Effect of corticosteroid injection, physiotherapy or both on clinical outcomes in patients with lateral epicondylalgia: A randomized controlled trial.

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Abstract

Context Corticosteroid injection and physiotherapy, common treatments for lateral epicondylalgia, are frequently combined in clinical practice. Study of their combined efficacy is lacking.

Objective To investigate the effectiveness of corticosteroid injection, multimodal physiotherapy, or both, in patients with unilateral lateral epicondylalgia.

Design, Setting and Patients A 2x2 factorial, randomized, injection blinded, placebo controlled trial was conducted at a single university research centre and 16 primary care settings in Brisbane, Australia. 165 patients with unilateral lateral epicondylalgia of greater than six weeks duration were enrolled between July 2008 and May 2010. One year follow-up was completed in May 2011.

Intervention Corticosteroid injection (n=43), placebo injection (n=41), corticosteroid injection plus physiotherapy (n=40) or placebo injection plus physiotherapy (n=41).

Main outcome measures Primary endpoint/outcomes were one year global rating of change scores of complete recovery/much improvement, as well as one year recurrence, defined as global rating of change scores of complete recovery/much improvement at 4 or 8 weeks, but not later, analysed on an intention to treat basis (P<0.01). Secondary time points included 4 and 26 weeks.

Results Compared to placebo injection, corticosteroid injection resulted in lower complete recovery/much improvement at one year (83% *v* 96%, RR 0.86 (99% CI 0.75 to 0.99), P=0.01) and greater recurrence (54% *v* 12%, RR 0.23 (0.10 to 0.51), P<0.001). Physiotherapy and no-physiotherapy groups did not differ on one year ratings of complete recovery/much improvement (91% *v* 88%, RR 1.04 (0.90 to 1.19), P=0.56) or recurrence (29% *v* 38%, RR 1.31 (0.73 to 2.35), P=0.25). A similar pattern was found at 26 weeks, with lower complete recovery/much improvement following corticosteroid than placebo injection (55% *v* 85%, RR 0.79 (0.62 to 0.99), P<0.001) and no difference between physiotherapy and no-physiotherapy (71% *v* 69%, RR 1.22 (0.97 to 1.53), P=0.84). At four weeks, there was an interaction between corticosteroid injection and physiotherapy (P=0.01) whereby in placebo injected patients physiotherapy resulted in greater complete recovery/much improvement than no-physiotherapy (39% *v* 10%, RR 4.00 (1.07 to 15.0), P=0.004), but not in corticosteroid injected patients (68% *v* 71%, RR 0.95 (0.65 to 1.38), P=0.57).

Conclusions Among patients with chronic unilateral epicondylalgia, after one year the use of corticosteroid injection compared with placebo resulted in worse clinical outcomes, and physiotherapy did not result in any significant difference.

Trial registration Australian Clinical Trials Registry (ACTRN12609000051246)

Introduction

There are increasing calls for medical practitioners to desist from using corticosteroid injections to treat lateral epicondylalgia,[1,2] which is likely based on evidence of long term inefficacy[3-5] and high recurrence.[3,6] In a recent randomized controlled trial with one year follow-up, recurrence was evident in 72% of corticosteroid injected patients, compared to 8% following physiotherapy.[3] To overcome the poor long term outcomes of injections, clinicians often recommend combining corticosteroid injection and physiotherapy interventions. This has only been evaluated in two small studies.[7,8] One reported no benefit at six months of corticosteroid injection when added to ice massage and physiotherapy prescribed exercise.[7] The other found no significant effect of a progressive graduated exercise program when added to corticosteroid injection, however this study was underpowered, reported a high drop-out rate and did not assess outcomes beyond seven weeks.[8] The long term effects of a combination of corticosteroid injection and physiotherapy are not known.

In contrast to the poor long term outcomes, corticosteroid injections produce substantial pain relief in the short term,[3,5,9] which is somewhat perplexing given their anti-inflammatory mode of action juxtaposed against the lack of inflammatory markers in tendinopathy.[10-12] A plausible explanation is that these injections are associated with strong placebo effects.[13] A recent systematic review found significant heterogeneity for studies comparing corticosteroid with placebo injection, with three out of four studies showing no difference,[14] though the use of lidocaine and bupivicaine injections as placebo comparators might have exerted a therapeutic effect.[13] There is a critical need to evaluate the efficacy of corticosteroid injection compared to a placebo injection of normal saline.

The primary objectives of this study were two-fold: to evaluate at one year the clinical efficacy of (1) corticosteroid injection compared to placebo injection, and (2) physiotherapy compared to no-physiotherapy in patients with unilateral lateral epicondylalgia. The primary outcomes were (a) patient rated global rating of change scores of complete recovery or much improvement, and (b) recurrence, defined as complete recovery/much improvement at 4 or 8 weeks, but not 8, 26 or 52 weeks.

Methods

Study design

A randomized control trial with 2x2 factorial design and one year follow-up was performed in a community setting in Brisbane, Australia, as per our previously published protocol.[13] Injection and physiotherapy factors were combined to constitute four treatment groups (1) corticosteroid injection; (2) placebo injection; (3) corticosteroid injection plus multimodal physiotherapy; (4) placebo injection plus multimodal physiotherapy. This trial was registered with the Australian Clinical Trials Registry (ACTRN12609000051246) and approved by the Medical Research Ethics Committee (University of Queensland).

