Efficacy and safety of corticosteroid injections and other injections for management of tendinopathy: a systematic review of randomised controlled trials

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Summary

Background Few evidence-based treatment guidelines for tendinopathy exist. We undertook a systematic review of randomised trials to establish clinical efficacy and risk of adverse events for treatment by injection.

Methods We searched eight databases without language, publication, or date restrictions. We included randomised trials assessing efficacy of one or more peritendinous injections with placebo or non-surgical interventions for tendinopathy, scoring more than 50% on the modified physiotherapy evidence database scale. We undertook meta-analyses with a random-effects model, and estimated relative risk and standardised mean differences (SMDs). The primary outcome of clinical efficacy was protocol-defined pain score in the short term (4 weeks, range 0–12), intermediate term (26 weeks, 13–26), or long term (52 weeks, ≥52). Adverse events were also reported.

Findings 3824 trials were identified and 41 met inclusion criteria, providing data for 2672 participants. We showed consistent findings between many high-quality randomised controlled trials that corticosteroid injections reduced pain in the short term compared with other interventions, but this effect was reversed at intermediate and long terms. For example, in pooled analysis of treatment for lateral epicondylalgia, corticosteroid injection had a large effect (defined as SMD>0·8) on reduction of pain compared with no intervention in the short term (SMD 1·44, 95% CI 1·17–1·71, p<0·0001), but no intervention was favoured at intermediate term (–0·40, –0·67 to –0·14, p<0·003) and long term (–0·31, –0·61 to –0·01, p=0·05). Short-term efficacy of corticosteroid injections for rotator-cuff tendinopathy is not clear. Of 991 participants who received corticosteroid injections in studies that reported adverse events, only one (0·1%) had a serious adverse event (tendon rupture). By comparison with placebo, reductions in pain were reported after injections of sodium hyaluronate (short [3·91, 3·54–4·28, p<0·0001], intermediate [2·89, 2·58–3·20, p<0·0001], and long [3·91, 3·55–4·28, p<0·0001] terms), botulinum toxin (short term [1·23, 0·67–1·78, p<0·0001]), and prolotherapy (intermediate term [2·62, 1·36–3·88, p<0·0001]) for treatment of lateral epicondylalgia. Lauromacrogol (polidocanol), aprotinin, and platelet-rich plasma were not more efficacious than was placebo for Achilles tendinopathy, while prolotherapy was not more effective than was eccentric exercise.

Interpretation Despite the effectiveness of corticosteroid injections in the short term, non-corticosteroid injections might be of benefit for long-term treatment of lateral epicondylalgia. However, response to injection should not be generalised because of variation in effect between sites of tendinopathy.

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Introduction

Overuse disorders of tendon or tendinopathies affect active young people (20–30 years old) and middle-aged people (40–60 years old) and are often difficult to manage successfully. These disorders are characterised by angiofibroblastic hyperplasia,[1] including hypercellularity, neovascularisation, increased protein synthesis, and disorganisation of matrix, but not inflammation.[2–4] This absence of inflammation, along with poor long-term outcomes[5] and adverse effects,[6,7] has led investigators to question the use of corticosteroid injections for treatment[8] and has contributed to increased use of other injection types, such as lauromacrogol (polidocanol), platelet-rich plasma, botulinum toxin, and proteinases. The large number of studies about these other injection types underpins the need for a synthesis of the evidence for injection therapies. We aimed to review the clinical efficacy and risk of adverse events of injections (including corticosteroids) for treatment of tendinopathy in the short term, intermediate term, and long term, and in different areas of tendinopathy.

Methods

Search strategy and selection criteria

We did this systematic review and reported it in accordance with Cochrane Collaboration[9] and PRISMA[10] guidelines. We systematically reviewed eight databases (Medline, Cinahl, Embase, Web of Knowledge, Allied and Complementary Medicine, SPORTDiscus, Cochrane Controlled Trial Register, and Physiotherapy Evidence Database) without language, publication, or date restrictions in March, 2010, with the search terms "tennis elbow", "Achilles tendon", "patellar ligament", "tendinopathy", "tendon injuries", "rotator cuff",

For the **original PEDro scale** see http://www.pedro.org.au/scale_item.html

"shoulder impingement syndrome", "epicondyl*", "golfers elbow", "supraspin*", or "jumpers knee" and "injections", "steroids", "anesthetics, local", "sclerosing solutions", "aprotinin", "platelet-rich plasma", "botulinum toxins", or "glycosaminoglycans". We searched reference lists for additional studies.

We included randomised controlled trials that compared one or more peritendinous injections with placebo or other non-surgical interventions. Intramuscular or intra-articular injections were beyond the scope of this review because pathological changes reported in tendinopathy are thought to occur in the tendon. We defined rotator-cuff tendinopathy as described in a previous systematic review,[11] excluding studies composed of a high proportion of adhesive capsulitis, full thickness tears, or rheumatological disease. Potentially relevant citations were assessed for inclusion by one investigator (BKC) and confirmed by a second investigator (LB).

Quality was assessed independently with a modified physiotherapy evidence database (PEDro) scale by two masked investigators (BKC and LB), and disagreement was resolved by consensus. Very good inter-rater reliability was achieved (6·9% initial disagreement, κ statistic 0·85). We added two items, which were consistency of timing of outcome measurement and documentation of adverse events, to the original PEDro scale. Studies were included if they scored more than the mean PEDro score (50%) for randomised controlled trials in physical therapy.[12]

The predefined outcomes of pain, function, and patient-rated overall improvement were extracted as measures of clinical efficacy. Frequency of all adverse events was recorded to assess treatment safety. We classified data according to duration and comparator intervention. Duration of follow-up was classified as short term (4 weeks, range 0–12 weeks), intermediate (26 weeks, 13–26 weeks), and long term (1 year, ≥52 weeks).[13] Comparison was made with placebo injection (saline or local anaesthetic), no-intervention (observation or wait and see), NSAIDs, physiotherapy, electrotherapy, or orthotic devices. Trial data were extracted by BKC and confirmed by BV. We contacted investigators for additional data if insufficient

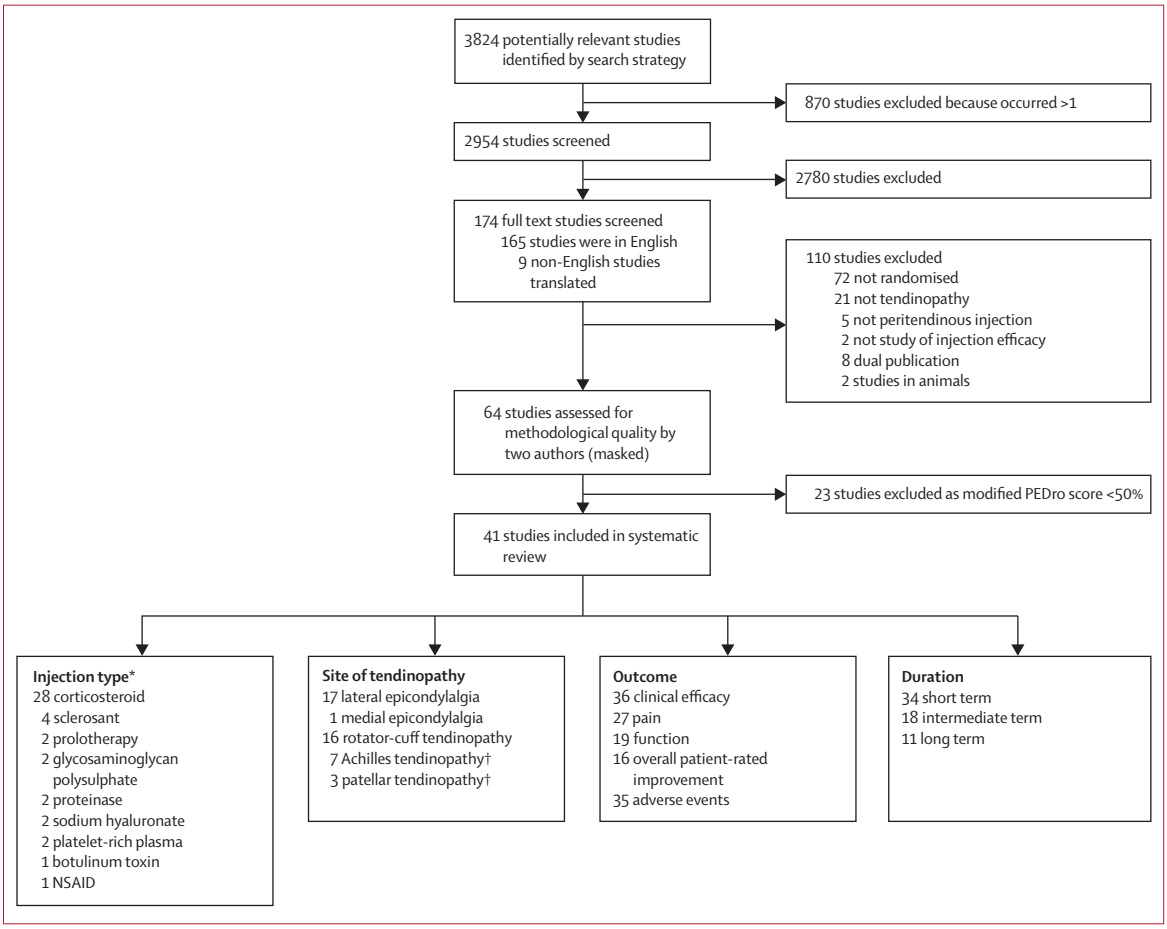

Figure 1: **Study selection**
*Three studies of more than one injection type. †One study investigated both Achilles and patellar tendinopathy. NSAID=non-steroidal anti-inflammatory drug.

information was provided. Investigators were not contacted to seek confirmation of their data.

Statistical analysis

We used RevMan statistical software version 5.0 (Nordic Cochrane Centre, Copenhagen, Denmark) to derive summary statistics with a random-effects model. We calculated relative risk (RR) for dichotomous data and the standardised mean difference (SMD; difference in mean effects between groups divided by the pooled SD) for continuous data.[9] If the difference in mean effects between groups was not available, the SMD was calculated from the postintervention mean scores and corresponding SD. For adverse events, we calculated RR and number needed to harm (NNH), which was the number of patients treated for the occurrence of one additional adverse event in the treatment group compared with the control group.

