A Network Meta-Analysis of Randomized Controlled Trials Directed at Treating Lateral Epicondylalgia

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ORIGINAL RESEARCH

Abstract

Background: Lateral epicondylosis is the most prevalent cause of lateral elbow pain, occurring in 4 per 1000 patients. The aim of most treatments is to reduce inflammation even with histological evidence demonstrating that lateral epicondylosis is a non-inflammatory condition.

Objective: To determine the relative merits of the different regimens used to diminish lateral epicondylosis pain using a mixed treatment comparison/network meta-analysis (NMA).

Methods: A thorough literature search was performed. The eligibility criteria for this mixed treatment comparison were: randomized controlled clinical trials; human subjects; working age population (16 to 70 years); the outcome measure was an objective pain assessment; measured at a 1- to 3-month follow-up. The NMA were performed using the GeMTC user interface for automated NMA utilizing a Bayesian Hierarchical Model of random effects. The evaluation of confidence in the findings from NMA was performed using a semi-automated platform called CINeMA (Confidence in Network Meta-Analysis).

Results: The model suggests that articulation technique is the most effective measure for decreasing lateral epicondylalgia followed by topical nitrates, acupuncture, kinesiology taping and low-level laser therapy, respectively. Muscle energy technique, local corticosteroid injection, prolotherapy and counterforce bracing displayed a trend toward being less effective than placebo.

Conclusions: The results suggest that the most effective modalities for improving lateral epicondylalgia are those that decrease muscle tone and those that improve circulation, while measures meant to decrease inflammation appear to be of no or limited benefit.

Introduction

Lateral epicondylitis is better defined as a progression of tendinosis rather than tendinitis. Therefore, it is more appropriate to call this disorder lateral epicondylosis. Lateral epicondylosis is the most prevalent cause of lateral elbow pain, occurring in 4 per 1000 patients.

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Disclosures: none reported.

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Submitted for publication February 6, 2020; manuscript accepted for publication April 14, 2021; final revision received July 19, 2021.

Each year 1% to 3% of adults are diagnosed with lateral epicondylosis, with an equal prevalence between men and women. Patients usually present in the fourth to fifth decade of life with symptoms more commonly in their dominant elbow.[1]

The results of a 2016 meta-analysis strongly support the hypothesis of an association between strenuous manual tasks utilizing the elbow and/or hand with a combination of force at work and incidence of lateral epicondylosis.[2] The extensor carpi radialis brevis origin is felt to be the specific site of pathology. The origin of the extensor carpi radialis brevis tendon impinges on the lateral edge of the capitellum during elbow extension and flexion in vulnerable individuals. Patients frequently describe slow onset and increase of pain with no history of a discernable traumatic event. Pain is characteristically located anterior or slightly distal to the lateral epicondyle. Patients often report a sharp pain intensified by carrying items in their hand, particularly with the hand in prone position. On physical examination, patients report tenderness to palpation over the origin of the extensor carpi radialis brevis.[1]

Histological specimens initially exhibit fibroblastic hyperplasia, followed by vascular hyperplasia and the production of abnormal

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collagen. The accumulation of internal microtears leads to a cellular response characterized by a noninflammatory, degenerative and avascular process termed angiofibroblastic tendinosis.[1] Although the precise cause is still unknown, several theories have been suggested. One theory proposes that 2 regions of hypovascularity identified within the common extensor origin on the lateral epicondyle play a role in the etiology of lateral epicondylitis.[3] These hypovascular regions are posited to impede the normal inflammatory cascade and healing response to microtearing in this region.

Even with histological evidence demonstrating that lateral epicondylosis is a non-inflammatory condition, the aim of most treatments is still to reduce inflammation. Hundreds of trials have been performed to compare treatments for lateral epicondylosis, but because each has compared only 2 or 3 treatments, it is difficult to integrate information on the relative efficacy of all tested therapeutic measures. This study will examine treatments for lateral epicondylosis using a mixed treatment comparison/network meta-analysis to determine the relative merits of the different regimens used to diminish lateral epicondylosis pain.

Methods

A thorough literature search was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. Studies were identified by searching the PubMed, OVID, Cochrane Central, PEDro and OSTMED.DR databases, scanning reference lists of articles, and using the Canadian Agency for Drugs and Technologies in Health (CADTH) grey literature checklist. The search was limited to English language publications. The dates of coverage for each database search were from the creation of the database through August 2018. The following search terms were used to search each database: *lateral epicondylitis*; *clinical trial*; *human*; and *English*.

Eligibility assessment was performed in an unblinded standardized manner by a single reviewer. The eligibility criteria for this mixed treatment comparison were: randomized controlled clinical trials; human subjects; working age population (16 to 70 years); the outcome measure was an objective pain assessment; measured at a 1- to 3-month follow-up.

The author developed a data extraction sheet based on the National Institute for Health and Care Excellence (NICE) methodology checklist for reviewing randomized controlled trials. Information was extracted from each included trial on: characteristics of trial participants (including age and sex); type of intervention and the comparison (placebo, nothing, or another intervention); type of outcome measure; presented results; and potential sources of bias. The outcome measure chosen for this network meta-analyses was the Visual Analogue Scale (VAS).

As there was only one reviewer, the NICE checklist was adapted to add a quantifiable measure for determining suitability. Each category of bias was initially assigned a numerical value of 1. One point was added for each "No" or "Unclear" answer. The remaining value is the quality measure for the given type of potential bias (4 = high risk, 3 = moderate-high risk, 2 = low-moderate risk, 1 = low risk). The quality measures were summed and then divided by 4. The average of quality measures for studies were then rounded to the nearest integer. Studies with an average value of 3 were eliminated from the network meta-analysis due to a high risk of bias. The remaining studies with low and moderate risk of bias were used to generate the mixed treatment comparison model, and to perform Confidence In the results of Network Meta-Analysis (CINeMA) within-study bias assessment.

The network meta-analysis (NMA) was performed using the GeMTC user interface for automated NMA utilizing a Bayesian Hierarchical Model of random effects.[4,5] The primary outcome measure was the mean difference in VAS scores. Heterogeneity priors were determined automatically by the software. Multi-arm trials were handled automatically by GeMTC by modelling treatment effects relative to the reference treatment using a multivariate normal distribution where the covariance elements are assumed have homogeneous between-study variances treatment contrasts.[6]

The network geometry is presented visually as a figure. Potential scale reduction factor (PSRF) was calculated to assess for adequate convergence within the network. The results were presented in a league table of the relative effect of each treatment compared to each other treatment, on the scale of measurement implied by the chosen outcome measure. The relative effects were also assessed visually using the relative effects plots. In both cases, placebo was selected as the baseline against which all other treatments were compared. Differences between treatments were considered significant (at the 5% level) if their confidence intervals did not overlap the no-effect line. In addition to relative effects, the Bayesian analysis produced rank probabilities, or the probability for each treatment to obtain each possible rank in terms of their relative effects. This assessment generated a rank probabilities table.

The evaluation of confidence in the findings from network meta-analysis was performed using a semi-automated platform called CINeMA (Confidence in Network Meta-Analysis). It is based on a methodological framework described by the Grading of Recom-

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mendations Assessment, Development and Evaluation (GRADE) Working Group.[7] CINeMA considers 6 domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence.

The mean difference of 2 was assigned as the value of the clinically important size of effect. Thus, relative effect estimates below -2.000 and above 2.000 were considered clinically important.

Results

The search of PubMed, OVID, Cochrane Central, PEDro, and OSTMED.DR databases, as well as the grey literature checklist search, provided at total of 823 citations. After removing duplicate citations, 474 remained. Of these, 444 studies were excluded because, after reviewing the abstracts, it appeared that these studies clearly did not meet the defined inclusion criteria. The full text of the remaining 30 citations was examined and data was extracted. Each study was evaluated using the NICE checklist and 4 studies were excluded (Table 1). Each study had a mean quality measure greater than 2.5. One study exhibited moderate to high risk of bias in each NICE checklist category. One study displayed moderate to high risk of selection, performance, and detection biases, and low to moderate risk of attrition bias. One study had high risk of performance bias, and moderate to high risk of selection, attrition, and detection biases. Finally, one study exhibited high risk of selection bias, and moderate to high risk of attrition and detection biases. This left 26 studies for the NMA (Figure 1).

