.51	0.44	64	-0.21	0.45	30	32.2%	-0.67 [-1.12 , -0.23]
Subtotal (95% CI)			**181**			**103**	**100.0%**	**-0.77 [-1.02 , -0.52]**
Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 2 (P = 0.86); I² = 0%								
Test for overall effect: Z = 5.99 (P < 0.00001)								
1.3.5 LCI+LA versus LA								
Karadaş 2011	-2.47	0.88	40	-0.95	0.82	20	100.0%	-1.74 [-2.37 , -1.12]
Subtotal (95% CI)			**40**			**20**	**100.0%**	**-1.74 [-2.37 , -1.12]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.45 (P < 0.00001)								
1.3.6 LCI+LA+splints versus splints								
Ucan 2006	-1.38	0.42	23	-1.27	0.23	23	100.0%	-0.32 [-0.90 , 0.26]
Subtotal (95% CI)			**23**			**23**	**100.0%**	**-0.32 [-0.90 , 0.26]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.08 (P = 0.28)								
Test for subgroup differences: Chi² = 13.81, df = 5 (P = 0.02), I² = 63.8%								



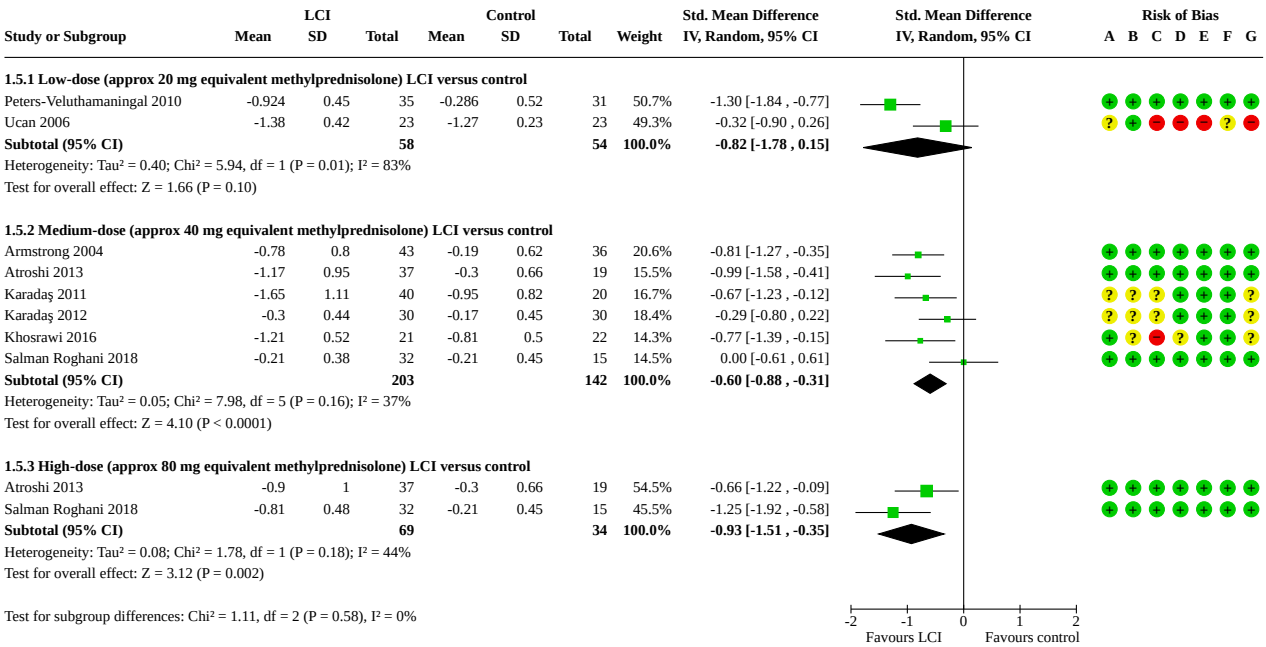


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.4. Comparison 1: Local corticosteroid injection (LCI) versus control: improvement in symptoms, Outcome 4: Symptoms > 3 months by LA use



Analysis 1.5. Comparison 1: Local corticosteroid injection (LCI) versus control: improvement in symptoms, Outcome 5: Symptoms ≤ 3 months by corticosteroid dose

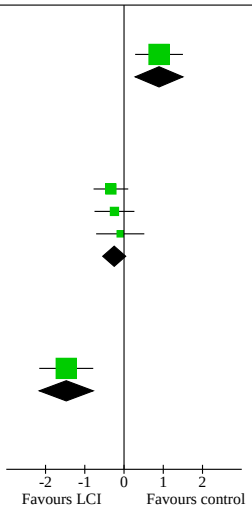


Study or Subgroup	LCI Mean	LCI SD	LCI Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
1.5.1 Low-dose (approx 20 mg equivalent methylprednisolone) LCI versus control									
Peters-Veluthamaningal 2010	-0.924	0.45	35	-0.286	0.52	31	50.7%	-1.30 [-1.84 , -0.77]	+ + + + + + +
Ucan 2006	-1.38	0.42	23	-1.27	0.23	23	49.3%	-0.32 [-0.90 , 0.26]	? + - - - ? -
Subtotal (95% CI)			**58**			**54**	**100.0%**	**-0.82 [-1.78 , 0.15]**	
Heterogeneity: Tau² = 0.40; Chi² = 5.94, df = 1 (P = 0.01); I² = 83%									
Test for overall effect: Z = 1.66 (P = 0.10)									
1.5.2 Medium-dose (approx 40 mg equivalent methylprednisolone) LCI versus control									
Armstrong 2004	-0.78	0.8	43	-0.19	0.62	36	20.6%	-0.81 [-1.27 , -0.35]	+ + + + + + +
Atroshi 2013	-1.17	0.95	37	-0.3	0.66	19	15.5%	-0.99 [-1.58 , -0.41]	+ + + + + + +
Karadaş 2011	-1.65	1.11	40	-0.95	0.82	20	16.7%	-0.67 [-1.23 , -0.12]	? ? ? + + + ?
Karadaş 2012	-0.3	0.44	30	-0.17	0.45	30	18.4%	-0.29 [-0.80 , 0.22]	? ? ? + + + ?
Khosrawi 2016	-1.21	0.52	21	-0.81	0.5	22	14.3%	-0.77 [-1.39 , -0.15]	+ ? - ? + + ?
Salman Roghani 2018	-0.21	0.38	32	-0.21	0.45	15	14.5%	0.00 [-0.61 , 0.61]	+ + + + + + +
Subtotal (95% CI)			**203**			**142**	**100.0%**	**-0.60 [-0.88 , -0.31]**	
Heterogeneity: Tau² = 0.05; Chi² = 7.98, df = 5 (P = 0.16); I² = 37%									
Test for overall effect: Z = 4.10 (P < 0.0001)									
1.5.3 High-dose (approx 80 mg equivalent methylprednisolone) LCI versus control									
Atroshi 2013	-0.9	1	37	-0.3	0.66	19	54.5%	-0.66 [-1.22 , -0.09]	+ + + + + + +
Salman Roghani 2018	-0.81	0.48	32	-0.21	0.45	15	45.5%	-1.25 [-1.92 , -0.58]	+ + + + + + +
Subtotal (95% CI)			**69**			**34**	**100.0%**	**-0.93 [-1.51 , -0.35]**	
Heterogeneity: Tau² = 0.08; Chi² = 1.78, df = 1 (P = 0.18); I² = 44%									
Test for overall effect: Z = 3.12 (P = 0.002)									
Test for subgroup differences: Chi² = 1.11, df = 2 (P = 0.58), I² = 0%									

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.6. Comparison 1: Local corticosteroid injection (LCI) versus control: improvement in symptoms, Outcome 6: Symptoms > 3 months by corticosteroid dose

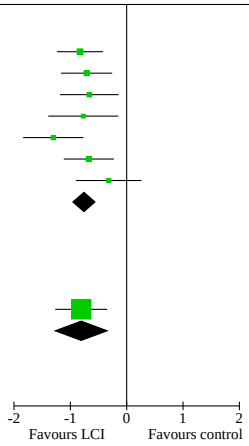
Study or Subgroup	LCI Mean	LCI SD	LCI Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
1.6.1 Low-dose (approx 20 mg equivalent methylprednisolone) LCI versus control									
Ucan 2006	-0.83	0.4	23	-1.12	0.21	23	100.0%	0.89 [0.28 , 1.50]	? + − − − ? −
Subtotal (95% CI)			**23**			**23**	**100.0%**	**0.89 [0.28 , 1.50]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 2.87 (P = 0.004)									
1.6.2 Medium-dose (approx 40 mg equivalent methylprednisolone) LCI versus control									
Karadaş 2011	-0.75	1.05	40	-0.45	0.69	40	44.0%	-0.33 [-0.78 , 0.11]	? ? ? + + + ?
Karadaş 2012	-0.27	0.43	30	-0.16	0.46	30	33.2%	-0.24 [-0.75 , 0.26]	? ? ? + + + ?
Salman Roghani 2018	-0.46	0.38	32	-0.42	0.46	15	22.8%	-0.10 [-0.71 , 0.52]	+ + + + + + +
Subtotal (95% CI)			**102**			**85**	**100.0%**	**-0.25 [-0.54 , 0.04]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.38, df = 2 (P = 0.83); I² = 0%									
Test for overall effect: Z = 1.67 (P = 0.09)									
1.6.3 High-dose (approx 80 mg equivalent methylprednisolone) LCI versus control									
Salman Roghani 2018	-1.14	0.49	32	-0.42	0.46	15	100.0%	-1.47 [-2.16 , -0.78]	+ + + + + + +
Subtotal (95% CI)			**32**			**15**	**100.0%**	**-1.47 [-2.16 , -0.78]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 4.20 (P < 0.0001)									
Test for subgroup differences: Chi² = 25.61, df = 2 (P < 0.00001), I² = 92.2%									



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

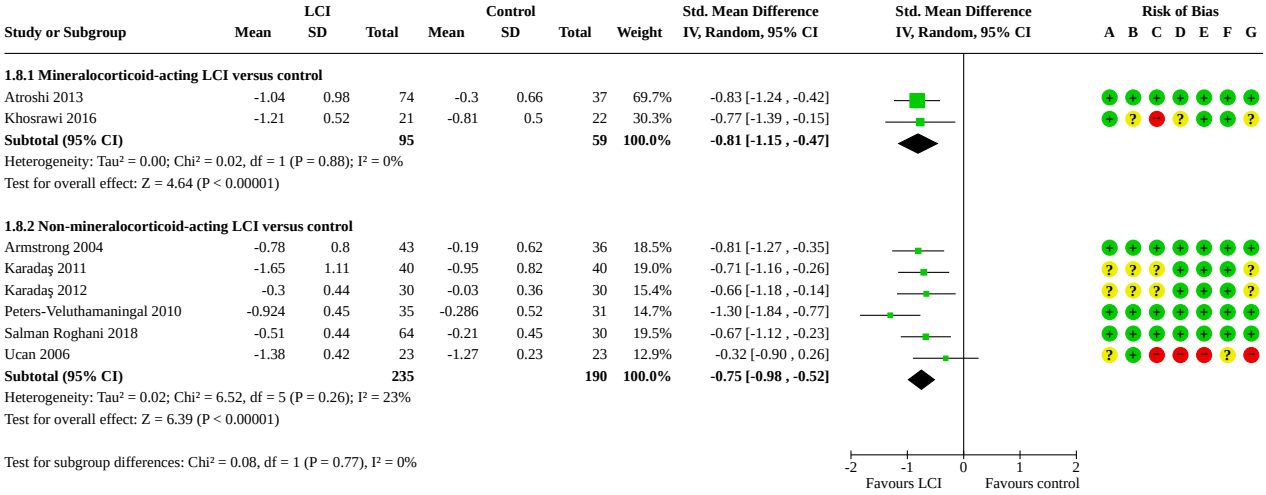
Analysis 1.7. Comparison 1: Local corticosteroid injection (LCI) versus control: improvement in symptoms, Outcome 7: Symptoms ≤ 3 months by duration of action of corticosteroid