Point estimates of effect were statistically significant when the CI did not cross 1 for RR or 0 for SMD. Results favoured the primary injection when SMD was positive or RR was more than 1, and favoured the control when SMD was negative or RR was less than 1. SMD of less than 0·5 and RR of less than 1·25 (but more than 1) or more than 0·8 (but less than 1) were defined as a small effect, SMD 0·5–0·8 and RR 1·25–2 or 0·5–0·8 were defined as a medium effect, and SMD of more than 0·8 and RR more than 2 or less than 0·5 were defined as a large effect.[14] Pooled estimates were calculated with RevMan when subgroups of trials displayed sufficient clinical and statistical homogeneity ($p<0·05$) as assessed with the I^2 statistic.[15] Publication bias was not assessed because of the small numbers of trials that could be pooled. For outcomes that could not be pooled because of heterogeneity, the strength of evidence was guided by the following criteria of scientific evidence: strong (consistent findings between many high-quality randomised controlled trials), moderate (one high-quality randomised controlled trial), conflicting (inconsistent findings between many randomised controlled trials), or no evidence.[16]

Role of the funding source

There was no funding source for this study. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the process of study selection, leading to the inclusion of 41 studies in the systematic review. Quality rating scores ranged from 2 of 13 to 13 of 13 (see webappendix) and were not dependent on anatomical site. 23 articles were excluded from the systematic review because of low modified PEDro scores (<50%). Table 1 shows study populations, interventions, and extracted outcome measures for eligible trials. Tables 2 and 3 show clinical outcomes in the eligible studies. We discuss only pain outcomes for the studies in which pain outcomes were representative of all outcome measurements.

18 analyses from 12 trials were done to assess the efficacy of corticosteroid injection for lateral epicondylalgia in 1171 participants. Figure 2 shows pain data for the eight trials that compared corticosteroid injection with non-corticosteroid injections. All individuals in the study populations had clinically diagnosed lateral epicondylalgia of 3–6 months median duration, apart from one study,[20] in which participants had clinically diagnosed lateral epicondylalgia for less than 4 weeks. Efficacy of one injection was investigated in seven trials, up to three injections in four trials, and one trial compared one injection with repeated injections.[21] Compared with non-injection interventions, there was strong evidence for benefit of corticosteroid injections in the short term across all outcome measures for treatment of lateral epicondylalgia. Estimates of effect of corticosteroid injections were large by comparison with no intervention,[5,25,26] NSAIDs,[18] physiotherapy,[5,25–27] and orthotic devices (table 2).[17] Although findings were consistent (mainly in favour of corticosteroid injections), significant heterogeneity was noted in studies that compared corticosteroid injection with physiotherapy, because of different physiotherapy protocols between studies, and placebo injection, which restricted pooling of data. Investigators from one trial of 87 participants[23] reported a large effect of corticosteroid injection compared with local anaesthetic (placebo) injection for reduction of pain (table 2), whereas investigators from two trials[19,20] of 64 and 39 participants showed no difference in effect from the two injections. One of these two studies had a 25% loss to follow-up in both groups,[19] and in the other all patients received concomitant physiotherapy.[20] A third trial[24] reported no difference in overall improvement compared with saline injection combined with NSAID. A trial[22] of corticosteroid injection versus platelet-rich plasma injection reported a small effect of reduction in pain in favour of corticosteroid injection in 100 participants (table 2).

Strong evidence suggests that corticosteroid injections are less beneficial than are other interventions for treatment of lateral epicondylalgia at 26 weeks. Inferior reductions in pain were reported after corticosteroid injection compared with no intervention,[5,25] NSAIDs,[18] physiotherapy,[5,25] and platelet-rich plasma injections.[22] These negative effects remained significant at 1 year, apart from for corticosteroid injection versus NSAIDs, which did not differ (table 2).[18] Doses and suspensions of corticosteroid did not alter outcomes.[23] However, repeated corticosteroid injections (average of 4·3 injections, range of three to six in 18 months) were associated with a poorer long-term effect on reduction in pain than were interventions with one injection.[21]

See Online for webappendix

14 analyses from ten trials were done to assess efficacy of corticosteroid injection for treatment of rotator-cuff tendinopathy in 780 participants. Figure 3 shows pain data for nine trials that compared corticosteroid injection with non-corticosteroid injections. Population characteristics differed between included studies (table 1). Mean duration of symptoms varied from less than 4 weeks in 82% of patients in one trial[40] to 3·2 years in another trial.[30]

Evidence for short-term efficacy of corticosteroid injections for rotator-cuff tendinopathy is conflicting.

	PEDro score	Population characteristics	Interventions (number randomised)	Extracted outcome measures	Extracted time points (weeks)
Corticosteroid injection for lateral epicondylalgia					
Bisset[5]	11/13	Inclusion: clinical diagnosis of unilateral LE >6 weeks Exclusion: treatment in previous 6 months, other elbow abnormalities, radiculopathy, nerve involvement, surgery, fracture, dislocation, neurological disorders, or medication contraindication Mean pain VAS=57/100	1 mL triamcinolone acetonide 10 mg/mL plus 1 mL 1% lidocaine, one or two injections, 2-week interval (n=65); physiotherapy, 8×30 min sessions, elbow mobilisation with movement, concentric, eccentric or isometric or general arm exercise (n=66); wait-and-see (n=67)	Adverse events; pain VAS (0–100);* pain-free function scale (out of 100);* overall improvement (complete recovery or much improved; 6-point scale)	6, 26, 52
Haker[17]	7/13	Inclusion: clinical diagnosis of LE >1 month Exclusion: neck or shoulder dysfunction, arthritis, neurological abnormality, or nerve entrapment	0·2 mL triamcinolone acetonide 10 mg/mL plus 0·3 mL bupivacaine, one or two injections, 1-week interval (n=19); elbow band for 3 months (n=18); wrist splint for 3 months (n=19)	Adverse events; patient perceived change (excellent or good; 5-point scale)	2, 26, 52
Hay[18]	10/13	Inclusion: clinical diagnosis of LE (new episode) Exclusion: arthritis, gross structural abnormality, or medication contraindication Mean NRS=5·1/9	20 mg methylprednisolone plus 0·5 mL 1% lidocaine in one injection (n=53); 500 mg naproxen twice daily for 2 weeks (n=53); placebo tablets twice daily for 2 weeks (n=58)	Adverse events; pain NRS (0–9);† impairment of function NRS (0–9);† overall improvement (complete recovery; 5-point scale)	4, 26, 52
Lindenhovius[19]	11/13	Inclusion: LE <6 months, clinical diagnosis with substantial relief following lidocaine injection Exclusion: surgery, inflammatory disease, pregnancy, restricted elbow motion, neurological signs, or previous steroid use	1 mL of 4 mg/mL dexamethasone plus 1 mL 1% lidocaine without epinephrine (n=31); 2 mL 1% lidocaine without epinephrine injection (n=33); one injection, co-intervention allowed	Adverse events; pain VAS (0–10);† DASH scale (out of 100)†	4, 26
Newcomer[20]	11/13	Inclusion: clinical diagnosis of acute, unilateral LE <4 weeks Exclusion: previous treatment, nerve entrapment, history of trauma or previous LE, inflammatory disorders, workers' compensation, or systemic steroids	5 mL betamethasone (6 mg/mL) plus 0·25% bupivacaine (n=20); 5 mL 0·25% bupivacaine (n=19); one injection, co-intervention of rehabilitation (strength and stretch exercises) and ice	Pain VAS (0–100)*‡	4, 26
Okcu[21]	7/13	Inclusion: clinical diagnosis of LE Exclusion: steroid injection in previous year, inflammatory disorders, cervical origin, or elbow trauma Mean pain VAS=83/100	0·5 mL 4·53 mg betamethasone plus 0·5 mL 5 mg prilocaine; one injection (n=22); multiple injections (n=30), minimum 4-week intervals and mean 4·3 injections at 18 months; co-intervention NSAID tenoxicam 20 mg per day for 10 days	Adverse events; pain VAS (0–100);† subjective satisfaction (pleased; 3-point scale)	6, 78
Peerbooms[22]	10/13	Inclusion: clinical diagnosis of LE >6 months and pain VAS>50/100, normal radiograph Exclusion: <18 years of age, pregnancy, history of carpal tunnel, cervical radiculopathy, systemic disorders (eg diabetes, rheumatoid arthritis, or hepatitis), or steroid injection or surgery in past 6 months Mean pain VAS=67/100	4 mL 40 mg/mL triamcinolone plus bupivacaine 0·5% with epinephrine (n=49); 4 mL platelet-rich plasma injection (n=51); one injection with peppering technique; co-intervention physiotherapy (rest 24 h, stretching 2 weeks, followed by eccentric strengthening exercise)	Adverse events; pain VAS (0–100);† DASH scale†	4, 26, 52
Price[23]	11/13	Inclusion: clinical diagnosis of LE, previous treatment accepted Mean pain VAS in study 1=49/100 Mean pain VAS in study 2=65/100	Study 1: 2 mL 10 mg triamcinolone plus 1% lidocaine (n=29); 2 mL 25 mg hydrocortisone plus 1% lidocaine (n=29); 2 mL of 1% lidocaine (n=29); Study 2: 2 mL 10 mg triamcinolone plus 1% lidocaine (n=23); 2 mL 20 mg triamcinolone plus 1% lidocaine (n=28)	Adverse events; pain VAS (0–100)†	4, 24
Saartok[24]	8/13	Inclusion: clinical diagnosis of LE Exclusion: treatment within previous 5 weeks	1 mL 6 mg betamethasone plus 0·5 mL 1% prilocaine, one injection plus placebo tablets (n=11); 1·5 mL saline injection plus 250 mg NSAID naproxen twice daily, initial dose 500 mg for 2 weeks (n=10)	Adverse events; patient perceived assessment (cured or strikingly improved; 6-point scale)	2
Smidt[25]	11/13	Inclusion: clinical diagnosis of unilateral LE >6 weeks Exclusion: injections or physiotherapy in previous 6 months, radiculopathy, elbow deformity, surgery, trauma, neurological disorders, or medication contraindication Median day pain=60/100	1 mL triamcinolone acetonide 10 mg/mL plus 1 mL 2% lidocaine, one to three injections for 6 weeks (n=62); physiotherapy of 8×30 min sessions, US, friction massage, stretches, and strength and occupational exercise (n=64); wait and see (n=59)	Adverse events; pain during day NRS (0–100);* modified pain-free function scale (out of 100);* overall improvement (complete recovery or much improved; 6-point scale)	3, 26, 52
Tonks[26]	8/13	Inclusion: clinical diagnosis of unilateral LE Exclusion: treatment in previous 6 months; cervical or other arm abnormalities, trauma, surgery, systemic steroids, or injection contraindication	1 mL triamcinolone 10 mg/mL plus 2% lidocaine in one injection (n=12); 1 mL triamcinolone 10 mg/mL plus 2% lidocaine with physiotherapy (n=12); physiotherapy, strength and stretch exercise (n=12); observation (n=12)	Adverse events; PRFEQ pain subscale (0–50);* PRFEQ function subscale (0–100)*	7