Patients

Adults aged 18 years or over with unilateral lateral epicondylalgia of duration longer than six weeks, who responded to public advertisement between August 2008 and May 2010, were invited to participate. Inclusion criteria were pain over the lateral humeral epicondyle of severity greater than 30 on a 100mm visual analogue scale (VAS), provoked by at least two of: gripping, palpation, resisted wrist or middle finger extension or stretching of forearm extensor muscles with reduced pain-free grip. Exclusion criteria were injection (preceding six months); course of physiotherapy (preceding three months); concomitant neck or other arm pain necessitating treatment or preventing participation in usual work or recreational activities (preceding six months); symptoms suggesting radicular, neurological or systemic arthritic conditions; pregnancy; breastfeeding; or contraindication to injection. Eligibility was determined by telephone interview and physical examination by one researcher and confirmed by a second researcher.

Randomization

Following written informed consent, randomization was performed by concealed allocation using a computer-generated schedule, developed by the Queensland Clinical Trials Centre, an independent offsite organisation. Randomization was stratified according to pain severity greater or less than 57.5mm on a 100mm VAS, based on the mean score from a previous study.[3] A research assistant not involved in data collection or analysis, administered the randomization schedule and arranged all study appointments.

Blinding

The researcher who assessed outcomes and performed intention to treat analysis was blinded to both injection and physiotherapy assignment. Patients were masked to injection content, but not to physiotherapy due to its nature. To evaluate the success of blinding, patients were

asked at eight weeks whether they were confident of which injection they received, and those who responded yes were asked to nominate the injection. The outcome assessor guessed both injection and physiotherapy assignment of all patients.

Interventions

Injection

Patients received a single injection of either placebo (0.5ml, 0.9% isotonic saline) or corticosteroid and local anaesthetic medication (1ml, 10mg/ml Triamcinolone Acetonide, *Kencort A10*, with 1ml, 1% Lignocaine) by one of five medical practitioners within 10 days of randomization. The injection was applied to the site of greatest palpable tenderness at the common extensor origin. All patients received standardized advice to avoid activities that caused or provoked pain and to rest from strenuous activity for two weeks post-injection. Following this gradual return to normal activities was encouraged, even if substantial initial relief was obtained, to minimise potential recurrence. Patients could use analgesic or anti-inflammatory medication, heat/cold or braces as needed, but were discouraged from seeking treatments other than those assigned.

Physiotherapy

Physiotherapy groups underwent eight, thirty-minute sessions of treatment over an eight week period, with the first session scheduled prior to the injection. Eleven physiotherapy practitioners with post-graduate qualification underwent two hours of training (by BKC and BV) to standardize the treatment according to a previously published protocol,[13] which comprised local elbow manual therapy and exercise. To individualise treatment, practitioners chose manual therapy and exercises from the protocol and progressed the program based on the patients' capabilities to allow for optimal exercise volume and load setting without exacerbating pain. The specific elbow manipulation (mobilisation with movement) techniques were applied in combination with gripping as described by Vicenzino.[15] The comprehensive exercise program included twice daily sensorimotor retraining of gripping and concentric and eccentric exercise to progressively load the wrist extensors using resistive theraband. The home program was regularly reviewed and exercise diaries were monitored to facilitate program adherence.

Outcome measures

Patients estimated at each trial visit (4,8,12,26,52 weeks) their global rating of change since commencing the study using a 6-point Likert scale, ranging from "complete recovery" to "much worse".[3,13] *A priori* primary endpoint/outcomes were one year global rating of change scores of complete recovery/ much improvement, as well as one year recurrence, defined as global rating of change scores of complete recovery/much improvement at 4 or 8 weeks, but not 8, 26 or 52 weeks.

Secondary time points/outcomes were: global rating of change scores of complete recovery/much improvement (4 and 26 weeks); severity of current resting pain and worst pain over the preceding week (100mm VAS); a condition-specific, validated questionnaire of pain and disability (Patient-rated Tennis Elbow Evaluation, PRTEE, ranging from 0 to 100, where 100 represents worst imaginable pain with a very significant functional disability)[16,17]; health-related quality of life (EuroQol EQ-5D, ranging from 0 to 1, where 1 represents perfect health)[18] (4, 26 and 52 weeks); use of analgesic or anti-inflammatory medication or other non-allocated treatments and adverse events. Minimum clinically important changes in pain and disability (as measured using the PRTEE) of 37% of baseline scores are reported for clinical significance defined as 'much better' or 'completely recovered' in patients with lateral epicondylalgia.[19]

Statistical analysis

The primary hypotheses of this 2x2 factorial design study were that after one year, clinical outcomes would be worse in patients receiving injection of corticosteroid (than placebo), while better in those receiving physiotherapy (than no-physiotherapy). At the outset of the trial, we did not anticipate an interaction between the two interventions.[20] A total sample size of 120 patients (α=0.05, β=0.2) was initially estimated to detect a clinically meaningful difference of 25% for the two factorial (at-margin) comparisons (corticosteroid *v* placebo; physiotherapy *v* no-physiotherapy) for all primary hypotheses based on previous studies.[3,5] At a trial steering committee meeting (before recruitment ended), however, we decided to inflate the sample size to 165 to permit adequate power for the following *a priori* pairwise comparisons:[21] corticosteroid injection *v* placebo injection alone; corticosteroid injection plus physiotherapy *v* placebo injection plus physiotherapy; placebo injection *v* placebo injection plus physiotherapy; and corticosteroid injection *v* corticosteroid injection plus physiotherapy, as well as account for loss to follow-up. No interim analyses were performed during the study period.