Study or Subgroup	LCI Mean	LCI SD	LCI Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
1.7.1 Intermediate-acting (12–36 hours) LCI versus control									
Atroshi 2013	-1.04	0.98	74	-0.3	0.66	37	20.1%	-0.83 [-1.24 , -0.42]	+ + + + + + +
Karadaş 2011	-1.65	1.11	40	-0.95	0.82	40	16.9%	-0.71 [-1.16 , -0.26]	? ? ? + + + ?
Karadaş 2012	-0.3	0.44	30	-0.03	0.36	30	13.1%	-0.66 [-1.18 , -0.14]	? ? ? + + + ?
Khosrawi 2016	-1.21	0.52	21	-0.81	0.5	22	9.4%	-0.77 [-1.39 , -0.15]	+ ? − ? + + ?
Peters-Veluthamaningal 2010	-0.924	0.45	35	-0.286	0.52	31	12.5%	-1.30 [-1.84 , -0.77]	+ + + + + + +
Salman Roghani 2018	-0.51	0.44	64	-0.21	0.45	30	17.4%	-0.67 [-1.12 , -0.23]	+ + + + + + +
Ucan 2006	-1.38	0.42	23	-1.27	0.23	23	10.7%	-0.32 [-0.90 , 0.26]	? + − − − ? −
Subtotal (95% CI)			**287**			**213**	**100.0%**	**-0.76 [-0.96 , -0.56]**	
Heterogeneity: Tau² = 0.01; Chi² = 6.59, df = 6 (P = 0.36); I² = 9%									
Test for overall effect: Z = 7.56 (P < 0.00001)									
1.7.2 Long-acting (> 48 hours) LCI versus control									
Armstrong 2004	-0.78	0.8	43	-0.19	0.62	36	100.0%	-0.81 [-1.27 , -0.35]	+ + + + + + +
Subtotal (95% CI)			**43**			**36**	**100.0%**	**-0.81 [-1.27 , -0.35]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 3.43 (P = 0.0006)									
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.85), I² = 0%									



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

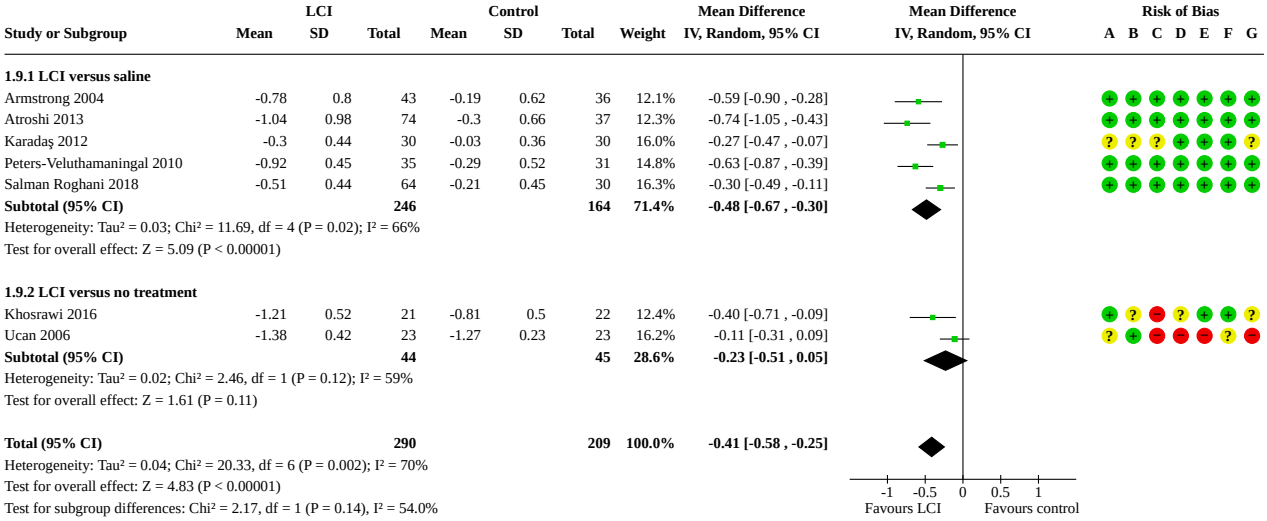
Analysis 1.8. Comparison 1: Local corticosteroid injection (LCI) versus control: improvement in symptoms, Outcome 8: Symptoms ≤ 3 months by type corticosteroid



Study or Subgroup	LCI Mean	LCI SD	LCI Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.8.1 Mineralocorticoid-acting LCI versus control								
Atroshi 2013	-1.04	0.98	74	-0.3	0.66	37	69.7%	-0.83 [-1.24 , -0.42]
Khosrawi 2016	-1.21	0.52	21	-0.81	0.5	22	30.3%	-0.77 [-1.39 , -0.15]
Subtotal (95% CI)			**95**			**59**	**100.0%**	**-0.81 [-1.15 , -0.47]**
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%								
Test for overall effect: Z = 4.64 (P < 0.00001)								
1.8.2 Non-mineralocorticoid-acting LCI versus control								
Armstrong 2004	-0.78	0.8	43	-0.19	0.62	36	18.5%	-0.81 [-1.27 , -0.35]
Karadaş 2011	-1.65	1.11	40	-0.95	0.82	40	19.0%	-0.71 [-1.16 , -0.26]
Karadaş 2012	-0.3	0.44	30	-0.03	0.36	30	15.4%	-0.66 [-1.18 , -0.14]
Peters-Veluthamaningal 2010	-0.924	0.45	35	-0.286	0.52	31	14.7%	-1.30 [-1.84 , -0.77]
Salman Roghani 2018	-0.51	0.44	64	-0.21	0.45	30	19.5%	-0.67 [-1.12 , -0.23]
Ucan 2006	-1.38	0.42	23	-1.27	0.23	23	12.9%	-0.32 [-0.90 , 0.26]
Subtotal (95% CI)			**235**			**190**	**100.0%**	**-0.75 [-0.98 , -0.52]**
Heterogeneity: Tau² = 0.02; Chi² = 6.52, df = 5 (P = 0.26); I² = 23%								
Test for overall effect: Z = 6.39 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.77), I² = 0%								

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

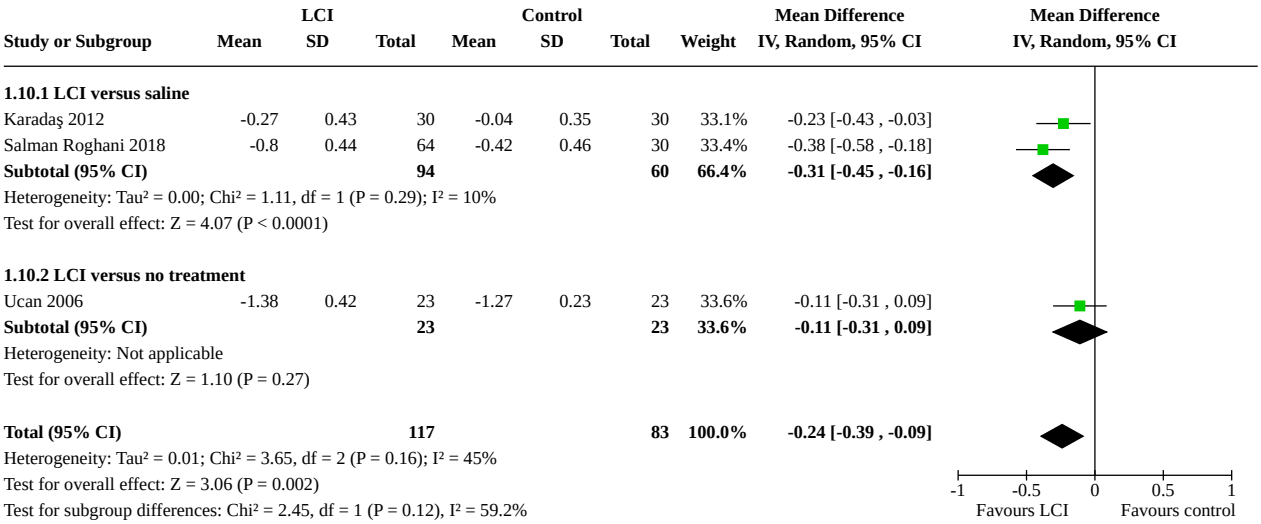
Analysis 1.9. Comparison 1: Local corticosteroid injection (LCI) versus control: improvement in symptoms, Outcome 9: Boston Carpal Tunnel Questionnaire (Symptom Severity Scale) ≤ 3 months



Study or Subgroup	LCI Mean	LCI SD	LCI Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.9.1 LCI versus saline								
Armstrong 2004	-0.78	0.8	43	-0.19	0.62	36	12.1%	-0.59 [-0.90 , -0.28]
Atroshi 2013	-1.04	0.98	74	-0.3	0.66	37	12.3%	-0.74 [-1.05 , -0.43]
Karadaş 2012	-0.3	0.44	30	-0.03	0.36	30	16.0%	-0.27 [-0.47 , -0.07]
Peters-Veluthamaningal 2010	-0.92	0.45	35	-0.29	0.52	31	14.8%	-0.63 [-0.87 , -0.39]
Salman Roghani 2018	-0.51	0.44	64	-0.21	0.45	30	16.3%	-0.30 [-0.49 , -0.11]
Subtotal (95% CI)			**246**			**164**	**71.4%**	**-0.48 [-0.67 , -0.30]**
Heterogeneity: Tau² = 0.03; Chi² = 11.69, df = 4 (P = 0.02); I² = 66%								
Test for overall effect: Z = 5.09 (P < 0.00001)								
1.9.2 LCI versus no treatment								
Khosrawi 2016	-1.21	0.52	21	-0.81	0.5	22	12.4%	-0.40 [-0.71 , -0.09]
Ucan 2006	-1.38	0.42	23	-1.27	0.23	23	16.2%	-0.11 [-0.31 , 0.09]
Subtotal (95% CI)			**44**			**45**	**28.6%**	**-0.23 [-0.51 , 0.05]**
Heterogeneity: Tau² = 0.02; Chi² = 2.46, df = 1 (P = 0.12); I² = 59%								
Test for overall effect: Z = 1.61 (P = 0.11)								
Total (95% CI)			**290**			**209**	**100.0%**	**-0.41 [-0.58 , -0.25]**
Heterogeneity: Tau² = 0.04; Chi² = 20.33, df = 6 (P = 0.002); I² = 70%								
Test for overall effect: Z = 4.83 (P < 0.00001)								
Test for subgroup differences: Chi² = 2.17, df = 1 (P = 0.14), I² = 54.0%								

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.10. Comparison 1: Local corticosteroid injection (LCI) versus control: improvement in symptoms, Outcome 10: Boston Carpal Tunnel Questionnaire (Symptom Severity Scale) > 3 months



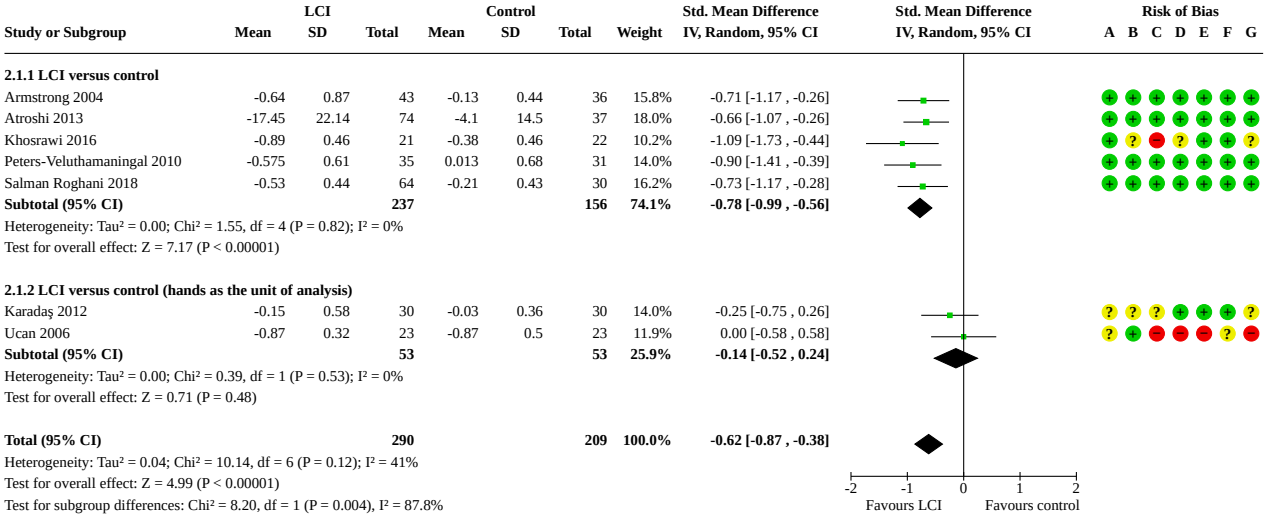
Comparison 2. Local corticosteroid injection (LCI) versus control: improvement in function