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	PEDro score	Population characteristics	Interventions (number randomised)	Extracted outcome measures	Extracted time points (weeks)
(Continued from previous page)					
Verhaar[27]	9/13	Inclusion: clinical diagnosis of LE Exclusion: surgery, arthritis, neurological disorder, more than three steroid injections in previous 6 months, or previous Cyriax physiotherapy	1 mL 1% triamcinolone plus 1 mL 1% lidocaine in one to three injections at 2 week intervals (n=53); Cyriax physiotherapy (n=53) for 12 sessions for 4 weeks, transverse friction massage, Mills manipulation; co-intervention of combination therapy (20%) or surgery (30%)	Adverse events; patient perceived satisfaction (satisfied; 3-point scale)	6, 52
Corticosteroid injection for rotator-cuff tendinopathy					
Adebajo[28]	10/13	Inclusion: acute (<3 months) RC tendinitis of painful arc, pain with resisted abduction or rotation, and normal passive motion Exclusion: systemic inflammation, glenohumeral or acromioclavicular arthritis, bicipital tendinitis, or suspected RC tear Mean pain VAS=6·5/10	1 mL 80 mg/mL triamcinolone plus 2 mL 0·5% lidocaine plus placebo tablet (n=20); 3 mL 0·5% lidocaine plus NSAID diclofenac 50 mg (n=20); 3 mL 0·5% lidocaine plus placebo tablet (n=20); one injection, tablets thrice daily for 28 days; co-intervention of pendular or wall climb exercises	Adverse events; pain VAS (0–10);* restricted function (0–3)*	4
Akgün[29]	9/13	Inclusion: clinical and MRI diagnosis of subacromial impingement syndrome: positive impingement tests, positive subacromial injection test, and MRI stage 2 Exclusion: MRI stage 3 (complete tear), frozen shoulder, calcific tendinitis, dislocation, cervical pain, fibromyalgia, or treatment in previous 3 months Mean activity pain with activity VAS=6/10	40 mg methylprednisolone plus 10 mL 1% lidocaine plus 500 mg NSAID naproxen (n=16); 10 mL 1% lidocaine plus 500 mg NSAID naproxen (n=16); two injections, 10 day interval; NSAIDs twice-daily for 15 days; co-intervention of pendular or strength or stretch exercises	Activity pain VAS (0–10);† total constant score (function; 0–100)†	4
Alvarez[30]	11/13	Inclusion: chronic (>6 months) tendinosis or partial cuff tear, pain on palpation of cuff insertion, decreased or painful shoulder motion, positive Neer impingement sign, positive subacromial injection test, failed 2 week trial NSAIDs, or failed 6 week physical therapy Exclusion: full thickness tear on US Mean pain VAS with Neers test=58/100	1 mL 6 mg betamethasone plus 4 mL 2% xylocaine (n=31); 5 mL 2% xylocaine (n=31); one injection	Pain with Neers test VAS (0–100);† DASH scale†	2, 26
Alvarez-Nemegyei[31]	9/13	Inclusion: RC tendinitis, positive subacromial lidocaine injection test Exclusion: acromioclavicular sprain or osteophytes, calcium deposits on radiograph, allergy, rheumatological disease, hypertension, or uncontrolled diabetes Mean pain VAS=57·5/100	2 mL 40 mg/mL methylprednisolone plus 1 mL 1% lidocaine (n=27); 3 mL 1% lidocaine (n=29); co-intervention of standard physiotherapy rehabilitation and NSAIDs	Adverse events; pain VAS (0–100);*‡ shoulder disability questionnaire (0–23)*	4, 24
Blair[32]	8/13	Inclusion: subacromial impingement syndrome >3 months, positive lidocaine injection test Exclusion: previous steroid injection, os acromiale on radiograph, workers' compensation claim, or full thickness tear (contrast arthrography)	2 mL of 40 mg/mL triamcinolone plus 4 mL 1% lidocaine without epinephrine (n=19); 6 mL 1% lidocaine without epinephrine (n=21); one subacromial injection; co-intervention of physical therapy (passive, assisted, active, or Theraband strength exercise)	Adverse events; patient perception of pain change (decreased pain; 3-point scale): data not extracted because of range of follow-up 12–55 weeks (mean 30 weeks)	..
Cloke[33]	7/13	Inclusion: painful arc with active shoulder abduction <6 months Exclusion: neck referred pain, systemic inflammatory arthritis, severe loss of motion (capsulitis), glenohumeral or acromioclavicular arthritis, incompetant RC (pronounced weakness), injection in previous 3 months, or medication contraindication	40 mg methylprednisolone plus 10 mL 1% lidocaine, three injections, 6 week intervals (n=27); NSAIDs or simple analgesia (n=20); six sessions of physiotherapy, in a maximum of 18 weeks, exercise, and manual therapy (n=22)	Oxford shoulder score (12–60);*‡ patient perception of outcome (better; 3-point scale): insufficient data	6, 18, 52
Ekeberg[34]	12/13	Inclusion: clinical diagnosis of RC disease >3 months, pain on abduction, <50% reduced glenohumeral motion in no more than one direction, and positive impingement signs Exclusion: acromioclavicular or glenohumeral arthritis, cervical or organ referral, generalised pain syndrome, arthritis, diabetes, fractures, surgery, medication contraindication, or corticosteroids in previous month SPADI score <30	2 mL triamcinolone 10 mg/mL plus 5 mL lidocaine 10 mg/mL US-guided subacromial injection plus 4 mL lidocaine; 10 mg/mL intramusclar (buttock) injection (n=53); 5 mL lidocaine 10 mg/mL US-guided subacromial injection plus 2 mL triamcinolone 10 mg/mL plus 2 mL lidocaine 10 mg/mL intramuscular injection (n=53); co-intervention of physiotherapy continued if attending at baseline	Adverse events; pain during activity NRS (0–9): insufficient data; SPADI (out of 100)†	2
Hay[35]	10/13	Inclusion: clinical diagnosis of unilateral shoulder pain (new episode), exacerbated by active or passive shoulder movement Exclusion: inflammatory disorder, gross structural or neurological abnormality, medication contraindication, red flags, RC rupture, fracture, surgery, physical therapy in previous year, or pregnancy Mean day pain NRS=5·1/9	40 mg methylprednisolone plus 4 mL lidocaine, one or two subacromial injections (n=104); physiotherapy of 8×20 min sessions for 6 weeks, active shoulder exercise with or without US or manual therapy (n=103)	Day pain NRS (0–9);†‡ Shoulder Disability Questionnaire;*‡ overall improvement (completely recovered; 5-point scale)	6, 26

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	PEDro score	Population characteristics	Interventions (number randomised)	Extracted outcome measures	Extracted time points (weeks)
(Continued from previous page)					
Karthikeyan[36]	11/13	Inclusion: clinical radiograph diagnosis of subacromial impingment >3 months, pain at shoulder worse with overhead activity, arc pain, tenderness, positive Hawkins–Kennedy impingement sign; positive Neers injection test Exclusion: other abnormalities (eg, arthritis), adhesive capsulitis, major tear, injection in previous 6 months, regular NSAIDs or steroids or medication contraindicated, legal proceedings, or pregnant or breastfeeding	40 mg methylprednisolone plus 5 mL 1% lidocaine injection (n=27); 20 mg NSAID tenoxicam plus 5 mL 1% lidocaine injection (n=31); one subacromial anterolateral injection; co-intervention of standardised outpatient physiotherapy	Adverse events; DASH questionnaire (out of 100);* overall assessment (much better or slightly better; 5-point scale)	4
McInerney[37]	10/13	Inclusion: post-traumatic shoulder impingement, age older than 16 years, painful arc, pain on resisted abduction, normal radiographs, full abduction power, positive Neers injection test Exclusion: complete RC tear, acromioclavicular tenderness, chronic shoulder disease, shoulder crepitus, loss of external rotation, diabetes, or anticoagulated	40 mg methylprednisolone plus 2 mL 0·5% bupivacaine, one subacromial injection; Neers injection test prior: 8 mL 0·5% bupivacaine (n=54); Neers injection test: 8 mL 0·5% bupivacaine (n=44); co-intervention of pendular or wall climb exercises	Adverse events; pain VAS (0–10): insufficient data	..
Petri[38]	11/13	Inclusion: shoulder pain with at least two of painful abduction, painful arc or tenderness to palpation supraspinatus tendon; positive lidocaine injection test Exclusion: bicipital tendinitis, tears (radiograph), frozen shoulder, arthritis, or injection in previous 3 months	1 mL 40 mg/mL triamcinolone plus 3 mL 1% lidocaine plus placebo tablets (n=25); 1 mL 40 mg/mL triamcinolone plus 3 mL 1% lidocaine plus 500 mg naproxen (n=25); 4 mL 1% lidocaine plus naproxen 500 mg (n=25); 4 mL 1% lidocaine plus placebo tablets (n=25); one injection, tablets twice daily for 30 days; co-intervention of range of motion exercise, heat and cold	Adverse events; pain VAS (0–5);* Restricted function VAS (0–5)*	4
Vecchio[39]	9/13	Inclusion: clinical diagnosis of acute RC tendinitis, pain with resisted shoulder movement, passive motion normal Exclusion: frozen shoulder, bicipital tendinitis, acromioclavicular arthritis, RC tears, local infection, or previous steroid injection	1 mL of 40 mg/mL methylprednisolone plus 1 mL 1% lidocaine (n=28); 1 mL 1% lidocaine (n=25); one subacromial injection; co-intervention of pendular or wall climb home exercise	Adverse events; combined day and night pain VAS: insufficient data	12
White[40]	7/13	Inclusion: acute RC tendinitis (<12 weeks), painful arc, positive lidocaine injection test Exclusion: calcific tendinitis, frozen shoulder, systemic inflammatory or acromioclavicular arthritis, biceps tendinitis, major RC tear, or injection in previous 6 months Mean day pain VAS=6/9	1 mL of 40 mg/mL triamcinalone plus placebo tablets (n=15); 1 mL saline injection plus 25 mg oral indomethacin (n=15); one to two injections, 3-week interval, tablets four times daily; subacromial injection of 3 mL 1% lidocaine 10 min before; co-intervention of physical therapy (pendular, wall climb, and slow abduction home exercise)	Adverse events; total pain (day and night) VAS (0–18)*	3–6
Corticosteroid injection for medial epicondylalgia					
Stahl[41]	11/13	Inclusion: clinical and radiography diagnosis of medial epicondylalgia Exclusion: ulnar neuropathy or other upper limb disorders Mean pain VAS=3·6/10	1 mL 40 mg methylprednisolone plus 1 mL 1% lidocaine, one injection (n=30); 1 mL 1% lidocaine plus 1 mL saline 0·9% (n=30); co-intervention of NSAIDs and physical therapy	Adverse events; pain VAS (0–10)†	6, 52
Corticosteroid Injection for Achilles and patellar tendinopathy					
Capasso[42]	7/13	Inclusion: clinical and US diagnosis of PT Exclusion: cardiovascular, metabolic, and musculoskeletal disease Mean pain VAS after 10-min run=67/100	40 mg methylprednisolone plus 2·5 mL 1% lidocaine (n=39); 62 500 U aprotinin plus 2·5 mL 1% lidocaine (n=38); 5 mL 9% saline (n=39); two to four paratendinous injections every 2 weeks	Adverse events; pain after 10-min run VAS: insufficient data	..
Fredberg[43]	9/13	Inclusion: chronic (≥6 months) midsubstance ACH and PT, clinical and US diagnosis (stage 3A or 3B, tendon thickening >1 mm) Exclusion: part or total rupture, previous steroid treatment, infection, surgery, diabetes, or inflammatory disease Mean walking pain VAS=3·1/10	0·5 mL 20 mg triamcinolone plus 3·5 mL 10 mg/mL lidocaine (n=24); 3·5 mL 1% lidocaine plus 0·5 mL 20% intraplipid (n=24); two to three US-guided injections at days 0, 7, and 21; co-intervention of stretch or strength exercises; crossover for placebo group offered at 3 weeks if athlete did not feel improvement	Adverse events; walking pain VAS (0–10)*‡	3§
Alternative injections for lateral epicondylalgia					
Akermark[44]	11/13	Inclusion: clinical diagnosis LE >3 months Exclusion: nerve entrapment, neck disorders, injection in previous 8 weeks, or NSAIDs in previous 7 days Mean pain VAS=60/100	1 mL 50 mg/mL glycosaminoglycan polysulfate (n=34); 1 mL 0·9% saline (n=31); five injections, 1-week intervals; co-intervention of 6 weeks of rest followed by stretch and strength exercises	Adverse events; pain VAS (0–100)†	3, 26
Petrella[45]	8/13	Inclusion: clinical or radiographic diagnosis of LE >3 months, new referrals only Exclusion: previous injections or acupuncture, nerve entrapment, or systemic neuromuscular disorders Mean pain at rest VAS=8·5/10	1·2 mL sodium hyaluronate (n= 165); 1·2 mL saline (n=166); two injections, once a week	Adverse events; pain at rest VAS (0–10);† patient overall satisfaction (Likert scale 0–5; 0=not satisfied, 5=fully satisfied)	4, 13, 52

