Effect of Corticosteroid Injection, Physiotherapy, or Both on Clinical Outcomes in Patients With Unilateral Lateral Epicondylalgia

A Randomized Controlled Trial

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Importance Corticosteroid injection and physiotherapy, common treatments for lateral epicondylalgia, are frequently combined in clinical practice. However, evidence on 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 2×2 factorial, randomized, injection-blinded, placebo-controlled trial was conducted at a single university research center and 16 primary care settings in Brisbane, Australia. A total of 165 patients aged 18 years or older with unilateral lateral epicondylalgia of longer than 6 weeks' duration were enrolled between July 2008 and May 2010; 1-year follow-up was completed in May 2011.

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

Main Outcome Measures The 2 primary outcomes were 1-year global rating of change scores for complete recovery or much improvement and 1-year recurrence (defined as complete recovery or much improvement at 4 or 8 weeks, but not later) analyzed on an intention-to-treat basis ($P<.01$). Secondary outcomes included complete recovery or much improvement at 4 and 26 weeks.

Results Corticosteroid injection resulted in lower complete recovery or much improvement at 1 year vs placebo injection (83% vs 96%, respectively; relative risk [RR], 0.86 [99% CI, 0.75-0.99]; $P=.01$) and greater 1-year recurrence (54% vs 12%; RR, 0.23 [99% CI, 0.10-0.51]; $P<.001$). The physiotherapy and no physiotherapy groups did not differ on 1-year ratings of complete recovery or much improvement (91% vs 88%, respectively; RR, 1.04 [99% CI, 0.90-1.19]; $P=.56$) or recurrence (29% vs 38%; RR, 1.31 [99% CI, 0.73-2.35]; $P=.25$). Similar patterns were found at 26 weeks, with lower complete recovery or much improvement after corticosteroid injection vs placebo injection (55% vs 85%, respectively; RR, 0.79 [99% CI, 0.62-0.99]; $P<.001$) and no difference between the physiotherapy and no physiotherapy groups (71% vs 69%, respectively; RR, 1.22 [99% CI, 0.97-1.53]; $P=.84$). At 4 weeks, there was a significant interaction between corticosteroid injection and physiotherapy ($P=.01$), whereby patients receiving the placebo injection plus physiotherapy had greater complete recovery or much improvement vs no physiotherapy (39% vs 10%, respectively; RR, 4.00 [99% CI, 1.07-15.00]; $P=.004$). However, there was no difference between patients receiving the corticosteroid injection plus physiotherapy vs corticosteroid alone (68% vs 71%, respectively; RR, 0.95 [99% CI, 0.65-1.38]; $P=.57$).

Conclusion and Relevance Among patients with chronic unilateral lateral epicondylalgia, the use of corticosteroid injection vs placebo injection resulted in worse clinical outcomes after 1 year, and physiotherapy did not result in any significant differences.

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USE OF CORTICOSTEROID INjections to treat lateral epicondylalgia is increasingly discouraged,[1,2] partly because evidence of long-term efficacy has not been found,[3-5] and due to high recurrence rates.[3,6] In a randomized controlled trial with 1-year follow-up,[3] recurrence was evident in 72% of patients receiving corticosteroid injection compared with 8% after physiotherapy.

Combining corticosteroid injection with physiotherapy to compensate for the poor long-term outcomes of corticosteroid injections has been evaluated only in 2 small studies.[7,8] One of the studies reported no benefit at 6 months after corticosteroid injection when added to ice massage plus physiotherapy-prescribed exercise.[7] The other study found no significant effect of a progressive resistance training and graduated exercise program when added to corticosteroid injection; however, this study was underpowered, reported a high dropout rate, and did not assess outcomes beyond 7 weeks.[8] The long-term effects of corticosteroid injection combined with 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 counterintuitive, given their anti-inflammatory mode of action juxtaposed against the lack of inflammatory markers in tendinopathy.[10-12] A plausible explanation is that

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these corticosteroid injections are associated with strong placebo effects.[13] A systematic review[14] found significant heterogeneity for studies comparing corticosteroid injection with placebo injection, with 3 of the 4 studies showing no difference. However, the use of lidocaine and bupivacaine injections as placebo comparators might have exerted a therapeutic effect.[13] There is a critical need to evaluate the efficacy of corticosteroid injection compared with a placebo injection of normal saline.

The primary objectives of this study were 2-fold: to evaluate at 1 year the clinical efficacy of (1) corticosteroid injection vs placebo injection and (2) physiotherapy vs no physiotherapy in patients with unilateral lateral epicondylalgia. The primary outcomes were (1) patient-rated 1-year global change scores for complete recovery or much improvement and (2) 1-year recurrence (defined as complete recovery or much improvement at 4 or 8 weeks, but not at 8, 12, 26, or 52 weeks).

METHODS

A randomized, blinded, placebo-controlled trial with a 2 × 2 factorial design and 1 year of follow-up was performed in a community setting in Brisbane, Australia, as per the published protocol.[13] Injection and physiotherapy factors were combined to constitute 4 treatment groups: (1) corticosteroid injection, (2) placebo injection, (3) corticosteroid injection plus multimodal physiotherapy, and (4) placebo injection plus multimodal physiotherapy. This trial was approved by the University of Queensland medical research ethics committee.