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Function ≤ 3 months	7	499	Std. Mean Difference (IV, Random, 95% CI)	-0.62 [-0.87, -0.38]
2.1.1 LCI versus control	5	393	Std. Mean Difference (IV, Random, 95% CI)	-0.78 [-0.99, -0.56]
2.1.2 LCI versus control (hands as the unit of analysis)	2	106	Std. Mean Difference (IV, Random, 95% CI)	-0.14 [-0.52, 0.24]
2.2 Function > 3 months	3	200	Std. Mean Difference (IV, Random, 95% CI)	0.01 [-0.43, 0.46]
2.2.1 LCI versus control	1	94	Std. Mean Difference (IV, Random, 95% CI)	-0.16 [-0.59, 0.28]
2.2.2 LCI versus control (hands as unit of analysis)	2	106	Std. Mean Difference (IV, Random, 95% CI)	0.13 [-0.64, 0.90]
2.3 Function ≤ 3 months by local anaesthetic (LA) use	7		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.3.1 LCI versus saline	2	111	Std. Mean Difference (IV, Random, 95% CI)	-0.61 [-1.23, 0.01]
2.3.2 LCI versus LA	1	45	Std. Mean Difference (IV, Random, 95% CI)	-0.05 [-0.67, 0.57]
2.3.3 LCI versus no treatment	1	43	Std. Mean Difference (IV, Random, 95% CI)	-1.09 [-1.73, -0.44]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3.4 LCI+LA versus saline+LA	3	284	Std. Mean Difference (IV, Random, 95% CI)	-0.70 [-0.95, -0.45]
2.3.5 LCI+LA+splints versus splints	1	46	Std. Mean Difference (IV, Random, 95% CI)	0.00 [-0.58, 0.58]
2.4 Function > 3 months by LA use	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.4.1 LCI versus saline	1	45	Std. Mean Difference (IV, Random, 95% CI)	-0.27 [-0.89, 0.36]
2.4.2 LCI versus LA	1	45	Std. Mean Difference (IV, Random, 95% CI)	-0.05 [-0.67, 0.57]
2.4.3 LCI+LA versus saline+LA	1	94	Std. Mean Difference (IV, Random, 95% CI)	-0.16 [-0.59, 0.28]
2.4.4 LCI+LA+splints versus splints	1	46	Std. Mean Difference (IV, Random, 95% CI)	0.54 [-0.05, 1.13]
2.5 Function ≤ 3 months by dose of corticosteroid	6		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.5.1 Low-dose (approx 20 mg equivalent methylprednisolone) LCI versus control	2	112	Std. Mean Difference (IV, Random, 95% CI)	-0.46 [-1.35, 0.42]
2.5.2 Medium-dose (approx 40 mg equivalent methylprednisolone) LCI versus control	4	206	Std. Mean Difference (IV, Random, 95% CI)	-0.52 [-0.93, -0.10]
2.5.3 High-dose (approx 80 mg equivalent methylprednisolone) LCI versus control	2	103	Std. Mean Difference (IV, Random, 95% CI)	-0.93 [-1.58, -0.29]
2.6 Function > 3 months by dose of corticosteroid	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.6.1 Low-dose (approx 20 mg equivalent methylprednisolone) LCI versus control	1	46	Std. Mean Difference (IV, Random, 95% CI)	0.54 [-0.05, 1.13]
2.6.2 Medium-dose (approx 40 mg equivalent methylprednisolone) LCI versus control	2	107	Std. Mean Difference (IV, Random, 95% CI)	-0.18 [-0.58, 0.21]
2.6.3 High-dose (approx 80 mg equivalent methylprednisolone) LCI versus control	1	47	Std. Mean Difference (IV, Random, 95% CI)	-1.45 [-2.14, -0.76]
2.7 Function ≤ 3 months by duration of action of corticosteroid	7		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only

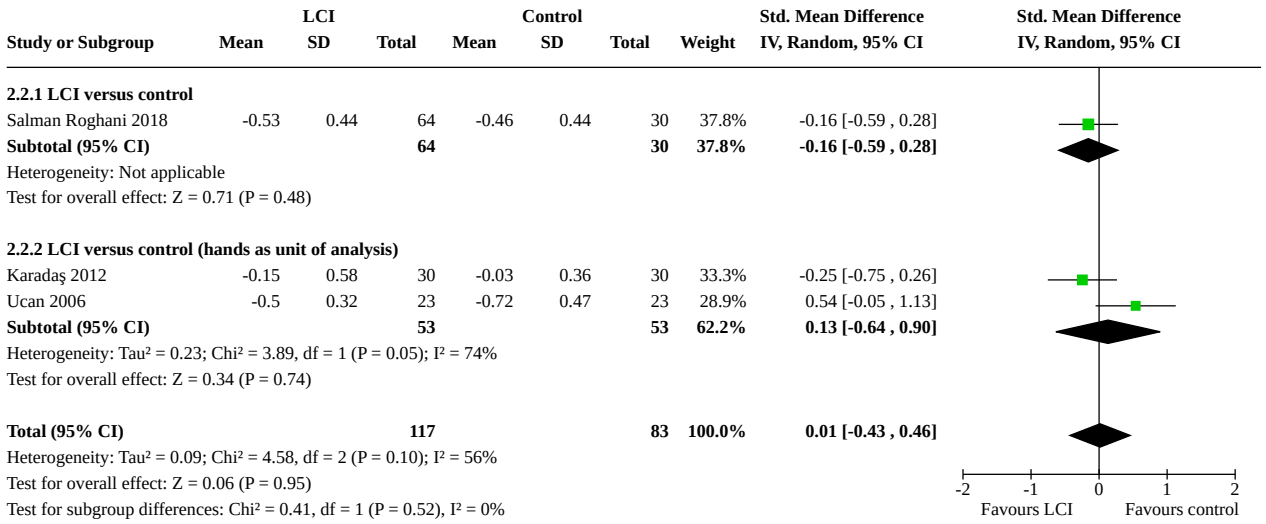
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.7.1 Intermediate-acting (12–36 hours) LCI versus control	6	420	Std. Mean Difference (IV, Random, 95% CI)	-0.60 [-0.89, -0.31]
2.7.2 Long-acting (> 48 hours) LCI versus control	1	79	Std. Mean Difference (IV, Random, 95% CI)	-0.71 [-1.17, -0.26]
2.8 Function ≤ 3 months by type of corticosteroid	7		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.8.1 Mineralocorticoid-acting LCI versus control	2	154	Std. Mean Difference (IV, Random, 95% CI)	-0.80 [-1.19, -0.41]
2.8.2 Non-mineralocorticoid-acting LCI versus control	5	345	Std. Mean Difference (IV, Random, 95% CI)	-0.54 [-0.85, -0.23]
2.9 Boston Carpal Tunnel Questionnaire (Functional Status Scale) ≤ 3 months	6	388	Mean Difference (IV, Random, 95% CI)	-0.33 [-0.51, -0.14]
2.9.1 LCI versus saline	4	299	Mean Difference (IV, Random, 95% CI)	-0.36 [-0.56, -0.17]
2.9.2 LCI versus no treatment	2	89	Mean Difference (IV, Random, 95% CI)	-0.25 [-0.75, 0.25]
2.10 Boston Carpal Tunnel Questionnaire (Functional Status Scale) > 3 months	3	200	Mean Difference (IV, Random, 95% CI)	0.01 [-0.19, 0.21]
2.10.1 LCI versus saline	2	154	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.24, 0.06]
2.10.2 LCI versus no treatment	1	46	Mean Difference (IV, Random, 95% CI)	0.22 [-0.01, 0.45]

Analysis 2.1. Comparison 2: Local corticosteroid injection (LCI) versus control: improvement in function, Outcome 1: Function ≤ 3 months

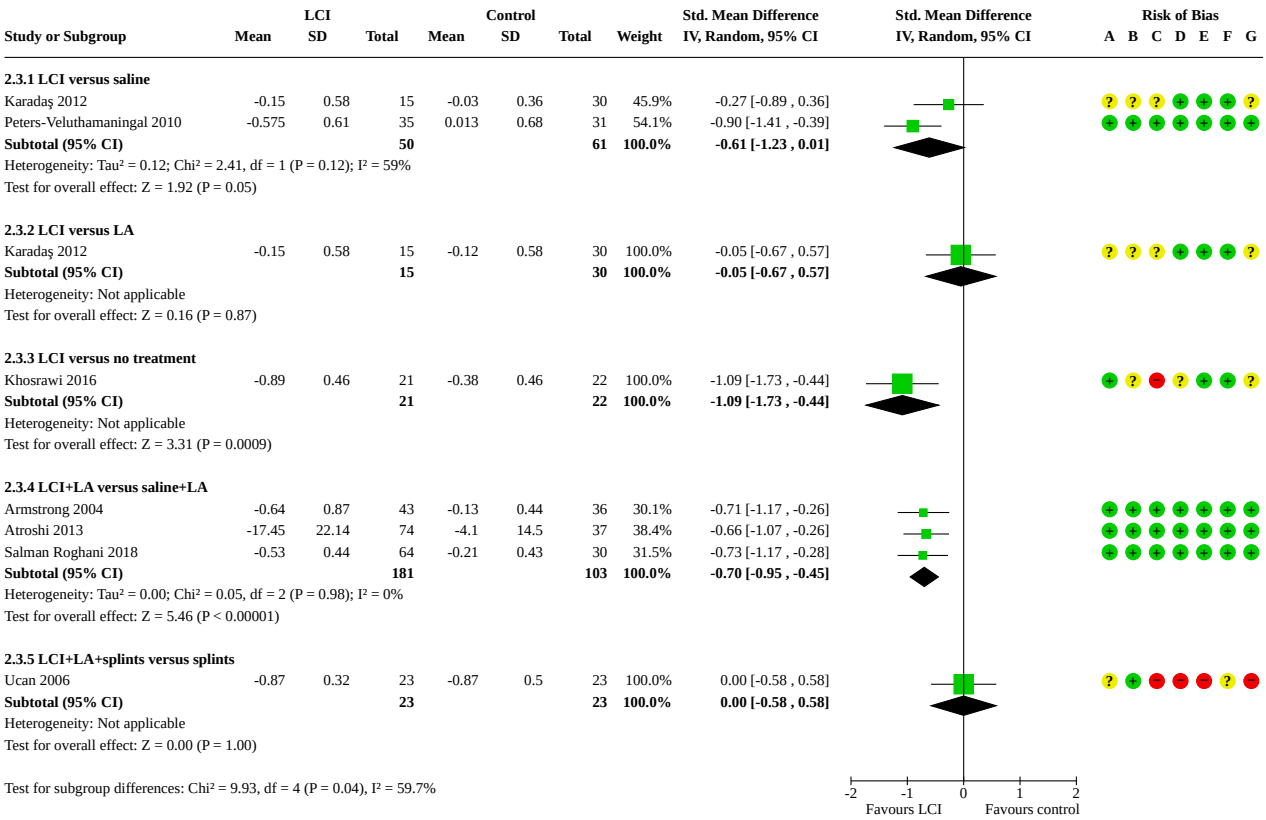


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.2. Comparison 2: Local corticosteroid injection (LCI) versus control: improvement in function, Outcome 2: Function > 3 months