(Continues on next page)

	PEDro score	Population characteristics	Interventions (number randomised)	Extracted outcome measures	Extracted time points (weeks)
(Continued from previous page)					
Scarpone[46]	10/13	Inclusion: clinical diagnosis of LE >6 months, failure with physical therapy, NSAIDs, and two steroid injections Exclusion: steroid injection in previous 6 weeks or immunocompromised Mean resting pain NRS=4·8/10	1·5 mL prolotherapy, 50% dextrose, 5% sodium morrhuate, 4% lidocaine, 0·5% sensorcaine (n=12); 1·5 mL 0·9% saline (n=12); three injections at 4 week intervals	Adverse events; resting pain NRS (0–10)†	8, 16
Wong[47]	12/13	Inclusion: clinical diagnosis of LE >3 months Exclusion: previous injection or acupuncture, nerve entrapment, systemic neuromuscular disorders Mean pain VAS=66/100	60 U botulinum toxin (n=30); 60 U 0·9% saline (n=30); one injection, 1 cm from lateral epicondyle	Adverse events; pain VAS (0–100)†	4
Zeisig[48]	12/13	Inclusion: clinical diagnosis of chronic LE (>3 months) Exclusion: interventions in previous 3 months, arthritis, synovitis, or radiculopathy Mean pain VAS=69/100	0·5 mL lauromacrogol 10 mg/mL (n=18); 0·5 mL lidocaine 10 mg/mL plus epinephrine (n=18); 5 µg/mL; one US-guided injection; crossover of control group >3 months	Adverse events; pain with gripping VAS (0–100);† Satisfaction with treatment (satisfied; dichotomous scale)	12§
Alternative injections for rotator-cuff tendinopathy					
Sengul[49]	7/13	Inclusion: shoulder impingement syndrome, clinical and MRI diagnosis, positive subacromial injection test Exclusion: positive drop arm test, adhesive capsulitis, calcific tendinitis, cervical spondylosis, radiculopathy, RC tear, fracture, dislocation, inflammatory disease, severe cardiac or pulmonary disease, or malignant disease	2 mL 20 mg sodium hyaluronate, three subacromial injections, 1-week intervals (n=25); local modalities daily for 2 weeks: analgesic current 25 W, 50 Hz, 10 min, US (n=25); co-intervention of pendulum and pain-free active assisted exercises	Adverse events; constant Murley scale pain subscore;† ASES function score;† patient overall assessment (much better; 4-point scale)	5
Alternative injections for Achilles and patellar tendinopathy					
Alfredson[50]	9/13	Inclusion: chronic midsubstance ACH, clinical and US diagnosis (neovascularisation) Exclusion: previous injection Mean pain VAS with load=71/100	Lauromacrogol 5 mg/mL (n=10); lidocaine 5 mg/mL plus epinephrine 5 µg/mL (n=10); one or two US-guided injections at a 3–6 week interval; crossover of control group >3 months	Adverse events; pain with load VAS (0–100);† patient satisfaction with treatment (satisfied; dichotomous)	12§
Brown[51]	9/13	Inclusion: clinical diagnosis ACH >6 weeks Exclusion: paratendinitis, bursitis, enthesopathy, significant cardiovascular, or renal or hepatic disease Mean VISA=60·6/100	3 mL aprotinin plus 1 mL xylocaine 1% plain (n=15); 3 mL 0·9% saline plus 1 mL xylocaine 1% plain (n=18); three injections, 1-week intervals; co-intervention of eccentric exercise	Adverse events; tenderness pain VAS (0–10);*‡ VISA (0–100);*‡ patient-rated change VAS (0–10)*‡	4, 52
de Vos[52]	12/13	Inclusion: clinical diagnosis ACH >2 months, midportion, aged 18–70 years, thickened tendon Exclusion: other musculoskeletal or inflammatory disorder, tendon rupture, specific medications causing tendinopathy, previous eccentric exercise programme, or injection with platelet-rich plasma	Platelet-rich plasma injection(n=27); 4 mL isotonic saline (n=27); one, US-guided masked peritendinous injection, 2 mL 0·5% bupivacaine injection before; co-intervention of eccentric exercise programme begun 1 week after injection	Adverse events; VISA-A* (0–100); patient satisfaction (good or excellent; 4-point scale)	6, 24
Hoksrud[53]	13/13	Inclusion: PT >3 months, clinical and US diagnosis (neovascularisation), VISA <75/100 Exclusion: patellofemoral pain syndrome, inflammatory joint conditions Mean VISA=54/100	2 mL lauromacrogol 10 mg/mL (n=17); 2 mL lidocaine plus epinephrine 5 mg/mL plus 5 µg/mL (n=16); one to three US-guided injections at 3–5-week intervals; crossover of control group at 4 months	Adverse events; VISA (0–100);*‡ overall satisfaction VAS (0–10)*‡	16§
Sundqvist[54]	7/13	Inclusion: clinical diagnosis of ACH Exclusion: local injection previous 40 days, systemic steroids, NSAIDs previous 7 days, or medication contraindication	1 mL 50 mg/mL glycosaminoglycan polysulfate injection plus placebo tablets (n=29); 1 mL saline 0·9% injection plus 50 mg NSAID indomethacin tablets (n=30); six peritendinous injections (three per week)	Adverse events; impediment to function VAS (0–10): insufficient data	..
Yelland[55]	10/13	Inclusion: clinical and US diagnosis of midportion ACH >6 weeks, aged older than 18 years, VISA <80/100 for participants in sport or VISA <70/90 for participants not involved in sport Exclusion: previous steroid or prolotherapy injections or surgery, previous completion of >50% of Achilles eccentric exercise protocol, or allergies or medical conditions restricting treatment	Prolotherapy of ≤5 mL 20% glucose, 0·1% lidocaine, 0·1% ropivacaine (n=14); subcutaneous peritendinous injection every week for 4–12 treatments; eccentric loading exercises based on Alfredson protocol, three review sessions (n=15); prolotherapy plus eccentric loading exercises (n=14)	Adverse events; VISA-A;† worst pain during the last week NRS (0–10);† PGIC (7 point Likert scale; very much worse to very much better)	6 (VISA-A, NRS), 12 (PGIC), 26, 52
Willberg[56]	10/13	Inclusion: chronic ACH, by clinical and US diagnosis (neovascularisation) Exclusion: previous injection Mean pain VAS during activity=66/100	5 mg/mL lauromacrogol (n=26); 10 mg/mL lauromacrogol (n=26); one to three US-guided injections at 6–8-week intervals	Adverse events; pain during activity VAS (0–100);† patient satisfication (satisfied; dicotomous scale)	Follow-up after one to three injections

LE=lateral epicondylalgia. RC=rotator-cuff tendinopathy. ACH=Achilles tendinopathy. PT=patellar tendinopathy. VAS=visual analogue scale. ..=not applicable. SPADI=shoulder pain and disability index. US=ultrasonography. NSAID=non-steroidal anti-inflammatory drug. NRS=numerical rating scale. VISA=Victorian Institute of Sports Assessment. DASH=Disabilities of the shoulder, arm, and hand. PRFEQ=Patient-rated forearm evaluation questionnaire. ASES=American shoulder and elbow surgeons. PGIC=Patient global impression of change. *Change score. †Final score. ‡Additional data supplied by investigators. §Data not extracted after crossover of placebo group.