Patients

Adults aged 18 years or older with unilateral lateral epicondylalgia of longer than 6 weeks' duration, who responded to public advertisements between August 2008 and May 2010, were invited to participate. Inclusion criteria were pain over the lateral humeral epicondyle with pain severity of greater than 30 mm on a 100-mm visual analog scale (VAS), provoked by at least 2 of the following: gripping, palpation, resisted wrist or middle finger extension, or stretching of forearm extensor muscles with reduced pain-free grip.

Exclusion criteria were receipt of injection (during preceding 6 months); receipt of a course of physiotherapy (during preceding 3 months); concomitant neck or other arm pain necessitating treatment or preventing participation in usual work or recreational activities (during preceding 6 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 (B.K.C.) and confirmed by a second researcher (B.V.).

Randomization

After written informed consent was obtained, randomization was performed by concealed allocation using a computer-generated schedule developed by the Queensland Clinical Trials Center, an independent, offsite organization. Randomization was stratified according to pain severity of greater or less than 57.5 mm on a 100-mm VAS, which was 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 the intention-to-treat analysis was blinded to both injection and physiotherapy assignment. Patients were masked to injection type (corticosteroid or placebo) but not to physiotherapy due to its nature. To evaluate the success of blinding, patients were asked at 8 weeks whether they were confident of which injection they received, and those who responded yes were asked to report the suspected injection type. The outcome assessor guessed both injection and physiotherapy assignment of all patients.

Interventions

Injection Types. Patients received a single injection of either placebo (0.5 mL of 0.9% isotonic saline) or corticosteroid and local anesthetic medication (10 mg/mL of triamcinolone acetonide in a 1 mL injection plus 1 mL of 1% lignocaine) by 1 of 5 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 refrain from performing strenuous activity for 2 weeks after receipt of injection. Following this 2-week period, a gradual return to normal activities was encouraged (even if substantial initial relief was obtained) to minimize potential recurrence. Patients could use an analgesic or anti-inflammatory medication, heat or cold pack, or braces as needed, but were discouraged from seeking treatments other than those assigned.

Physiotherapy. The physiotherapy groups underwent eight 30-minute sessions of treatment during an 8-week period, with the first session scheduled prior to the injection. Eleven physiotherapy practitioners with postgraduate qualifications underwent 2 hours of training with 2 of the authors (B.K.C. and B.V.) to standardize the treatment according to a published protocol,[13] which comprised local elbow manual therapy and exercise.

To individualize 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 (mobilization 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 elastic latex bands. The home program was regularly reviewed and exercise diaries were monitored to facilitate program adherence.

Outcome Measures

Patients estimated their global rating of change at each trial visit (at 4, 8, 12, 26, and 52 weeks) using a 6-point Likert scale, ranging from "complete recovery" to "much worse."[3,13] A priori primary outcomes were 1-year global rating of change scores of complete recovery or much improvement and 1-year recurrence (defined as global rating of change scores of complete recovery or much improvement at 4 or 8 weeks, but not at 8, 12, 26, or 52 weeks).

The secondary outcomes were global rating of change scores of complete recovery or much improvement at 4 and 26 weeks; severity of current resting pain and worst pain over the preceding week (on a 100-mm VAS); a condition-specific, validated questionnaire of pain and disability (Patient-Rated Tennis Elbow Evaluation score range: 0-100, in which 100 represents the worst imaginable pain with a very significant functional disability)[16,17]; health-related quality of life (EuroQol EQ-5D score range: 0-1, in which 1 represents perfect health)[18] at 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 Patient-Rated Tennis Elbow Evaluation) 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 2×2 factorial study design were that after 1 year, clinical outcomes would be worse in patients receiving an injection of corticosteroid (vs placebo), whereas outcomes would be better in those receiving physiotherapy (vs no physiotherapy). At the outset of the trial, we did not anticipate an interaction between the 2 interventions.[20] A total sample size of 120 patients ($\alpha = .05$, $\beta = .20$) was initially estimated to detect a clinically meaningful difference of 25% for the 2 factorial (at margin) comparisons (corticosteroid vs placebo; physiotherapy vs no physiotherapy) for all primary hypotheses based on previous studies.[3,5]

However, at a trial steering committee meeting (before recruitment ended), we decided to inflate the sample size to 165 to permit adequate power for the following a priori pairwise comparisons[21]: corticosteroid injection vs placebo injection alone; corticosteroid injection plus physiotherapy vs placebo injection plus physiotherapy; placebo injection vs placebo injection plus physiotherapy; and corticosteroid injection vs corticosteroid injection plus physiotherapy; and to account for loss to follow-up. No interim analyses were performed during the study period.