Analysis 2.3. Comparison 2: Local corticosteroid injection (LCI) versus control: improvement in function, Outcome 3: Function ≤ 3 months by local anaesthetic (LA) use

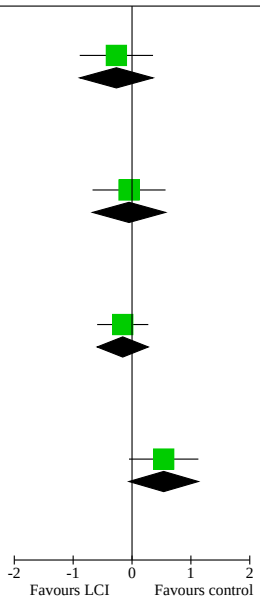


Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.4. Comparison 2: Local corticosteroid injection (LCI) versus control: improvement in function, Outcome 4: Function > 3 months by LA use

Study or Subgroup	LCI Mean	LCI SD	LCI Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
2.4.1 LCI versus saline									
Karadaş 2012	-0.15	0.58	15	-0.03	0.36	30	100.0%	-0.27 [-0.89 , 0.36]	? ? ? + + + ?
Subtotal (95% CI)			**15**			**30**	**100.0%**	**-0.27 [-0.89 , 0.36]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.84 (P = 0.40)									
2.4.2 LCI versus LA									
Karadaş 2012	-0.15	0.58	15	-0.12	0.58	30	100.0%	-0.05 [-0.67 , 0.57]	? ? ? + + + ?
Subtotal (95% CI)			**15**			**30**	**100.0%**	**-0.05 [-0.67 , 0.57]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.16 (P = 0.87)									
2.4.3 LCI+LA versus saline+LA									
Salman Roghani 2018	-0.53	0.44	64	-0.46	0.44	30	100.0%	-0.16 [-0.59 , 0.28]	+ + + + + + +
Subtotal (95% CI)			**64**			**30**	**100.0%**	**-0.16 [-0.59 , 0.28]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.71 (P = 0.48)									
2.4.4 LCI+LA+splints versus splints									
Ucan 2006	-0.5	0.32	23	-0.72	0.47	23	100.0%	0.54 [-0.05 , 1.13]	? + − − − ? −
Subtotal (95% CI)			**23**			**23**	**100.0%**	**0.54 [-0.05 , 1.13]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.79 (P = 0.07)									

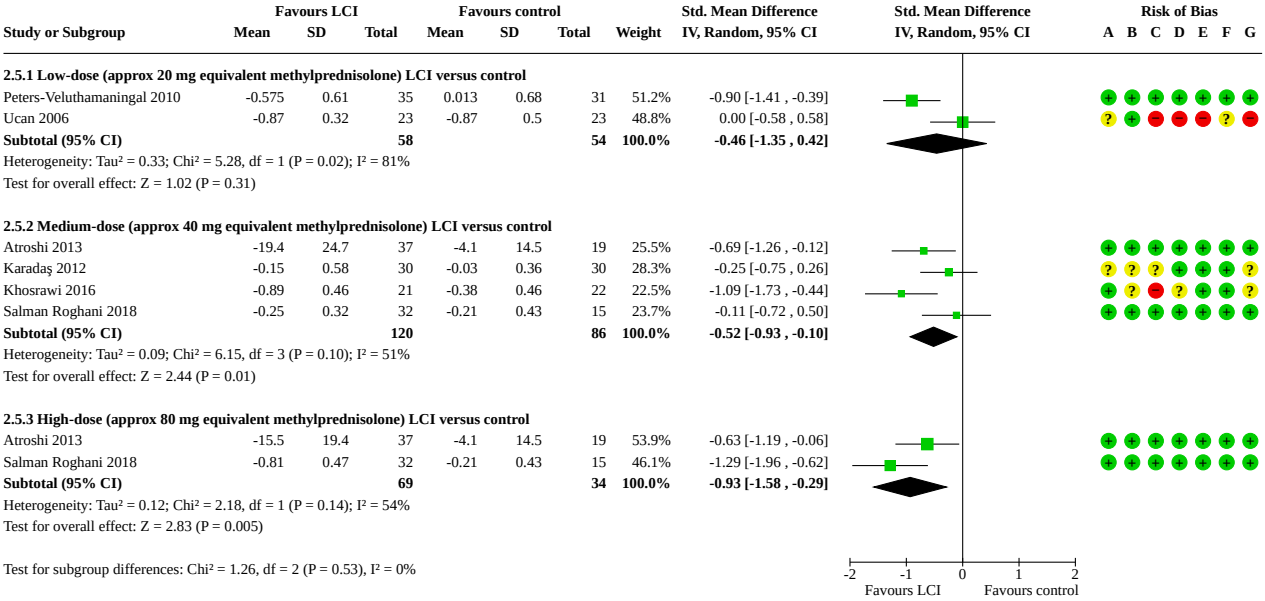


Test for subgroup differences: Chi² = 4.43, df = 3 (P = 0.22), I² = 32.3%

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

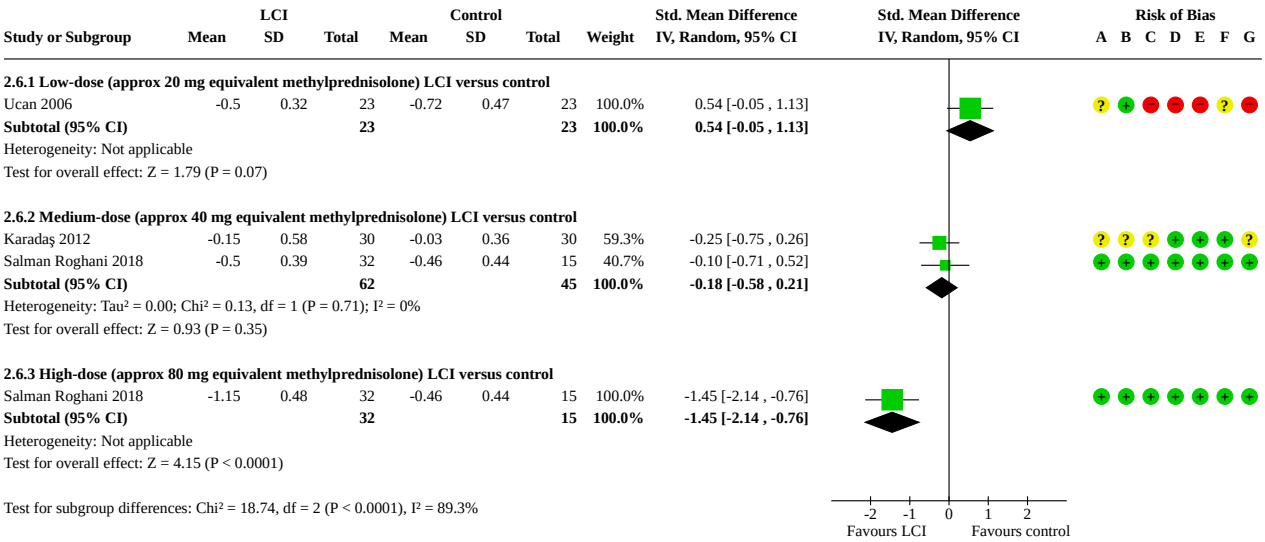
Analysis 2.5. Comparison 2: Local corticosteroid injection (LCI) versus control: improvement in function, Outcome 5: Function ≤ 3 months by dose of corticosteroid



Study or Subgroup	Favours LCI Mean	SD	Total	Favours control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.5.1 Low-dose (approx 20 mg equivalent methylprednisolone) LCI versus control								
Peters-Veluthamaningal 2010	-0.575	0.61	35	0.013	0.68	31	51.2%	-0.90 [-1.41 , -0.39]
Ucan 2006	-0.87	0.32	23	-0.87	0.5	23	48.8%	0.00 [-0.58 , 0.58]
Subtotal (95% CI)			**58**			**54**	**100.0%**	**-0.46 [-1.35 , 0.42]**
Heterogeneity: Tau² = 0.33; Chi² = 5.28, df = 1 (P = 0.02); I² = 81%								
Test for overall effect: Z = 1.02 (P = 0.31)								
2.5.2 Medium-dose (approx 40 mg equivalent methylprednisolone) LCI versus control								
Atroshi 2013	-19.4	24.7	37	-4.1	14.5	19	25.5%	-0.69 [-1.26 , -0.12]
Karadaş 2012	-0.15	0.58	30	-0.03	0.36	30	28.3%	-0.25 [-0.75 , 0.26]
Khosrawi 2016	-0.89	0.46	21	-0.38	0.46	22	22.5%	-1.09 [-1.73 , -0.44]
Salman Roghani 2018	-0.25	0.32	32	-0.21	0.43	15	23.7%	-0.11 [-0.72 , 0.50]
Subtotal (95% CI)			**120**			**86**	**100.0%**	**-0.52 [-0.93 , -0.10]**
Heterogeneity: Tau² = 0.09; Chi² = 6.15, df = 3 (P = 0.10); I² = 51%								
Test for overall effect: Z = 2.44 (P = 0.01)								
2.5.3 High-dose (approx 80 mg equivalent methylprednisolone) LCI versus control								
Atroshi 2013	-15.5	19.4	37	-4.1	14.5	19	53.9%	-0.63 [-1.19 , -0.06]
Salman Roghani 2018	-0.81	0.47	32	-0.21	0.43	15	46.1%	-1.29 [-1.96 , -0.62]
Subtotal (95% CI)			**69**			**34**	**100.0%**	**-0.93 [-1.58 , -0.29]**
Heterogeneity: Tau² = 0.12; Chi² = 2.18, df = 1 (P = 0.14); I² = 54%								
Test for overall effect: Z = 2.83 (P = 0.005)								
Test for subgroup differences: Chi² = 1.26, df = 2 (P = 0.53), I² = 0%								

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.6. Comparison 2: Local corticosteroid injection (LCI) versus control: improvement in function, Outcome 6: Function > 3 months by dose of corticosteroid

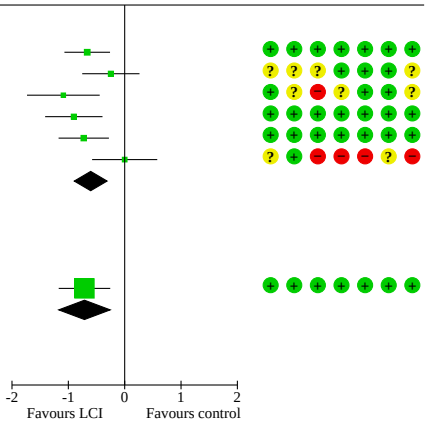


Study or Subgroup	LCI Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.6.1 Low-dose (approx 20 mg equivalent methylprednisolone) LCI versus control								
Ucan 2006	-0.5	0.32	23	-0.72	0.47	23	100.0%	0.54 [-0.05 , 1.13]
Subtotal (95% CI)			**23**			**23**	**100.0%**	**0.54 [-0.05 , 1.13]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.79 (P = 0.07)								
2.6.2 Medium-dose (approx 40 mg equivalent methylprednisolone) LCI versus control								
Karadaş 2012	-0.15	0.58	30	-0.03	0.36	30	59.3%	-0.25 [-0.75 , 0.26]
Salman Roghani 2018	-0.5	0.39	32	-0.46	0.44	15	40.7%	-0.10 [-0.71 , 0.52]
Subtotal (95% CI)			**62**			**45**	**100.0%**	**-0.18 [-0.58 , 0.21]**
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.71); I² = 0%								
Test for overall effect: Z = 0.93 (P = 0.35)								
2.6.3 High-dose (approx 80 mg equivalent methylprednisolone) LCI versus control								
Salman Roghani 2018	-1.15	0.48	32	-0.46	0.44	15	100.0%	-1.45 [-2.14 , -0.76]
Subtotal (95% CI)			**32**			**15**	**100.0%**	**-1.45 [-2.14 , -0.76]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.15 (P < 0.0001)								
Test for subgroup differences: Chi² = 18.74, df = 2 (P < 0.0001), I² = 89.3%								