Statistical analysis was done on a blinded intention to treat basis using SPSS version 20.0 (IBM, Somers, New York, USA) with *a priori* P<0.01 (two-sided) significance because of multiple comparisons. The effects of injection and physiotherapy on complete recovery/much improvement and recurrence were analysed using binary logistic regression, including as a covariate baseline worst pain (VAS), which is a recognised prognostic factor.[22] We investigated for interactions between injection and physiotherapy factors and interpreted results of pairwise comparisons when a significant interaction was found. We calculated the relative risk (RR, 99% CI) of complete recovery/much improvement by dividing the corticosteroid (or physiotherapy) risk by the placebo (or no-physiotherapy) risk. We also calculated the RR of recurrence by dividing the placebo (or no-physiotherapy) risk by the corticosteroid (or physiotherapy) risk. Numbers needed to treat (NNT, 99% CI) were generated as a meaningful indicator of treatment efficacy for practitioners.[23] Continuous outcomes were analysed using linear regression, including baseline values of the dependent variable as a covariate. Main effects or pairwise comparisons (where significant interaction)[21] were expressed as standardised mean differences (SMD, 99% CI), calculated using RevMan statistical software version 5.0.[24] A beneficial effect of corticosteroid and physiotherapy were defined as RR>1, or SMD and NNT >0, while a harmful effect of corticosteroid and physiotherapy were defined as RR<1, or SMD and NNT <0. A SMD 0.2- 0.5 was defined as a small effect, SMD 0.5-0.8 as a medium effect and greater than 0.8 as a large effect.[25]

Results

165 patients were enrolled between July 2008 and May 2010. Figure 1 summarizes patient recruitment, participation and attrition. The most common reasons for exclusion of patients with suspected lateral epicondylalgia were recent treatment (27%), declined to participate (21%), concomitant neck or shoulder pain (17%), bilateral elbow pain (15%) or resolution of lateral epicondylalgia (8%). Elbow surgery, a history of repeated corticosteroid injection, neurological symptoms and other contraindications made up the remaining 12% of excluded patients. The trial was completed in May 2011, with 163 patients (99%) completing primary outcomes at one year and two unrelated deaths from cancer recorded. Due to the small proportion of missing values (n=3, 2%) we decided not to do any imputation. The omitted cases were similar in baseline characteristics to the total sample. No significant differences in baseline characteristics were found between the four groups (Table 1). The median duration

of lateral epicondylalgia was 16 weeks (range six weeks to four years) with 76% presenting with their first episode.

Four patients did not receive the allocated injection (1 placebo, 3 corticosteroid) due to non-attendance (n=2, 1%) or alternative medical advice (n=2, 1%). The mean (SD) number of physiotherapy sessions attended was 7.5 (1.9). Seven patients (9%) completed less than four physiotherapy sessions, due to non-attendance, moving interstate or recovery. Seventy percent of patients were compliant with their home exercise program on at least five out of seven weeks. Two (2%) corticosteroid injected patients had an additional corticosteroid injection, while seven (8%) patients not allocated to physiotherapy, pursued physiotherapy external to the trial. Injection and physiotherapy allocation was correctly guessed by the outcome assessor in 53% (20/38) of cases receiving placebo injection only, 39% (16/41) of placebo injection plus physiotherapy, 44% (18/41) of corticosteroid injection only, 44%(15/38) of corticosteroid injection plus physiotherapy. Thirty-seven percent (50/137) of patients stated they were confident of which injection they received, with correct responses identified by 71% (20/28) of corticosteroid injected patients and 73% (16/22) of placebo injected patients. No differences were found between interventions.

Descriptive statistics for the four randomized groups for a priori time points (4, 26 and 52 weeks) are presented in Table 2, while additional data is provided online (eTable 1). Primary outcomes

There was no interaction between injection and physiotherapy at one year (P=0.99). Our first hypothesis was supported, with corticosteroid injection demonstrating lower complete recovery/much improvement (68/82 (83%) *v* 78/81 (96%), RR 0.86 (99% CI 0.75 to 0.99), NNT -7.5 (99% CI -150.9 to -3.7), P=0.01) and greater recurrence (44/81 (54%) *v* 10/81 (12%), RR 0.23 (0.10 to 0.51), NNT -2.4 (-4.3 to -1.8), P<0.001) compared to placebo injection at one year (Figure 2A). The second hypothesis was not supported, with no differences between physiotherapy and no-physiotherapy for complete recovery/much improvement (73/80 (91%) *v* 73/83 (88%), RR 1.04 (0.90 to 1.19), P=0.56) or recurrence (23/80 (29%) *v* 31/82 (38%), RR 1.31 (0.73 to 2.35), P=0.25) (Figure 2B).