The statistical analyses were performed on a blinded, intention-to-treat basis using SPSS version 20.0 (SPSS Inc) with a priori 2-sided significance as a *P* value of less than .01 due to the multiple comparisons. The effects of injection and physiotherapy on complete recovery or much improvement and 1-year recurrence were analyzed using binary logistic regression, including baseline worst pain as a covariate (measured by the VAS), which is a recognized 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) of complete recovery or 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. The numbers needed to treat (NNT) were generated as a meaningful indicator of treatment efficacy for practitioners.[23]

Continuous outcomes were analyzed using linear regression, including baseline values of the dependent variable as a covariate. Main effects or pairwise comparisons (when there was a significant interaction)[21] were expressed as standardized mean differences (SMDs) and calculated using RevMan statistical software version 5.0 (Nordic Cochrane Centre, Cochrane Collaboration). A beneficial effect of corticosteroid and physiotherapy were defined as a RR of greater than 1, or a SMD and NNT of greater than 0, whereas a harmful effect of corticosteroid injection and physiotherapy were defined as a RR of less than 1, or a SMD and NNT of less than 0. A SMD between 0.2 and 0.5 was defined as a small effect, a SMD between 0.5 and 0.8 as a medium effect, and a SMD of greater than 0.8 as a large effect.[24]

RESULTS

A total of 165 patients with unilateral lateral epicondylalgia 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 (22%), other elbow condition (19%), concomitant neck or shoulder pain (14%), refused to participate (13%), bilateral elbow pain (12%), or resolution of lateral epicondylalgia (5%). Elbow surgery, a history of repeated corticosteroid injection, neurological symptoms, and other contraindications made up the remaining 15% of excluded patients.

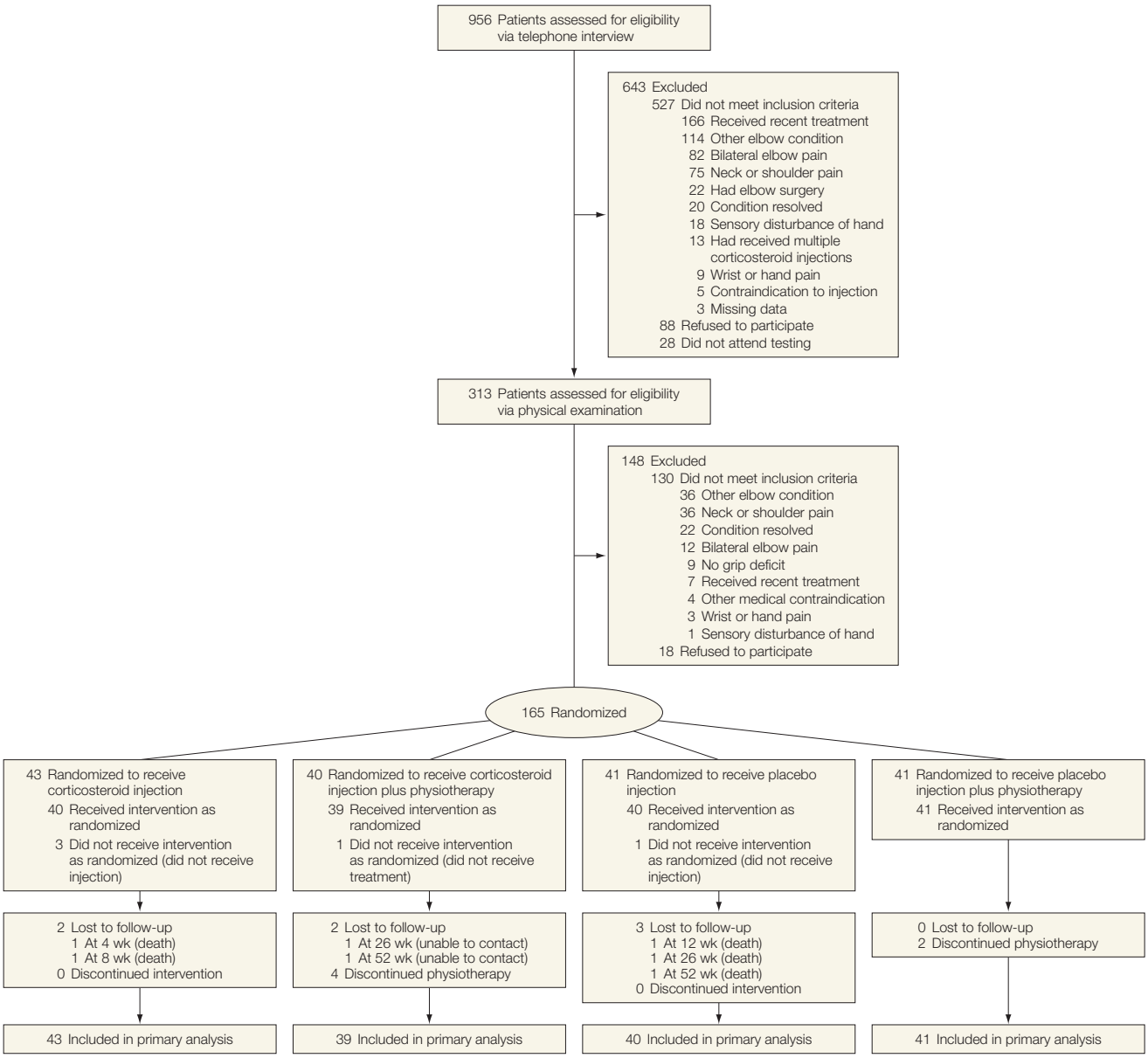
The trial was completed in May 2011, with 163 patients (99%) completing primary outcomes at 1 year; there were 2 deaths due to cancer. Because of the small proportion of missing values (n=3; 2%), we did not perform any data imputation. The omitted cases had similar baseline characteristics as the total sample. No significant differences in baseline characteristics were found among the 4 study groups (TABLE 1). The median duration of lateral epicon-

dylalgia was 16 weeks (range: 6 weeks-4 years) and 76% presented with their first episode.