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.7. Comparison 2: Local corticosteroid injection (LCI) versus control: improvement in function, Outcome 7: Function ≤ 3 months by duration of action of corticosteroid

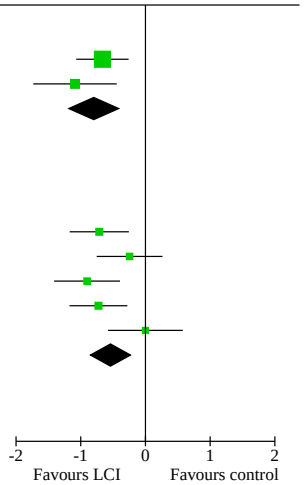
Study or Subgroup	LCI Mean	LCI SD	LCI Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.7.1 Intermediate-acting (12–36 hours) LCI versus control								
Atroshi 2013	-17.45	22.14	74	-4.1	14.5	37	20.5%	-0.66 [-1.07 , -0.26]
Karadaş 2012	-0.15	0.58	30	-0.03	0.36	30	16.7%	-0.25 [-0.75 , 0.26]
Khosrawi 2016	-0.89	0.46	21	-0.38	0.46	22	12.7%	-1.09 [-1.73 , -0.44]
Peters-Veluthamaningal 2010	-0.575	0.61	35	0.013	0.68	31	16.7%	-0.90 [-1.41 , -0.39]
Salman Roghani 2018	-0.53	0.44	64	-0.21	0.43	30	18.9%	-0.73 [-1.17 , -0.28]
Ucan 2006	-0.87	0.32	23	-0.87	0.5	23	14.5%	0.00 [-0.58 , 0.58]
Subtotal (95% CI)			**247**			**173**	**100.0%**	**-0.60 [-0.89 , -0.31]**
Heterogeneity: Tau² = 0.07; Chi² = 9.97, df = 5 (P = 0.08); I² = 50%								
Test for overall effect: Z = 4.06 (P < 0.0001)								
2.7.2 Long-acting (> 48 hours) LCI versus control								
Armstrong 2004	-0.64	0.87	43	-0.13	0.44	36	100.0%	-0.71 [-1.17 , -0.26]
Subtotal (95% CI)			**43**			**36**	**100.0%**	**-0.71 [-1.17 , -0.26]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.06 (P = 0.002)								
Test for subgroup differences: Chi² = 0.16, df = 1 (P = 0.69), I² = 0%								



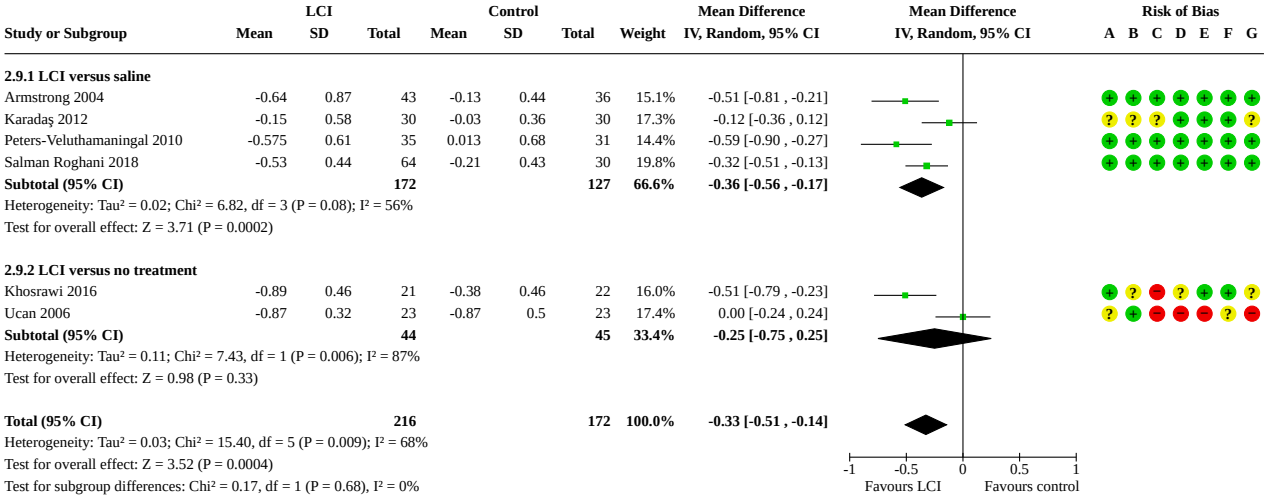
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.8. Comparison 2: Local corticosteroid injection (LCI) versus control: improvement in function, Outcome 8: Function ≤ 3 months by type of corticosteroid

Study or Subgroup	LCI Mean	LCI SD	LCI Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.8.1 Mineralocorticoid-acting LCI versus control								
Atroshi 2013	-17.45	22.14	74	-4.1	14.5	37	68.3%	-0.66 [-1.07 , -0.26]
Khosrawi 2016	-0.89	0.46	21	-0.38	0.46	22	31.7%	-1.09 [-1.73 , -0.44]
Subtotal (95% CI)			**95**			**59**	**100.0%**	**-0.80 [-1.19 , -0.41]**
Heterogeneity: Tau² = 0.01; Chi² = 1.19, df = 1 (P = 0.28); I² = 16%								
Test for overall effect: Z = 4.05 (P < 0.0001)								
2.8.2 Non-mineralocorticoid-acting LCI versus control								
Armstrong 2004	-0.64	0.87	43	-0.13	0.44	36	21.7%	-0.71 [-1.17 , -0.26]
Karadaş 2012	-0.15	0.58	30	-0.03	0.36	30	19.6%	-0.25 [-0.75 , 0.26]
Peters-Veluthamaningal 2010	-0.575	0.61	35	0.013	0.68	31	19.5%	-0.90 [-1.41 , -0.39]
Salman Roghani 2018	-0.53	0.44	64	-0.21	0.43	30	22.2%	-0.73 [-1.17 , -0.28]
Ucan 2006	-0.87	0.32	23	-0.87	0.5	23	16.9%	0.00 [-0.58 , 0.58]
Subtotal (95% CI)			**195**			**150**	**100.0%**	**-0.54 [-0.85 , -0.23]**
Heterogeneity: Tau² = 0.06; Chi² = 7.79, df = 4 (P = 0.10); I² = 49%								
Test for overall effect: Z = 3.42 (P = 0.0006)								
Test for subgroup differences: Chi² = 1.04, df = 1 (P = 0.31), I² = 4.2%								



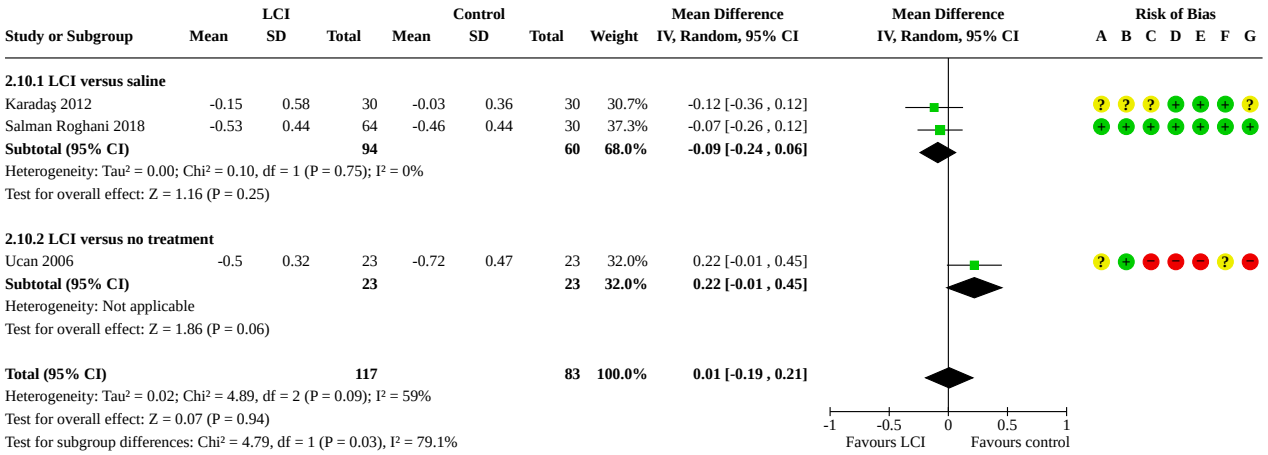
Analysis 2.9. Comparison 2: Local corticosteroid injection (LCI) versus control: improvement in function, Outcome 9: Boston Carpal Tunnel Questionnaire (Functional Status Scale) ≤ 3 months



Study or Subgroup	LCI Mean	LCI SD	LCI Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
2.9.1 LCI versus saline								
Armstrong 2004	-0.64	0.87	43	-0.13	0.44	36	15.1%	-0.51 [-0.81 , -0.21]
Karadaş 2012	-0.15	0.58	30	-0.03	0.36	30	17.3%	-0.12 [-0.36 , 0.12]
Peters-Veluthamaningal 2010	-0.575	0.61	35	0.013	0.68	31	14.4%	-0.59 [-0.90 , -0.27]
Salman Roghani 2018	-0.53	0.44	64	-0.21	0.43	30	19.8%	-0.32 [-0.51 , -0.13]
Subtotal (95% CI)			**172**			**127**	**66.6%**	**-0.36 [-0.56 , -0.17]**
Heterogeneity: Tau² = 0.02; Chi² = 6.82, df = 3 (P = 0.08); I² = 56%								
Test for overall effect: Z = 3.71 (P = 0.0002)								
2.9.2 LCI versus no treatment								
Khosrawi 2016	-0.89	0.46	21	-0.38	0.46	22	16.0%	-0.51 [-0.79 , -0.23]
Ucan 2006	-0.87	0.32	23	-0.87	0.5	23	17.4%	0.00 [-0.24 , 0.24]
Subtotal (95% CI)			**44**			**45**	**33.4%**	**-0.25 [-0.75 , 0.25]**
Heterogeneity: Tau² = 0.11; Chi² = 7.43, df = 1 (P = 0.006); I² = 87%								
Test for overall effect: Z = 0.98 (P = 0.33)								
Total (95% CI)			**216**			**172**	**100.0%**	**-0.33 [-0.51 , -0.14]**
Heterogeneity: Tau² = 0.03; Chi² = 15.40, df = 5 (P = 0.009); I² = 68%								
Test for overall effect: Z = 3.52 (P = 0.0004)								
Test for subgroup differences: Chi² = 0.17, df = 1 (P = 0.68), I² = 0%								

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.10. Comparison 2: Local corticosteroid injection (LCI) versus control: improvement in function, Outcome 10: Boston Carpal Tunnel Questionnaire (Functional Status Scale) > 3 months



Study or Subgroup	LCI Mean	LCI SD	LCI Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
2.10.1 LCI versus saline								
Karadaş 2012	-0.15	0.58	30	-0.03	0.36	30	30.7%	-0.12 [-0.36 , 0.12]
Salman Roghani 2018	-0.53	0.44	64	-0.46	0.44	30	37.3%	-0.07 [-0.26 , 0.12]
Subtotal (95% CI)			**94**			**60**	**68.0%**	**-0.09 [-0.24 , 0.06]**
Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.75); I² = 0%								
Test for overall effect: Z = 1.16 (P = 0.25)								
2.10.2 LCI versus no treatment								
Ucan 2006	-0.5	0.32	23	-0.72	0.47	23	32.0%	0.22 [-0.01 , 0.45]
Subtotal (95% CI)			**23**			**23**	**32.0%**	**0.22 [-0.01 , 0.45]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.86 (P = 0.06)								
Total (95% CI)			**117**			**83**	**100.0%**	**0.01 [-0.19 , 0.21]**
Heterogeneity: Tau² = 0.02; Chi² = 4.89, df = 2 (P = 0.09); I² = 59%								
Test for overall effect: Z = 0.07 (P = 0.94)								
Test for subgroup differences: Chi² = 4.79, df = 1 (P = 0.03), I² = 79.1%								