Secondary time points/ outcomes

Four weeks

At 4 weeks, there was a significant interaction between injection and physiotherapy for complete recovery/much improvement (P=0.01; Figure 2), as well as worst pain (P<0.001), pain and disability (P<0.001) and quality of life (P =0.004) (Figure 3). In the absence of physiotherapy, complete recovery/much improvement was greater following corticosteroid than placebo injection (RR 7.32 (99% CI 2.1 to 25.5), NNT 1.6 (99% CI 1.3 to 2.9), P<0.001), and was associated with large benefits for all secondary outcomes- worst pain (SMD 1.77 (99% CI 1.09 to 2.44), P<0.001), resting pain (SMD 0.87 (0.28 to 1.46); P<0.001), pain and disability (SMD 1.81 (1.13 to 2.48), P<0.001) and quality of life (SMD 1.14 (0.53 to 1.76), P<0.001). This was not the case for most outcomes when physiotherapy was present, with no differences in complete recovery/much improvement (RR 1.73 (0.97 to 3.08), P=0.02), worst pain (SMD 0.51 (-0.08 to 1.09), P=0.03), resting pain (SMD 0.21 (-0.36 to 0.79), P=0.29) or quality of life (SMD 0.30 (-0.27 to 0.88), P=0.08), but there was a medium-sized benefit of corticosteroid injection on pain and disability (SMD 0.63 (0.04 to 1.22), P<0.001). In corticosteroid injected patients, physiotherapy had no effect on any outcome (complete recovery/much improvement RR 0.95 (0.65 to 1.38), P=0.57; worst pain SMD -0.38 (-0.96 to 0.19), P=0.10; resting pain SMD -0.05 (-0.62 to 0.52), P=0.91); pain and disability SMD -0.40 (-0.97 to 0.18), P=0.12; quality of life SMD -0.30 (-0.88 to 0.27), P=0.29). This contrasted with placebo injected patients, in which physiotherapy resulted in greater complete recovery/much improvement (RR 4.00 (1.07 to 15.0), NNT 3.4 (2.0 to 21.4), P=0.004), along with medium-sized benefits of worst pain (SMD 0.88 (0.29 to 1.48), P<0.001), resting pain (SMD 0.60 (0.02 to 1.19), P=0.01) and pain and disability (SMD 0.77 (0.18 to 1.37), P=0.001).

26 weeks

There were no significant interaction effects at 26 weeks. Corticosteroid injection demonstrated lower complete recovery/much improvement than placebo injection (45/82 (55%) *v* 69/81 (85%), RR 0.79 (0.62 to 0.99), NNT -5.5 (-123.1 to -2.9), P<0.001), supported by medium-sized deficits on all other outcomes - worst pain (SMD -0.77 (-1.19 to -0.35), P<0.001), resting pain (SMD -0.61 (-1.02 to -0.19), P<0.001), pain and disability (SMD -0.76 (-1.18 to -0.34), P<0.001) and quality of life (SMD -0.55 (-0.97 to -0.14), P=0.004). Physiotherapy demonstrated no effect on any outcome (complete recovery/much improvement 57/80 *v* 57/83, RR 1.22 (0.97 to 1.53), P=0.84; worst pain SMD 0.04 (-0.36 to 0.44), P=0.79; resting pain SMD 0.05 (-0.35 to 0.46), P=0.74; pain and disability SMD 0.07 (-0.33 to 0.48), P=0.25; quality of life SMD 0.33 (-0.08 to 0.74), P=0.13).

52 weeks

There were no significant interaction effects at 52 weeks. Consistent with primary outcomes, worst pain remained significantly higher for corticosteroid than placebo injection at one year, although differences were small (SMD -0.44 (-0.85 to -0.03), *P*=0.005). No differences were found between injection types for resting pain (SMD -0.17 (-0.58 to 0.23), *P*=0.29), pain and disability (SMD -0.36 (-0.76 to 0.05), *P*=0.02) or quality of life (SMD -0.22 (-0.63 to 0.18), *P*=0.21). Physiotherapy demonstrated no effect on any outcome (complete recovery/much improvement 73/80 *v* 73/83, RR 1.04 (0.90 to 1.19), *P*=0.56; worst pain SMD -0.07 (-0.47 to 0.34), *P*=0.66; resting pain SMD -0.07 (-0.47 to 0.34), *P*=0.64; pain and disability SMD 0.05 (-0.36 to 0.45), *P*=0.51; quality of life SMD 0.00 (-0.40 to 0.40), *P*=0.70).

Use of analgesic or anti-inflammatory medication (Table 2) did not differ between injection of corticosteroid or placebo (26/83 (31%) *v* 23/82 (28%); *P*=0.57), while was less frequently used by patients allocated to physiotherapy than those not allocated to physiotherapy (16/81 (20%) *v* 33/84 (39%), NNT 5.1 (2.8 to 84.8), *P*=0.008). Non-protocol medical consultations did not differ between injection (15/83 (8%) *v* 8/82 (10%), *P*=0.13) or physiotherapy (7/81 (9%) v 16/84 (19%), *P*=0.06) factors.

Adverse events reported in this study were minor, transient and not significantly different between injection or physiotherapy factors (Table 2). Skin depigmentation (4/83, 5%) and subcutaneous atrophy (3/83, 4%) occurred exclusively in patients receiving corticosteroid injection, showed a delayed onset (evident on examinations at 8 or 12 weeks) and was resolved by 26 weeks.

Comment

In this placebo-controlled study, a single, blinded injection of corticosteroid medication was associated with poorer long term outcomes and higher recurrence rates one year following injection in patients with lateral epicondylalgia. Eight weeks of multimodal physiotherapy, comprising elbow mobilisation with movement and exercise, did not optimise long term outcomes, but was beneficial in the short term in the absence of corticosteroid injection. Significantly fewer patients receiving physiotherapy consumed analgesic or anti-inflammatory medication.