Table 1: **Characteristics of included studies**

Pooled data for three studies[28,30,38] comparing corticosteroid injections with placebo injection showed a medium effect of corticosteroid injection for reduction of pain (table 2). A large effect of corticosteroid injection for overall improvement was noted in one study[36] compared with injection of tenoxicam (an NSAID; table 2). By contrast, no difference in effect was shown in all studies in which oral NSAIDs[28,29,31,33,38,40] were prescribed. Trials comparing corticosteroid injection with physiotherapy reported no differences in pain[35] or function,[33] although more patients reported overall improvement after corticosteroid injection at 6 weeks in one study (table 2).[35] Efficacy did not differ in

	Overall improvement RR (95%CI)			Pain SMD (95% CI)			Function SMD (95% CI)		
	Short term	Intermediate	Long term	Short term	Intermediate	Long term	Short term	Intermediate	Long term
CSI for lateral epicondylalgia									
CSI *vs* NI									
Smidt[25]	2·85 (1·96 to 4·16)*	..	0·84 (0·68 to 1·02)	1·50 (1·09 to 1·90)*	−0·27 (−0·63 to 0·09)	−0·15 (−0·51 to 0·21)	1·44 (1·04 to 1·84)*	−0·48 (−0·85 to −0·12)*	−0·36 (−0·72 to −0·00)*
Bisset[5]	4·72 (2·55 to 8·75)*	0·55 (0·41 to 0·73)*	0·75 (0·62 to 0·90)*	1·32 (0·92 to 1·72)*	−0·54 (−0·90 to −0·18)*	−0·46 (−0·81 to −0·11)*	1·60 (1·18 to 2·01)*	−0·53 (−0·89 to −0·16)*	−0·27 (−0·62 to 0·08)
Tonks[26]	..	..	..	1·88 (0·84 to 2·92)*	..	..	1·26 (0·32 to 2·19)*	..	..
Pooled	3·47 (2·11 to 5·69)*	..	0·79 (0·69 to 0·90)*	1·44 (1·17 to 1·71)*	−0·40 (−0·67 to −0·14)*	−0·31 (−0·61 to −0·01)*	1·50 (1·22 to 1·77)*	−0·51 (−0·76 to −0·25)*	−0·32 (−0·57 to −0·06)*
Heterogeneity	p=0·16, I^2=50%	..	p=0·44, I^2=0%	p=0·57, I^2=0%	p=0·3, I^2=8%	p=0·23, I^2=31%	p=0·76, I^2=0%	p=0·86, I^2=0%	p=0·73, I^2=0%
CSI *vs* NSAIDs									
Hay[18]	7·47 (2·38 to 23·46)*	..	..	1·02 (0·61 to 1·43)*	−0·52 (−0·92 to −0·13)*	−0·19 (−0·58 to 0·19)	0·92 (0·51 to 1·32)*	−0·29 (−0·68 to 0·10)	−0·19 (−0·58 to 0·19)
CSI *vs* PI									
Saartok[24]	0·83 (0·25 to 2·76)	..	..	..	..	..	..	..	..
Price[23]	..	..	..	0·95 (0·41 to 1·50)*	−0·42 (−0·97 to 0·14)	..	..	..	..
Lindenhovius[19]	..	..	..	0·25 (−0·31 to 0·80)	−0·27 (−0·84 to 0·30)	..	0·14 (−0·42 to 0·69)	−0·25 (−0·82 to 0·32)	..
Newcomer[20]	..	..	..	−0·06 (−0·69 to 0·57)	0·57 (−0·11 to 1·25)	..	..	..	..
Pooled	..	..	..	Significant heterogeneity	−0·07 (−0·63 to 0·50)	..	..	..	..
Heterogeneity	..	..	..	p=0·04, I^2=68%	p=0·07, I^2=63%	..	..	..	..
CSI *vs* physiotherapy									
Verhaar[27]	2·45 (1·51 to 3·98)*	..	0·87 (0·60 to 1·24)	..	..	..	..	..	..
Smidt[25]	1·96 (1·50 to 2·57)*	..	0·77 (0·64 to 0·92)*	1·48 (1·08 to 1·87)*	−0·52 (−0·88 to −0·17)*	−0·40 (−0·76 to −0·05)*	1·20 (0·82 to 1·58)*	−0·63 (−0·99 to −0·27)*	−0·57 (−0·93 to −0·22)*
Bisset[5]	3·18 (2·00 to 5·07)*	0·52 (0·39 to 0·70)*	0·72 (0·60 to 0·87)*	0·79 (0·43 to 1·15)*	−0·60 (−0·96 to −0·24)*	−0·56 (−0·91 to −0·20)*	1·37 (0·98 to 1·76)*	−0·65 (−1·02 to −0·29)*	−0·57 (−0·92 to −0·21)*
Tonks[26]	..	..	..	1·15 (0·17 to 2·13)*	..	..	1·39 (0·38 to 2·41)*	..	..
Pooled	2·37 (1·75 to 3·21)*	..	0·76 (0·67 to 0·85)*	Significant heterogeneity	−0·56 (−0·82 to −0·31)*	−0·48 (−0·73 to −0·23)*	1·29 (1·03 to 1·55)*	−0·64 (−0·90 to −0·39)*	−0·57 (−0·82 to −0·32)*
Heterogeneity	p=0·17, I^2=43%	..	p=0·65, I^2=0%	p=0·04, I^2=68%	p=0·76, I^2=0%	p=0·56, I^2=0%	p=0·81, I^2=0%	p=0·93, I^2=0%	p=0·98, I^2=0%
CSI *vs* orthotic devices (EB or WS)									
Haker[17]	EB 6·16 (1·61 to 23·56)*	0·59 (0·24 to 1·47)	0·81 (0·34 to 1·96)	..	..	..	..	..	..
Haker[17]	WS 13·0 (1·88 to 89·74)*	0·50 (0·21 to 1·19)	0·75 (0·32 to 1·75)	..	..	..	..	..	..
Low-dose (10 mg) *vs* high-dose (20 mg) CSI†									
Price[23]	..	..	..	0·04 (−0·51 to 0·59)	−0·06 (−0·63 to 0·50)	..	..	..	..
TI *vs* HI‡									
Price[23]	..	..	..	0·45 (−0·07 to 0·97)	0·21 (−0·33 to 0·75)	..	..	..	..

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	Overall improvement RR (95%CI)			Pain SMD (95% CI)			Function SMD (95% CI)		
	Short term	Intermediate	Long term	Short term	Intermediate	Long term	Short term	Intermediate	Long term
(Continued from previous page)									
One *vs* more than one CSIs§									
Okcu[21]	0·92 (0·74 to 1·13)	..	0·43 (0·25 to 0·75)*	1·71 (1·06 to 2·36)*	..	–10·11 (–12·2 to –8·01)*	..	..	..
CSI *vs* PRPI¶									
Peerbooms[22]	..	..	..	0·44 (0·04 to 0·84)*	–0·86 (–1·27 to –0·45)*	–0·83 (–1·24 to –0·42)*	0·52 (0·12 to 0·92)*	–0·48 (–0·88 to –0·08)*	–0·69 (–1·09 to –0·28)*
CSI for rotator-cuff tendinopathy									
CSI *vs* PI									
Petri[38]	..	..	..	0·65 (0·08 to 1·22)*	..	..	0·40 (–0·16 to 0·96)	..	..
Adebajo[28]	..	..	..	1·07 (0·40 to 1·73)*	..	..	0·94 (0·29 to 1·60)*	..	..
Alvarez[30]	..	..	..	0·47 (–0·05 to 0·99)	–0·08 (–0·60 to 0·43)	..	0·41 (–0·11 to 0·93)	0·01 (–0·50 to 0·53)	..
Pooled	..	..	..	0·68 (0·35 to 1·01)*	..	..	0·62 (0·29 to 0·95)*	..	..
Heterogeneity	..	..	..	p=0·38, I^2=0%	..	..	p=0·45, I^2=0%	..	..
CSI *vs* NSAID injection									
Karthikeyan[36]	1·54 (1·02 to 2·33)*	..	..	..	..	..	0·98 (0·42 to 1·54)*	..	..
CSI *vs* NSAIDs									
Cloke[33]	..	..	..	..	..	..	0·32 (–0·24 to 0·87)	0·19 (–0·42 to 0·79)	–0·02 (–0·71 to 0·67)
CSI *vs* PI+NSAIDs									
Adebajo[28]	..	..	..	0·42 (–0·21 to 1·05)	..	..	0·00 (–0·62 to 0·62)	..	..
Petri[38]	..	..	..	0·18 (–0·38 to 0·73)	..	..	–0·05 (–0·60 to 0·51)	..	..
White[40]	..	..	..	–0·17 (–0·89 to 0·55)	..	..	..	..	..
Pooled	..	..	..	0·17 (–0·19 to 0·53)	..	..	–0·03 (–0·44 to 0·39)	..	..
Heterogeneity	..	..	..	p=0·48, I^2=0%	..	..	p=0·91, I^2=0%	..	..
CSI+NSAIDs *vs* PI+NSAIDs									
Petri[38]	..	..	..	0·11 (–0·44 to 0·67)	..	..	–0·06 (–0·62 to 0·49)	..	..
Akgün[29]	..	..	..	0·61 (–0·10 to 1·33)		..	0·35 (–0·35 to 1·05)		..
Alvarez-Nemegyei[31]	..	..	..	–0·34 (–0·87 to 0·20)	–0·21 (–0·90 to 0·49)	..	–0·21 (–0·74 to 0·32)	–0·17 (–0·86 to 0·53)	..
Pooled	..	..	..	0·09 (–0·43 to 0·60)	..	..	–0·03 (–0·36 to 0·31)	..	..
Heterogeneity	..	..	..	p=0·11, I^2=56%	..	..	p=0·45, I^2=0%	..	..
CSI *vs* physiotherapy									
Hay[35]	3·06 (1·27 to 7·39)*	0·75 (0·43 to 1·32)	..	–0·04 (–0·32 to 0·24)	–0·23 (–0·51 to 0·05)	..	0·08 (–0·20 to 0·36)	–0·25 (–0·53 to 0·03)	..
Cloke[33]	..	..	..	..	..	..	0·12 (–0·41 to 0·64)	0·35 (–0·21 to 0·92)	–0·19 (–0·85 to 0·48)
Pooled	..	..	..	..	..	..	0·09 (–0·16 to 0·33)	–0·00 (–0·58 to 0·58)	..
Heterogeneity	..	..	..	..	..	..	p=0·91, I^2=0%	p=0·06, I^2=71%	..
Local *vs* systemic CSI‖									
Ekeberg[34]	..	..	..	..	..	..	–0·17 (–0·55 to 0·22)	..	..