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

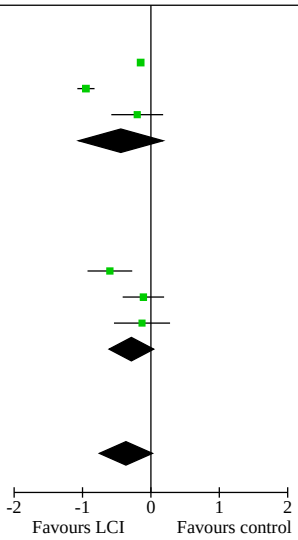
Comparison 3. Local corticosteroid injection (LCI) versus control: improvement in neurophysiological parameters

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Median nerve distal motor latency (DML) ≤ 3 months	6	359	Mean Difference (IV, Random, 95% CI)	-0.37 [-0.75, 0.02]
3.1.1 LCI versus control	3	216	Mean Difference (IV, Random, 95% CI)	-0.44 [-1.06, 0.18]
3.1.2 LCI versus control (hands as unit of analysis)	3	143	Mean Difference (IV, Random, 95% CI)	-0.29 [-0.61, 0.04]
3.2 Median nerve DML > 3 months	3	200	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.32, 0.09]
3.2.1 LCI versus control	1	94	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.53, 0.33]
3.2.2 LCI versus control (hands as unit of analysis)	2	106	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.36, 0.13]
3.3 Median nerve DML ≤ 3 months by local anaesthetic (LA) use	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.3.1 LCI versus saline	1	45	Mean Difference (IV, Random, 95% CI)	-0.60 [-0.99, -0.21]
3.3.2 LCI versus LA	1	45	Mean Difference (IV, Random, 95% CI)	-0.27 [-0.66, 0.12]
3.3.3 LCI versus no treatment	1	43	Mean Difference (IV, Random, 95% CI)	-0.95 [-1.08, -0.82]
3.3.4 LCI+LA versus saline+LA	2	173	Mean Difference (IV, Random, 95% CI)	-0.15 [-0.16, -0.14]
3.3.5 LCI+LA+splints versus splints	2	83	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.36, 0.13]
3.4 Median nerve DML ≤ 3 months by dose of corticosteroid	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.4.1 Low-dose (approx 20 mg equivalent methylprednisolone) LCI versus control	1	46	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.41, 0.19]
3.4.2 Medium-dose (approx 40 mg equivalent methylprednisolone) LCI versus control	4	229	Mean Difference (IV, Random, 95% CI)	-0.47 [-1.00, 0.07]
3.4.3 High-dose (approx 80 mg equivalent methylprednisolone) LCI versus control	1	47	Mean Difference (IV, Random, 95% CI)	-0.29 [-0.83, 0.25]
3.5 Median nerve DML > 3 months by dose of corticosteroid	3		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.5.1 Low-dose (approx 20 mg equivalent methylprednisolone) LCI versus control	1	46	Mean Difference (IV, Random, 95% CI)	0.01 [-0.32, 0.34]
3.5.2 Medium-dose (approx 40 mg equivalent methylprednisolone) LCI versus control	2	107	Mean Difference (IV, Random, 95% CI)	-0.18 [-0.46, 0.10]
3.5.3 High-dose (approx 80 mg equivalent methylprednisolone) LCI versus control	1	47	Mean Difference (IV, Random, 95% CI)	-0.23 [-0.84, 0.38]
3.6 Median nerve DML ≤ 3 months by duration of action of corticosteroid	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.6.1 Intermediate-acting (12–36 hours) LCI versus control	4	243	Mean Difference (IV, Random, 95% CI)	-0.48 [-0.94, -0.02]
3.6.2 Long-acting (> 48 hours) LCI versus control	2	116	Mean Difference (IV, Random, 95% CI)	-0.15 [-0.16, -0.14]
3.7 Median nerve DML ≤ 3 months by type of corticosteroid	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.7.1 Mineralocorticoid-acting LCI versus control	1	43	Mean Difference (IV, Random, 95% CI)	-0.95 [-1.08, -0.82]
3.7.2 Non-mineralocorticoid-acting LCI versus control	5	316	Mean Difference (IV, Random, 95% CI)	-0.21 [-0.37, -0.06]
3.8 Median nerve sensory nerve conduction velocity (SNCV) ≤ 3 months	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.8.1 LCI versus control	1	43	Mean Difference (IV, Random, 95% CI)	1.94 [0.82, 3.06]
3.8.2 LCI versus control (hands as the unit of analysis)	3	143	Mean Difference (IV, Random, 95% CI)	1.96 [-1.30, 5.22]
3.9 Median nerve SNCV > 3 months	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.9.1 LCI versus saline	1	60	Mean Difference (IV, Random, 95% CI)	3.06 [1.34, 4.78]
3.9.2 LCI versus no treatment	1	46	Mean Difference (IV, Random, 95% CI)	-1.78 [-3.46, -0.10]

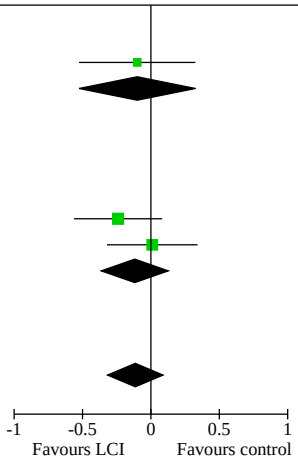
Analysis 3.1. Comparison 3: Local corticosteroid injection (LCI) versus control: improvement in neurophysiological parameters, Outcome 1: Median nerve distal motor latency (DML) ≤ 3 months

Study or Subgroup	LCI Mean	LCI SD	LCI Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
3.1.1 LCI versus control								
Armstrong 2004	-0.26	0.035	43	-0.11	0.032	36	18.4%	-0.15 [-0.16 , -0.14]
Khosrawi 2016	-1.67	0.26	21	-0.72	0.14	22	18.0%	-0.95 [-1.08 , -0.82]
Salman Roghani 2018	-0.44	0.79	64	-0.24	0.91	30	15.6%	-0.20 [-0.58 , 0.18]
Subtotal (95% CI)			**128**			**88**	**52.0%**	**-0.44 [-1.06 , 0.18]**
Heterogeneity: Tau² = 0.28; Chi² = 153.63, df = 2 (P < 0.00001); I² = 99%								
Test for overall effect: Z = 1.40 (P = 0.16)								
3.1.2 LCI versus control (hands as unit of analysis)								
Karadaş 2012	-0.59	0.61	30	0.01	0.68	30	16.2%	-0.60 [-0.93 , -0.27]
Ucan 2006	-0.61	0.39	23	-0.5	0.63	23	16.5%	-0.11 [-0.41 , 0.19]
Wu 1991	-0.84	0.58	18	-0.71	0.69	19	15.2%	-0.13 [-0.54 , 0.28]
Subtotal (95% CI)			**71**			**72**	**48.0%**	**-0.29 [-0.61 , 0.04]**
Heterogeneity: Tau² = 0.05; Chi² = 5.40, df = 2 (P = 0.07); I² = 63%								
Test for overall effect: Z = 1.72 (P = 0.09)								
Total (95% CI)			**199**			**160**	**100.0%**	**-0.37 [-0.75 , 0.02]**
Heterogeneity: Tau² = 0.21; Chi² = 160.68, df = 5 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 1.85 (P = 0.06)								
Test for subgroup differences: Chi² = 0.19, df = 1 (P = 0.66), I² = 0%								



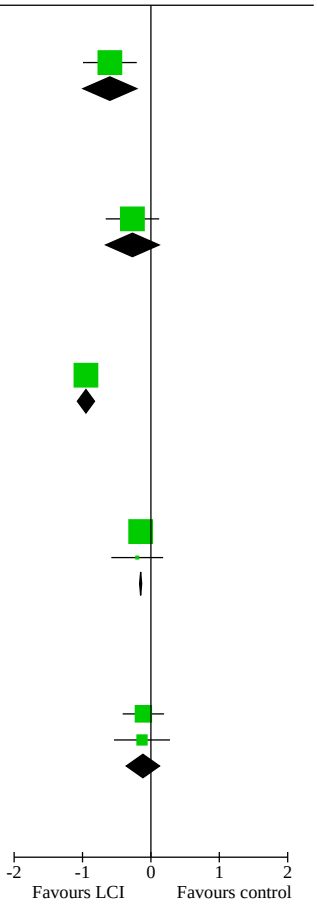
Analysis 3.2. Comparison 3: Local corticosteroid injection (LCI) versus control: improvement in neurophysiological parameters, Outcome 2: Median nerve DML > 3 months

Study or Subgroup	LCI Mean	LCI SD	LCI Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
3.2.1 LCI versus control								
Salman Roghani 2018	-0.63	0.84	64	-0.53	1.04	30	22.8%	-0.10 [-0.53 , 0.33]
Subtotal (95% CI)			**64**			**30**	**22.8%**	**-0.10 [-0.53 , 0.33]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.46 (P = 0.64)								
3.2.2 LCI versus control (hands as unit of analysis)								
Karadaş 2012	-0.43	0.59	30	-0.19	0.68	30	39.7%	-0.24 [-0.56 , 0.08]
Ucan 2006	-0.41	0.39	23	-0.42	0.71	23	37.6%	0.01 [-0.32 , 0.34]
Subtotal (95% CI)			**53**			**53**	**77.2%**	**-0.12 [-0.36 , 0.13]**
Heterogeneity: Tau² = 0.00; Chi² = 1.13, df = 1 (P = 0.29); I² = 11%								
Test for overall effect: Z = 0.94 (P = 0.34)								
Total (95% CI)			**117**			**83**	**100.0%**	**-0.11 [-0.32 , 0.09]**
Heterogeneity: Tau² = 0.00; Chi² = 1.13, df = 2 (P = 0.57); I² = 0%								
Test for overall effect: Z = 1.10 (P = 0.27)								
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.94), I² = 0%								



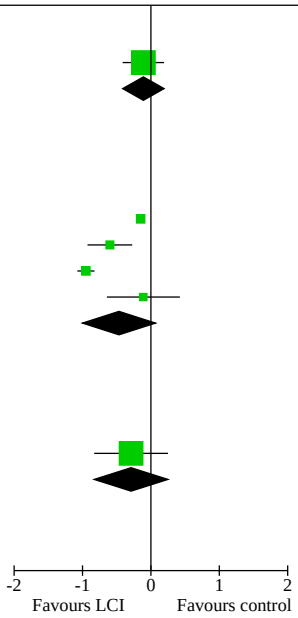
Analysis 3.3. Comparison 3: Local corticosteroid injection (LCI) versus control: improvement in neurophysiological parameters, Outcome 3: Median nerve DML ≤ 3 months by local anaesthetic (LA) use

Study or Subgroup	LCI Mean	LCI SD	LCI Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
3.3.1 LCI versus saline								
Karadaş 2012	-0.59	0.61	15	0.01	0.68	30	100.0%	-0.60 [-0.99 , -0.21]
Subtotal (95% CI)			**15**			**30**	**100.0%**	**-0.60 [-0.99 , -0.21]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.99 (P = 0.003)								
3.3.2 LCI versus LA								
Karadaş 2012	-0.59	0.61	15	-0.32	0.67	30	100.0%	-0.27 [-0.66 , 0.12]
Subtotal (95% CI)			**15**			**30**	**100.0%**	**-0.27 [-0.66 , 0.12]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.35 (P = 0.18)								
3.3.3 LCI versus no treatment								
Khosrawi 2016	-1.67	0.26	21	-0.72	0.14	22	100.0%	-0.95 [-1.08 , -0.82]
Subtotal (95% CI)			**21**			**22**	**100.0%**	**-0.95 [-1.08 , -0.82]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 14.82 (P < 0.00001)								
3.3.4 LCI+LA versus saline+LA								
Armstrong 2004	-0.26	0.035	43	-0.11	0.032	36	99.8%	-0.15 [-0.16 , -0.14]
Salman Roghani 2018	-0.44	0.79	64	-0.24	0.91	30	0.2%	-0.20 [-0.58 , 0.18]
Subtotal (95% CI)			**107**			**66**	**100.0%**	**-0.15 [-0.16 , -0.14]**
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.80); I² = 0%								
Test for overall effect: Z = 19.90 (P < 0.00001)								
3.3.5 LCI+LA+splints versus splints								
Ucan 2006	-0.61	0.39	23	-0.5	0.63	23	64.7%	-0.11 [-0.41 , 0.19]
Wu 1991	-0.84	0.58	18	-0.71	0.69	19	35.3%	-0.13 [-0.54 , 0.28]
Subtotal (95% CI)			**41**			**42**	**100.0%**	**-0.12 [-0.36 , 0.13]**
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%								
Test for overall effect: Z = 0.94 (P = 0.35)								
Test for subgroup differences: Chi² = 158.77, df = 4 (P < 0.00001), I² = 97.5%								