A recent systematic review (search date March 2010)[4] reported that it was not possible to make a definitive declaration regarding the efficacy of corticosteroid injection beyond placebo, largely due to significant heterogeneity for studies making this comparison. Our current study provides evidence of the short term effectiveness of corticosteroid injection compared to placebo injection, when injected alone. Notwithstanding this, differences in complete recovery/much improvement were not significant when patients also received physiotherapy, a finding echoed by Newcomer et al. in a study of lateral epicondylalgia of less than six weeks duration.[7] This evidence does not support the clinical opinion that corticosteroid injection be used to facilitate active rehabilitation.

Results were reversed at six months, with corticosteroid injection displaying moderate to large inferior effects consistently across measures of complete recovery/much improvement, pain, disability and quality of life. At one year, most (90%) patients reported complete recovery/much improvement, which reflects the natural history of the condition.[3,5,9] However, significantly fewer patients reported being completely recovered or much improved, and worst pain levels remained higher one year following corticosteroid injection. Furthermore, over half of all patients treated with a single corticosteroid injection experienced a recurrence, substantially greater than placebo. In clinical terms, this represented a NNT of 2.4, i.e., for every two or three people treated with corticosteroid injection (in comparison to placebo), one person experienced recurrence over the year. Whilst high recurrence rates following corticosteroid injection have been previously reported,[3,5] this study provides evidence that it may be the effect of the medication and not merely a manifestation of the disease or the injection.

The biological basis for the clinical effect of corticosteroids in lateral epicondylalgia is still largely unknown. Corticosteroids are potent in suppressing inflammation,[26] but the prevailing opinion is that no histological evidence of acute inflammation has been documented,[11,12,27,28] although inflammatory cells have been detected by newer studies using immunohistochemistry.[29,30] The early response of corticosteroids may be due to an analgesic effect on the neuropeptides, calcitonin gene-related peptide and substance P, which are increased in tendinopathy.[28] Recurrence may occur as corticosteroids do not address key features of tendinopathy, which is traditionally thought to be associated with overuse or

cumulative trauma weakening collagen cross-linking and the non-collagenous matrix and vascular elements of tendon.[28] Indeed, the medication might be deleterious to the tendon through an effect on fibroblasts' role in collagen and extracellular matrix protein production.[26] Others have proposed that the poor long term clinical effect of corticosteroid injection might be related to the immediate pain relief and conceivable excessive or inappropriate early activity.[3,28] {Fredberg, 2008 #64;Bisset, 2006 #1}

Contrary to our hypothesis and to a generally held clinical view,[2] we found that multimodal physiotherapy provided no beneficial long term effect on complete recovery/much improvement, recurrence, pain, disability or quality of life, thereby not supporting the hypothesis that the combined approach is superior. However, physiotherapy should not be dismissed altogether, because in the absence of corticosteroid, it provided short term benefit across all outcomes, as well as the lowest recurrence rates (4.9%) and 100% complete recovery/much improvement at one year. At four weeks, the magnitude of improvement on PRTEE, a validated, condition-specific measure of pain and disability, exceeded previously reported minimum clinically important differences[19] for patients receiving corticosteroid injection and/or physiotherapy, but not those receiving placebo injection alone. A previous study showed a similar multimodal physiotherapy program was superior to wait and see in the short term.[3]

The strengths of this study lie in the high retention (99.8%) of patients after extended follow-up and consistency of findings across validated condition-specific and generic outcomes. It also has limitations. First, results may not be generalized to other clinical contexts where treatments are reserved for specific individuals or combined in a different sequence or manner, for example; injection of patients who have not recovered following a period of wait and see or physiotherapy; or treatment with physiotherapy in patients with poor late outcomes following injection. Secondly, it is not uncommon for lateral epicondylalgia to present bilaterally or be associated with concomitant symptoms of the neck or upper limb.[22] We limited our study population to patients with unilateral lateral epicondylalgia, without significant neck or other upper limb symptoms, which needs to be considered in applying our findings to clinical practice. In addition, we excluded patients who had received recent treatment or repeated corticosteroid injection as these may have biased findings. Excluding prior corticosteroid injection suggests that our findings are best case scenario in terms of its long term outcomes. A previous study found a poorer long term effect of repeated

401 corticosteroid injection (mean 4.3 injections in 18 months) on reduction of pain than
402 treatment with one injection.[31] It should be acknowledged that while the assessor was blinded
403 to treatments received by the patients, the lack of patient and therapist blinding to
404 physiotherapy might have biased estimates of the benefit of physiotherapy, the mitigation of
405 which should be considered in future study designs.[31]
406
407
408 In conclusion, among patients with chronic unilateral epicondylalgia, one year after
409 corticosteroid injection there was a worse clinical outcome compared with placebo, despite
410 its short term benefits. Physiotherapy did not result in any significant 1-year difference.