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	Overall improvement RR (95%CI)			Pain SMD (95% CI)			Function SMD (95% CI)		
	Short term	Intermediate	Long term	Short term	Intermediate	Long term	Short term	Intermediate	Long term
(Continued from previous page)									
CSI for medial epicondylalgia									
CSI *vs* PI									
Stahl[41]	..	..	..	0·43 (–0·08 to 0·94)	..	0·10 (–0·40 to 0·61)	0·63 (0·11 to 1·15)*	..	0·10 (–0·41 to 0·60)
CSI for Achilles and patellar tendinopathy									
CSI *vs* PI									
Fredberg[43]	..	..	..	ACH/PT 0·81 (0·22 to 1·40);* ACH=0·73 (–0·11 to 1·56); and PT=0·91 (0·06 to 1·76)*	..	..	..	..	..

RR=relative risk. SMD=standardised mean difference. CSI=corticosteroid injection. NI=no intervention. NSAID=non-steroidal anti-inflammatory drug. ..=not applicable. PI=placebo injection. EB=elbow band. WS=wrist splint. TI=triamcinolone injection. HI=hydrocortisone injection. PRPI=platelet-rich plasma injection. ACH=Achilles tendinopathy. PT=patellar tendinopathy. *Significant effect (p<0·05). †SMD>0 favours low dose. ‡SMD >0 favours triamcinolone injection. §RR >1 and SMD >0 favour more than one injection; RR <1 and SMD <0 favour one injection. ¶SMD >0 favours corticosteroid injection; SMD <1 favours PRPI. ||SMD <1 favours systemic corticosteroid injection.

Table 2: **Clinical effectiveness of corticosteroid injections for tendinopathy**

all studies of intermediate[29–31,33,35] and long-term outcomes[33] after treatment for rotator-cuff tendinopathy. Short-term outcomes were not affected by local or systemic injection sites for this tendinopathy.[34] Alternative dose schedules have not been studied in rotator-cuff tendinopathy.

Only one investigation[41] of corticosteroid versus placebo injection for medial epicondylalgia met the criteria for inclusion, and showed no short-term effect of corticosteroid injection on a visual analogue score of pain (table 2). However, there was a medium beneficial effect on a composite measure of pain and function (Nirschl and Pettrone pain phase;[41] data not shown). Outcomes did not differ at 1 year (table 2).

Two trials[42,43] were done to assess corticosteroid injection for tendinopathies affecting the leg, but only one trial[43] had enough data for analysis (table 1). A large effect of pain reduction was shown in the short term for corticosteroid injection (table 2) compared with placebo. In a subgroup analysis of tendon sites, a beneficial effect was noted for patellar tendons, but not for Achilles tendons.

We identified 15 trials that investigated non-corticosteroid injections, but two[42,54] did not use predefined outcomes of interest. Comparison was made with placebo injection in nine trials (figure 4), eccentric exercise in one,[55] and electrotherapy methods in one.[49] Investigators in one study[56] compared different doses of lauromacrogol.[44]

Ultrasonography-guided injection of lauromacrogol, a sclerosing solution, was compared with saline injection in three trials.[48,50,53] A large overall improvement was reported for patellar tendinopathy at 16 weeks in a study of 33 participants (table 3),[53] whereas this was not the case for 20 participants with Achilles tendinopathy (p=0·07)[50] or 36 participants with lateral epicondylalgia (table 3).[48] Efficacy did not differ between high-dose and low-dose lauromacrogol in Achilles tendinopathy.[56]

Two trials[22,52] were done to assess efficacy of platelet-rich plasma for treatment of tendinopathy. Outcomes did not differ in the short or intermediate term between platelet-rich plasma or placebo injections in 54 participants with chronic (≥2 months) midsubstance Achilles tendinopathy.[52] In one study,[22] corticosteroid injection had a small beneficial effect in the short term compared with platelet-rich plasma injection,[22] but a large effect in favour of platelet-rich plasma injection was noted at intermediate and long terms (table 2).

Sodium hyaluronate was much better for pain relief in the short, intermediate, and long terms than was placebo injection for treatment of lateral epicondylalgia (table 3).[45] No short-term benefit was noted for any outcomes with sodium hyaluronate injection by comparison with electrotherapy methods for rotator-cuff tendinopathy.[49]

One study[46] of 24 participants compared a series of three prolotherapy injections (solution of hypertonic glucose and local anaesthetic) in 8 weeks with placebo injection for chronic (average duration of 1·9 years) lateral epicondylalgia. Although no effect was seen in the short term (immediately before the third injection), a large effect of reduction in pain was reported in the intermediate term (table 3). Another study[55] of 43 participants assessed a series of four to 12 prolotherapy injections in patients with Achilles tendinopathy (table 1). Compared with eccentric exercise, outcomes after prolotherapy or a combination of prolotherapy and eccentric exercise did not differ for participants in the short, intermediate, or long term (table 3).

	Site	Overall improvement RR (95%CI)			Pain SMD (95% CI)			Function SMD (95% CI)		
		Short term	Intermediate	Long term	Short term	Intermediate	Long term	Short term	Intermediate	Long term
Lauromacrogol *vs* PI										
Zeisig[48]	LE	0·80 (0·44 to 1·45)	..	..	–0·20 (–0·88 to 0·47)	..	..	..	..	..
Alfredson[50]	ACH	11·00 (0·69 to 175)	..	..	0·84 (–0·08 to 1·77)	..	..	..	..	..
Hoksrud[53]	PT	..	SMD: 1·69 (0·88 to 2·5)*	..	..	..	..	..	0·60 (–0·10 to 1·30)	..
Low-dose (5 mg) *vs* high-dose (10 mg) lauromacrogol injection†										
Willberg[56]	ACH	1·02 (0·88 to 1·18)	..	..	0·03 (–0·51 to 0·58)	..	..	..	..	..
Platelet-rich plasma *vs* PI										
de Vos[52]	ACH	1·00 (0·44 to 2·28)	0·88 (0·57 to 1·38)	..	..	..	..	0·18 (–0·35 to 0·72)	0·05 (–0·48 to 0·59)	..
Aprotinin *vs* PI										
Brown[51]	ACH	SMD: 0·26 (–0·42 to 0·95)	..	SMD: –0·05 (–0·81 to 0·72)	0·06 (–0·63 to 0·74)	..	0·00 (–0·77 to 0·77)	0·05 (–0·67 to 0·77)	..	0·06 (–0·71 to 0·83)
Arteparon *vs* PI										
Akermark[44]	LE	..	..	..	0·21 (–0·30 to 0·72)	0·38 (–0·13 to 0·89)	..	..	..	..
Sodium hyaluronate vs PI										
Petrella[45]	LE	SMD: 1·62 (1·37 to 1·87)*	SMD: 6·11 (5·59 to 6·62)*	SMD: 2·59 (2·30 to 2·88)*	3·91 (3·54 to 4·28)*	2·89 (2·58 to 3·20)*	3·91 (3·55 to 4·28)*	..	..	..
Sodium hyaluronate injection *vs* electrotherapy										
Sengul[49]	RC	2·25 (0·80 to 6·36)	..	..	0·49 (–0·08 to 1·05)	..	..	0·38 (–0·18 to 0·94)	..	..
Prolotherapy *vs* PI										
Scarpone[46]	LE	..	..	..	0·27 (–0·61 to 1·15)	2·62 (1·36 to 3·88)*	..	..	..	..
Prolotherapy *vs* eccentric exercise										
Yelland[55]	ACH	1·69 (0·92 to 3·12)	1·27 (0·80 to 2·02)	1·00 (0·72 to 1·39)	..	..	..	..	..	..
Botulinum toxin vs PI										
Wong[47]	LE	..	..	..	1·23 (0·67 to 1·78)*	..	..	..	..	..

RR=relative risk. SMD=standardised mean difference. PI=placebo injection. LE=lateral epicondylalgia. ACH=Achilles tendinopathy. PT=patellar tendinopathy. ..=not applicable. RC=rotator-cuff tendinopathy. *Significant effect (p<0·05). †RR >1 and SMD >0 favours high dose.

Table 3: **Clinical effectiveness of non-corticosteroid injections for tendinopathy**

Arteparon,[44] aprotinin,[51] and botulinum toxin[47] were compared with placebo injection in individual trials (table 3). No significant short-term or intermediate-term effects on pain were reported for a series of five injections once a week of arteparon for lateral epicondylalgia.[44] A series of three injections once a week of the proteinase, aprotinin, also had no beneficial short-term or long-term effects on any outcomes for Achilles tendinopathy.[51] Wong and colleagues[47] investigated peritendinous injection of botulinum toxin in chronic lateral epicondylalgia (average duration 1·25 years), and showed a large beneficial effect on pain in the short term compared with placebo injection.