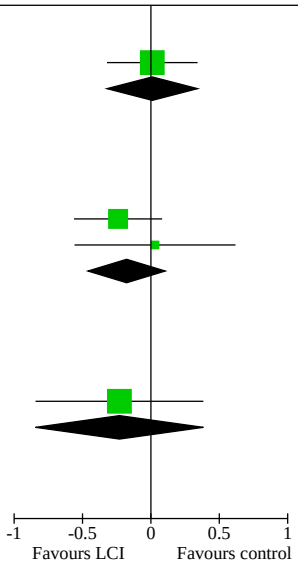
Analysis 3.4. Comparison 3: Local corticosteroid injection (LCI) versus control: improvement in neurophysiological parameters, Outcome 4: Median nerve DML ≤ 3 months by dose of corticosteroid

Study or Subgroup	LCI Mean	LCI SD	LCI Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
3.4.1 Low-dose (approx 20 mg equivalent methylprednisolone) LCI versus control								
Ucan 2006	-0.61	0.39	23	-0.5	0.63	23	100.0%	-0.11 [-0.41 , 0.19]
Subtotal (95% CI)			**23**			**23**	**100.0%**	**-0.11 [-0.41 , 0.19]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.71 (P = 0.48)								
3.4.2 Medium-dose (approx 40 mg equivalent methylprednisolone) LCI versus control								
Armstrong 2004	-0.26	0.035	43	-0.11	0.032	36	27.2%	-0.15 [-0.16 , -0.14]
Karadaş 2012	-0.59	0.61	30	0.01	0.68	30	24.7%	-0.60 [-0.93 , -0.27]
Khosrawi 2016	-1.67	0.26	21	-0.72	0.14	22	26.8%	-0.95 [-1.08 , -0.82]
Salman Roghani 2018	-0.35	0.78	32	-0.24	0.91	15	21.4%	-0.11 [-0.64 , 0.42]
Subtotal (95% CI)			**126**			**103**	**100.0%**	**-0.47 [-1.00 , 0.07]**
Heterogeneity: Tau² = 0.27; Chi² = 160.54, df = 3 (P < 0.00001); I² = 98%								
Test for overall effect: Z = 1.71 (P = 0.09)								
3.4.3 High-dose (approx 80 mg equivalent methylprednisolone) LCI versus control								
Salman Roghani 2018	-0.53	0.81	32	-0.24	0.91	15	100.0%	-0.29 [-0.83 , 0.25]
Subtotal (95% CI)			**32**			**15**	**100.0%**	**-0.29 [-0.83 , 0.25]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.05 (P = 0.29)								
Test for subgroup differences: Chi² = 1.39, df = 2 (P = 0.50), I² = 0%								



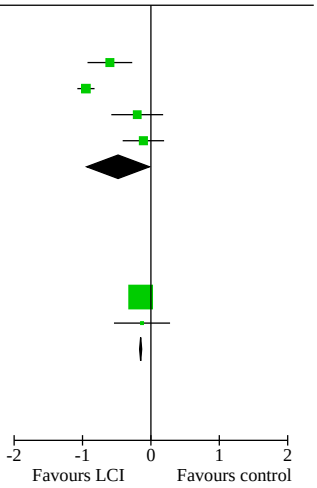
Analysis 3.5. Comparison 3: Local corticosteroid injection (LCI) versus control: improvement in neurophysiological parameters, Outcome 5: Median nerve DML > 3 months by dose of corticosteroid

Study or Subgroup	LCI Mean	LCI SD	LCI Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
3.5.1 Low-dose (approx 20 mg equivalent methylprednisolone) LCI versus control								
Ucan 2006	-0.41	0.39	23	-0.42	0.71	23	100.0%	0.01 [-0.32 , 0.34]
Subtotal (95% CI)			**23**			**23**	**100.0%**	**0.01 [-0.32 , 0.34]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.06 (P = 0.95)								
3.5.2 Medium-dose (approx 40 mg equivalent methylprednisolone) LCI versus control								
Karadaş 2012	-0.43	0.59	30	-0.19	0.68	30	76.9%	-0.24 [-0.56 , 0.08]
Salman Roghani 2018	-0.5	0.76	32	-0.53	1.04	15	23.1%	0.03 [-0.56 , 0.62]
Subtotal (95% CI)			**62**			**45**	**100.0%**	**-0.18 [-0.46 , 0.10]**
Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 1 (P = 0.43); I² = 0%								
Test for overall effect: Z = 1.23 (P = 0.22)								
3.5.3 High-dose (approx 80 mg equivalent methylprednisolone) LCI versus control								
Salman Roghani 2018	-0.76	0.91	32	-0.53	1.04	15	100.0%	-0.23 [-0.84 , 0.38]
Subtotal (95% CI)			**32**			**15**	**100.0%**	**-0.23 [-0.84 , 0.38]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.73 (P = 0.46)								
Test for subgroup differences: Chi² = 0.87, df = 2 (P = 0.65), I² = 0%								



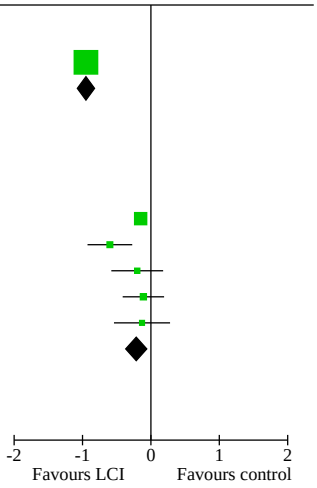
Analysis 3.6. Comparison 3: Local corticosteroid injection (LCI) versus control: improvement in neurophysiological parameters, Outcome 6: Median nerve DML ≤ 3 months by duration of action of corticosteroid

Study or Subgroup	LCI Mean	LCI SD	LCI Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
3.6.1 Intermediate-acting (12–36 hours) LCI versus control								
Karadaş 2012	-0.59	0.61	30	0.01	0.68	30	24.4%	-0.60 [-0.93 , -0.27]
Khosrawi 2016	-1.67	0.26	21	-0.72	0.14	22	27.3%	-0.95 [-1.08 , -0.82]
Salman Roghani 2018	-0.44	0.79	64	-0.24	0.91	30	23.4%	-0.20 [-0.58 , 0.18]
Ucan 2006	-0.61	0.39	23	-0.5	0.63	23	24.9%	-0.11 [-0.41 , 0.19]
Subtotal (95% CI)			**138**			**105**	**100.0%**	**-0.48 [-0.94 , -0.02]**
Heterogeneity: Tau² = 0.20; Chi² = 35.79, df = 3 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 2.05 (P = 0.04)								
3.6.2 Long-acting (> 48 hours) LCI versus control								
Armstrong 2004	-0.26	0.035	43	-0.11	0.032	36	99.9%	-0.15 [-0.16 , -0.14]
Wu 1991	-0.84	0.58	18	-0.71	0.69	19	0.1%	-0.13 [-0.54 , 0.28]
Subtotal (95% CI)			**61**			**55**	**100.0%**	**-0.15 [-0.16 , -0.14]**
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%								
Test for overall effect: Z = 19.89 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.99, df = 1 (P = 0.16), I² = 49.7%								



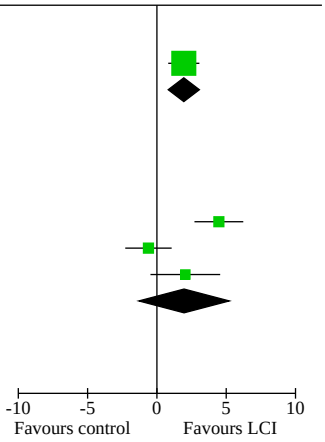
Analysis 3.7. Comparison 3: Local corticosteroid injection (LCI) versus control: improvement in neurophysiological parameters, Outcome 7: Median nerve DML ≤ 3 months by type of corticosteroid

Study or Subgroup	LCI Mean	LCI SD	LCI Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
3.7.1 Mineralocorticoid-acting LCI versus control								
Khosrawi 2016	-1.67	0.26	21	-0.72	0.14	22	100.0%	-0.95 [-1.08 , -0.82]
Subtotal (95% CI)			**21**			**22**	**100.0%**	**-0.95 [-1.08 , -0.82]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 14.82 (P < 0.00001)								
3.7.2 Non-mineralocorticoid-acting LCI versus control								
Armstrong 2004	-0.26	0.035	43	-0.11	0.032	36	45.7%	-0.15 [-0.16 , -0.14]
Karadaş 2012	-0.59	0.61	30	0.01	0.68	30	14.9%	-0.60 [-0.93 , -0.27]
Salman Roghani 2018	-0.44	0.79	64	-0.24	0.91	30	12.1%	-0.20 [-0.58 , 0.18]
Ucan 2006	-0.61	0.39	23	-0.5	0.63	23	16.5%	-0.11 [-0.41 , 0.19]
Wu 1991	-0.84	0.58	18	-0.71	0.69	19	10.8%	-0.13 [-0.54 , 0.28]
Subtotal (95% CI)			**178**			**138**	**100.0%**	**-0.21 [-0.37 , -0.06]**
Heterogeneity: Tau² = 0.01; Chi² = 7.41, df = 4 (P = 0.12); I² = 46%								
Test for overall effect: Z = 2.73 (P = 0.006)								
Test for subgroup differences: Chi² = 52.68, df = 1 (P < 0.00001), I² = 98.1%								



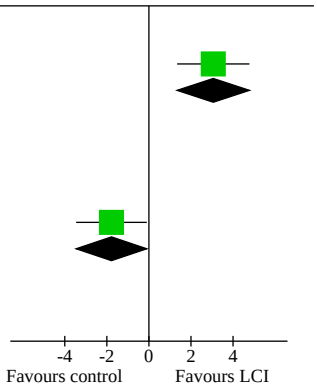
Analysis 3.8. Comparison 3: Local corticosteroid injection (LCI) versus control: improvement in neurophysiological parameters, Outcome 8: Median nerve sensory nerve conduction velocity (SNCV) ≤ 3 months

Study or Subgroup	LCI Mean	LCI SD	LCI Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
3.8.1 LCI versus control								
Khosrawi 2016	10.98	1.84	21	9.04	1.92	22	100.0%	1.94 [0.82 , 3.06]
Subtotal (95% CI)			**21**			**22**	**100.0%**	**1.94 [0.82 , 3.06]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.38 (P = 0.0007)								
3.8.2 LCI versus control (hands as the unit of analysis)								
Karadaş 2012	4.05	3.93	30	-0.42	2.96	30	34.3%	4.47 [2.71 , 6.23]
Ucan 2006	-0.05	2.93	23	0.56	2.86	23	34.6%	-0.61 [-2.28 , 1.06]
Wu 1991	3.34	3.55	18	1.29	4.24	19	31.1%	2.05 [-0.46 , 4.56]
Subtotal (95% CI)			**71**			**72**	**100.0%**	**1.96 [-1.30 , 5.22]**
Heterogeneity: Tau² = 7.26; Chi² = 16.83, df = 2 (P = 0.0002); I² = 88%								
Test for overall effect: Z = 1.18 (P = 0.24)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² = 0%								



Analysis 3.9. Comparison 3: Local corticosteroid injection (LCI) versus control: improvement in neurophysiological parameters, Outcome 9: Median nerve SNCV > 3 months