Four patients did not receive the allocated injection (1 in the placebo group and 3 in the corticosteroid group) due to nonattendance (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 4 physiotherapy sessions; the reasons included nonattendance, moving interstate, or recovery from pain. Of patients in the physiotherapy groups, 70% were compliant with their home exercise program during at least 5 of 7 weeks. Two patients (2%) in the corticosteroid group received an additional corticosteroid injection, and 7 patients (8%) not allocated to physiotherapy, pursued physiotherapy outside of the trial.

Treatment allocation was correctly guessed by the outcome assessor in 53% (20/38) of cases receiving the placebo

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. The corticosteroid injection was 10 mg/mL of triamcinolone acetonide in a 1 mL injection plus 1 mL of 1% lignocaine. The placebo injection was 0.5 mL of 0.9% isotonic saline.

injection only, 39% (16/41) of cases receiving the placebo injection plus physiotherapy, 44% (18/41) of cases receiving the corticosteroid injection only, and 39% (15/38) of cases receiving the corticosteroid injection plus physiotherapy. Of 137 patients, 50 (37%) stated they were confident of which injection they received and correct responses were identified by 71% (20/28) of patients in the corticosteroid injection group and 73% (16/22) of patients in the placebo injection group. No differences were found among the 4 interventions.

Descriptive statistics for the 4 randomized groups for a priori time points (at 4, 26, and 52 weeks) are presented in TABLE 2 and TABLE 3 while additional data are provided online (eTable at http://www.jama.com).

Table 1. Baseline Demographic and Clinical Characteristics

	Corticosteroid Injection		Placebo Injection		
	Alone (n = 43)	Plus Physiotherapy (n = 40)	Alone (n = 41)	Plus Physiotherapy (n = 41)	Total (N = 165)
Age, mean (SD), y	49.3 (8.9)	50.8 (8.5)	49.9 (7.4)	48.7 (7.7)	49.7 (8.1)
Female sex, No. (%)	16 (37)	15 (38)	17 (42)	15 (37)	63 (38)
Duration of symptoms, median (IQR), wk	16 (10-27)	15 (10-26)	16 (8-32)	16 (8-24)	16 (10-26)
Pain score on VAS (range: 0-100 mm), mm[a]					
Resting, median (IQR)	4.5 (0-18)	9 (0-15)	9 (0-22)	7 (0-11)	7.5 (0-15)
Worst, mean (SD)	62.0 (20.3)	59.0 (15.8)	62.4 (19.8)	63.2 (18.0)	61.7 (18.5)
Score, mean (SD)					
Pain and disability on PRTEE (range: 0-100)[b]	42.0 (14.4)	38.1 (13.8)	41.6 (14.4)	36.4 (13.3)	39.5 (14.1)
Health-related quality of life (EuroQol 5ED range: 0-1)[c]	0.68 (0.20)	0.74 (0.09)	0.74 (0.13)	0.74 (0.12)	0.73 (0.14)

Abbreviations: IQR, interquartile range; PRTEE, Patient-Rated Tennis Elbow Evaluation; VAS, visual analog scale.
[a] A higher score indicates a higher level of pain.
[b] A score of 100 represents worst imaginable pain with a very significant functional disability.
[c] A score of 1 represents perfect health.

Primary Outcomes

There was no interaction between injection (corticosteroid vs placebo) and physiotherapy (yes vs no) at 1 year ($P=.99$). Corticosteroid injection demonstrated lower complete recovery or much improvement at 1 year compared with placebo injection (68/82 [83%] vs 78/81 [96%], respectively; RR, 0.86 [99% CI, 0.75 to 0.99]; NNT, −7.5 [99% CI, −150.9 to −3.7]; $P=.01$) and greater recurrence (44/81 [54%] vs 10/81 [12%]; RR, 0.23 [99% CI, 0.10 to 0.51]; NNT, −2.4 [−4.3 to −1.8]; $P<.001$) (FIGURE 2).

There were no differences between physiotherapy and no physiotherapy at 1 year for complete recovery or much improvement (73/80 [91%] vs 73/83 [88%], respectively; RR, 1.04 [99% CI, 0.90-1.19]; $P=.56$) or recurrence (23/80 [29%] vs 31/82 [38%]; RR, 1.31 [99% CI, 0.73-2.35]; $P=.25$) (Figure 2).

Secondary Outcomes

At 4 Weeks. There was a significant interaction at 4 weeks between corticosteroid injection and physiotherapy for complete recovery or much improvement ($P=.01$; Figure 2), worst pain ($P<.001$), pain and disability ($P<.001$), and quality of life ($P=.004$) (FIGURE 3).