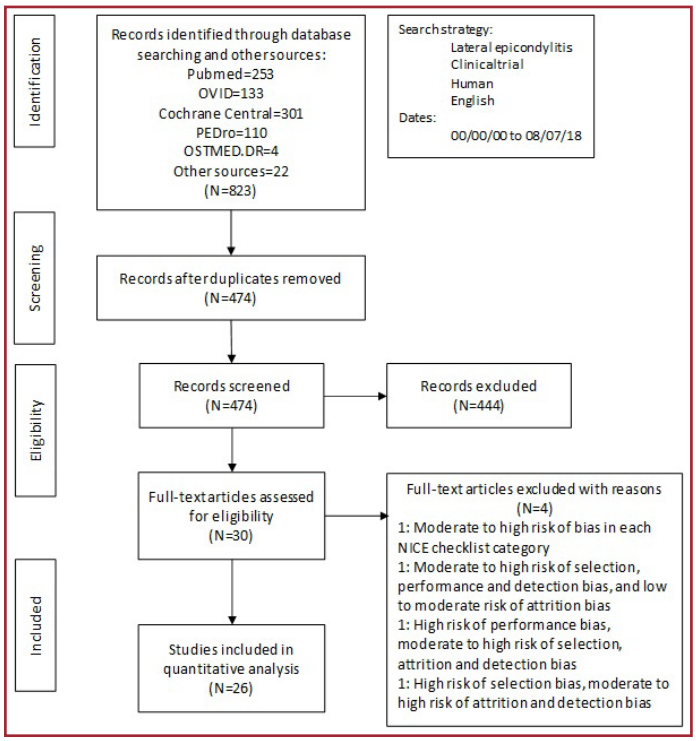

Figure 1. *Study selection flow diagram*

Study	Selection bias	Performance bias	Attrition bias	Detection bias	CINeMA RoB
Akin (2010)[8]	1	1	2	1	1
Arik (2014)[9]	3	3	1	3	2
Blanchette (2011)[10]	3	4	3	3	3
Capan (2016)[11]	1	2	1	1	1
Carayannopoulos (2011)[12]	2	1	1	1	1
Chung (2004)[13]	2	2	2	1	2
Chung (2005)[14]	4	2	3	3	3
Emanet (2010)[15]	1	2	1	1	1
Eraslan (2018)[16]	2	2	2	2	2
Fink (2002)[17]	1	2	1	3	2
Gautam (2015)[18]	4	4	1	1	2
Gosens (2011)[19]	1	2	1	1	1
Gündüz (2012)[20]	1	4	1	1	2
Hsu (2016)[21]	1	4	2	3	2
Küçükşen (2013)[22]	1	3	1	1	1
Labelle (1997)[23]	2	1	1	2	1
Lam (2007)[24]	2	2	1	3	2
Lundeberg (1988)[25]	4	2	1	1	2
Murtezani (2015)[26]	1	3	1	1	1
Öken (2008)[27]	3	3	1	3	2
Ozden (2014)[28]	3	2	1	1	2
Peerbooms (2010)[29]	1	1	1	1	1
Peterson (2011)[30]	1	3	1	1	1
Shakeri (2018)[31]	1	2	1	2	1
Spacca (2005)[32]	2	3	1	3	2
Speed (2002)[33]	3	2	1	1	2
Thanasas (2011)[34]	1	2	1	1	1
Uygur (2017)[35]	3	3	3	3	3
Wolf (2011)[36]	2	2	1	3	2
Yadav (2015)[37]	3	3	2	3	3

Low risk of bias	1	Low risk of bias	1
Low to moderate risk of bias	2	Moderate risk of bias	2
Moderate to high risk of bias	3	High risk of bias	3
High risk of bias	4		

Table 1. *Risk of bias within studies as per NICE methodology checklist for randomized controlled trials for this network meta-analysis.*

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Figure 2 shows the network geometry comparing treatments for lateral epicondylosis. Each of the PSRF point estimates were less than 1.05 indicating acceptable convergence of the network comparisons (Table 2). The NMA included a total of 1,078 lateral epicondylosis patients who received active treatment. The most commonly studied treatments were local corticosteroid injection (n = 9 trials; patients receiving treatment = 257), extracorporeal shockwave therapy (n = 6 trials; patients receiving treatment = 160), and platelet rich plasma injection (n = 4; patients receiving treatment = 129). Placebo was used as a comparator arm in 13 studies (patients receiving placebo = 351). Local corticosteroid injection (n = 6 trials; number of patients = 188), wait-and-see (n = 2 trials; number of patients = 74), whole blood injection (n = 2 trials; number of patients 54), and extracorporeal shockwave therapy (n = 1 trial; number of patients = 15) were also used as comparator arms. None of the studies were sponsored by pharmaceutical or biotechnology companies.

Table 3 presents the available demographics and mean VAS values for each included study. Mean age of included studies ranged from 31.62 years to 52.5 years. The interventions included pharmacological and manual medicine treatments. The male to female ratio of the included studies ranged from 0 to 0.98. Mean VAS scores ranged from 0.05 to 6.7.

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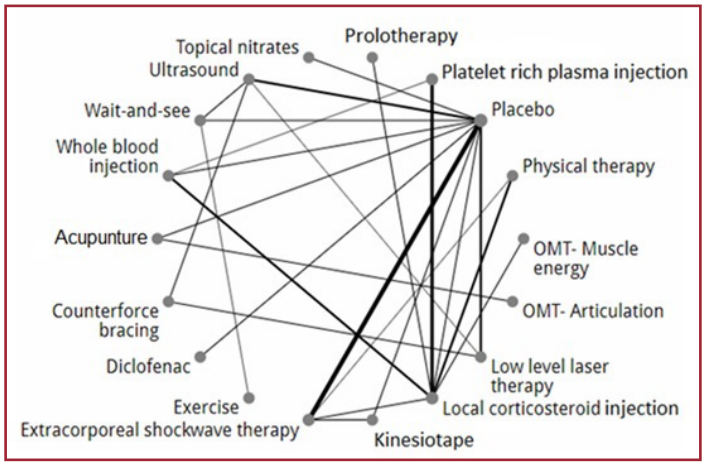

Figure 2. *Presentation of network geometry for lateral epicondylalgia treatments.*

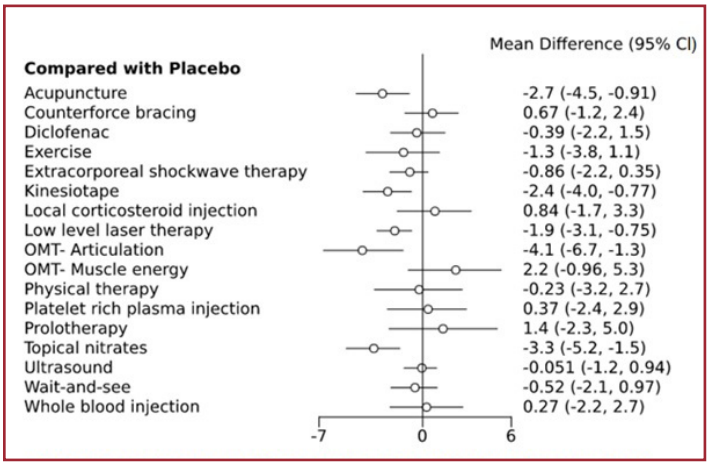

Figure 3. *Relative effects plot of the mean difference of visual analog score of pain for studied treatments of lateral epicondylalgia compared to placebo.*

Parameter	Standard deviation	Time-series S.E.	Potential scale reduction factor (PSRF)	
			Point estimate	97.5% quantile
Acupuncture, OMT: Articulation	1.0844	0.012593	0.99982	1
Extracorporeal Shockwave Therapy, Physical Therapy	1.4745	0.027196	1.0043	1.014
Laser (LLLT), Counterforce Bracing	0.88696	0.0099448	1.0001	1.0005
Local Corticosteroid Injection, OMT: Muscle energy	1.0349	0.011685	1.001	1.003
Local Corticosteroid Injection, Platelet Rich Plasma Injection	0.52339	0.0061688	1.001	1.0032
Local Corticosteroid Injection, Prolotherapy	1.4415	0.018161	1.0006	1.0019
Placebo, Acupuncture	0.98804	0.011095	1.0002	1.0008
Placebo, Extracorporeal Shockwave Therapy	0.61596	0.0076447	0.9999	1.0004
Placebo, Kinesiotape	0.86462	0.0098911	1.0011	1.0039
Placebo, Laser (LLLT)	0.65278	0.0072995	1.0004	1.0004
Placebo, Local Corticosteroid Injection	1.2231	0.023525	1.0027	1.009
Placebo, NSAID: Diclofenac	1.0129	0.011321	1.0002	1.001
Placebo, Topical Nitrates	0.99327	0.011099	0.99998	1.0004
Placebo, Ultrasound	0.60917	0.0068884	1.0008	1.0029
Placebo, Wait-and-see	0.8352	0.0093356	1.0006	1.0025
Placebo, Whole Blood Injection	1.2561	0.022798	1.0023	1.0075
Wait-and-see, Exercise	1.0526	0.012151	1.0003	1.0016
Random effects standard deviation	0.30566	0.0051789	1.0009	1.0022