All trials of non-corticosteroid injections reported adverse events, whereas only 23 (82%) of 28 trials did so for corticosteroid injection (table 4). Of the 416 participants who received corticosteroid injections in placebo-injection comparison trials, there were 38 (9%) cases of atrophy, 31 (8%) cases of pain, two (<1%) cases of depigmentation, and one (<1%) case of tendon rupture of the Achilles tendon.[43] By comparison with placebo injection, corticosteroid injection had a significant RR of atrophy for Achilles and patellar tendons,[43] but not elbow tendons (table 4).[23]

No adverse events, apart from pain, were reported after injections with lauromacrogol (97 participants),[48,50,53,56] sodium hyaluronate (356),[45,49] prolotherapy (40),[46,55] or platelet-rich plasma (78).[22,52] Injections of botulinum toxin and aprotinin were associated with harm compared with placebo injections. Aprotinin injection was associated with a significant RR of itching[51] and burning (table 4).[42] Botulinum toxin was associated with a significant RR of total adverse events compared with saline injection,[47] probably

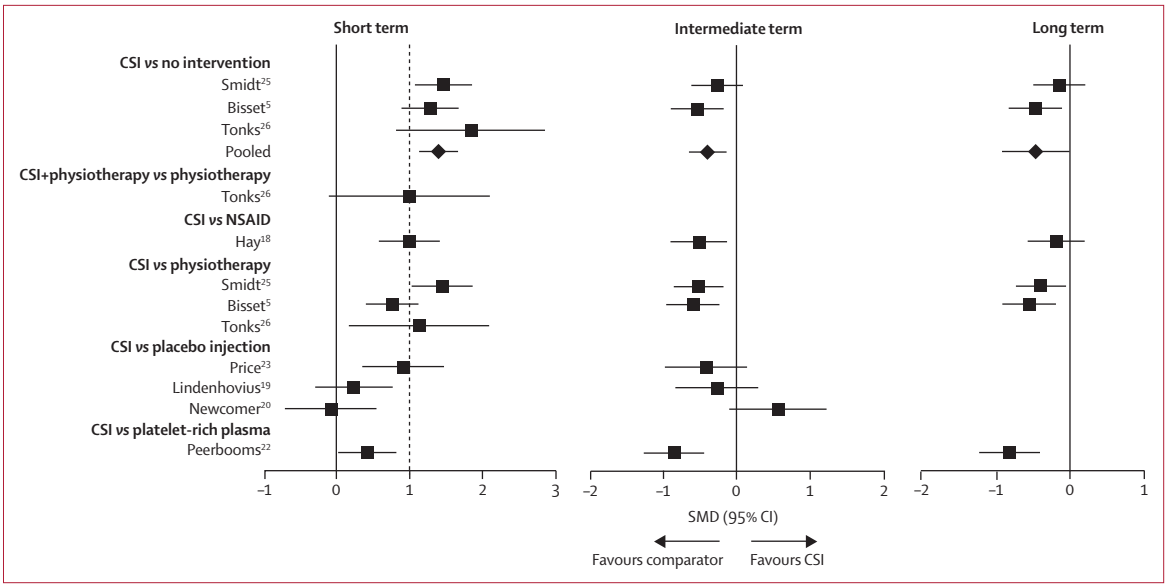

Figure 2: **Standardised mean difference for improvement in pain after corticosteroid injection for lateral epicondylalgia**
SMD=standardised mean difference. CSI=corticosteroid injection. NSAID=non-steroidal anti-inflammatory drug. PRPI=platelet-rich plasma injection.

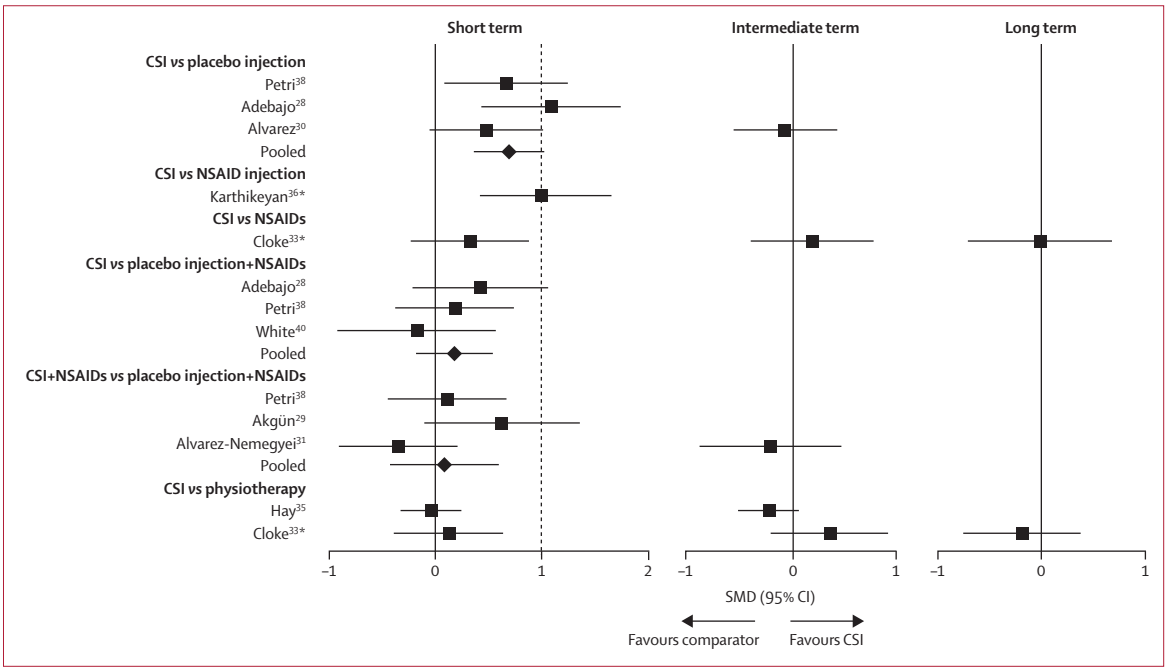

Figure 3: **Standardised mean difference for improvement in pain or function after corticosteroid injection for rotator-cuff tendinopathy**
SMD=standardised mean difference. CSI=corticosteroid injection. NSAID=non-steroidal anti-inflammatory drug. PRPI=platelet-rich plasma injection. *Function study.

because of many reports of weakness (33%) and paresis (13%).

Injection-related pain varied between trials and the type of placebo injection. Post-injection pain was reported more frequently after corticosteroid injection than it was after placebo (table 4).[23] In one study,[46] all patients receiving a series of five injections of either prolotherapy or saline solutions reported pain. Gastrointestinal disorders, vertigo, and rash were more common after placebo injection combined with oral NSAIDs than they were after corticosteroid injection[38] or arteparon injection.[54]

Discussion

We have shown strong evidence that corticosteroid injection is beneficial in the short term for treatment of

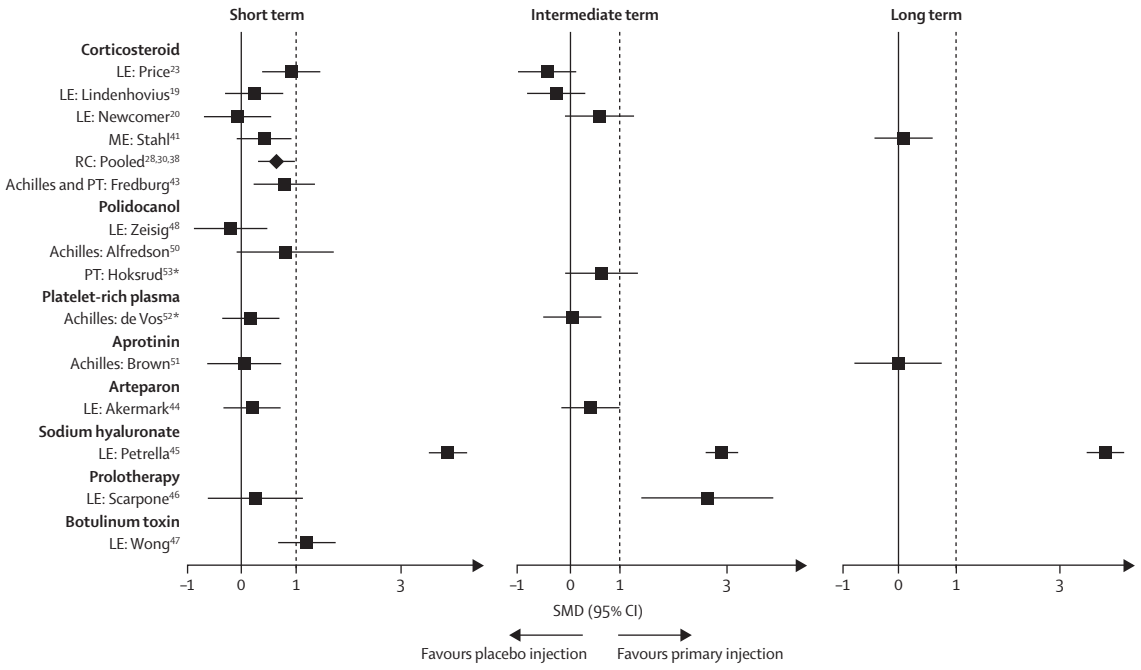

Figure 4: **Standardised mean difference for improvement in pain or function after any injection type versus placebo injection for lateral epicondylalgia, medial epicondylalgia, rotator-cuff, patellar, or Achilles tendinopathy**
LE=lateral epicondylalgia tendinopathy. ME=medial epicondylalgia tendinopathy. RC=rotator-cuff tendinopathy. PT=patellar tendinopathy. *Function study.

	Study	Site	Trial injection adverse events incidence	Placebo injection adverse events incidence	Relative risk (95% CI)	NNH
Corticosteroid						
Tendon rupture	Fredberg[43]	ACH, PT	1/48 (2%)	0/24	1·53 (0·06–36·23)	48
Postinjection pain	Price[23]	LE	30/59 (51%)	9/29 (31%)	1·64 (0·90–2·98)	5
Intense pain	Alvarez-Nemegyei[31]	RC	1/27 (4%)	0/27	3·00 (0·13–70·53)	27
Pain with injection	Capasso[42]	PT	0/39	1/39 (3%)	0·33 (0·01–7·94)	39†
Burning sensation	Capasso[42]	PT	4/39 (13%)	5/39 (13%)	0·80 (0·23–2·76)	39†
Atrophy	Price[23]	LE	18/59 (31%)	5/29 (17%)	1·77 (0·73–4·29)	8
Atrophy	Fredberg[43]	ACH, PT	20/48 (42%)	0/24	20·92 (1·32–331·74)*	2
Depigmentation	Lindenhovius[19]	LE	1/31 (3%)	2/33 (6%)	0·53 (0·05–5·58)	35†
Depigmentation	Petri[38]	RC	1/50 (2%)	0/50‡	3·00 (0·13–71·92)	50
Eczema	Capasso[42]	PT	1/39 (3%)	0/39	3·00 (0·13–71·46)	39
Rash	Petri[38]	RC	0/50	2/50 (4%)‡	0·20 (0·01–4·06)	25†
Facial flushing	Stahl[41]	ME	1/30 (3%)	0/30	3·00 (0·13–70·83)	30
Gastrointestinal upset	White[40]	RC	1/20 (5%)	2/20 (10%)‡	0·50 (0·05–5·08)	20†
Vasovagal reaction	Petri[38]	RC	0/50	1/50 (2%)‡	0·33 (0·01–7·99)	50†
Postmenopausal bleeding	Petri[38]	RC	0/50	1/50 (2%)‡	0·33 (0·01–7·99)	50†
None (apart from pain)	McInerney,[37] Vecchio,[39] Alvarez-Nemegyei,[31] Saartok,[24] and Blair[32]	RC or LE	0/139	0/129	..	..
Lauromacrogol (sclerosant)						
None	Alfredson,[50] Hoksrud,[53] and Zeisig[48]	ACH, PT, or LE	0/45	0/42	..	..
Platelet-rich plasma						
None	de Vos[52]	ACH	0/27	0/27	..	..