In the absence of physiotherapy, complete recovery or much improvement was greater following corticosteroid injection compared with the placebo injection (RR, 7.32 [99% CI, 2.1-25.5]; NNT, 1.6 [99% CI, 1.3-2.9]; $P<.001$). Corticosteroid injection alone was associated with large benefits for all secondary outcomes: worst pain (SMD, 1.77 [99% CI, 1.09-2.44]; $P<.001$), resting pain (SMD, 0.87 [99% CI, 0.28-1.46]; $P<.001$), pain and disability (SMD, 1.81 [99% CI, 1.13-2.48]; $P<.001$), and quality of life (SMD, 1.14 [99% CI, 0.53-1.76]; $P<.001$).

When physiotherapy was present, there were no differences between the corticosteroid injection and placebo injection groups for the outcomes of complete recovery or much improvement (RR, 1.73 [99% CI, 0.97 to 3.08]; $P=.02$), worst pain (SMD, 0.51 [99% CI, −0.08 to 1.09]; $P=.03$), resting pain (SMD, 0.21 [99% CI, −0.36 to 0.79]; $P=.29$), and quality of life (SMD, 0.30 [99% CI, −0.27 to 0.88]; $P=.08$). There was a medium-sized benefit for pain and disability when physiotherapy was combined with corticosteroid injection (vs placebo injection combined with physiotherapy) (SMD, 0.63 [99% CI, 0.04 to 1.22]; $P<.001$).

Physiotherapy plus corticosteroid (vs corticosteroid alone) had no effect on the outcomes of complete recovery or much improvement (RR, 0.95 [99% CI, 0.65 to 1.38]; $P=.57$), worst pain (SMD, −0.38 [99% CI, −0.96 to 0.19]; $P=.10$), resting pain (SMD, −0.05 [99% CI, −0.62 to 0.52]; $P=.91$), pain and disability (SMD, −0.40 [99% CI, −0.97 to 0.18]; $P=.12$), and quality of life (SMD, −0.30 [99% CI, −0.88 to 0.27]; $P=.29$).

Patients who received the placebo injection plus physiotherapy had greater complete recovery or much improvement compared with the no physiotherapy group (RR, 4.00 [99% CI, 1.07-15.00]; NNT, 3.4 [99% CI, 2.0-21.4], $P=.004$), and medium-sized benefits for worst pain (SMD, 0.88 [99% CI, 0.29-1.48]; $P<.001$), resting pain (SMD, 0.60 [99% CI, 0.02-1.19]; $P=.01$), and pain and disability (SMD, 0.77 [99% CI, 0.18-1.37]; $P=.001$).

At 26 Weeks. There were no significant interaction effects at 26 weeks. The corticosteroid injection demonstrated lower complete recovery or much improvement compared with the placebo injection (45/82 [55%] vs 69/81 [85%], respectively; RR, 0.79 [99% CI, 0.62 to 0.99]; NNT −5.5 [99% CI, −123.1 to −2.9]; $P<.001$).

Table 2. Descriptive Statistics for Primary Outcomes and Adverse Events

	Corticosteroid Injection				Placebo Injection			
	Alone		Plus Physiotherapy		Alone		Plus Physiotherapy	
	No. of Events/ Total Sample	% (99% CI)	No. of Events/ Total Sample	% (99% CI)	No. of Events/ Total Sample	% (99% CI)	No. of Events/ Total Sample	% (99% CI)
Complete recovery or much improvement								
At 4 wk	30/42	71 (52-85)	27/40	68 (47-83)	4/41	10 (3-28)	16/41	39 (22-59)
At 26 wk	24/43	56 (37-73)	21/39	54 (34-72)	33/40	83 (63-93)	36/41	89 (69-96)
At 52 wk	36/43	84 (65-93)	32/39	82 (62-93)	37/40	93 (75-98)	41/41	100 (86-100)
Recurrence at 52 wk[a]	23/42	55 (36-73)	21/39	54 (34-72)	8/40	20 (9-40)	2/41	5 (1-21)
Adverse events								
Pain after injection								
Severe	0/43	0 (0-13)	0/40	0 (0-14)	1/41	2 (0-18)	3/41	7 (2-25)
Lasting >48 h	2/43	5 (1-21)	1/40	3 (0-18)	8/41	20 (8-39)	5/41	12 (4-31)
Lasting >7 d	1/43	2 (0-17)	0/40	0 (0-14)	1/41	2 (0-18)	3/41	7 (2-25)
Pain after physiotherapy								
Lasting >24 h	NA		2/40	5 (1-22)	NA		3/41	7 (2-25)
Lasting >7 d	NA		1/40	3 (0-18)	NA		0/41	0 (0-14)
Skin depigmentation	3/43	7 (2-24)	1/40	3 (0-18)	0/41	0 (0-14)	0/41	0 (0-14)
Subcutaneous atrophy	2/43	5 (1-21)	1/40	3 (0-18)	0/41	0 (0-14)	0/41	0 (0-14)
Hand numbness	1/43	2 (0-17)	0/40	0 (0-14)	1/41	2 (0-18)	0/41	0 (0-14)
Vomiting	0/43	0 (0-13)	0/40	0 (0-14)	0/41	0 (0-14)	1/41	2 (0-18)
Swelling	0/43	0 (0-13)	0/40	0 (0-14)	0/41	0 (0-14)	1/41	2 (0-18)
Skin irritation from taping	NA		1/40	3 (0-18)	NA		0/41	0 (0-14)
Nonprotocol treatment								
Analgesic or NSAID medication	17/43	40 (23-59)	9/40	23 (10-43)	16/41	39 (22-59)	7/41	17 (7-36)
Medical consultation	10/43	23 (11-43)	5/40	13 (4-31)	6/41	15 (5-34)	2/41	5 (1-21)

Abbreviations: NA, data not applicable; NSAID, nonsteroidal anti-inflammatory drug.
[a]Defined as complete recovery or much improvement at 4 or 8 weeks, but not at 8, 12, 26, or 52 weeks.

Table 3. Scores on Pain Scales and Health-Related Quality-of-Life Questionnaire by Time

	Scores on Pain Scales, Median (IQR)[a]			
	Corticosteroid Injection		Placebo Injection	
	Alone	Plus Physiotherapy	Alone	Plus Physiotherapy
Worst pain on VAS, mm				
At 4 wk	5 (0-22)	1 (10-25)	56 (30-70)	35 (15-45)
At 26 wk	10 (2-58)	2.0 (5.5-48.5)	5 (0-22)	5 (0-10)
At 52 wk	0.5 (0-10.0)	5 (0-18)	0 (0-5)	0 (0-3)
Resting pain on VAS, mm				
At 4 wk	0 (0-2)	0 (0-0)	5 (0-22)	0 (0-10)
At 26 wk	0 (0-14)	0 (0-8)	0 (0-0)	0 (0-0)
At 52 wk	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
Pain and disability on PRTEE				
At 4 wk	6.5 (2.5-12.0)	7.0 (2.5-16.0)	31.8 (20.5-43.8)	22.5 (9.5-28.5)
At 26 wk	10.5 (3.5-22.5)	7.5 (4.0-21.0)	6.5 (2.8-12.0)	3.5 (1.0-6.0)
At 52 wk	3.0 (0-8.5)	3 (0-6)	0.5 (0-5.8)	1.0 (0-4.5)
Health-related quality of life on EuroQol 5ED[b]				
At 4 wk	0.91 (0.87-0.96)	0.89 (0.84-0.95)	0.77 (0.71-0.83)	0.84 (0.79-0.89)
At 26 wk	0.83 (0.78-0.89)	0.88 (0.83-0.94)	0.90 (0.84-0.96)	0.93 (0.89-0.98)
At 52 wk	0.93 (0.89-0.98)	0.92 (0.85-1.00)	0.94 (0.89-0.98)	0.97 (0.93-1.00)

Abbreviations: PRTEE, Patient-Rated Tennis Elbow Evaluation; VAS, visual analog scale.
[a]Unless otherwise indicated.
[b]Quality of life expressed as mean (99% CI).

Patients who received the corticosteroid injection had medium-sized deficits for worst pain (SMD, −0.77 [99% CI, −1.19 to −0.35]; $P<.001$), resting pain (SMD, −0.61 [99% CI, −1.02 to −0.19]; $P<.001$), pain and disability (SMD, −0.76 [99% CI, −1.18 to −0.34]; $P<.001$), and quality of life (SMD, −0.55 [99% CI, −0.97 to −0.14]; $P=.004$).

Physiotherapy compared with no physiotherapy demonstrated no effects on the outcomes of complete recovery or much improvement (57/80 [71%] vs 57/83 [69%], respectively; RR, 1.22 [99% CI, 0.97 to 1.53]; $P=.84$), worst pain (SMD, 0.04 [99% CI, −0.36 to 0.44]; $P=.79$), resting pain (SMD, 0.05 [99% CI, −0.35 to 0.46]; $P=.74$), pain and disability (SMD, 0.07 [99% CI, −0.33 to 0.48]; $P=.25$), and quality of life (SMD, 0.33 [99% CI, −0.08 to 0.74]; $P=.13$).

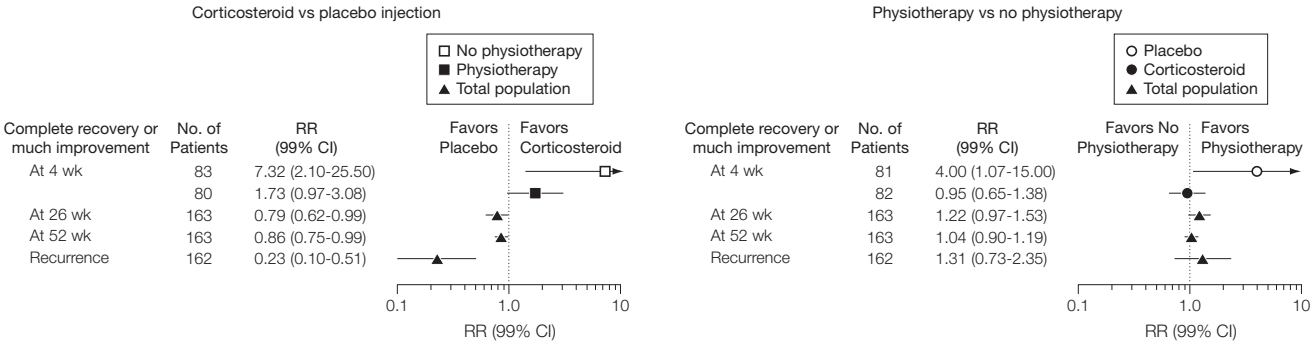
At 52 Weeks. There were no significant interaction effects at 52 weeks. Consistent with the primary out-

comes, worst pain remained significantly higher for the corticosteroid injection compared with the placebo injection at 1 year, although the differences were small (SMD, −0.44 [99% CI, −0.85 to −0.03]; *P*=.005).