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Author Contributions: Professor Vicenzino had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Coombes, Bisset, Vicenzino
Acquisition of data: Coombes, Vicenzino
Analysis and interpretation of data: Coombes, Bisset, Khan, Vicenzino
Drafting of the manuscript: Coombes, Khan, Vicenzino
Critical revision of the manuscript for important intellectual content: Coombes, Bisset, Brooks, Khan, Vicenzino
Statistical analysis: Coombes, Khan, Vicenzino
Obtained funding: Bisset, Vicenzino, Brooks
Study supervision: Bisset, Vicenzino

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Additional contributions: We also thank all of the patients for their valuable contributions to the study

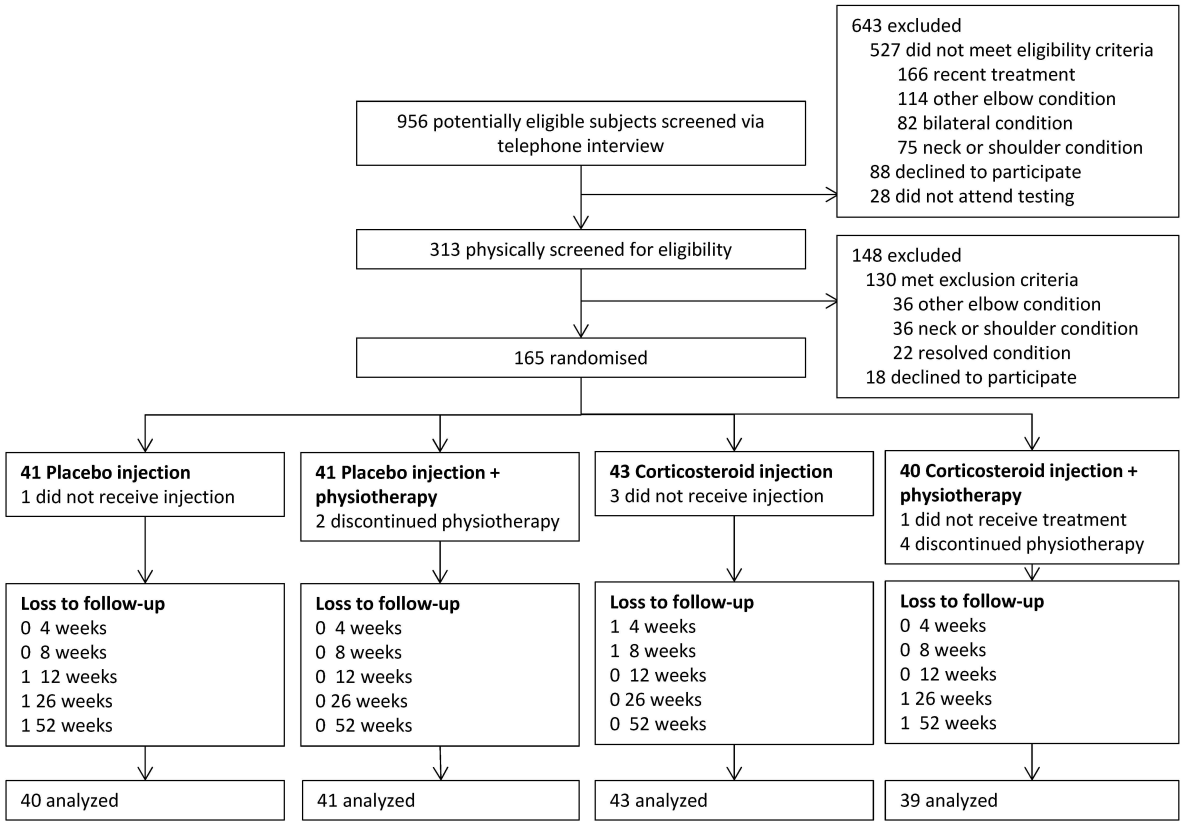

Figure 1: Study flow diagram

Patients were lost to follow-up if they did not provide global rating of change scores. Patients who discontinued treatment had the opportunity to provide follow-up data.

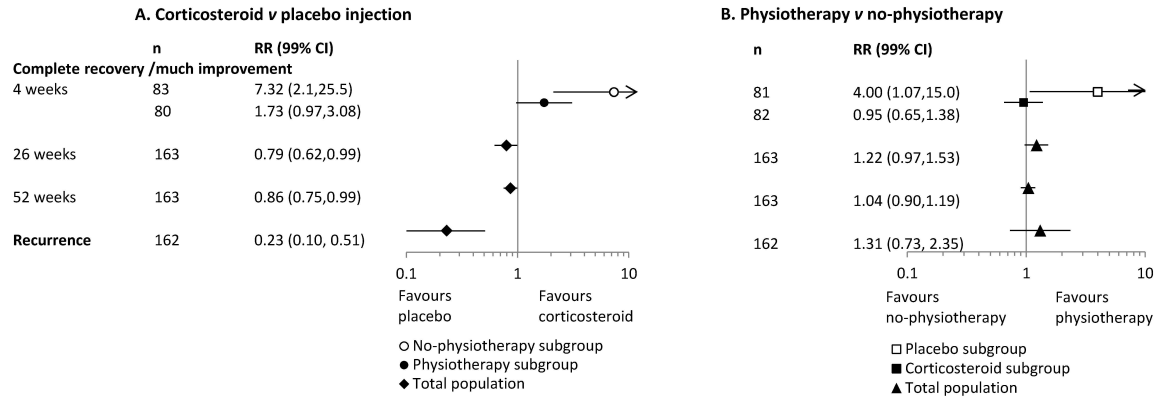

Figure 2: Relative risk (RR) of complete recovery or much improvement and recurrence and 99% confidence interval (CI) for (A) corticosteroid injection relative to placebo injection and (B) for addition of physiotherapy relative to no-physiotherapy.

Effect statistics are for the total population (diamond or triangle) or in the case of significant interaction, for the following subgroups: no-physiotherapy (white circle), physiotherapy (black circle), placebo injection (white square) or corticosteroid injection (black square). Scores greater than one indicate outcomes in favour of the active intervention.

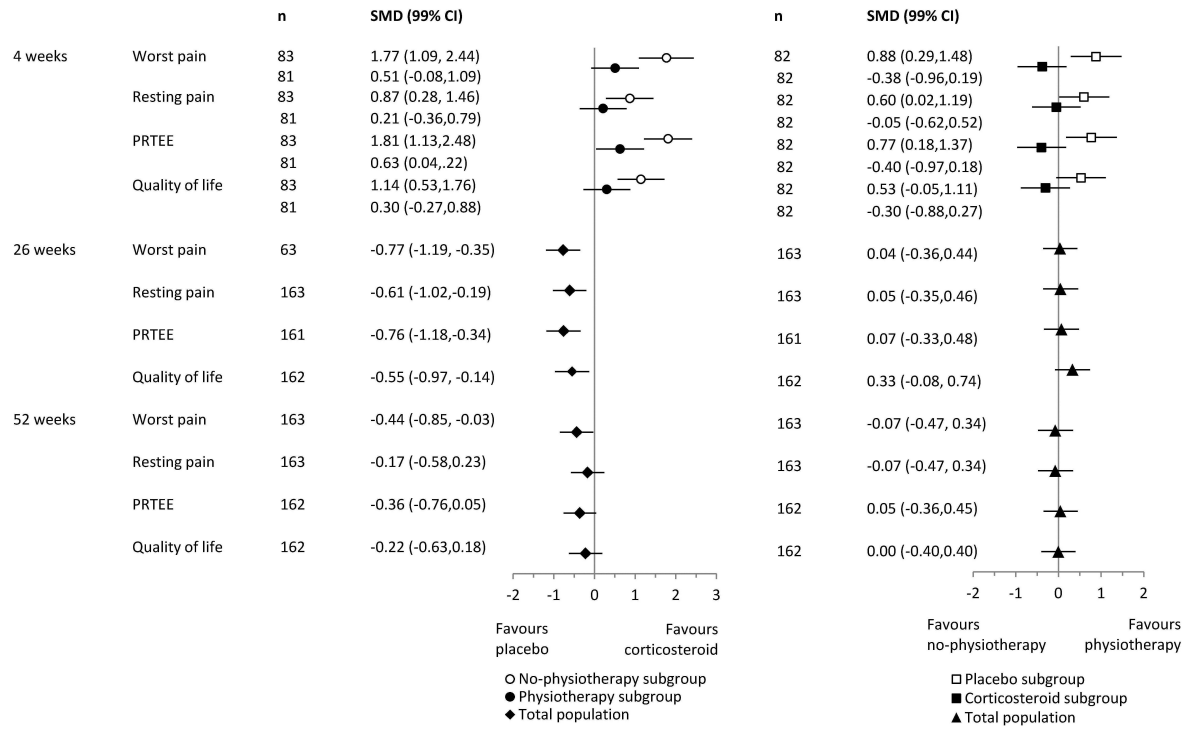

Figure 3: Standardised mean differences (SMD) and 99% confidence interval (CI) for (A) corticosteroid injection relative to placebo injection and (B) for addition of physiotherapy relative to no-physiotherapy.

Effect statistics are for the total population (diamond or triangle) or in the case of significant interaction, for the following subgroups: no-physiotherapy (white circle), physiotherapy (black circle), placebo injection (white square) or corticosteroid injection (black square). Positive scores indicate outcomes in favour of the active intervention. PRTEE: Patient-rated tennis elbow evaluation.

461 **Table 1: Baseline demographic and clinical characteristics**

Characteristic	Placebo injection	Placebo injection + physiotherapy	Corticosteroid injection	Corticosteroid injection + physiotherapy	Total
Patients, n	41	41	43	40	165
Age (years) [a]	49·9 (7·4)	48·7 (7·7)	49·3 (8·9)	50·8 (8·5)	49·7 (8·1)
Female [b]	17 (42%)	15 (37%)	16 (37%)	15 (38%)	63 (38%)
Duration of symptoms (weeks) [c]	16 (8 to 32)	16 (8 to 24)	16 (10 to 27)	15 (10 to 26)	16 (10 to 26)
Resting pain VAS (0-100) [c]	9 (0 to 22)	7 (0 to 11)	4.5 (0 to 18)	9 (0 to 15)	7.5 (0 to 15)
Worst pain VAS (0-100) [a]	62·4 (19·8)	63·2 (18·0)	62·0 (20·3)	59·0 (15·8)	61·7 (18·5)
Pain and disability (PRTEE: 0-100) [a]	41·6 (14·4)	36·4 (13·3)	42·0 (14·4)	38·1 (13·8)	39·5 (14·1)
Quality of life (EQ-5ED: 0-1) [a]	0·74 (0·13)	0·74 (0·12)	0·68 (0·20)	0·74 (0·09)	0·73 (0·14)

462 Data represents mean (SD)[a], count (%)[b], median (IQR)[c]. VAS = Visual analogue scale;

463 PRTEE = Patient rated tennis elbow evaluation

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Table 2: Descriptive statistics for primary and secondary outcomes at a priori time points.