Table 2. *Per-parameter convergence diagnostics.*

Study	Treatment	Mean age	Male : Female	Mean VAS	Standard Deviation	Sample size
Akin 2010[8]	Ultrasound	46.7	.76	4.8	2.3	30
	Placebo	45.4	.84	5.4	2.2	30
Arik 2014[9]	Local corticosteroid injection	46.7	.44	3.7	1.9	40
	Whole blood injection	43.7	.48	2.1	1.1	40
Capan 2016[11]	Extracorporeal shockwave therapy	48.4	.3	3.3	2.4	23
	Placebo	46.2	.14	4.6	3.1	22
Carayannopoulos 2011[12]	Prolotherapy	49		2.38	1.6	8
	Local corticosteroid injection	46		1.83	2.85	9
Chung 2004[13]	Extracorporeal shockwave therapy	46.8	.72	2.4	4.5	31
	Placebo	45.5	.84	3.3	4.47	29
Emanet 2010[15]	Low level laser therapy	45.52	.35	2.53	1.35	25
	Placebo	49.52	.22	3.95	2.12	25
Eraslan 2018[16]	Kinesiotape	48.5		1.8	1.8	15
	Extracorporeal shockwave therapy	48		3.5	2.2	15
Fink 2002[17]	Acupuncture	52.5	.81	6.01	1.36	20
	Placebo	51.6	.52	8.73	1.3	20
Gautam 2015[18]	Platelet rich plasma injection			1.8	0.6	15
	Local corticosteroid injection			1.7	0.5	15
Gosens 2011[19]	Platelet rich plasma injection	46.8	.98	4.02	2.75	51
	Local corticosteroid injection	47.3	.98	4.55	2.71	49
Gündüz 2012[20]	Local corticosteroid injection	45.7	.34	2	8.55	20
	Extracorporeal shockwave therapy	44.9	.34	2	8.3	20
	Physical therapy	43.6	.22	2	8.55	19
Hsu 2016[21]	OMT- Articulation	44.81	.22	1.597	1.26	16
	Acupuncture	45.89	.18	2.968	2.15	19
Küçükşen 2013[22]	OMT- Muscle energy	46.17	.77	4.38	2.08	40
	Local corticosteroid injection	43.78	.81	2.98	2.49	40
Labelle 1997[23]	Diclofenac			2.31	2.63	64
	Placebo			2.7	2.74	64
Lam 2007[24]	Low level laser therapy	46.1	.38	1.48	1.36	21
	Placebo	48.9	.3	4.28	2.11	18
Lundeberg 1988[25]	Ultrasound			2.8	0.3	33
	Placebo			2.4	0.3	33
	Wait-and-see			2.1	0.5	33
Murtezani 2015[26]	Physical therapy	51.6	.67	1.8	0.9	25
	Local corticosteroid injection	51	.51	2.9	0.9	24
Öken 2008[27]	Low level laser therapy	45.1	.14	4.3	1.2	20
	Counterforce bracing	44.5	.1	6.7	2.2	20
	Ultrasound	46.5	.18	5.7	0.09	18
Ozden 2014[28]	Topical nitrates	42.9	.55	3.15	1.53	20
	Placebo	43.5	.63	6.45	0.75	20
Peerbooms 2010[29]	Platelet rich plasma injection	46.9	.88	3.87	2.72	49
	Local corticosteroid injection	47.3	.96	4.42	2.71	51
Peterson 2011[30]	Exercise	49.1	.13	1.95	2.11	40
	Wait-and-see	47.4	.97	2.7	2.79	41
Shakeri 2018[31]	Kinesiotape	37.6	0	2.53	1.89	15
	Placebo	31.62	0	4.66	1.89	15
Spacca 2005[32]	Extracorporeal shockwave therapy	46.82	.68	0.05	3.41	31
	Placebo	47.03	.68	5	7.5	31
Speed 2002[33]	Extracorporeal shockwave therapy	46.5	.81	4.79	3.14	40
	Placebo	48.2	.6	5.15	3.24	35
Thanasas 2011[34]	Platelet rich plasma injection	35.9	.22	1.92	0.88	14
	Whole blood injection	36.6	.13	2.78	0.87	14
Wolf 2011[36]	Local corticosteroid injection			3	3	9
	Placebo			3	2.5	9
	Whole blood injection			4	2.7	10

Table 3. *Assessed studies and available population characteristics.*

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Table 4 presents comparisons of the studied interventions as the mean difference and 95% confidence intervals. Each cell in the league table represents the effect of column-defining intervention relative to the row-defining intervention. The relative effects plot graphically presents the VAS mean difference and 95% confidence intervals for each treatment relative to placebo (Figure 3). The model results suggest that OMT-articulation, topical nitrates, acupuncture, and kinesiology taping outperform placebo, with 2 being the defined clinically important mean difference. Low-level laser therapy nears clinical importance, with its mean difference being -1.9 relative to placebo. However, it should be noted that the 95% confidence interval for each of these treatments cross into the -2.000 to 0 range.

Rank probabilities substantiated that OMT-articulation was the most effective treatment for lateral epicondylalgia presented in this mixed treatment comparison (Table 5). The next most effective treatment was topical nitrates, followed by acupuncture, kinesiology taping, and low-level laser therapy, respectively. However, there is some uncertainty of rank order for ranks 9 through 14.

The results of the Confidence in Network Meta-Analysis (CINeMA) assessment are presented in Table 6. The scores from the risk-of-bias assessment used for selecting studies to be included in the NMA

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Acupuncture	3.395 (0.512, 6.100)	1.397 (-2.109, 4.738)	1.594 (-0.763, 3.780)	0.265 (-2.318, 2.727)	0.842 (-1.561, 3.103)	3.217 (-0.034, 6.192)	2.344 (-0.555, 5.163)	-1.345 (-3.499, 0.809)	4.604 (0.755, 8.162)	2.133 (-1.426, 5.522)	2.722 (0.688, 4.626)	2.683 (-0.648, 5.747)	3.774 (-0.497, 7.832)	-0.577 (-3.358, 2.074)	2.599 (0.192, 4.797)	2.167 (-0.495, 4.730)	2.853 (-0.276, 5.882)
	Counterforce Bracing	-1.956 (-5.208, 1.074)	-1.783 (-4.125, 0.397)	-3.139 (-5.735, -0.595)	-2.545 (-4.343, -0.781)	-0.164 (-3.340, 2.857)	-1.019 (-3.811, 1.823)	-4.724 (-8.087, -1.179)	1.244 (-2.585, 4.902)	-1.256 (-4.732, 2.171)	-0.663 (-2.537, 1.293)	-0.704 (-3.935, 2.447)	0.410 (-3.924, 4.420)	-3.952 (-6.656, -1.154)	-0.771 (-2.673, 1.034)	-1.210 (-3.630, 1.232)	-0.530 (-3.670, 2.564)
		Exercise	0.176 (-2.785, 3.176)	-1.156 (-4.302, 2.123)	-0.581 (-3.434, 2.392)	1.817 (-1.802, 5.379)	0.928 (-2.442, 4.490)	-2.756 (-6.679, 1.356)	3.200 (-0.973, 7.356)	0.726 (-3.179, 4.622)	1.316 (-1.316, 4.165)	1.258 (-2.447, 5.015)	2.345 (-2.209, 6.773)	-1.989 (-5.299, 1.374)	1.198 (-1.484, 3.936)	0.767 (-1.350, 2.934)	1.444 (-2.008, 5.106)
			Extracorporeal Shockwave Therapy	-1.331 (-3.012, 0.422)	-0.760 (-2.475, 1.023)	1.644 (-1.000, 4.112)	0.766 (-1.529, 3.112)	-2.943 (-5.960, 0.316)	3.048 (-0.312, 6.217)	0.528 (-2.412, 3.460)	1.140 (-0.022, 2.349)	1.092 (-1.614, 3.722)	2.217 (-1.676, 5.842)	-2.172 (-4.419, 0.148)	1.036 (-0.688, 2.739)	0.587 (-1.513, 2.706)	1.285 (-1.336, 3.789)
				Kinesiotape	0.595 (-1.547, 2.639)	2.973 (0.076, 5.749)	2.095 (-0.567, 4.737)	-1.609 (-4.858, 1.790)	4.360 (0.742, 7.714)	1.866 (-1.351, 5.073)	2.478 (0.816, 4.088)	2.433 (-0.537, 5.346)	3.524 (-0.501, 7.401)	-0.839 (-3.346, 1.735)	2.370 (0.181, 4.377)	1.925 (-0.472, 4.302)	2.609 (-0.269, 5.427)
					Laser (LLLT)	2.387 (-0.378, 5.062)	1.508 (-0.822, 3.934)	-2.179 (-5.254, 0.976)	3.791 (0.356, 7.182)	1.293 (-1.840, 4.390)	1.887 (0.655, 3.168)	1.851 (-1.039, 4.628)	2.963 (-1.096, 6.750)	-1.420 (-3.701, 0.961)	1.772 (0.249, 3.263)	1.332 (-0.688, 3.315)	2.019 (-0.661, 4.737)
						Local Corticosteroid Injection	-0.845 (-3.933, 2.360)	-4.560 (-8.153, -0.671)	1.398 (-0.668, 3.459)	-1.094 (-2.829, 0.688)	-0.481 (-2.847, 1.964)	-0.540 (-1.574, 0.521)	0.539 (-2.262, 3.333)	-3.805 (-6.800, -0.657)	-0.618 (-3.257, 2.129)	-1.043 (-3.910, 1.935)	-0.370 (-1.590, 0.995)
							NSAID: Diclofenac	-3.705 (-7.253, -0.111)	2.284 (-1.596, 5.880)	-0.232 (-3.752, 3.236)	0.366 (-1.695, 2.413)	0.321 (-3.076, 3.539)	1.433 (-2.818, 5.526)	-2.933 (-5.706, -0.191)	0.266 (-2.175, 2.613)	-0.161 (-2.957, 2.484)	0.499 (-2.739, 3.650)
								OMT: Articulation	5.970 (1.516, 10.123)	3.493 (-0.681, 7.456)	4.077 (1.123, 6.950)	4.021 (0.033, 7.738)	5.123 (0.329, 9.629)	0.764 (-2.773, 4.198)	3.953 (0.702, 7.046)	3.512 (0.126, 6.849)	4.207 (0.396, 7.858)
									OMT: ME	-2.485 (-5.168, 0.255)	-1.904 (-4.939, 1.403)	-1.936 (-4.240, 0.403)	-0.834 (-4.331, 2.545)	-5.224 (-8.721, -1.460)	-2.015 (-5.356, 1.520)	-2.441 (-5.943, 1.253)	-1.755 (-4.164, 0.749)
										Physical Therapy	0.599 (-2.262, 3.511)	0.559 (-1.565, 2.550)	1.635 (-1.680, 4.916)	-2.727 (-6.121, 0.749)	0.482 (-2.648, 3.604)	0.049 (-3.295, 3.442)	0.722 (-1.405, 2.908)
											Placebo	-0.050 (-2.626, 2.474)	1.058 (-2.728, 4.602)	-3.297 (-5.234, -1.369)	-0.108 (-1.409, 1.061)	-0.551 (-2.297, 1.110)	0.129 (-2.308, 2.513)
												Platelet Rich Plasma Injection	1.088 (-1.944, 4.023)	-3.277 (-6.364, -0.036)	-0.084 (-2.858, 2.745)	-0.495 (-3.468, 2.613)	0.162 (-1.139, 1.600)
													Prolotherapy	-4.350 (-8.323, -0.153)	-1.173 (-4.870, 2.732)	-1.594 (-5.483, 2.462)	-0.926 (-3.949, 2.199)
														Topical Nitrates	3.198 (0.826, 5.447)	2.748 (0.149, 5.317)	3.459 (0.282, 6.452)
															Ultrasound	-0.438 (-2.071, 1.287)	0.258 (-2.463, 2.907)
																Wait-and-see	0.671 (-2.230, 3.676)
																	Whole Blood Injection

Table 4. *GeMTC Comparison of the included interventions: mean difference (95% CI). Each cell gives the effect of the column-defining intervention relative to the row-defining intervention.*

(continued from page 22)

were inputted into CINeMA to assess for bias for each mixed and indirect comparison in the final model. None of the comparisons were deemed to have "major concerns." However, most of the comparisons were considered to have "some concerns." The comparison-adjusted funnel plot demonstrated considerable visual asymmetry relative to the funnel shape (Figure 4). CINeMA found "no concerns" for indirectness for any of the network comparisons. However, several studies failed to report age and/or sex for the studied populations. Therefore, the indirectness determination was manually upgraded to "some concerns" for the comparisons made by each of these studies (Table 6). Imprecision was found to be of "some concern" or of "major concern" for many of the mixed and indirect comparisons (Table 6). Imprecision is also suggested by the uncertainty in the relative ranking order of the examined treatments, as noted in Table 5. Several mixed comparisons had "some concerns" for important heterogeneity. As a result, many of the indirect comparisons also had "some concerns" for important heterogeneity (Table 6 and Table 7). The platelet-rich-plasma injection: whole blood injection and the ultrasound: wait-and-see comparisons were deemed to have "major concerns" for important heterogeneity. CINeMA did not find any concerns related to incoherence for any of the comparisons included in this model. This statistic suggests the model met the assumption for transitivity.

(continued on page 28)

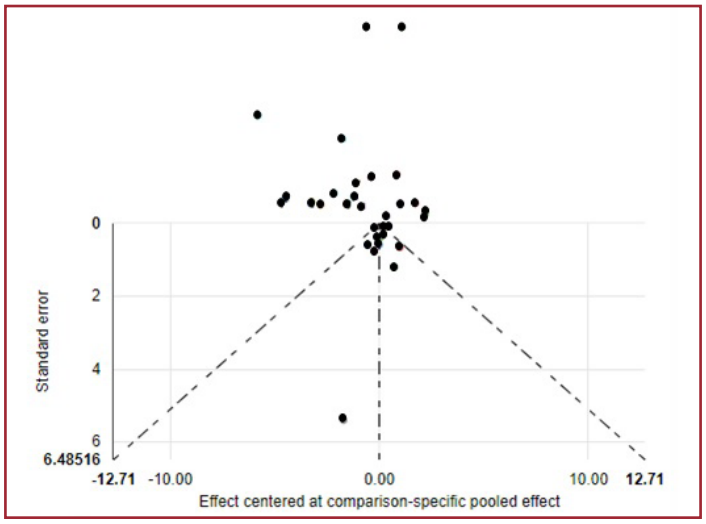

Figure 4. *Comparison-adjusted funnel plot*

	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7	Rank 8	Rank 9	Rank 10	Rank 11	Rank 12	Rank 13	Rank 14	Rank 15	Rank 16	Rank 17	Rank 18
Acupuncture	0.020	0.234	**0.295**	0.197	0.105	0.055	0.033	0.020	0.012	0.010	0.007	0.005	0.003	0.002	0.002	0.002	0.000	0.000
Counterforce Bracing	0.001	0.000	0.000	0.001	0.003	0.008	0.014	0.027	0.033	0.044	0.052	0.092	0.090	0.078	0.095	0.139	**0.172**	0.151
Exercise	0.026	0.041	0.059	0.089	0.120	**0.132**	0.115	0.087	0.066	0.048	0.044	0.040	0.030	0.026	0.023	0.024	0.019	0.011
Extracorporeal Shockwave Therapy	0.000	0.002	0.010	0.026	0.085	0.190	**0.208**	0.157	0.110	0.072	0.052	0.035	0.023	0.017	0.008	0.004	0.001	0.000
Kinesiotape	0.057	0.140	0.206	**0.245**	0.159	0.084	0.046	0.024	0.016	0.009	0.007	0.003	0.002	0.001	0.001	0.001	0.001	0.000
Laser (LLLT)	0.008	0.031	0.086	0.176	**0.273**	0.186	0.101	0.061	0.031	0.018	0.014	0.008	0.004	0.002	0.001	0.001	0.000	0.000
Local Corticosteroid Injection	0.000	0.000	0.000	0.002	0.005	0.006	0.014	0.026	0.035	0.049	0.065	0.076	0.082	0.119	0.181	**0.232**	0.103	0.006
NSAID: Diclofenac	0.002	0.005	0.009	0.020	0.036	0.066	0.089	0.093	**0.099**	0.085	0.086	0.085	0.066	0.060	0.058	0.056	0.054	0.033
OMT: Articulation	**0.619**	0.189	0.076	0.041	0.024	0.015	0.009	0.007	0.006	0.004	0.003	0.002	0.002	0.001	0.001	0.001	0.001	0.001
OMT: ME	0.000	0.000	0.001	0.002	0.002	0.004	0.006	0.005	0.007	0.010	0.016	0.019	0.025	0.028	0.040	0.075	0.234	**0.526**
Physical Therapy	0.011	0.018	0.031	0.045	0.060	0.083	0.088	0.091	**0.093**	0.078	0.071	0.081	0.092	0.055	0.048	0.033	0.018	0.005
Placebo	0.000	0.000	0.000	0.000	0.000	0.000	0.005	0.025	0.063	0.128	**0.165**	0.147	0.129	0.121	0.108	0.074	0.031	0.005
Platelet Rich Plasma Injection	0.001	0.004	0.008	0.013	0.022	0.037	0.056	0.072	0.078	0.087	0.086	0.093	0.118	**0.140**	0.107	0.055	0.021	0.003
Prolotherapy	0.004	0.006	0.008	0.011	0.014	0.022	0.024	0.031	0.031	0.035	0.030	0.040	0.050	0.054	0.064	0.102	**0.240**	0.234
Topical Nitrates	0.251	**0.325**	0.201	0.113	0.052	0.025	0.011	0.007	0.006	0.003	0.003	0.002	0.003	0.001	0.000	0.000	0.000	0.000
Ultrasound	0.000	0.000	0.001	0.001	0.004	0.015	0.032	0.062	0.108	**0.140**	0.136	0.102	0.096	0.095	0.087	0.076	0.038	0.009
Wait-and-see	0.000	0.002	0.005	0.012	0.023	0.050	0.113	**0.152**	0.139	0.105	0.085	0.077	0.069	0.058	0.047	0.034	0.022	0.008
Whole Blood Injection	0.001	0.002	0.004	0.008	0.013	0.023	0.036	0.056	0.070	0.075	0.081	0.095	0.118	**0.144**	0.128	0.093	0.046	0.008

Table 5. *Rank probabilities table for studied treatments of lateral epicondylalgia. Numbers in bold type are the highest rank probability for each treatment.*

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision*	Heterogeneity**	Incoherence	Confidence rating
Mixed evidence								
Acupuncture:OMT- Articulation	1	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Acupuncture:Placebo	1	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
Counterforce bracing:Low level laser therapy	1	Some concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	High
Counterforce bracing:Ultrasound	1	Some concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	High
Diclofenac:Placebo	1	No concerns	Suspected	Some concerns	Some concerns	Some concerns	No concerns	High
Exercise:Wait-and-see	1	No concerns	Suspected	No concerns	Some concerns	Some concerns	No concerns	High
Extracorporeal shockwave therapy:Kinesiotape	1	Some concerns	Undetected	Some concerns	Some concerns	No concerns	No concerns	High
Extracorporeal shockwave therapy:Local corticosteroid injection	1	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
Extracorporeal shockwave therapy:Physical therapy	1	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	High
Extracorporeal shockwave therapy:Placebo	4	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	High
Kinesiotape:Placebo	1	No concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	High
Local corticosteroid injection:OMT- Muscle energy	1	No concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	High
Local corticosteroid injection:Physical therapy	2	No concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	High
Local corticosteroid injection:Placebo	1	Some concerns	Suspected	Some concerns	Some concerns	Some concerns	No concerns	High
Local corticosteroid injection:Platelet rich plasma injection	3	No concerns	Suspected	Some concerns	No concerns	Some concerns	No concerns	High
Local corticosteroid injection:Prolotherapy	1	No concerns	Suspected	Some concerns	Major concerns	No concerns	No concerns	High
Local corticosteroid injection:Whole blood injection	2	Some concerns	Suspected	Some concerns	No concerns	Some concerns	No concerns	High
Low level laser therapy:Placebo	2	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	High
Low level laser therapy:Ultrasound	1	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	High
Placebo:Topical nitrates	1	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
Placebo:Ultrasound	2	Some concerns	Undetected	Some concerns	No concerns	Some concerns	No concerns	High
Placebo:Wait-and-see	1	Some concerns	Undetected	Some concerns	Some concerns	No concerns	No concerns	High
Placebo:Whole blood injection	1	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	High
Platelet rich plasma injection:Whole blood injection	1	No concerns	Undetected	No concerns	No concerns	Major concerns	No concerns	High
Ultrasound:Wait-and-see	1	Some concerns	Undetected	Some concerns	No concerns	Major concerns	No concerns	High
Indirect evidence								
Acupuncture:Counterforce bracing	0	Some concerns		No concerns	No concerns	Some concerns	No concerns	High
Acupuncture:Diclofenac	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
Acupuncture:Exercise	0	Some concerns		No concerns	Some concerns	Some concerns	No concerns	High
Acupuncture:Extracorporeal shockwave therapy	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
Acupuncture:Kinesiotape	0	Some concerns		No concerns	Major concerns	No concerns	No concerns	High
Acupuncture:Local corticosteroid injection	0	Some concerns		No concerns	No concerns	Some concerns	No concerns	High
Acupuncture:Low level laser therapy	0	Some concerns		No concerns	Some concerns	Some concerns	No concerns	High
Acupuncture:OMT- Muscle energy	0	Some concerns		No concerns	No concerns	No concerns	No concerns	High
Acupuncture:Physical therapy	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High

Table 6. *Confidence In the results of Network Meta-Analysis (CINeMA) table of results following the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.*

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision*	Heterogeneity**	Incoherence	Confidence rating
Indirect evidence (continued)								
Acupuncture:Platelet rich plasma injection	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
Acupuncture:Prolotherapy	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
Acupuncture:Topical nitrates	0	Some concerns		No concerns	Some concerns	Some concerns	No concerns	High
Acupuncture:Ultrasound	0	Some concerns		No concerns	No concerns	Some concerns	No concerns	High
Acupuncture:Wait-and-see	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
Acupuncture:Whole blood injection	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
Counterforce bracing:Diclofenac	0	Some concerns		No concerns	Some concerns	Some concerns	No concerns	High
Counterforce bracing:Exercise	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
Counterforce bracing:Extracorporeal shockwave therapy	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
Counterforce bracing:Kinesiotape	0	Some concerns		No concerns	No concerns	Some concerns	No concerns	High
Counterforce bracing:Local corticosteroid injection	0	Some concerns		No concerns	Major concerns	No concerns	No concerns	High
Counterforce bracing:OMT- Articulation	0	Some concerns		No concerns	No concerns	No concerns	No concerns	High
Counterforce bracing:OMT- Muscle energy	0	Some concerns		No concerns	Major concerns	No concerns	No concerns	High
Counterforce bracing:Physical therapy	0	Some concerns		No concerns	Some concerns	Some concerns	No concerns	High
Counterforce bracing:Placebo	0	Some concerns		No concerns	Some concerns	Some concerns	No concerns	High
Counterforce bracing:Platelet rich plasma injection	0	Some concerns		No concerns	Major concerns	No concerns	No concerns	High
Counterforce bracing:Prolotherapy	0	Some concerns		No concerns	Major concerns	No concerns	No concerns	High
Counterforce bracing:Topical nitrates	0	Some concerns		No concerns	No concerns	No concerns	No concerns	High
Counterforce bracing:Wait-and-see	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
Counterforce bracing:Whole blood injection	0	Some concerns		No concerns	Major concerns	No concerns	No concerns	High
Diclofenac:Exercise	0	No concerns		No concerns	Major concerns	No concerns	No concerns	High
Diclofenac:Extracorporeal shockwave therapy	0	No concerns		No concerns	Some concerns	Some concerns	No concerns	High
Diclofenac:Kinesiotape	0	No concerns		No concerns	Some concerns	No concerns	No concerns	High
Diclofenac:Local corticosteroid injection	0	Some concerns		No concerns	Major concerns	No concerns	No concerns	High
Diclofenac:Low level laser therapy	0	No concerns		No concerns	Some concerns	No concerns	No concerns	High
Diclofenac:OMT- Articulation	0	Some concerns		No concerns	No concerns	Some concerns	No concerns	High
Diclofenac:OMT- Muscle energy	0	No concerns		No concerns	Some concerns	Some concerns	No concerns	High
Diclofenac:Physical therapy	0	No concerns		No concerns	Major concerns	No concerns	No concerns	High
Diclofenac:Platelet rich plasma injection	0	No concerns		No concerns	Major concerns	No concerns	No concerns	High
Diclofenac:Prolotherapy	0	No concerns		No concerns	Major concerns	No concerns	No concerns	High
Diclofenac:Topical nitrates	0	Some concerns		No concerns	No concerns	Some concerns	No concerns	High
Diclofenac:Ultrasound	0	No concerns		No concerns	Some concerns	Some concerns	No concerns	High
Diclofenac:Wait-and-see	0	Some concerns		No concerns	Major concerns	No concerns	No concerns	High
Diclofenac:Whole blood injection	0	Some concerns		No concerns	Major concerns	No concerns	No concerns	High
Exercise:Extracorporeal shockwave therapy	0	Some concerns		No concerns	Major concerns	No concerns	No concerns	High

Table 6 (continued). *Confidence In the results of Network Meta-Analysis (CINeMA) table of results following the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.*

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision*	Heterogeneity**	Incoherence	Confidence rating
Indirect evidence (continued)								
Exercise:Kinesiotape	0	No concerns		No concerns	Some concerns	Some concerns	No concerns	High
Exercise:Local corticosteroid injection	0	Some concerns		No concerns	Some concerns	Some concerns	No concerns	High
Exercise:Low level laser therapy	0	Some concerns		No concerns	Major concerns	No concerns	No concerns	High
Exercise:OMT- Articulation	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
Exercise:OMT- Muscle energy	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
Exercise:Physical therapy	0	Some concerns		No concerns	Major concerns	No concerns	No concerns	High
Exercise:Placebo	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
Exercise:Platelet rich plasma injection	0	Some concerns		No concerns	Major concerns	No concerns	No concerns	High
Exercise:Prolotherapy	0	Some concerns		No concerns	Some concerns	Some concerns	No concerns	High
Exercise:Topical nitrates	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
Exercise:Ultrasound	0	Some concerns		No concerns	Some concerns	Some concerns	No concerns	High
Exercise:Whole blood injection	0	Some concerns		No concerns	Some concerns	Some concerns	No concerns	High
Extracorporeal shockwave therapy:Low level laser therapy	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
Extracorporeal shockwave therapy:OMT-Articulation	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
Extracorporeal shockwave therapy:OMT-Muscle energy	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
Extracorporeal shockwave therapy:Platelet rich plasma injection	0	Some concerns		No concerns	Some concerns	Some concerns	No concerns	High
Extracorporeal shockwave therapy:Prolotherapy	0	Some concerns		No concerns	Some concerns	Some concerns	No concerns	High
Extracorporeal shockwave therapy:Topical nitrates	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
Extracorporeal shockwave therapy:Ultrasound	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
Extracorporeal shockwave therapy:Wait-and-see	0	Some concerns		No concerns	Some concerns	Some concerns	No concerns	High
Extracorporeal shockwave therapy:Whole blood injection	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
Kinesiotape:Local corticosteroid injection	0	Some concerns		No concerns	No concerns	Some concerns	No concerns	High
Kinesiotape:Low level laser therapy	0	No concerns		No concerns	Some concerns	Some concerns	No concerns	High
Kinesiotape:OMT- Articulation	0	Some concerns		No concerns	Some concerns	Some concerns	No concerns	High
Kinesiotape:OMT- Muscle energy	0	No concerns		No concerns	No concerns	No concerns	No concerns	High
Kinesiotape:Physical therapy	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
Kinesiotape:Platelet rich plasma injection	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
Kinesiotape:Prolotherapy	0	No concerns		No concerns	Some concerns	No concerns	No concerns	High
Kinesiotape:Topical nitrates	0	Some concerns		No concerns	Some concerns	Some concerns	No concerns	High
Kinesiotape:Ultrasound	0	Some concerns		No concerns	No concerns	Some concerns	No concerns	High
Kinesiotape:Wait-and-see	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
Kinesiotape:Whole blood injection	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
Local corticosteroid injection:Low level laser therapy	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
Local corticosteroid injection:OMT-Articulation	0	Some concerns		No concerns	No concerns	No concerns	No concerns	High
Local corticosteroid injection:Topical nitrates	0	Some concerns		No concerns	No concerns	No concerns	No concerns	High

Table 6 (continued). *Confidence In the results of Network Meta-Analysis (CINeMA) table of results following the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.*

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision*	Heterogeneity**	Incoherence	Confidence rating
Indirect evidence (continued)								
Local corticosteroid injection:Ultrasound	0	Some concerns		No concerns	Some concerns	Some concerns	No concerns	High
Local corticosteroid injection:Wait-and-see	0	Some concerns		No concerns	Some concerns	Some concerns	No concerns	High
Low level laser therapy:OMT- Articulation	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
Low level laser therapy:OMT- Muscle energy	0	Some concerns		No concerns	No concerns	Some concerns	No concerns	High
Low level laser therapy:Physical therapy	0	Some concerns		No concerns	Some concerns	Some concerns	No concerns	High
Low level laser therapy:Platelet rich plasma injection	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
Low level laser therapy:Prolotherapy	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
Low level laser therapy:Topical nitrates	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
Low level laser therapy:Wait-and-see	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
Low level laser therapy:Whole blood injection	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
OMT- Articulation:OMT- Muscle energy	0	Some concerns		No concerns	No concerns	No concerns	No concerns	High
OMT- Articulation:Physical therapy	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
OMT- Articulation:Placebo	0	Some concerns		No concerns	No concerns	No concerns	No concerns	High
OMT- Articulation:Platelet rich plasma injection	0	Some concerns		No concerns	No concerns	Some concerns	No concerns	High
OMT- Articulation:Prolotherapy	0	Some concerns		No concerns	No concerns	Some concerns	No concerns	High
OMT- Articulation:Topical nitrates	0	Some concerns		No concerns	Major concerns	No concerns	No concerns	High
OMT- Articulation:Ultrasound	0	Some concerns		No concerns	No concerns	No concerns	No concerns	High
OMT- Articulation:Wait-and-see	0	Some concerns		No concerns	No concerns	Some concerns	No concerns	High
OMT- Articulation:Whole blood injection	0	Some concerns		No concerns	No concerns	Some concerns	No concerns	High
OMT- Muscle energy:Physical therapy	0	No concerns		No concerns	No concerns	Some concerns	No concerns	High
OMT- Muscle energy:Placebo	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
OMT- Muscle energy:Platelet rich plasma injection	0	No concerns		No concerns	Some concerns	No concerns	No concerns	High
OMT- Muscle energy:Prolotherapy	0	No concerns		No concerns	Major concerns	No concerns	No concerns	High
OMT- Muscle energy:Topical nitrates	0	Some concerns		No concerns	No concerns	No concerns	No concerns	High
OMT- Muscle energy:Ultrasound	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
OMT- Muscle energy:Wait-and-see	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
OMT- Muscle energy:Whole blood injection	0	No concerns		No concerns	Some concerns	No concerns	No concerns	High
Physical therapy:Placebo	0	Some concerns		No concerns	Major concerns	No concerns	No concerns	High
Physical therapy:Platelet rich plasma injection	0	No concerns		No concerns	Some concerns	Some concerns	No concerns	High
Physical therapy:Prolotherapy	0	No concerns		No concerns	Some concerns	Some concerns	No concerns	High
Physical therapy:Topical nitrates	0	Some concerns		No concerns	Some concerns	No concerns	No concerns	High
Physical therapy:Ultrasound	0	Some concerns		No concerns	Major concerns	No concerns	No concerns	High
Physical therapy:Wait-and-see	0	Some concerns		No concerns	Major concerns	No concerns	No concerns	High
Physical therapy:Whole blood injection	0	No concerns		No concerns	Some concerns	Some concerns	No concerns	High
Placebo:Platelet rich plasma injection	0	Some concerns		No concerns	Major concerns	No concerns	No concerns	High
Placebo:Prolotherapy	0	Some concerns		No concerns	Major concerns	No concerns	No concerns	High

Table 6 (continued). *Confidence In the results of Network Meta-Analysis (CINeMA) table of results following the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.*

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision*	Heterogeneity**	Incoherence	Confidence rating
Indirect evidence (continued)								
Platelet rich plasma injection:Prolotherapy	0	No concerns		No concerns	Some concerns	Some concerns	No concerns	High
Platelet rich plasma injection:Topical nitrates	0	Some concerns		No concerns	No concerns	Some concerns	No concerns	High
Platelet rich plasma injection:Ultrasound	0	Some concerns		No concerns	Major concerns	No concerns	No concerns	High
Platelet rich plasma injection:Wait-and-see	0	Some concerns		No concerns	Major concerns	No concerns	No concerns	High
Prolotherapy:Topical nitrates	0	Some concerns		No concerns	No concerns	Some concerns	No concerns	High
Prolotherapy:Ultrasound	0	Some concerns		No concerns	Major concerns	No concerns	No concerns	High
Prolotherapy:Wait-and-see	0	Some concerns		No concerns	Major concerns	No concerns	No concerns	High
Prolotherapy:Whole blood injection	0	No concerns		No concerns	Major concerns	No concerns	No concerns	High
Topical nitrates:Ultrasound	0	Some concerns		No concerns	No concerns	No concerns	No concerns	High
Topical nitrates:Wait-and-see	0	Some concerns		No concerns	No concerns	Some concerns	No concerns	High
Topical nitrates:Whole blood injection	0	Some concerns		No concerns	No concerns	Some concerns	No concerns	High
Ultrasound:Whole blood injection	0	Some concerns		No concerns	Major concerns	No concerns	No concerns	High
Wait-and-see:Whole blood injection	0	Some concerns		No concerns	Major concerns	No concerns	No concerns	High

Clinically important mean deference defined as 2
Relative effect estimates below-2.000 and above 2.000 are considered clinically important
CI = confidence interval; PI = prediction interval
*Imprecision: If 95% CI of NMA estimate does not cross clinically important effect then NO CONCERNS; If 95% CI of NMA estimate extends into clinically important effects than SOME CONCERNS; If 95% CI of NMA estimate extends into clinically important effects in both directions then MAJOR CONCERNS.
**Heterogeneity: If 95% CI and 95% PI agree in relation to clinically important effect then NO CONCERN; If 95% PI of NMA estimate extends into clinically important effects then SOME CONCERNS; If 95% CI and 95% PI of NMA estimate extend into clinically important effects then MAJOR CONCERNS

Table 6 (continued). *Confidence In the results of Network Meta-Analysis (CINeMA) table of results following the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.*

(continued from page 23)

Discussion

The articulation technique used in the study performed by Hsu et al[21] was aimed at treating an anterior radial head with restricted pronation and biceps brachii hypertonicity. The biceps brachii tendon inserts on the radial tuberosity and functions to flex the elbow and supinate the forearm. Hypertonicity of the biceps brachii leads to supination and anterior dysfunction of the radial head. This dysfunction appears to increase lateral collateral ligament and annular ligament tension. These ligaments blend in with the deep portion of the extensor carpi radialis brevis tendon.[21]

The technique used by Hsu is performed with the patient sitting upright with the involved elbow flexed and forearm fully supinated. The physician stands slightly to the affected side, facing the patient. The physician grasps the affected radial head with his or her thumb and forefinger with the hand closest to the patient's elbow. The thumb is on the anterolateral aspect of the radial head and the forefinger in on the posterior aspect of the radial head. The physician grasps the patient's wrist with the other hand (Figure 5). The physician then simultaneously pronates the forearm, extends the elbow, and internally rotates the radial head by rolling it between the thumb and forefinger. At the point of full elbow extension, the physician plucks the biceps brachii tendon by rapidly extending the thumb that was being used to internally rotate the radial head (Figure 6). This final action is meant to restore the alpha-gamma efferent balance of the biceps brachii muscle. The maneuver is repeated after 30 seconds. The treatment protocol was performed twice per week for 2 weeks.[21] This modality may also be releasing extensor carpi radialis brevis tendon impingement on the lateral edge of the capitellum or impingement of the lateral synovial fringe, as well as correcting radial head dysfunction.

Muscle energy technique was clearly the least effective treatment in this evaluation. The technique used in the study by Küçükşen et al[22] was directed at treating restricted supination. The procedure began with the patient sitting with the elbow flexed 90 degrees, and the physician standing slightly to the affected side facing the patient. The physician stabilized the patient's affected elbow by holding

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Comparison	NMA mean difference (95% CI)	Direct mean difference (95% CI)	Indirect mean difference (95% CI)	Difference of mean differences (95% CI)	P value
Counterforce bracing: Low level laser therapy	2.570 (0.732, 4.408)	2.400 (0.459, 4.341)	4.043 (-1.674, 9.761)	-1.643 (-7.682, 4.395)	0.594
Counterforce bracing: Ultrasound	0.860 (-0.937, 2.657)	1.000 (-0.869, 2.869)	-0.850 (-7.386, 5.685)	1.850 (-4.947, 8.648)	0.594
Extracorporeal shockwave therapy: Kinesiotape	1.301 (-0.310, 2.912)	1.700 (-0.452, 3.852)	0.791 (-1.638, 3.221)	0.908 (-2.337, 4.154)	0.583
Extracorporeal shockwave therapy: Local corticosteroid injection	-1.654 (-4.093, 0.785)	0.000 (-5.462, 5.462)	-2.066 (-4.792, 0.660)	2.066 (-4.039, 8.170)	0.507
Extracorporeal shockwave therapy: Physical therapy	-0.581 (-3.378, 2.217)	0.000 (-5.529, 5.529)	-0.780 (-4.024, 2.463)	0.780 (-5.630, 7.191)	0.811
Extracorporeal shockwave therapy: Placebo	-1.208 (-2.346, -0.070)	-1.426 (-2.688, -0.164)	-0.262 (-2.892, 2.368)	-1.164 (-4.082, 1.753)	0.434
Kinesiotape: Placebo	-2.509 (-4.109, -0.908)	-2.130 (-4.226, -0.034)	-3.038 (-5.517, -0.560)	0.908 (-2.337, 4.154)	0.583
Local corticosteroid injection: Physical therapy	1.073 (-0.518, 2.665)	1.009 (-0.598, 2.617)	4.219 (-7.071, 15.508)	-3.209 (-14.613, 8.194)	0.581
Local corticosteroid injection: Placebo	0.446 (-1.843, 2.734)	0.000 (-3.012, 3.012)	1.054 (-2.465, 4.574)	-1.054 (-5.687, 3.578)	0.655
Local corticosteroid injection: Platelet rich plasma injection	0.536 (-0.418, 1.489)	0.281 (-0.768, 1.330)	1.741 (-0.541, 4.023)	-1.460 (-3.972, 1.051)	0.255
Local corticosteroid injection: Whole blood injection	0.366 (-0.834, 1.566)	0.957 (-0.552, 2.466)	-0.652 (-2.632, 1.328)	1.609 (-0.881, 4.098)	0.205
Low level laser therapy: Placebo	-1.879 (-3.018, -0.740)	-2.080 (-3.438, -0.723)	-1.401 (-3.495, 0.694)	-0.679 (-3.175, 1.817)	0.594
Low level laser therapy: Ultrasound	-1.710 (-2.953, -0.467)	-1.400 (-3.085, 0.285)	-2.079 (-3.920, -0.238)	0.679 (-1.817, 3.175)	0.594
Placebo: Ultrasound	0.170 (-0.909, 1.248)	0.001 (-1.243, 1.245)	0.680 (-1.484, 2.844)	-0.679 (-3.175, 1.817)	0.594
Placebo: Wait-and-see	0.585 (-0.914, 2.084)	0.300 (-1.313, 1.913)	2.388 (-1.670, 6.445)	-2.087 (-6.454, 2.279)	0.349
Placebo: Whole blood injection	-0.080 (-2.404, 2.244)	-1.000 (-3.834, 1.834)	1.809 (-2.251, 5.870)	-2.809 (-7.761, 2.142)	0.266
Platelet rich plasma injection: Whole blood injection	-0.170 (-1.424, 1.084)	-0.860 (-2.587, 0.867)	0.600 (-1.224, 2.424)	-1.460 (-3.972, 1.051)	0.255
Ultrasound: Wait-and-see	0.415 (-1.084, 1.914)	0.700 (-0.913, 2.313)	-1.387 (-5.445, 2.670)	2.087 (-2.279, 6.454)	0.349
$\chi 2$ statistic: 7.261 (7 degrees of freedom), P value: 0.402					

Table 7. *Incoherence assessment.*

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the distal humerus with 1 hand. The physician held the patient's wrist with the other hand and supinated the forearm until met by resistance or discomfort. The patient then performed an isometric forearm pronation effort against an unyielding counterforce for 5 seconds. Then the physician increased forearm supination to the new barrier. After a 5 second pause, the procedure was repeated. This was done 3 to 5 times during each treatment session. The protocol called for performing the technique twice weekly for 4 weeks.[22]

The techniques used in these 2 studies are treating opposing dysfunctions. The Küçükşen et al[22] study failed to provide a justification for treating restricted supination of the radial head. This choice may be the reason for the underperformance of muscle energy technique in the current meta-analysis.

Acupuncture appears to be an effective option. Though the mechanisms underlying the effects of acupuncture have not been fully delineated, acupuncture appears to prompt the release of endogenous opioids in brain-stem, subcortical, and limbic structures. Acupuncture has been shown to increase μ-opioid receptor binding potential for several days in some of the same brain areas and to stimulate limbic and basal forebrain areas involved in pain processing.[38] It also seems to induce pituitary secretion of adrenocorticotropic hormone and cortisol, which may provide systemic anti-inflammatory effects. Acupuncture also seems to act locally by stimulating type I collagen production, releasing adenosine, and increasing local blood flow.[39]

The included studies that investigated the effectiveness of acupuncture for treating lateral epicondylalgia used the same treatment protocol. As local points, they selected one Ashi point, LI 10, and LI 11 over the muscular origin of the lateral extensor group of the forearm, and Lu 5 in the cubital region. As regional points, they selected LI 4 and SJ 5 for the treatment of pain in the upper limb. The needles

Figure 5: *Starting position for articulation procedure of the radial head. The patient sits upright with the involved elbow flexed and forearm supinated. The physician stands on the affected side, facing the patient. The physician grasps the affected radial head with his or her thumb and forefinger. The thumb is on the anterolateral aspect of the radial head and the forefinger in on the posterior aspect of the radial head. The physician grasps the patient's wrist with the other hand.*

Figure 6: *The physician simultaneously pronates the forearm, extends the elbow and internally rotates the radial head by rolling it between the thumb and forefinger. At full elbow extension, the physician plucks the biceps brachii tendon by rapidly extending the thumb that was being used to internally rotate the radial head.*

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were inserted down to the musculature and twisted until the De Qi sensation was felt. The needles remained *in situ* for 25 minutes.[17,21]

Topical nitrate therapy also seemed to be quite effective. It is posited that when glyceryl trinitrate is applied, free nitrite ions are released and converted to nitric oxide. Nitric oxide appears to positively affect fibroblast proliferation, collagen synthesis, and contraction of collagen lattices.[40] Topical nitrate therapy may also produce local vasodilation and improve circulation to the zones of relative hypovascularity within the common extensor tendon.

The treatment group in the included nitrate trial received glyceryl trinitrate (GTN) transdermal patches that delivered 1.25 mg GTN every 24 hours. They used GTN patches (Nitroderm® 5 mg; Novartis) cut into 4 equal parts and applied to the area of maximal tenderness once a day. Patches were worn until the symptoms subsided or up to 6 months.[28]

Kinesiology taping also outperformed placebo in this analysis. Kinesiology taping is thought to lift the skin and increase the subdermal interstitial space, thus increasing blood flow and lymphatic circulation akin to myofascial release.[41] Other proposed mechanisms of action for kinesiology taping are modulation of nociceptive processing and stimulation of cutaneous mechanoreceptors. One of the included studies used the taping method described by Kase in "Clinical therapeutic applications of the Kinesio taping methods."[16,42] The other study used the diamond tape technique for an identified myofascial trigger point.[31,43]

Photobiomodulation using low-level laser therapy is a growing field used to treat many conditions requiring stimulation of healing and restoration of function. Photons of red and near-infrared wavelengths are absorbed by mitochondrial chromophores to stimulate electron transport, adenosine triphosphate and nitric oxide release, blood flow, reactive oxygen species increase, and diverse signaling pathways to increase tissue repair and healing.[44]

The studies included in this analysis used gallium-arsenide lasers that emit 905 nm wavelength light. The pulse frequency of the beams ranged from 1000 Hz to 5000 Hz. The dosages ranged from 1 j/cm^2 for 2 mins per applied point 5 days per week, to 2.4 j/cm^2 for 11 seconds per applied point 3 days per week. Protocols were continued for 3 weeks for each study.[15,24,27]

Each of the remaining treatment modalities had confidence intervals that crossed the zero point. This included the proinflammatory modalities: extracorporeal shockwave therapy, prolotherapy, platelet rich plasma injection, and whole blood injection. This is not surprising as the inflammatory process that facilitates healing also involves mediators that trigger a nociceptive response. This is not meant to imply that these measures impair healing or adversely affect function.

There was insufficient evidence to support the use of physical therapy to decrease pain in this phase of follow-up. Nor was there evidence to support the use of ultrasound or counterforce bracing (tennis elbow band), both commonly used by physical therapists. These findings are supported by a Cochran review noting that there is insufficient evidence for most physiotherapy interventions for lateral epicondylosis,[45] as well as another review determining that no definitive conclusions can be drawn regarding efficacy of orthotic devices for lateral epicondylosis.[46]

The model also suggests that there is insufficient evidence to recommend local corticosteroid injections for the treatment of lateral epicondylosis. This finding is supported by studies that have suggested local corticosteroid injections do not improve function to a measurable degree. There is also evidence that at 12-months, the functional outcomes following local corticosteroid injections are worse than with other options.[47]

The only NSAID study meeting inclusion criteria examined the effectiveness of oral diclofenac. It was found to be no more effective than placebo. Per another Cochrane review, there is limited evidence regarding the benefits or harms of topical or oral NSAIDs in treating lateral elbow pain. Although data from 5 placebo-controlled trials suggest that topical NSAIDs may be beneficial in improving pain (for up to 4 weeks), methodological issues precluded firm conclusions. Evidence of the benefits of oral NSAIDs have been inconsistent.[48]

This study has several limitations. Most of the comparisons in this model had "some concerns" for within study bias. The investigated treatments make it difficult to blind individuals administering care, as well as patients receiving treatment. This inability to "double-blind" increased the risk of performance bias and was the major factor leading to concern for within study bias for most of the model's comparisons. Another contributing factor was that some studies failed to report the age and sex of the participants. While studies at low risk of bias are expected to provide more credible results, it is often impractical to restrict the analysis to such studies. In general, it is not desirable to derive judgements by considering only the risk of bias, as most studies in a network contribute some indirect information to every estimate of a relative treatment effect.

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The funnel plot exhibited significant asymmetry. Such a finding is often attributed to publication bias, but there are other possible explanations.[49] These include other types of reporting bias, such as selective outcome reporting and selective analysis reporting. Asymmetry may also be explained by poor methodological quality leading to spuriously inflated effects in smaller studies, true heterogeneity between comparisons, artifact, or chance.

There are "some concerns" for indirectness or differences in the studied populations. These concerns were not identified by the software but were related to the risk of selection bias for a few of the studies. Imprecision of rank order was noted for several of the treatments. However, the clinical importance is questionable, as none of those treatments performed better than placebo. There were 2 comparisons with "major concerns" of heterogeneity and there were "some concerns" of heterogeneity for several other comparisons. This is common with mixed treatment comparisons. A random effects model was utilized over a fixed effects model to mitigate the effects of anticipated heterogeneity. Despite these shortcomings, the model did meet the assumption of transitivity for each comparison within the model demonstrating "no concerns" for incoherence.

Conclusions

The results of this mixed treatment comparison appear to suggest that the most effective modalities for improving lateral epicondylalgia are those that decrease muscle tone and those that improve circulation, while measures meant to decrease inflammation appear to be of no or limited benefit. This analysis suggests that articulation technique is the most effective measure for decreasing lateral epicondylalgia, followed by topical nitrates, acupuncture, kinesiology taping and low-level laser therapy, respectively. Each of the remaining treatments included in this model appeared to be no better than placebo for improving lateral epicondylosis. Muscle energy technique, local corticosteroid injection, prolotherapy, and counterforce bracing displayed a trend toward being less effective than placebo.

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