No differences were found between the 2 injection types for resting pain (SMD, −0.17 [99% CI, −0.58 to 0.23]; *P*=.29), pain and disability (SMD, −0.36 [99% CI, −0.76 to 0.05]; *P*=.02), and quality of life (SMD, −0.22 [99% CI, −0.63 to 0.18]; *P*=.21). Physiotherapy compared with no physiotherapy demonstrated no effects on the outcomes of complete recovery or much improvement (73/80 [91%] vs 73/83 [88%], respectively; RR, 1.04 [99% CI, 0.90 to 1.19]; *P*=.56), worst pain (SMD, −0.07 [99% CI, −0.47 to 0.34]; *P*=.66), resting pain (SMD, −0.07 [99% CI, −0.47 to 0.34]; *P*=.64), pain and disability (SMD, 0.05 [99% CI, −0.36 to 0.45]; *P*=.51), and quality of life (SMD, 0.00 [99% CI, −0.40 to 0.40]; *P*=.70).

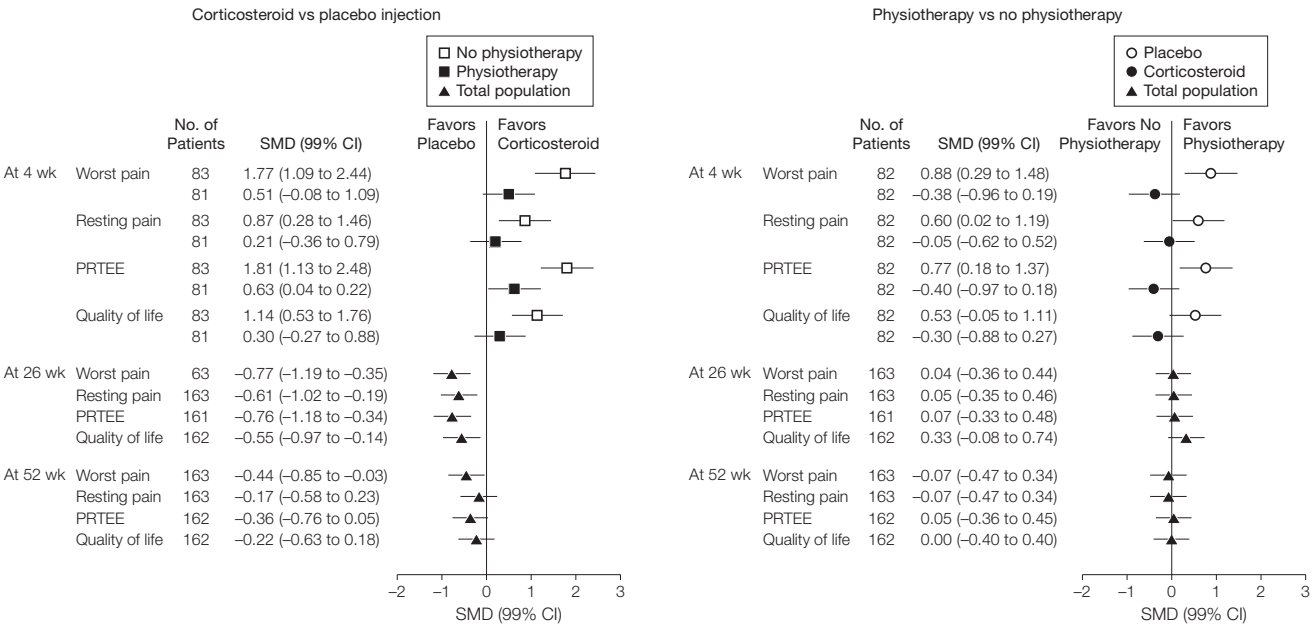
Use of an analgesic or anti-inflammatory medication did not differ between injection of corticosteroid or placebo (26/83 [31%] vs 23/82 [28%], respectively; *P*=.57), whereas it was less frequently used by patients allocated to physiotherapy compared with those not allocated to physiotherapy (16/81 [20%] vs 33/84 [39%], respectively; NNT, 5.1 [99% CI, 2.8-84.8]; *P*=.008) (Table 2). Nonprotocol medical consultations did not significantly differ between injection types (corticosteroid vs placebo) (15/83 [18%] vs 8/82 [10%], respectively; *P*=.13) or physiotherapy (yes vs no) (7/81 [9%] vs 16/84 [19%], respectively; *P*=.06).

Figure 2. Relative Risk (RR) of Complete Recovery or Much Improvement and 1-Year Recurrence



Scores greater than 1 indicate outcomes in favor of the corticosteroid injection or physiotherapy.

Figure 3. Standardized Mean Differences (SMDs) for Secondary Outcomes



Positive scores indicate outcomes in favor of the corticosteroid injection or physiotherapy. PRTEE indicates Patient-Rated Tennis Elbow Evaluation.

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 1 year after receiving an injection in patients with unilateral lateral epicondylalgia. Eight weeks of multimodal physiotherapy, comprising elbow mobilization with movement and exercise, did not optimize long-term outcomes, but was beneficial in the short-term in the absence of corticosteroid injection. Significantly fewer patients receiving physiotherapy consumed an analgesic or antiinflammatory medication.

A systematic review (search date: March 2010)[4] reported 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 alone compared with placebo injection. Notwithstanding this, differences in complete recovery or much improvement were not significant when patients also received physiotherapy, a finding echoed by Newcomer et al[7] in a study of lateral epicondylalgia of less than 6 weeks' duration. This evidence does not support the clinical practice of using corticosteroid injection to facilitate active rehabilitation.

Results were reversed at 6 months, with corticosteroid injection displaying moderate to large inferior effects consistently across measures of complete recovery or much improvement, pain, disability, and quality of life. At 1 year, most patients (90%) in the study reported complete recovery or much improvement, which reflects the natural history of the condition.[3,5,9] However, in patients who received the corticosteroid injection, significantly fewer reported being completely recovered or much improved, and worst pain levels remained higher 1 year after receipt of the corticosteroid injection.

Furthermore, more than half of all patients treated with a single corticosteroid injection experienced a recurrence, a substantially greater proportion than the placebo group. In clinical terms, this represented an NNT of 2.4 (ie, for every 2 or 3 people treated with corticosteroid injection vs placebo, 1 person experienced recurrence during the year). While high recurrence rates after corticosteroid injection have been previously reported,[3,5] our current study provides evidence that it may be the effect of the medication and not merely a manifestation of the condition 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,[25] but the prevailing opinion is that no histological evidence of acute inflammation has been documented,[11,12,26,27] although inflammatory cells have been detected by newer studies using immunohistochemistry.[28,29] 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.[27]

Recurrence may occur because corticosteroids do not address key features of tendinopathy, which is traditionally thought to be associated with overuse, cumulative trauma weakening the collagen cross-linking, and the noncollagenous matrix and vascular elements of the tendon.[27] Corticosteroids might be deleterious to the tendon through an effect on fibroblasts' role in collagen and extracellular matrix protein production.[25] 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.[3,27]

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 or 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 the corticosteroid, it provided short-term benefit across all outcomes, as well as the lowest recurrence rates (4.9%) and 100% complete recovery or much improvement at 1 year.

At 4 weeks, the magnitude of improvement on the Patient-Rated Tennis Elbow Evaluation, 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 for 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 the consistency of findings across validated condition-specific and generic outcomes.

This study also has limitations. First, results may not be generalized to other clinical contexts in which treatments are reserved for specific individuals or combined in a different sequence or manner (for example, injection of patients who have not recovered after a period of wait and see or physiotherapy; or treatment with physiotherapy in patients with poor late outcomes after injection).

Second, it is common 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 epicondy-

lalgia without significant neck or other upper limb symptoms, which needs to be considered in applying our findings to clinical practice.

Third, we excluded patients who had received recent treatment or repeated corticosteroid injection because inclusion may have biased the findings. Excluding patients who received prior corticosteroid injection suggests that our findings are the best-case scenario in terms of long-term outcomes. A previous study found a poorer long-term effect of repeated corticosteroid injection (mean of 4.3 injections in 18 months) on reduction of pain vs treatment with a single injection.[30]

Fourth, it should be acknowledged that while the assessor was blinded to treatments received by the patients, the lack of patient and therapist blinding to physiotherapy might have biased estimates of the benefit of physiotherapy, the mitigation of which should be considered in future study designs.[31]

In conclusion, among patients with chronic unilateral lateral epicondylalgia, there was a worse clinical outcome 1 year after corticosteroid injection compared with placebo, despite its short-term benefits. Physiotherapy did not result in any significant 1-year differences.

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Author Contributions: Dr 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, Brooks, Vicenzino.
Acquisition of data: Coombes, Bisset, Vicenzino.
Analysis and interpretation of data: Coombes, Bisset, Brooks, Khan, Vicenzino.
Drafting of the manuscript: Coombes, Brooks, Vicenzino.
Critical revision of the manuscript for important intellectual content: Coombes, Bisset, Brooks, Khan, Vicenzino.
Statistical analysis: Coombes, Khan, Vicenzino.
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Study supervision: Bisset, Vicenzino.
Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Bisset reported receiving payment from the Australian Catholic University for lectures on physiotherapy assessment and management of the elbow. Dr Vicenzino reported receiving payment from various conferences for lectures on a range of musculoskeletal and sports health-related topics, including lateral epicondylalgia, physiotherapy, injections, and exercise; receiving travel reimbursement when serving as a keynote speaker or when providing workshop presentations; and receiving royalties from Elsevier for a book that covers some of the treatments in the treatment program described in this article. No other authors reported disclosures.
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