(Continues on next page)

	Study	Site	Trial injection adverse events incidence	Placebo injection adverse events incidence	Relative risk (95% CI)	NNH
(Continued from previous page)						
Aprotinin (proteinase)						
Postinjection pain	Brown[51]	ACH	3/45 (7%)	9/54 (17%)	0·40 (0·12–1·39)	10†
Pain with injection	Capasso[42]	PT	2/38 (5%)	1/39 (3%)	2·05 (0·19–21·71)	37
Itch	Brown[51]	ACH	18/45 (40%)	4/54 (7%)	5·40 (1·97–14·81)*	3
Itch	Capasso[42]	PT	2/38 (5%)	0/39	5·13 (0·25–103·43)	19
Burning	Capasso[42]	PT	15/38 (39%)	5/39 (13%)	3·08 (1·24–7·64)*	3
Arteparon (glycosaminoglycan polysulfate)						
Overall	Sundqvist[54]	ACH	6/29 (21%)	10/30 (33%)‡	0·62 (0·26–1·49)	7†
Local pain	Akermark[44]	LE	13/32 (41%)	5/28 (18%)	2·27 (0·93–5·58)	4
Local tenderness and swelling	Sundqvist[54]	ACH	5/29 (17%)	4/30 (13%)‡	1·29 (0·38–4·34)	25
Haematoma	Akermark[44]	LE	2/32 (6%)	0/28	4·39 (0·22–87·82)	16
Gastrointestinal	Sundqvist[54]	ACH	0/29	6/30 (20%)‡	0·08 (0·00–1·35)	5†
Vertigo	Sundqvist[54]	ACH	0/29	4/30 (13%)‡	0·11 (0·01–2·04)	7†
Rash	Sundqvist[54]	ACH	0/29	4/30 (13%)‡	0·11 (0·01–2·04)	7†
Sodium hyaluronate						
Pain	Petrella[45]	LE	3/165 (1·8%)	5/166 (3%)	0·60 (0·15–2·48)	84†
Prolotherapy						
Pain	Scarpone[46]	LE	10/10 (100%)	10/10 (100%)	..	..
Local irritation	Scarpone[46]	LE	2/10 (20%)	0/10	5·00 (0·27–92·62)	5
Botulinum toxin						
Overall	Wong[47]	LE	19/30 (63%)	9/30 (30%)	2·11 (1·15–3·89)*	3
Postinjection pain	Wong[47]	LE	2/30 (7%)	1/30 (3%)	2·00 (0·19–20·90)	30
Nausea	Wong[47]	LE	0/30	1/30 (3%)	0·33 (0·01–7·87)	30†
Finger weakness	Wong[47]	LE	10/30 (33%)	6/30 (20%)	1·67 (0·69–4·00)	7
Paresis	Wong[47]	LE	4/30 (13%)	0/30	9·00 (0·51–160·17)	7

Data are number of adverse events/number of patients (%), relative risk (95% CI), or NNH. NSAID=non-steroidal anti-inflammatory drug. NNH=needed to harm. ..=not estimable. ACH=Achilles. PT=patellar. LE=lateral epicondylalgia. RC=rotator cuff. *Significant (p<0·05) effect. †NNH for greater number of adverse events for placebo intervention than trial intervention. ‡Placebo injections with NSAIDs.

Table 4: **Adverse events after trial injections compared with placebo injections or placebo injections combined with NSAIDs**

tendinopathy, but is worse than are other treatment options in the intermediate and long terms. Use of corticosteroid injections, which are potent anti-inflammatories,[57] poses a clinical dilemma because consistent findings suggest good short-term effects but tendinopathy does not have an inflammatory pathogenesis. Altered release of toxins and inhibition of collagen, extracellular matrix molecules, and granulation tissue might provide a biological basis for this effect.[57] Our systematic review challenges continued use of corticosteroid injections by providing strong evidence that they are worse in the long term than are most conservative interventions for tendinopathy.

Strong evidence for a large, beneficial effect of corticosteroid injection was shown for all outcomes in lateral epicondylalgia in the short term (<8 weeks), which is in agreement with previous meta-analyses.[58,59] Although previously alluded to,[58] our meta-analysis shows negative outcomes at 6 months, which remained 1 year after corticosteroid injection for lateral epicondylalgia. Corticosteroid injections had inconsistent effects for treatment of rotator-cuff tendinopathy, although analysis of a subgroup of three studies showed a medium beneficial effect by comparison with placebo injection alone, which concurs with previous meta-analyses.[59,60] Moderate evidence from one small high-quality trial[43] suggests short-term efficacy of corticosteroid injection for tendinopathies of the leg; however, reduction in pain might be restricted to patellar tendons and to the short term, given that many participants showed relapse within 6 months, which is much the same as we noted for lateral epicondylalgia.

In clinical practice, corticosteroid injection is commonly prescribed in combination with NSAIDs or physiotherapy, although we reported no differences in effect with these co-interventions.[20,26,29,31,38] Studies of sufficient size are needed to assess whether physiotherapy can reduce the high rates of recurrence associated with corticosteroid injection.[61,62]

Despite increasing popularity of new injection therapies for tendinopathy, many unanswered questions

remain about their therapeutic efficacy and physiological basis. Researchers have recently concentrated on injection of substances that are aimed at destruction of areas of neovascularisation within affected tendons. We suggest that ultrasonography-guided injection of lauromacrogol and prolotherapy injection of hypertonic glucose and local anaesthetic are potential therapeutic techniques, based on moderate evidence of improvements in the intermediate term for patellar tendinopathy and lateral epicondylalgia, respectively. Little evidence exists for administration of growth factors such as platelet-rich plasma to stimulate tendon healing. Although inferior in the short term, platelet-rich plasma injection was superior to corticosteroid injection in relieving pain for lateral epicondylalgia in the long term. The benefit of platelet-rich plasma compared with placebo for lateral epicondylalgia is unknown, although in one study this treatment was not more effective than was placebo for Achilles tendinopathy.[52] We found no randomised trials about injection of autologous blood for treatment of tendinopathy.

Petrella and colleagues[45] investigated injection of sodium hyaluronate, a naturally occurring biological substance, in 331 participants with chronic severe lateral epicondylalgia, and reported that it was largely effective in the short, intermediate, and long terms (moderate evidence). However, they reported no improvement in the placebo group during 12 months, which is inconsistent with most placebo-controlled studies of lateral epicondylalgia. There is moderate evidence that arteparon and aprotinin injections, which are posited to inhibit enzymes that degrade tendon ground substance, are not more effective than placebo injection.[44,51] Botulinum toxin injection into the painful area, 1 cm from the lateral epicondyle, was largely effective in the short term for lateral epicondylalgia (moderate evidence).[47] Although botulinum toxin injection is often used for neurological disorders, the underlying mechanism in tendinopathy in not known.

Injection into the tendon might weaken its structure and increase probability of rupture. A previous review[63] of ten studies in animals did not establish whether corticosteroid injections can cause damage to tendons. We noted a low frequency of serious adverse events after corticosteroid injection (only one case of tendon rupture), suggesting an acceptable risk. Although this position is in agreement with that of other investigators,[59,63,64] rigorous reporting of adverse events for all trials is needed to confirm the safety of corticosteroid injections. Minor complications such as postinjection pain, subcutaneous atrophy, and skin depigmentation were common; the RR of reversible atrophy of the lower limb was significantly higher after corticosteroid injection than it was after placebo injection.

Moderate evidence of harmful effects of repeated corticosteroid injection on pain was noted.[21] However, the optimum number of doses and interval between injections are not known. We urge patients and practitioners to consider results of corticosteroid treatment that might not be defined as adverse, including negative long-term outcomes and high recurrence rates.[5,25] Unique adverse-event profiles were recorded for alternative injection therapies. Lauromacrogol, prolotherapy, arteparon, sodium hyaluronate, and platelet-rich plasma injections were well tolerated. A high risk of burning and itching was associated with aprotinin injection, supply of which was suspended in 2007 after clinical trials associated it with an increased risk of death.[65]

Different types of injection led to different clinical effectiveness and adverse events between tendon sites, despite similar pathological changes.[66] Since many trials were restricted to selected subtypes of tendinopathy, application of the findings to clinical practice needs careful judgment. Difficulty associated with diagnosis of tendinopathy might account for heterogeneity of outcomes, especially for the rotator cuff, in which variation in eligibility criteria was evident between trials (table 1). Ultrasonography of tendon morphology might reduce the heterogeneity of included populations,[43] and was used to confirm diagnosis in six of nine trials of the lower limb, but in only one study[48] of lateral epicondylalgia and one study[34] of rotator-cuff tendinopathy. Only a third of athletes with clinically suspected Achilles or patellar tendinopathy were confirmed to have ultrasonically assessed thickening (>1 mm) of the symptomatic tendon.[43] Longitudinal studies are needed to establish whether abnormalities visible on ultrasonography correlate with clinical recovery.[67] Poor response to injection or side-effects, including raised intratendinous pressure, tendon degeneration, and deleterious effects on intra-articular cartilage, might be attributable to a misplaced injection. Ultrasonography-guided injection was done in all four studies of lauromacrogol to target areas of neovascularisation within the extensor tendon at the lateral elbow[48] or outside the Achilles and patellar tendons.[50,53,56] In two studies, ultrasonography-guided corticosteroid injection was used to avoid direct injection into the Achilles, patellar,[43] or rotator cuff[34] tendons. However, no difference in accuracy was seen between unguided and ultrasonography-guided subacromial injections, raising debate about its clinical use.[68]

Our systematic review has limitations. Meta-analysis was possible only for a few trials with sufficient homogeneity. Conclusions about corticosteroid injections and most other injection types in the lower limb were made on the basis of one randomised controlled trial, and their clinical usefulness needs further investigation. Furthermore, we restricted

this review to high quality randomised trials, as quantified by PEDro score, to improve probability of an unbiased assessment. We might therefore have excluded useful clinical information, although we note that the quality of trials did not substantially change our conclusions. To address these limitations, future studies should address methodological features such as concealed allocation, intention-to-treat, and treatment masking. Additionally, recruitment of large sample sizes, standardisation of co-interventions, long-term follow-up, and systematic reporting of recurrence and adverse events are needed.

Contributors

All authors contributed to the investigation and writing of this report.

Conflicts of interest

We declare that we have no conflicts of interest.

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