Outcome	Placebo injection	Placebo injection + physiotherapy	Corticosteroid injection	Corticosteroid injection + physiotherapy
Complete recovery or much improvement [a]				
4 weeks	4/41, 10% (3 to 28%)	16/41, 39% (22 to 59%)	30/42, 71% (52 to 85%)	27/40, 68% (47 to 83%)
26 weeks	33/40, 83% (63 to 93%)	36/41, 89% (69 to 96%)	24/43, 56% (37 to 73%)	21/39, 54% (34 to 72%)
52 weeks	37/40, 93% (75 to 98%)	41/41, 100% (86 to 100%)	36/43, 84% (65 to 93%)	32/39, 82% (62 to 93%)
Recurrence [a, b]				
52 weeks	8/40, 20% (9 to 40%)	2/41, 5% (1 to 21%)	23/42, 55% (36 to 73%)	21/39, 54% (34 to 72%)
Worst pain VAS [c]				
4 weeks	56 (30 to 70)	35 (15 to 45)	5 (0 to 22)	1 (10 to 25)
26 weeks	5 (0 to 22)	5 (0 to 10)	10 (2 to 58)	2 (5.5 to 48.5)
52 weeks	0 (0 to 5)	0 (0 to 3)	0.5 (0 to 10)	5 (0 to 18)
Resting pain VAS [c]				
4 weeks	5 (0 to 22)	0 (0 to 10)	0 (0 to 2)	0 (0 to 0)
26 weeks	0 (0 to 0)	0 (0 to 0)	0 (0 to 14)	0 (0 to 8)
52 weeks	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
Patient rated tennis elbow evaluation (PRTEE) [c]				
4 weeks	31.8 (20.5 to 43.8)	22.5 (9.5 to 28.5)	6.5 (2.5 to 12)	7 (2.5 to 16)
26 weeks	6.5 (2.8 to 12)	3.5 (1 to 6)	10.5 (3.5 to 22.5)	7.5 (4 to 21)
52 weeks	0.5 (0 to 5.8)	1 (0 to 4.5)	3 (0 to 8.5)	3 (0 to 6)
Health-related quality of life (EQ-5ED) [d]				
4 weeks	0.77 (0.71 to 0.83)	0.84 (0.79 to 0.89)	0.91 (0.87 to 0.96)	0.89 (0.84 to 0.95)
26 weeks	0.90 (0.84 to 0.96)	0.93 (0.89 to 0.98)	0.83 (0.78 to 0.89)	0.88 (0.83 to 0.94)
52 weeks	0.94 (0.89 to 0.98)	0.97 (0.93 to 1.00)	0.93 (0.89 to 0.98)	0.92 (0.85 to 1.00)
Adverse events [a]				
Severe post-injection pain	1/41, 2% (0 to 18%)	3/41, 7% (2 to 25%)	0/43, 0% (0 to 13%)	0/40, 0% (0 to 14%)
Pain post-injection > 48 hours	8/41, 20% (8 to 39%)	5/41, 12% (4 to 31%)	2/43, 5% (1 to 21%)	1/40, 3% (0 to 18%)
Pain post-injection> 7 days	1/41, 2% (0 to 18%)	3/41, 7% (2 to 25%)	1/43, 2% (0 to 17%)	0/40, 0% (0 to 14%)
Pain post-physio > 24 hours	NA	3/41, 7% (2 to 25%)	NA	2/40 , 5% (1 to 22%)
Pain post-physio > 7 days	NA	0/41, 0% (0 to 14%)	NA	1/40, 3% (0 to 18%)
Depigmentation	0/41, 0% (0 to 14%)	0/41, 0% (0 to 14%)	3/43, 7% (2 to 24%)	1/40, 3% (0 to 18%)
Subcutaneous atrophy	0/41, 0% (0 to 14%)	0/41, 0% (0 to 14%)	2/43, 5% (1 to 21%)	1/40, 3% (0 to 18%)
Numbness of hand	1/41, 2% (0 to 18%)	0/41, 0% (0 to 14%)	1/43, 2% (0 to 17%)	0/40, 0% (0 to 14%)
Vomiting	0/41, 0% (0 to 14%)	1/41, 2% (0 to 18%)	0/43, 0% (0 to 13%)	0/40, 0% (0 to 14%)
Swelling	0/41, 0% (0 to 14%)	1/41, 2% (0 to 18%)	0/43, 0% (0 to 13%)	0/40, 0% (0 to 14%)
Skin irritation from taping	NA	0/41, 0% (0 to 14%)	NA	1/40, 3% (0 to 18%)
Non-protocol treatment [a]				
Analgesic /NSAID medication	16/41, 39% (22 to 59%)	7/41, 17% (7 to 36%)	17/43, 40% (23 to 59%)	9/40, 23% (10 to 43%)
Medical consultation	6/41, 15% (5 to 34%)	2/41, 5% (1 to 21%)	10/43, 23% (11 to 43%)	5/40, 13% (4 to 31%)

[a] Number of events/total sample size, percentage (99% CI).
[b] Recurrence defined as complete recovery or much improvement at 4 or 8 weeks, but not later.
[c] Median (IQR)
[d] Mean (99% CI)
VAS = Visual analogue scale; PRTEE = Patient rated tennis elbow evaluation; EQ-5ED = Euroqol questionnaire

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