Study or Subgroup	LCI Mean	LCI SD	LCI Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
3.9.1 LCI versus saline								
Karadaş 2012	2.4	3.83	30	-0.66	2.9	30	100.0%	3.06 [1.34 , 4.78]
Subtotal (95% CI)			**30**			**30**	**100.0%**	**3.06 [1.34 , 4.78]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.49 (P = 0.0005)								
3.9.2 LCI versus no treatment								
Ucan 2006	-1.18	2.91	23	0.6	2.9	23	100.0%	-1.78 [-3.46 , -0.10]
Subtotal (95% CI)			**23**			**23**	**100.0%**	**-1.78 [-3.46 , -0.10]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.08 (P = 0.04)								
Test for subgroup differences: Chi² = 15.58, df = 1 (P < 0.0001), I² = 93.6%								

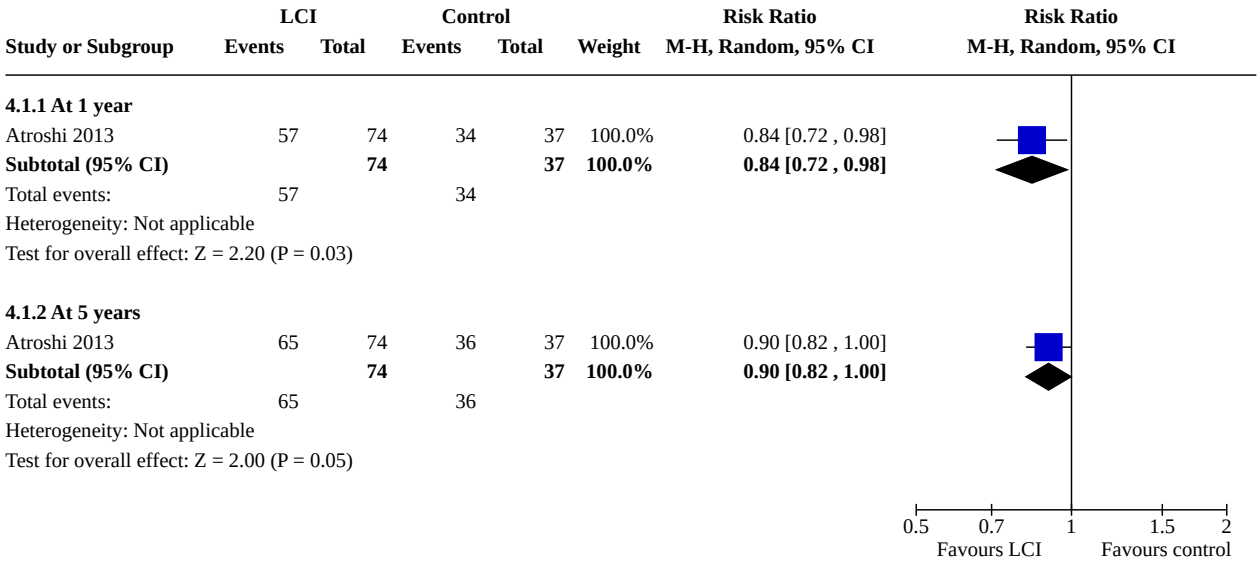


Comparison 4. Local corticosteroid injection (LCI) versus control: other outcomes

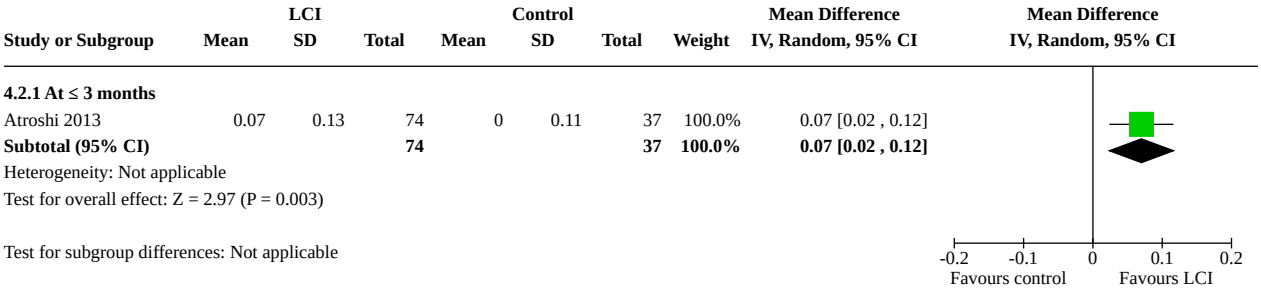
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Requirement for surgery	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1.1 At 1 year	1	111	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.72, 0.98]
4.1.2 At 5 years	1	111	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.82, 1.00]
4.2 Change in quality of life (Short-Form Six-Dimension Instrument)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2.1 At ≤ 3 months	1	111	Mean Difference (IV, Random, 95% CI)	0.07 [0.02, 0.12]

Analysis 4.1. Comparison 4: Local corticosteroid injection (LCI) versus control: other outcomes, Outcome 1: Requirement for surgery



Analysis 4.2. Comparison 4: Local corticosteroid injection (LCI) versus control: other outcomes, Outcome 2: Change in quality of life (Short-Form Six-Dimension Instrument)



APPENDICES

Appendix 1. Cochrane Neuromuscular Specialised Register via the Cochrane Register of Studies (CRS Web) search strategy

1 MeSH DESCRIPTOR Carpal Tunnel Syndrome AND INREGISTER 377

2 "carpal tunnel" AND INREGISTER 594

3 ("nerve entrapment" or "nerve compression" or "entrapment neuropath*") and carpal AND INREGISTER 42

4 #1 or #2 or #3 594

5 MeSH DESCRIPTOR Adrenal Cortex Hormones Explode All AND INREGISTER 346

6 steroid* or corticosteroid* or *asone or *olone or *isone or *onide AND INREGISTER 546

7 #5 or #6 682

8 #4 and #7 118

9 INREGISTER AND 07/06/2020_TO_26/05/2022:CRSCREATED 189

10 #8 AND #9 0

Appendix 2. Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies (CRS-Web) search strategy

1 MeSH DESCRIPTOR Carpal Tunnel Syndrome AND CENTRAL:TARGET 785

2 "carpal tunnel" AND CENTRAL:TARGET 1760

3 ("nerve entrapment" or "nerve compression" or "entrapment neuropath*") and carpal AND CENTRAL:TARGET 136

4 #1 or #2 or #3 1760

5 MeSH DESCRIPTOR Adrenal Cortex Hormones Explode All AND CENTRAL:TARGET 29305

6 steroid* or corticosteroid* or *asone or *olone or *isone or *onide AND CENTRAL:TARGET 56797

7 #5 or #6 74786

8 #4 and #7 328

9 07/06/2020_TO_26/05/2022:CRSINCENTRAL AND CENTRAL:TARGET 243239

10 #8 AND #9 70

Appendix 3. MEDLINE (OvidSP) search strategy

Database: Ovid MEDLINE(R) ALL <1946 to May 25, 2022>

1 ((randomized controlled trial or controlled clinical trial).pt. or (randomized or randomised or randomly or placebo or trial or groups).ab. or drug therapy.fs.) not (exp animals/ not humans.sh.) (4684563)

2 Carpal Tunnel Syndrome/ or Carpal Tunnel Syndrome.tw. or ((nerve entrapment or nerve compression or entrapment neuropath$) and carpal).mp. (11963)

3 exp adrenal cortex hormones/ or (corticosteroid$ or steroid$).mp. (747459)

4 1 and 2 and 3 (438)

5 limit 4 to ed=20200607-20221231 (37)

6 limit 4 to dt=20200607-20221231 (44)

7 5 or 6 (53)

Appendix 4. Embase (OvidSP) search strategy

Database: Embase <1974 to 2022 May 25>

1 (crossover procedure or double-blind procedure or single-blind procedure or randomized controlled trial).sh. or (random$ or crossover $ or cross over$ or placebo$ or (doubl$ adj blind$) or allocat$).tw,ot. or trial.ti. (2267673)

2 (animal/ or nonhuman/ or animal experiment/) and human/ (2354625)

3 animal/ or nonanimal/ or animal experiment/ (4382355)

4 3 not 2 (3561366)

5 1 not 4 (2082582)

6 limit 5 to (conference abstract or embase) (1741679)

7 Carpal Tunnel Syndrome/ or carpal tunnel syndrome.mp. or ((nerve entrapment or nerve compression or entrapment neuropath$) and carpal).mp. (17955)

8 exp corticosteroid/ or exp glucocorticoids/ or (corticosteroid$ or glucocorticoid$ or steroid$).mp. (1396810)

9 6 and 7 and 8 (269)

10 limit 9 to dc=20200607-20221231 (44)

Appendix 5. CINAHL Plus with Full Text (EBSCOhost) search strategy

Thursday, May 26, 2022 3:03:00 PM

S6 S4 AND S5 7

S5 EM 202006- 759,562

S4 S1 AND S2 AND S3 Limiters - Exclude MEDLINE records 38

S3 (MH "Adrenal Cortex Hormones+") OR (corticosteroid* or glucocorticoid* or steroid*) 98,770

S2 (MH "Carpal Tunnel Syndrome") OR carpal tunnel syndrome OR (nerve entrapment and carpal) OR (nerve compression and carpal) OR (entrapment neuropath* and carpal) 3,985

S1 (MH randomized controlled trials OR MH double-blind studies OR MH single-blind studies OR MH random assignment OR MH pretest-posttest design OR MH cluster sample OR (TI (randomised OR randomized)) OR AB (random*) OR TI (trial) OR (MH (sample size) AND AB (assigned OR allocated OR control)) OR MH (placebos) OR PT (randomized controlled trial) OR AB (control W5 group) OR (MH (crossover design) OR MH (comparative studies)) OR AB (cluster W3 RCT)) NOT ((MH animals+ OR MH (animal studies) OR TI (animal model*)) NOT MH (human)) 916,243

Appendix 6. US National Institutes for Health Clinical Trials Registry, ClinicalTrials.gov search strategy

Advanced Search

Condition or disease: Carpal Tunnel Syndrome

Study type: Interventional Studies (Clinical Trials)

First Posted From 06.07/2020 To 05/26/2022

60 Studies found

Appendix 7. WHO International Clinical Trials Registry Portal (ICTRP) search strategy

Advanced Search

Carpal Tunnel Syndrome in the Condition

Recruitment Status is ALL

500 records for 498 trials found

CONTRIBUTIONS OF AUTHORS

NA and JB drafted and edited the protocol and review.

Three pairs of authors (NA, GT, KC, JB, LA, AN) screened/selected/reviewed full text/extracted outcomes and assessed risk of bias.

All review authors approved the final protocol and review.

DECLARATIONS OF INTEREST

NA: none.

JB: none known. Dr Bland gives an annual lecture to students on a neuroscience MSc course, for which he is paid as an external lecturer. This activity has no relevance to this review.

KC: none.

GT: none.

LA: none.

AN: I received no money or sponsorship for my participation in this review. I am employed full-time as a Clinical Neurophysiologist and thus have an academic interest in carpal tunnel syndrome. I am a member of the British Society of Clinical Neurophysiologists who have published guidelines and recommendations with respect to carpal tunnel syndrome.

SOURCES OF SUPPORT

Internal sources

- None, Other

  We received no sources of support

External sources

- None, Other

  We received no sources of support

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes from our protocol (Ashworth 2020).

In the summary of findings table we reported on 'function' and 'neurophysiological measures' at three months or less instead of greater than three months that we originally planned because of lack of evidence at the longer follow-up.

We originally planned to not pool trials that used 'hands' as the unit of analysis together with those that used 'participants'; however, we realised that we had an important opportunity to determine if there truly was a difference in these types of trials. Therefore, we chose to ultimately report the two types of trials separately and to pool them if there was no difference between the two subgroups.

NOTES

This review is one of a series of reviews that replaces Marshall 2007. The published protocol is "Local corticosteroid injection for carpal tunnel syndrome" (Ashworth 2020).

INDEX TERMS

Medical Subject Headings (MeSH)

*Adrenal Cortex Hormones [adverse effects]; *Carpal Tunnel Syndrome [drug therapy]; Hand; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans