Meta-analysis

The Therapeutic Benefits of Saline Solution Injection for Lateral Epicondylitis: A Meta-analysis of Randomized Controlled Trials Comparing Saline Injections With Nonsurgical Injection Therapies

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Purpose: To quantify the effect of saline solution injections on patient-reported outcome measures (PROMs) and to determine whether this effect is clinically relevant by comparing it with minimal clinically important difference (MCID) criteria. **Methods:** A systematic search identified randomized controlled trials of lateral epicondylitis interventions comparing saline solution injections with nonsurgical injection therapies. Among included studies, saline solution was compared with platelet-rich plasma, autologous conditioned plasma, corticosteroid, and botulinum toxin injections. By use of data from included studies, a random-effects model was used to calculate overall mean differences (MDs) in pre- and post-injection PROMs in a pair-wise fashion. Calculated MDs were then compared with MCID criteria. **Results:** Of 458 identified studies, 10 met the inclusion criteria and encompassed 283 patients. At 1, 3, 6, and 12 months, statistically significant improvements in MDs in visual analog scale (VAS) scores were noted as follows: MD of 16.11 (95% confidence interval [CI], 8.29-23.93) at 1 month; MD of 22.50 (95% CI, 11.45-33.55) at 3 months; MD of 40.40 (95% CI, 27.48-53.32) at 6 months; and MD of 47.04 (95% CI, 39.43-54.66) at 12 months. At 6 months, Disabilities of the Arm, Shoulder and Hand scores showed a statistically significant improvement (MD, 23.92; 95% CI, 9.47-38.37). **Conclusions:** Improvements in Disabilities of the Arm, Shoulder and Hand scores at 6 months (23.92) surpassed MCID criteria for conservatively managed upper-extremity musculoskeletal pathology (10.83)—suggesting that saline solution injections have a clinically relevant effect. VAS MCID criteria are poorly established, but VAS scores at 6 and 12 months surpassed MCID criteria for conservative treatments for common orthopaedic conditions. In all but 1 study, no statistically significant difference in PROMs was found between saline solution and non–saline solution injections. **Level of Evidence:** Level II, meta-analysis of Level I and II randomized controlled trials.

The clinical course of lateral epicondylitis is variable, although it frequently responds to conservative management. When left untreated, lateral epicondylitis typically is associated with symptomatic improvement within 6 months to 2 years.[1] Treatment regimens for lateral epicondylitis vary but typically begin with conservative measures such as activity modification, nonsteroidal anti-inflammatory drugs (NSAIDs), bracing, or physiotherapy. If conservative measures fail, injection therapies are often used and may consist of platelet-rich plasma (PRP), autologous combined plasma, botulinum toxin, and glucocorticoids.[2] In randomized controlled trials (RCTs), injection therapies are often compared with a "placebo" saline solution injection. These saline solution injections, however, may have therapeutic benefits themselves. One recent study has shown that saline solution injections have quantifiable and clinically relevant therapeutic effects in patients with knee osteoarthritis.[3] It is hypothesized that this effect in knee osteoarthritis may be due to placebo or due to a biological effect.[3] The benefits of saline solution injections in lateral epicondylitis, however, have not yet been quantified.

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The purposes of this study were to quantify the effect of saline solution injections on patient-reported outcome measures (PROMs) and to determine whether this effect is clinically relevant by comparing it with minimal clinically important difference (MCID) criteria. We hypothesized that saline solution injections would show statistically significant improvements in PROMs in patients with lateral epicondylitis.

It should be noted that MCID criteria have not been established for all of the target PROMs used in this study for lateral epicondylitis. As a result, we compared certain PROMs analyzed in this study with MCIDs of related orthopaedic conditions.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were used to gather literature.[4] For internal validity, 2 reviewers (B.G., S.D.) independently conducted this study's searches on December 18, 2018. In the identification stage of our study, systematic literature searches of the PubMed (which includes MEDLINE databases) and Embase databases were conducted. The search terms used were as follows: "elbow" AND "injection" AND "lateral epicondylitis." Duplicates were removed using the automated duplicate removal feature in EndNote X8 (Clarivate Analytics, Philadelphia, PA). In some cases, Embase and PubMed list the same study record with different capitalization or abbreviations causing the automated duplicate removal feature to fail. In these cases, such duplicated records were removed during the screening stage. Articles were screened using either title or abstract. Studies were excluded if they were not randomized, prospective, saline solution injection placebo-controlled trials of Level I or II evidence published between January 1, 2007, and December 18, 2018. After screening, a full-text reading of non-excluded studies was completed to assess eligibility. Full-text articles were excluded during our eligibility phase if they did not report data regarding saline solution injections or if they were not RCTs. Studies that were not excluded during screening or full-text eligibility assessment were included in our quantitative and/or qualitative synthesis.

During the full-text eligibility phase, 1 supplemental abstract[5] and 1 trial protocol[6] were reviewed. These records appeared to meet our inclusion criteria, and the full-text versions of the completed trials were found[5,7] and reviewed using the aforementioned PRISMA guidelines. In our PRISMA flowchart (Fig 1), these 2 studies are accounted for in the "Additional records identified through other sources" box of the identification stage.[5,7]

From the final included studies, the following information was recorded: PROMs, whether PROMs improved with saline solution injection, and the number of patients who received saline solution injections (Table 1). In 1 study, the number of patients receiving saline solution was unavailable, so the number of elbows was recorded instead.[9] When we calculated the total number of patients receiving saline solution injections at baseline across all included studies, the number of elbows was assumed to equal the number of patients. This assumption was made because most patients with lateral epicondylitis (an estimated 88%) have unilateral lateral epicondylitis.[17]

Statistical Analysis

The following descriptive statistics were recorded or calculated from studies included in our statistical analysis: mean pre- and post-injection PROM scores (1-, 3-, 6-, or 12-month visual analog scale [VAS] score or 6-month Disabilities of the Arm, Shoulder and Hand [DASH] score), associated standard deviations, and the number of patients surveyed at each pre- and post-injection PROM time point. Only VAS scores measuring a patient's general pain were included in our statistical analysis, whereas VAS pain scores asking specifically about pain at rest or with activity were excluded (Table 1 shows each included study's reported PROMs). Other PROMs and time points were not used in the random-effects model because there did not exist 2 or more studies that reported the same PROMs at the same time points.

When VAS scores were reported on a scale from 0 to 10, these scores were scaled to a 0 to 100 scale. Schoffl et al.[10] reported DASH scores as a mean value with a plus/minus range but did not explicitly state whether this plus/minus range was a confidence interval (CI) in their study. Because they stated that they used 2-tailed tests at a 5% α value to test for significance, we assumed this plus/minus range was a 95% CI in our random-effects model. In other cases, if studies that met the PRISMA inclusion criteria did not report descriptive statistics, they were not included in the random-effects model.

By use of the descriptive statistics described earlier, a random-effects model was created to compare pre- and post-injection PROMs in a pair-wise fashion. Our model used an inverse variance approach, reported mean differences (MDs), and used the I^2 statistic to assess heterogeneity among included studies. Data analysis was completed using RevMan software (version 5.3; The Cochrane Collaboration, London, England). MDs from our model were then compared with previously published MCIDs.[18-21]

In addition, to further explore heterogeneity within our models, we calculated 95% predictive intervals using Stata software (version 15.1; StataCorp, College Station, TX). In estimating our τ^2 statistic, we used the 95th percentile t distribution with $k-2$ df (in which k is the number of studies present). Because the

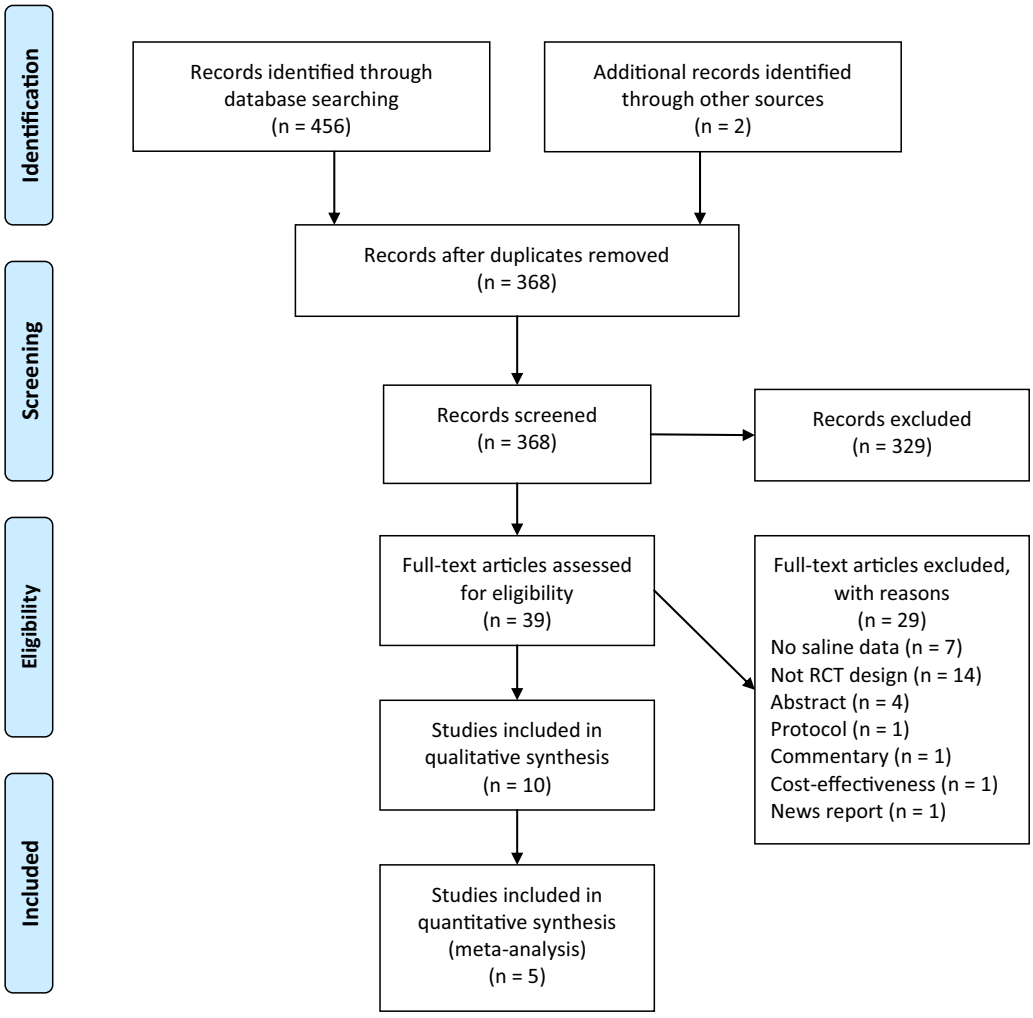

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Consolidated Standards of Reporting Trials (CONSORT) diagram for study selection. (RCT, randomized controlled trial.)

appropriate number of degrees of freedom is debated, we used the recommended compromise of Higgins et al.[22] of $k - 2$ *df*. This method, however, causes models with fewer than 3 pooled studies to have inestimable predictive intervals. As a result, we calculated predictive intervals only for models that used 3 or more studies (VAS score at 3-month follow-up and VAS score at 6-month follow-up).

To our knowledge, there are no well-established MCID criteria for the Oxford Elbow Score (OES), DASH score, and VAS score specific to lateral epicondylitis. For this study, we used DASH MCID criteria for patients with upper-extremity musculoskeletal pathology undergoing physical therapy (i.e., 10.83).[23] We chose MCID criteria for patients undergoing physical therapy because the standard of treatment for epicondylitis is nonoperative. Because no well-established nonoperative MCID criteria existed for the OES, we used OES MCID criteria for patients undergoing orthopaedic elbow surgery (i.e., 18 at 6 months).[19] Finally, because no well-established VAS MCID criteria were available for the elbow or upper extremity, we discuss MDs in VAS scores in the context of commonly encountered MCIDs related to orthopaedics or tendinopathy (osteoarthritic pain, patellofemoral pain, or postoperative pain).[18,20,21] These MCIDs are discussed to give a sense of the clinical importance of VAS score changes but not to definitively establish clinical significance. Statistical significance was defined as $P < .05$.

Risk-of-Bias Assessment

Although we used information only from the saline solution control arms for our quantitative and qualitative analyses, we still conducted a full risk-of-bias assessment for all included studies using the Cochrane Risk of Bias Tool (version 2.0).[24] The Cochrane Risk of Bias Tool has been both validated for the assessment of randomized clinical trials and recognized as being strong in its aim, developmental basis, and transparency

Table 1. Cohort and PROM Data From Included Studies

Authors, Year	PROMs*	No. of Patients at Baseline	Did Primary PROM Show Statistically Significant Improvement From Baseline ($P < .05$)†?	Injection Comparator
Yerlikaya et al.,[8] 2018	VAS (nocturnal pain and pain with motion), PRTEE	30	Yes; $P < .001$ (VAS score for nocturnal pain and for pain during motion at 8 wk of follow-up)	Leukocyte-poor PRP, leukocyte-rich PRP
Creuze et al.,[5] 2018	VAS for "usual pain," VAS for "decrease in quality of life," pain frequency (categorical rating), interference with daily activities, interference with sports activities, interference with professional activities, patient feeling totally cured Primary outcome: "percentage of patients whose initial pain intensity was relieved by > 50% at 3 months post-injection"; (based on VAS "usual pain" scores)	30	Yes; 25% of patients had >50% pain relief at 3 mo of follow-up based on VAS score (95% CI, 10%-44%)	Botulinum toxin
Seetharamaiah et al.,[9] 2017	VAS (unspecified), FPS	30 (elbows)	No; "saline group showed worsening of results in VAS score and in FPS score at 12 weeks and 24 weeks"	PRP, triamcinolone
Schoffl et al.,[10] 2017	DASH	18	No; $P = .13$ (DASH score at 6 mo of follow-up)‡	Autologous conditioned plasma
Montalvan et al.,[11] 2016	VAS (pain), Roles-Maudsley score	25	Yes; $P < .05$ (VAS score for pain at 6 mo and 12 mo of follow-up)	Autologous conditioned plasma
Olaussen et al.,[12] 2015	VAS (separate scores for elbow pain, affected function, and overall complaint), grip-related pain score, satisfaction, 6-point scale of "participants rating themselves much improved or completely recovered"	58	Yes; 24% (99% CI, 10%-39%) of patients rated themselves "much improved or completely recovered on a six-point scale"	Physiotherapy with 2 corticosteroid injections; "wait-and-see" technique (the saline solution arm also included physiotherapy in the study of Olaussen et al.)
Tahririan et al.,[13] 2014	VAS (pain), OES	39	Yes; $P < .05$ (OES at 24 wk)	40-mg Depo-Medrol injection alone; 40-mg Depo-Medrol injection with splinting; saline solution injection with splinting (the saline solution arm analyzed in this table was saline solution injection without splinting)
Krogh et al.,[14] 2013	PRTEE pain, PRTEE disability, tendon thickness, color Doppler activity	20	No; change in PRTEE score for pain from baseline was −1.7 (SE, 2.2) at 3 mo of follow-up	PRP, glucocorticoid
Wolf et al.,[15] 2011	DASH, PRFE, VAS (pain)	9	Yes; $P < .05$ (DASH score at 2 wk)‡	Corticosteroid, autologous blood injection
Espandar et al.,[16] 2010	VAS (pain at rest), grip-related pain score	24	Yes; $P < .05$ (VAS score for pain at rest at 4 wk)‡	Botulinum toxin

CI, confidence interval; DASH, Disabilities of the Arm, Shoulder and Hand; FPS, facial pain scale; OES, Oxford Elbow Score; PRFE, Patient-Related Forearm Evaluation; PROM, patient-reported outcome measure; PRP, platelet-rich plasma; PRTEE, Patient-Rated Tennis Elbow Evaluation; SE, standard error; VAS, visual analog scale.

*Some PROMs were not obtained at baseline or were incompletely obtained across follow-up. For completeness, any PROM that was reported during baseline or follow-up is listed here.

†If no PROM was specified as the primary outcome, the VAS or DASH score was chosen. VAS and DASH scores were chosen because they were adequately reported for our random-effects model. If no VAS or DASH score was reported, the study's standardized PROMs were evaluated.

‡Two-tailed *t* test comparing pre-therapy score versus PROM at listed follow-up.

of procedures. Furthermore, the Cochrane risk-of-bias assessment is commonly used to evaluate the quality of RCTs within the orthopaedic literature.[25,26] The Cochrane risk-of-bias assessment was independently performed by 2 researchers (B.G., L.V.R.). Each study was given an overall risk-of-bias rating based on the rating it most received across all domains. If a study received equal numbers of high, low, and unclear ratings, it was rated as having an overall "unclear" risk of bias. Full descriptions of each researcher's judgment and support for judgment are reported in Appendix Tables 1 through 10. Frequency-based and domain-based summaries of each rater's assessment were created using RevMan software (version 5.3) and are presented in Figure 2. Inter-rater agreement was measured across the 7 Cochrane risk-of-bias assessment domains using the percentage agreement. The Cohen κ statistic was also calculated as a secondary measure. Percentage agreement and κ statistics were calculated using Stata software (version 15). Percentage agreement was made our primary measure because the Cochrane risk-of-bias assessment carries inherent issues that can lower reliability scores. This is further discussed in the "Discussion" section.

Results

Study Characteristics

Of the 458 studies identified in our search, 10 met the inclusion criteria (Fig 1). Qualitative findings regarding these studies are summarized in Table 1. Altogether, these 10 studies encompassed 283 patients at baseline. Of the 10 included studies, 7 showed statistically significant improvements in primary PROMs with saline solution injections. The primary PROMs that showed improvements with saline solution injection were as follows: VAS scores ("usual"/overall pain, nocturnal pain, pain at rest, and pain during motion), DASH scores, OES values, and a 6-point scale on which participants rated themselves as "much improved or completely recovered." Among included studies, saline solution injections were compared with autologous conditioned plasma (ACP) (3 of 10 studies),

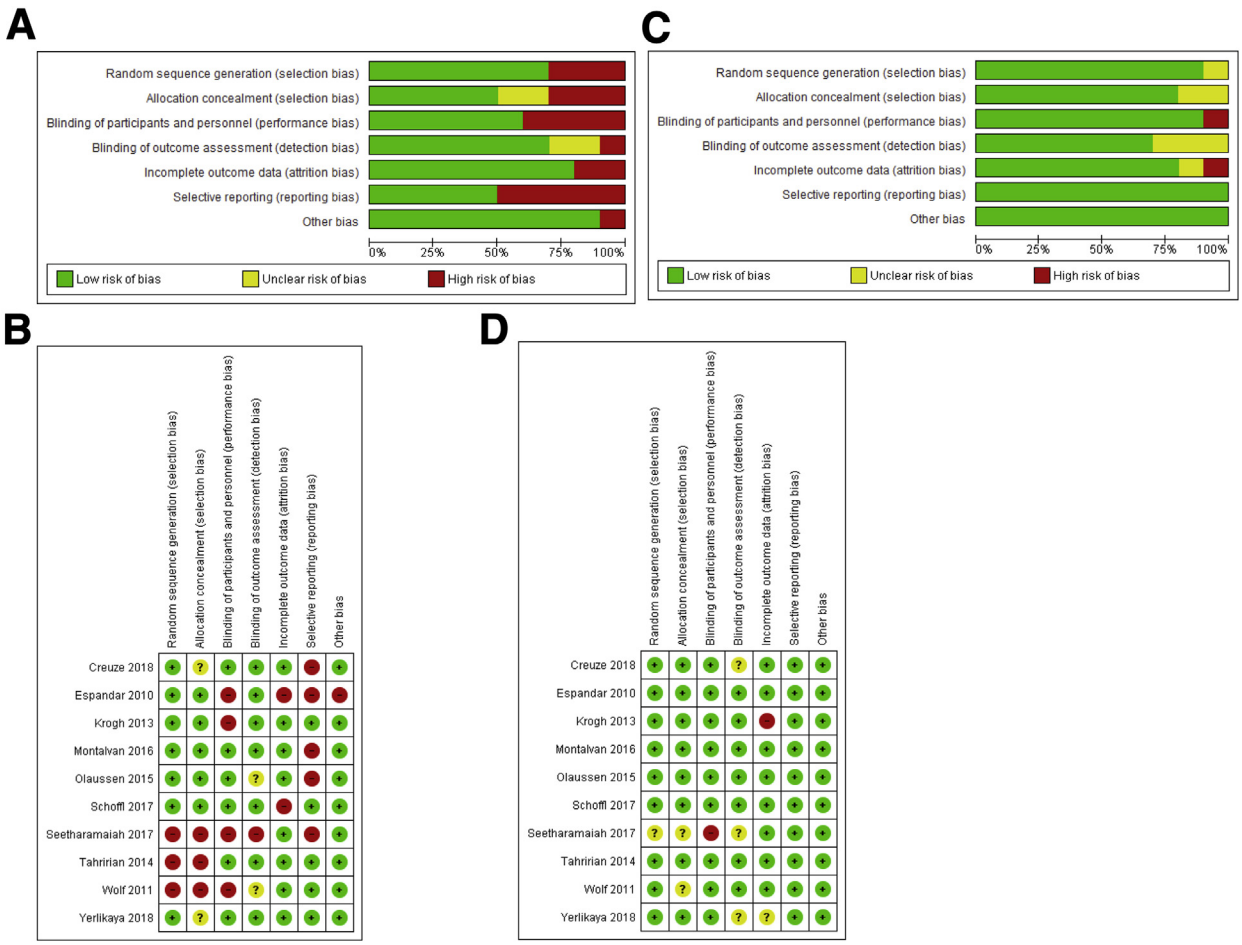

Fig 2. Cochrane risk-of-bias assessments. (A) Frequency summary for rater 1. (B) Domain summary for rater 1. (C) Frequency summary for rater 2. (D) Domain summary for rater 2.

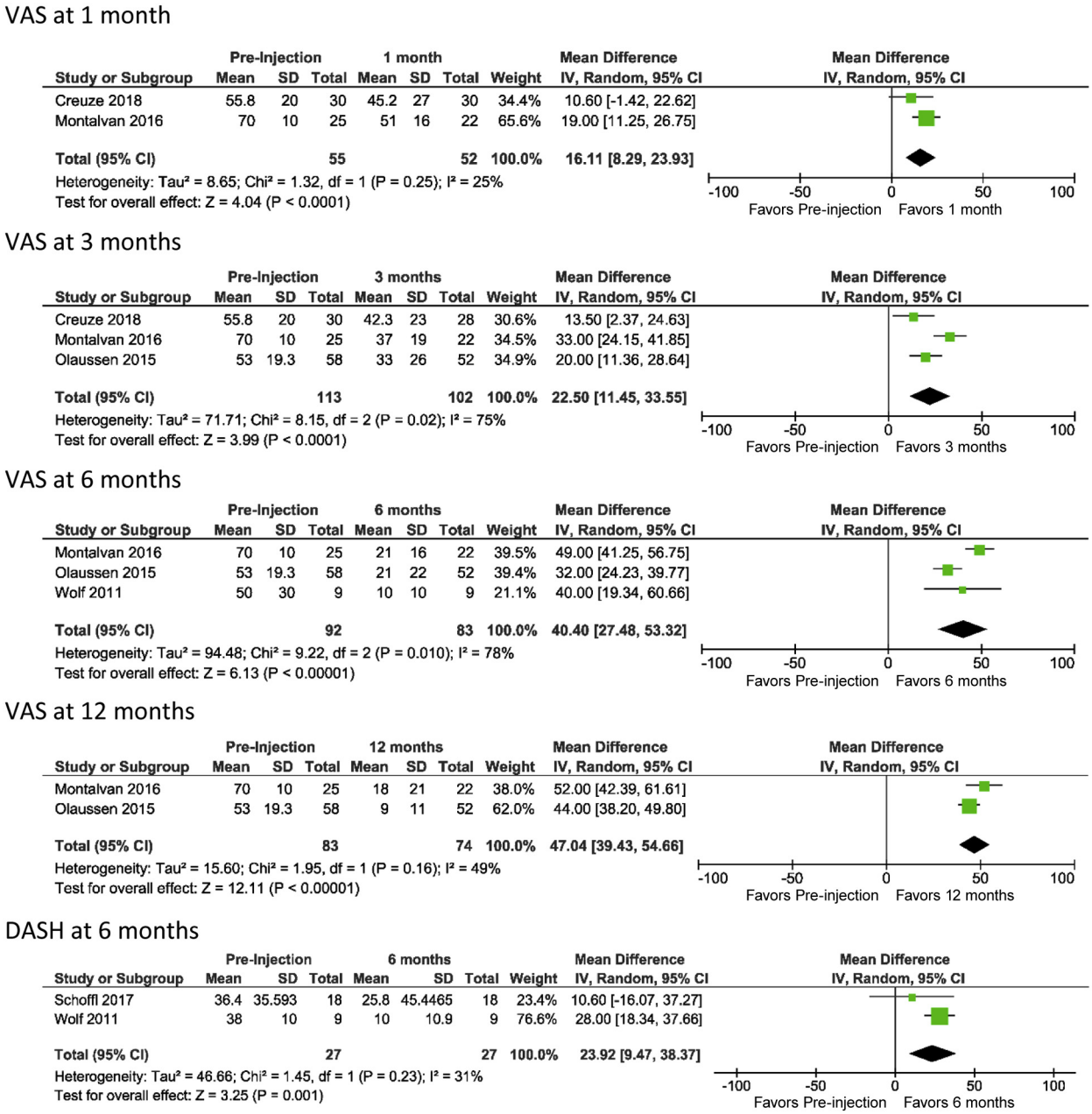

Fig 3. Visual analog scale (VAS) scores at 1, 3, 6, and 12 months and Disabilities of the Arm, Shoulder and Hand (DASH) scores at 6 months after saline solution injection. (CI, confidence interval; IV, inverse variance; SD, standard deviation.)

corticosteroids (4 of 10 studies), PRP (3 of 10 studies), and botulinum toxin (2 of 10 studies).[5,8-16]

Qualitative Review

On qualitative review, 3 studies compared PRP with saline solution and found conflicting results. One study found that greater statistically significant improvements in VAS and facial pain scale scores occurred at 12 and 24 weeks with PRP than with saline solution,[9] whereas the other 2 studies found no statistically significant difference between PRP and saline solution in Patient-Rated Tennis Elbow Evaluation (PRTEE) pain or disability scores at 1 and 3 months[9] or in 4- and 8-week VAS scores for nocturnal pain, VAS scores for pain with motion, or PRTEE scores.[8] Among the 3 studies comparing ACP with saline solution, ACP showed no statistically significant difference in post-injection DASH scores at 1, 3, or 6 months or VAS scores at 1, 3, 6, or 12 months.[10,11,15]

Studies comparing saline solution with corticosteroids found the two to be equivocal in effect. In a comparison of saline solution with corticosteroids, Olaussen et al.[12] found no statistically significant difference in VAS pain or function scores at 6 weeks, 3 months, 6 months, or 12 months. Other studies showed similar results, with glucocorticoid injections showing short-term

Table 2. Improvement in Outcome Variables and Comparison With MCID

Outcome Variable	Calculated or Reported Weighted Mean Improvement	MCID	Meets MCID
DASH score at 6 mo	23.92	10.83	Yes
OES at 24 wk	20.1	18	Yes
VAS score at 1 mo	16.11	10, 20, 25.4*	NA
VAS score at 3 mo	22.5	10, 20, 25.4*	NA
VAS score at 6 mo	40.4	10, 20, 25.4*	NA
VAS score at 12 mo	47.04	10, 20, 25.4*	NA

DASH, Disabilities of the Arm, Shoulder and Hand; MCID, minimal clinically important difference; NA, not applicable; OES, Oxford Elbow Score; VAS, visual analog scale.

*MCIDs of 10 for postoperative pain, 20 for patellofemoral pain at 6 weeks, and 25.4 for osteoarthritic pain.

improvements in VAS scores at 2 weeks and PRTEE pain scale scores at 1 month but no significant difference in VAS scores at 24 weeks or PRTEE pain scores at 3 months.[13,14] Finally, 2 studies compared botulinum toxin with saline solution.[5,16] One study found no difference in VAS pain scores at 30-day follow-up but did find a statistically significant difference in VAS pain scores at 90-day follow-up, with botulinum toxin producing lower VAS scores ($P = .032$).[5] The other study showed significant differences in VAS scores for pain at rest at 4, 8, and 16 weeks but showed no difference in grip strength or VAS scores for pain during grip[16]—suggesting that patients whose primary concern is improved function or function-related pain may not see additional benefits with botulinum toxin over saline solution. Altogether, of the 8 included studies, only 1 found a consistent statistically significant difference between saline solution injections and its comparator injection (PRP).[9]

Quantitative Review

Of 10 studies, 5 adequately reported PROMs for analysis within the random-effects model (Fig 3). These 5 studies encompassed 140 patients. Within these 5 studies, only DASH and VAS scores were reported adequately for analysis. An adequately reported PROM consisted of enough data such that we were able to calculate pre- and post-injection means and standard deviations, as well as numbers of surveyed patients. In addition, for any given PROM, 2 or more studies that reported the same PROM at the same time point were needed for analysis. The results of our model are summarized in Figure 3. At 1, 3, 6, and 12 months, statistically significant improvements in MDs among post-injection VAS scores compared with pre-injection scores were noted as follows: MD of 16.11 (95% CI, 8.29-23.93; $P < .0001$; $I^2 = 25\%$) at 1 month; MD of 22.50 (95% CI, 11.45-33.55; $P < .0001$; $I^2 = 75\%$; predictive interval, −106.77 to 151.77) at 3 months; MD of 40.40 (95% CI, 27.48-53.32; $P < .00001$; $I^2 = 78\%$; predictive interval, −108.83 to 189.62) at 6 months; and MD of 47.04 (95% CI, 39.43-54.66; $P < .0001$; $I^2 = 49\%$) at 12 months. At 6 months, post-injection DASH scores showed a statistically significant improvement compared with pre-injection scores (MD, 23.92; 95% CI, 9.47-38.37; $P = .001$; $I^2 = 31\%$). Outside of the random-effects model, 1 study reported OES values at 24 weeks, which showed an improvement by 20.1 points.[13]

MCID criteria and MD scores are summarized in Table 2. MCID criteria quantify the minimal change in an outcome measure that is associated with clinically significant improvements in a patient's function or symptoms.[18,23,27] Improvements in DASH scores at 6 months (23.92) and OES values at 24 weeks (20.1) surpassed DASH MCID criteria for conservatively managed upper-extremity musculoskeletal pathology (i.e., 10.83)[16] and OES MCID criteria for 6-month OES values in patients undergoing orthopaedic elbow surgery (i.e., 18).[19] These results suggest that improvements in DASH scores and OES values were clinically relevant in reducing patients' symptoms. Further interpretation is provided in our "Discussion" section.

At 6 months after injection, the MD in VAS scores was 40.40, and at 12 months, it was 47.04. To our knowledge, VAS MCID criteria for lateral epicondylitis and upper-extremity pathology are poorly established. In Table 2, however, we list VAS MCIDs for various conservative and medical treatments for common orthopaedic problems. We present this information to give the reader a sense of the minimal changes in VAS scores considered by patients and practitioners to be large enough to correspond to improved patients' symptoms—not for definitive evaluation of VAS scores with saline solution injections. The VAS MCID criterion for postoperative pain treated with analgesia[20] was 10; for chronic osteoarthritic pain treated with NSAIDs,[21] it was 24.5; and for patellofemoral pain treated with conservative physiotherapy or ultrasound treatment at 6 weeks,[18] it was 20. In comparison with such MCID criteria, saline solution injections provided much larger improvements in VAS scores. However, without MCID criteria specific to upper-extremity pathology or lateral epicondylitis, we caution against making definitive interpretations regarding the clinical relevance of saline solution injections based on VAS scores alone. This is discussed further in our "Discussion" section.

Risk of Bias

The Cochrane risk-of-bias assessments are summarized in Figure 2. The full Cochrane risk-of-bias assessment for each included study, including each rater's reasoning, is reported in Appendix Tables 1 through 10. Percentage agreement and κ statistics are summarized in Table 3. When assessments were compared between

Table 3. Inter-rater Agreement and Reliability of Cochrane Risk-of-Bias Assessment

Bias Domain	% Agreement	κ Statistic	SE for κ Statistic
Random sequence generation (selection bias)	70.00	0.1892	0.1175
Allocation concealment (selection bias)	50.00	0.1071	0.1764
Blinding of participants and personnel (performance bias)	70.00	0.2857	0.2213
Blinding of outcome assessment (detection bias)	60.00	0.0244	0.2263
Incomplete outcome data (attrition bias)	50.00	−0.1765	0.2382
Selective reporting (reporting bias)	50.00	0	0
Other bias	90.00	0	0

SE, standard error.

rater 1 and rater 2, rater 1 perceived higher risks of bias within each study. Rater 1 assessed 2 studies as having an overall high risk of bias,[9,16] 1 study as having an unclear risk of bias,[15] and 7 studies as having a low risk of bias.[5,8,10-14] Rater 2, meanwhile, assessed only 1 study as having an unclear risk of bias[9] and assessed all other studies as having a low risk of bias.[5,8,10-16] Among the assessments of rater 2, only 1 study contained fewer than 5 of 7 domains rated as being at a low risk of bias.[9] Rater 1 also rated this study as having several domains at a high or unclear risk of bias—rating it as being at a high risk of bias for 5 domains (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, and selective reporting) and at an unclear risk for the domain of incomplete outcome data.[9]

Among the 10 studies evaluated, both raters reported at least 50% of all risk-of-bias domains as having a low risk of bias. Among the assessments of rater 1, the domain most frequently rated (5 of 10 studies) as having a high risk of bias was selective reporting (reporting bias). Among the studies rated as being at a high risk of bias, all reported nonstandardized orthopaedic PROMs.[5,9,11,12,16] Nonvalidated questionnaires may skew results in favor of showing a therapeutic effect. This, however, is a subjective judgment, and rater 2 did not agree. In fact, rater 2 graded all studies as having a low risk of bias.

The average percentage agreement of all studies was 64.3% across all domains (range, 50%-90%). The domains with the highest percentage agreement were as follows: other bias (90% agreement), blinding of participants and personnel (performance bias) (70% agreement), and random sequence generation (selection bias) (70% agreement). The domains with the lowest agreement were allocation concealment (selection bias) (50% agreement) and selective reporting (reporting bias) (50% of domains). Reliability scores were low across all domains, with no domain receiving a score above 0.50.

Discussion

Our results suggest that in patients with lateral epicondylitis, saline solution injections can create significant measurable improvements in DASH scores at 6 months and VAS scores up to 12 months. Furthermore, when MDs at 1, 3, 6, and 12 months were tracked, VAS scores continued to improve as time went on—suggesting that saline solution injections may have benefits that improve over time.

The results of improvements in PROMs after saline solution injection compare favorably with related MCID criteria. Before we explore this comparison, however, it is important to note that MCID criteria are meant to be within-patient metrics. Thus, each patient's score should be compared with MCID criteria individually. However, owing to the nature of meta-analysis, it is not possible to know the individual patient-level improvements. Therefore, we compare MCID criteria with the mean improvement calculated from our meta-analysis or found during our qualitative review. In doing so, however, our comparisons with MCID criteria are vulnerable to outliers. For example, if 1 patient reported particularly high improvements with saline solution injection, this may cause the mean to increase above an MCID criterion that it otherwise would not have, and as a result, the entire group of patients would be deemed to have improved beyond a target MCID threshold. Despite this chance of bias, however, our random-effects model takes an inverse variance approach—thus weighting studies with low variance (and likely fewer outliers) more than studies with higher variance during pooling. Altogether then, there is a small but existent possibility that comparisons with MCID criteria in this study could be swayed in favor or against by an outlier.

When DASH score improvements are compared with MCID criteria, improvements in DASH scores appear to be clinically relevant. Comparing OES values at 24 weeks with MCID criteria also suggests that OES improvements are clinically relevant. We do, however, place caution on this interpretation because the best currently available OES MCID criteria are based on procedural intervention, and thus, we cannot definitively state that OES effect sizes are clinically relevant. Likewise, interpretation of VAS score improvements is challenging. Although the VAS effect sizes of saline solution injection surpass MCID criteria used for

conservative or medical treatments of common orthopaedic pathologies (analgesia for acute postoperative pain, NSAIDs for chronic osteoarthritic pain, and 6 weeks of conservative treatment for patellofemoral pain), these pathologies differ from conservatively managed upper-extremity pathology. The limits of the current orthopaedic literature prevent us from definitively stating that VAS scores show clinically relevant improvements. However, given the large VAS effect sizes, as well as the trend in DASH scores and OES values in relation to available MCID criteria, the VAS score improvements may be clinically relevant. Overall, the relation of DASH scores, OES values, and VAS scores to available MCID criteria suggests that the benefits of saline solution injections may have clinical significance.

The effects of saline solution injections are notable when compared with traditional therapies for lateral epicondylitis. Eccentric exercises have shown effect sizes of 1.0 on VAS pain scores and 0.6 on DASH scores.[28,29] NSAID therapy has shown a Cohen *d* effect size of 0.52 for VAS pain scores.[30] Furthermore, saline solution injections appear to have equivalent effects to other injection therapies. In all but 1 included RCT,[9] no statistically significant difference was found in PROMs between saline solution and non–saline solution injections. This is not to say that non–saline solution injections did not improve patients' symptoms—in fact, all RCTs found that non–saline solution injections provided improvements in PROMs. Rather, these results suggest that saline solution injections can achieve therapeutic effects similar to non–saline solution injections (PRP, ACP, corticosteroid, and botulinum toxin injections).

The therapeutic benefits of saline solution in our study are consistent with recently published work by Saltzman et al.[3] that showed that saline solution injections in patients with knee osteoarthritis create statistically and clinically significant improvements in patient-reported outcomes. Saltzman et al. discussed the possibility of saline solution injections providing a placebo effect for patients. Kaptchuk and Miller[31] defined a placebo effect as an improvement in a patient's symptoms not through direct intervention on a pathophysiological process but rather through a patient's "participation in [a] therapeutic encounter, with its rituals, symbols, and interactions." In this sense, many therapies known to improve patients' symptoms are also likely to use the placebo effect as a part of their healing.[32] The exact mechanism of how saline solution injections have shown statistically significant improvements in PROMs is unclear, but a placebo effect may be possible.

Naturally, the statistically significant improvements in PROMs in patients receiving saline solution injections may lead clinicians to wonder whether such injections should be incorporated into clinical practice. Although the results of this study suggest that such injections may indeed improve patients' symptoms, until the mechanism of action can be confirmed, we would hesitate to recommend saline solution injections as a first-line injection treatment. Furthermore, as discussed in our section regarding heterogeneity, the data pooled here are quite heterogeneous. As a result, more studies—and narrower prediction intervals—are required before any definitive recommendations can be made.

The results of this meta-analysis, however, should not be dismissed. Future studies comparing non–saline solution injection therapies with saline solution injections should be wary of this effect and consider the use of additional control arms such as physiotherapy or no injection, given the statistically significant effect size of saline solution injections.

Risk of Bias

Most constituent studies were rated as having an overall low risk of bias (7 of 10 studies by rater 1 and 9 of 10 by rater 2). This finding suggests that the results of this systematic review are at a relatively low risk of bias. It should be noted, however, that this study pooled only "control" arms, whereas the Cochrane risk-of-bias assessment evaluates the bias across an entire study. Thus, certain domains of bias—even if they were rated as high risk—were more likely to downwardly bias the effect size of our studied saline solution injections. For example, in studies that were rated as having a high risk of allocation concealment–related bias (by rater 1),[9,13,15] it was believed that there may be a possibility that the allocation of saline solution versus comparator injections would be known to either a patient or a treatment and/or evaluation team member. Such knowledge, however, may be more likely to benefit the comparator injection—because placebo injections may be thought of as having a lesser effect by patients and treatment teams at baseline. Similarly, this possibility includes studies that reported a high risk of bias for the domain of blinding of participants and personnel and the domain of blinding of outcome assessment.

The percentage agreement across domains between raters ranged from fair (50%) to excellent (90%), with an overall percentage agreement of 64.3%. This finding suggests that raters agreed across most domains. The Cochrane risk-of-bias assessment inherently causes disagreements because of the lack of gradations in its rating system. For example, raters must choose between the stark differences of a "low" risk of bias and a "high" risk of bias. If a study, however, presents a moderate risk of bias, then raters may choose different "grades" for their risk of bias but may be using similar support for their judgment and may be recognizing the same bias. Other times, if a study is unclear about its methods or does not make an explicit statement

regarding a domain, the rater may grade this as an unclear risk or may believe that the study authors omitted these details because appropriate measures were not taken to decrease this bias, leading to a grade of "high risk." For example, for the domain of random sequence generation, 1 study was rated as being at a high risk of bias by rater 1 because it did not provide details beyond the use of "randomization software."[9] Rater 2, however, gave this study a rating of unclear risk of bias for the same reason.[9] The difficulty of finding agreement in the Cochrane risk-of-bias assessment's 3-level rating system is detailed by Robertson et al.[33] in a study of the Cochrane risk-of-bias assessment's performance.

The Cochrane risk-of-bias assessment also can lead to poor reliability scores. In general, reliability score calculations rely on comparing the ratio of variability between scores to the variability of all scores.[34] Thus, if variability among risk-of-bias scores is low, reliability scores will also be low.[34] In our systematic review, low score variability likely occurred for 2 reasons: First, the range of scores is restricted because the Cochrane risk of bias allows for only 3 possible grades. Thus, the Cochrane risk-of-bias assessment is inherently at risk of lower reliability scores than studies that allow for a greater range of scores. Second, the prevalence of the "low" risk-of-bias score is very high. Thus, although our review may include a number of well-designed and -reported studies, the high prevalence of such studies causes low variability among scores and thus lowers our calculated reliability statistic. For example, in the domain of "other bias," rater 1 gave all studies but one[16] a low risk-of-bias rating and rater 2 gave all studies this rating. The κ statistic, meanwhile, calculates expected percentage agreement based on the observed distribution of scores. As such, the expected percentage agreement was equivalent to the actual percentage agreement—yielding a κ statistic of 0. Altogether then, although the κ statistics were low across domains, this is likely because of a combination of the limited number of grading levels within the Cochrane risk of bias and the high prevalence of low risk-of-bias scores across domains.

Random-Effects Model Heterogeneity

By use of the suggested categorizations of the I^2 statistic of Higgins et al.,[35] 2 models yielded I^2 statistics suggesting a low impact of study heterogeneity on study results (VAS score at 1-month follow-up, $I^2 = 25\%$; DASH score at 6-month follow-up, $I^2 = 31\%$); 1 model yielded an I^2 statistic suggesting a moderate impact of study heterogeneity on study results (VAS score at 12-month follow-up, $I^2 = 49\%$); and 2 models yielded I^2 statistics suggesting a high impact of study heterogeneity on study results (VAS score at 3-month follow-up, $I^2 = 75\%$; VAS score at 6-month follow-up, $I^2 = 78\%$). The source of heterogeneity in these final 2 models with I^2 statistics of 75% or greater is more likely because of clinical diversity than because of methodologic diversity. Among the studies included in the VAS score 3-month model, all were RCTs that were rated as having an overall low risk of bias by both raters.[5,11,12] Within each of these 3 studies, only the selective reporting domain was given a rating of a high risk of bias (by rater 1)—and this was only because these studies did not report a standardized orthopaedic PROM.[5,11,12] The VAS score 6-month follow-up model uses 2 of the same studies (Montalvan et al.[11] and Olaussen et al.[12]) as the VAS score 3-month follow-up but adds an additional study by Wolf et al.[15] The study by Wolf et al. received an overall rating of an unclear risk of bias (from rater 1), suggesting that their study may be at a higher risk of bias than the other studies included in the VAS score 6-month follow-up. This higher risk of bias may add to the methodologic diversity present in the VAS score 6-month follow-up model. However, it should be noted that rater 2 gave the study by Wolf et al. a low risk of bias across all domains.

When we analyzed the clinical diversity present in the 4 studies included in the random-effects models categorized as having high impact heterogeneity (VAS score at 3-month follow-up and VAS score at 6-month follow-up),[5,11,12,15] although all studies used saline solution injections, these injections all differed slightly in their administration. The study by Creuze et al.[5] used 0.4-mL saline solution injections guided with electromyographic stimulation tracking. The study by Montalvan et al.[11] used 2-mL saline solution injections with ultrasound guidance and 2 mL of 1% lidocaine (subcutaneously). The study by Wolf et al.[15] used multiple passes of 2-mL saline solution injections with 1 mL of lidocaine. The study by Olaussen et al.[12] used 2 injections of 1 mL of saline solution with 0.5 mL of 2% lidocaine; their patients also underwent mandatory stretching and massage routines with a physiotherapist. Altogether, although all pooled studies involve saline solution injection therapy, the differences in their administration and amount are possible sources of the heterogeneity represented in the I^2 statistic. We should note, however, that the impact of these differences on the clinical diversity present in these studies is speculative. For example, there may be no effective clinical difference in outcomes between using ultrasound guidance[11] and using electromyographic stimulation guidance[5] or between using 2 mL of 1% lidocaine[11] and using 0.5 mL of 2% lidocaine.[12]

Although significant heterogeneity exists in the VAS score 3-month follow-up and VAS score 6-month follow-up models, a random-effects model (as opposed to a fixed-effects model) was used to incorporate some of this heterogeneity. However, because

this heterogeneity may be due to clinical diversity, the results of these models may act as estimates of the average intervention effect and not the "best estimate" of the intervention effect.[36] This distinction is particularly important when interpreting the effect estimates of the VAS score 3-month model and VAS score 6-month model in the context of their predictive intervals. The VAS score 3-month model yielded a statistically significant MD of 22.50 (95% CI, 11.45-33.55). This finding suggests that the average effect size from the observed studies showed an improvement in VAS pain scores. However, the predictive interval of the VAS 3-month model was wide and included the null value (−106.77 to 151.77). Prediction intervals attempt to incorporate heterogeneity in effect estimates to convey the range of effects in a future study.[37,38] Alongside the large heterogeneity statistic ($I^2 = 75\%$), this predictive interval suggests that the heterogeneity of the included studies has a significant impact on effect estimates. Furthermore, the broad prediction interval suggests that although the average observed effect size showed statistically significant improvements in VAS scores (MD, 40.40; 95% CI, 27.48-53.32), there are theoretical settings in which a patient may experience no effect or a suboptimal effect from saline solution injections. These same interpretations apply to the VAS score 6-month model (MD, 40.40; 95% CI, 27.48-53.32; $P < .00001$; $I^2 = 78\%$; predictive interval, −108.83 to 189.62). The prediction intervals here should, however, be interpreted with caution. Meta-analyses that show statistically significant effects by analyzing continuous variables are more prone to showing predictive intervals that cross a no-effect threshold.[38] In addition, the predictive intervals are imprecise in models that contain fewer and smaller studies because between-study heterogeneity measurements may be less precise in such cases.[38]

Although not enough studies were available in the other models to calculate predictive intervals, the heterogeneity statistic in these studies was much lower. As a result, a narrower predictive interval would be expected from these models if such a predictive interval were estimable. It should also be noted that the 2 studies contained within the VAS score 12-month follow-up model ($I^2 = 49\%$) were also contained within the VAS score 3- and 6-month follow-up models discussed earlier,[11,12] and thus the same interpretations likely apply.

This systematic review has many strengths. First, our study incorporated rigorous analysis of bias within each included RCT and found only a low to moderate risk of bias in most studies. Second, in addition to providing evidence-based knowledge to the area of saline solution injections and lateral epicondylitis, our research suggests a change in direction for future injection-related research in orthopaedics. The statistically significant improvement in PROMs from saline solution injections, as well as the possibility that a biological effect exists from the injection of saline solution into the elbows of patients with lateral epicondylitis, suggests that future studies should not use saline solution injections alone as a placebo arm. Future studies should consider the use of a single needle stick as a sham placebo group.

Limitations

In addition to its strengths, our study has several limitations. First, saline solution injections themselves are not often the subject of study, and as a result, reporting of outcomes is limited and often heterogeneous. Further RCTs should be completed with saline solution injection arms and should report VAS scores, as well as commonly used scores of pain and function such as DASH scores. Second, the administration of saline solution injections has not been standardized. The amount of saline solution used, whether these injections are performed with lidocaine, whether a peppering injection technique is used, and whether additional conservative therapies such as splinting or physiotherapy are performed afterward may affect the therapeutic benefits of saline solution. Future research should seek to discover whether a particular style of administration of saline solution injections is superior to other styles. Third, MCID criteria for lateral epicondylitis are not well established and limit the ability to definitively establish the clinical relevance of the effects seen in this article. Fourth, tendinopathy can be chronic in nature, and pain and function can change throughout the course of a case of tendinopathy. As with any chronic disease, natural fluctuations in PROMs may confound estimates. Fifth, lateral epicondylitis is a self-limited problem, with symptom improvement typically occurring between 6 months and 2 years.[1] As a result, it is difficult to differentiate between the therapeutic effect of any injection therapy and the natural history of lateral epicondylitis. This difficulty is largely a result of the reporting in the current primary literature. Current literature reports follow-up periods at times during which improvement from injection therapy may coincide with spontaneous improvement in symptoms. To try to account for this, we attempted to pool follow-up in as many time points as possible, including early time points such as 3-month follow-up for VAS scores.

Conclusions

Improvements in DASH scores at 6 months (23.92) surpassed MCID criteria for conservatively managed upper-extremity musculoskeletal pathology (10.83)—suggesting that saline solution injections have a clinically relevant effect. VAS MCID criteria are poorly established, but VAS scores at 6 and 12 months surpassed MCID criteria for conservative treatments for

common orthopaedic conditions. In all but 1 study, no statistically significant difference in PROMs was found between saline solution and non−saline solution injections.

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Appendix Table 1. Cochrane Risk-of-Bias Assessment for Yerlikaya et al.[8] (2018)

	Rater 1		Rater 2	
Bias	Rater's Judgment	Support for Judgment	Rater's Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned into three groups (n = 30 in each) by using the block randomization method."	Low risk	"Patients were randomly assigned into three groups (n = 30 in each) by using the block randomization method." This information is vague but not a high risk.
Allocation concealment (selection bias)	Unclear risk	Although a small nonrandom block size was used (block size of 3), suggesting the possibility of selection bias, it was not specified whether the study groups or therapies were masked during the randomization process.	Low risk	Block randomization was appropriate, and there did not appear to be any foreknowledge of forthcoming allocations.
Blinding of participants and personnel (performance bias)	Low risk	"The treatment was performed by another investigator who had four years of experience. Both the patient and investigator were blinded to the treatment given."	Low risk	There was a slight possibility that patients may know whether they received saline solution versus PRP based on the way the injection was performed.
Blinding of outcome assessment (detection bias)	Low risk	"The treatment was performed by another investigator who had four years of experience. Both the patient and investigator were blinded to the treatment given."	Unclear risk	Physicians evaluating outcomes were blinded. However, they may have known if they had given patients saline solution. It is unclear whether this possibility affected the outcome.
Incomplete outcome data (attrition bias)	Low risk	No loss to follow-up occurred; no patients were excluded in outcome reporting.	Unclear risk	It does not appear that there was an explicit statement as to whether there was any attrition or dropout among the 90 original patients and, if so, why participants decided to quit.
Selective reporting (reporting bias)	Low risk	The PRTEE was used. The PRTEE is a standardized orthopaedic PROM specific to tennis elbow.	Low risk	Outcomes were not omitted.
Other bias	Low risk	—	Low risk	The follow-up period was short.

PROM, patient-reported outcome measure; PRP, platelet-rich plasma; PRTEE, Patient-Rated Tennis Elbow Evaluation.

Appendix Table 2. Cochrane Risk-of-Bias Assessment for Creuze et al.[5] (2018)

	Rater 1		Rater 2	
Bias	Rater's Judgment	Support for Judgment	Rater's Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	"Randomization (1:1) was performed after the enrollment visit, at which the patient's eligibility was confirmed (block randomization size of 4)."	Low risk	"Block randomization size of 4. The university pharmacist was responsible for preparation of injected products according to a randomized list, which was kept confidential."
Allocation concealment (selection bias)	Unclear risk	Although a small nonrandom block size was used ("block randomization size of 4")—suggesting the possibility of selection bias—it was not specified whether the study groups or therapies were masked during the randomization process.	Low risk	Block randomization was appropriate, and there did not appear to be any foreknowledge of forthcoming allocations.
Blinding of participants and personnel (performance bias)	Low risk	"We conducted a phase-III, single-center, randomized, double-blinded [study]… The university pharmacist was responsible for preparation of injected products according to a randomized list, which was kept confidential. Neither therapists nor patients were aware of which product was administered."	Low risk	A pharmacist prepared the injection products so that the therapist and patient were not aware of what was given.
Blinding of outcome assessment (detection bias)	Low risk	"We conducted a phase-III, single-center, randomized, double-blinded [study]… The university pharmacist was responsible for preparation of injected products according to a randomized list, which was kept confidential. Neither therapists nor patients were aware of which product was administered."	Unclear risk	No specific blinding measures were outlined outside of the authors writing that the pharmacists were the only ones to know what was in each syringe. However, the appearance of each syringe was not stated; thus, it is unclear whether the outcome assessor was able to identify the syringe contents by its appearance.
Incomplete outcome data (attrition bias)	Low risk	No loss to follow-up occurred at 30 days; 2 patients (of baseline 30 patients) were lost to follow-up at 90 days. Except for loss to follow-up, no patients were excluded in outcome reporting.	Low risk	Outcomes were very complete with a flowchart outlining patients excluded, attrition, and when "loss to follow-up" occurred.
Selective reporting (reporting bias)	High risk	No standardized orthopaedic questionnaires were used (excluding VAS).	Low risk	The primary outcome was pain as reported by the patient.
Other bias	Low risk	—	Low risk	There were no other concerns regarding bias.

VAS, visual analog scale.

Appendix Table 3. Cochrane Risk-of-Bias Assessment for Seetharamaiah et al.[9] (2017)

	Rater 1		Rater 2	
Bias	Rater's Judgment	Support for Judgment	Rater's Judgment	Support for Judgment
Random sequence generation (selection bias)	High risk	No further details were given beyond the following: "The patients were randomized into three groups according to the randomization software."	Unclear risk	"The patients were randomized into three groups according to the randomization software." Neither the software nor the technique was mentioned in the article.
Allocation concealment (selection bias)	High risk	No further details were given beyond the following: "The patients were randomized into three groups according to the randomization software."	Unclear risk	No details were given regarding concealment of intervention allocations.
Blinding of participants and personnel (performance bias)	High risk	No details were given regarding blinding.	High risk	No details were given regarding blinding providers, patients, or study assessors.
Blinding of outcome assessment (detection bias)	High risk	No details were given regarding blinding.	Unclear risk	It is unclear whether blinding was effective because it was not mentioned in the article. For this reason, rater 2 was unable to determine whether it was effective.
Incomplete outcome data (attrition bias)	Low risk	The CONSORT diagram was used. There was no loss to follow-up or exclusion of patients after randomization.	Low risk	Data were very complete with no patient attrition from the original 90 and a clear flowchart outlining the excluded patients.
Selective reporting (reporting bias)	High risk	No standardized orthopaedic questionnaires were used (excluding a VAS).	Low risk	Outcomes were appropriately reported. No outcomes were excluded from tables.
Other bias	Low risk	—	Low risk	Only 1 limitation of the study was acknowledged: The sample size needed for the study was not calculated.

CONSORT, Consolidated Standards of Reporting Trials; VAS, visual analog scale.

Appendix Table 4. Cochrane Risk-of-Bias Assessment for Schoffl et al.[10] (2017)

	Rater 1		Rater 2	
Bias	Rater's Judgment	Support for Judgment	Rater's Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	"With the help of Microsoft Excel, randomized numbers between 0 and 1 [0;1] were generated and listed. A randomized number smaller than 0.5 was specified as placebo therapy, [and] a randomized number higher than 0.5 was specified as ACP therapy. The patients list of 1 − 50 was then adjusted accordingly to produce two equal sample sizes of 25 patients."	Low risk	"The patients were externally randomized into the treatment or control (placebo) group by an independent statistician (S. Roloff, PhD). With the help of Microsoft Excel, randomized numbers between 0 and 1 [0;1] were generated and listed. A randomized number smaller than 0.5 was specified as placebo therapy, [and] a randomized number higher than 0.5 was specified as ACP therapy. The patients list of 1 − 50 was then adjusted accordingly to produce two equal sample sizes of 25 patients."
Allocation concealment (selection bias)	Low risk	"The patients were externally randomized into the treatment or control (placebo) group by an independent statistician (S. Roloff, PhD)."	Low risk	The sequence was concealed because it was generated randomly by a statistician not involved in the intervention or outcomes.
Blinding of participants and personnel (performance bias)	Low risk	A "prospective, double-blind, randomized controlled clinical trial" was performed.	Low risk	"The syringe was blinded by the study nurse through external coverage with adhesive and opaque tape wrapping, effectively preventing any influence of the applying physician on the administration of verum [*sic*] or falsum [*sic*] for any patient (double blinding)."
Blinding of outcome assessment (detection bias)	Low risk	"An independent physician's assistant obtained the blood sample from each patient and a study nurse then either produced ACP, as described through Arthrex, Naples FL, USA (www.arthrex.com) or used NaCl 0.9% to fill the inner syringe in accordance to the randomized protocol. The syringe was blinded by the study nurse through external coverage with adhesive and opaque tape wrapping, effectively preventing any influence of the applying physician on the administration of verum [*sic*] or falsum [*sic*] for any patient (double blinding). After the final evaluation at six months postinjection, each patient and the corresponding treating physician were informed about which therapy had been applied."	Low risk	The primary outcome analysis was self-rated by patients. Therefore, if they were blinded as they were stated to have been, their group assignment should not have generated detection bias.
Incomplete outcome data (attrition bias)	High risk	"[This] study had, in spite of the short time frame for follow up, a high drop out rate of 28% (14/40). This is based on incomplete questionnaires in 6 of the patients and in a patient loss for follow-up in 8 patients."	Low risk	The attrition rate (28%) was mentioned in the discussion as being a possible source of bias: "This is based on incomplete questionnaires in 6 of the patients and in a patient loss for follow-up in 8 patients. This was also based on the fact that some patients needed to travel a longer distance for check up and were not willing to do so, in others that they had moved elsewhere [*sic*]." Although there was attrition in this study, it was openly acknowledged, and rater 2 did not believe the attrition was large enough to warrant a rating of high risk.

(continued)

Appendix Table 4. Continued

	Rater 1		Rater 2	
Bias	Rater's Judgment	Support for Judgment	Rater's Judgment	Support for Judgment
Selective reporting (reporting bias)	Low risk	A standardized upper-extremity orthopaedic PROM was used (DASH score) and fully reported.	Low risk	Because of the attrition rates, it is theoretically possible that certain patients presenting with specific characteristics chose not to complete the surveys. However, rater 2 did not believe this risk of bias was high enough to warrant a high-risk rating.
Other bias	Low risk	—	Low risk	Arthrex was the study funder.

ACP, autologous conditioned plasma; DASH, Disabilities of the Arm, Shoulder and Hand; NaCl, sodium chloride; PROM, patient-reported outcome measure.

Appendix Table 5. Cochrane Risk-of-Bias Assessment for Montalvan et al.[11] (2016)

	Rater 1		Rater 2	
Bias	Rater's Judgment	Support for Judgment	Rater's Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	"The treatment was allocated according to a randomization list, with a block size of four with no stratification."	Low risk	"The treatment was allocated according to a randomization list, with a block size of four with no stratification."
Allocation concealment (selection bias)	Low risk	"The treatment was allocated according to a randomization list, with a block size of four with no stratification. The evaluator (P.G.) was blinded to treatment because he was not involved in the injection protocol."	Low risk	"The evaluator (P.G.) was blinded to treatment because he was not involved in the injection protocol. The patient was also blinded to treatment because the blood sample was collected from all patients and the syringe was hidden after preparation, before randomization." There was no appearance of foreknowledge of forthcoming allocations.
Blinding of participants and personnel (performance bias)	Low risk	"The evaluator (P.G.) was blinded to treatment because he was not involved in the injection protocol. The patient was also blinded to treatment because the blood sample was collected from all patients and the syringe was hidden after preparation, before randomization."	Low risk	Randomization was "performed" by the physician, but the syringe was hidden from patient viewing.
Blinding of outcome assessment (detection bias)	Low risk	"The evaluator (P.G.) was blinded to treatment because he was not involved in the injection protocol. The patient was also blinded to treatment because the blood sample was collected from all patients and the syringe was hidden after preparation, before randomization."	Low risk	The provider who conducted the clinical evaluation was a different doctor than the one who administered the injection and was blinded to the injection used.
Incomplete outcome data (attrition bias)	Low risk	Minimal loss of follow occurred. No results were excluded after randomization outside of those of patients who were lost to follow-up. "During the 12-month follow-up period, six patients were lost to follow-up or withdrew from the study because of protocol violation" (50 patients were randomized).	Low risk	The study flowchart was clear in outlining the reasons for attrition and the number of patients in each group; exclusions were also reported. The chart stated that all 50 patients were analyzed (despite dropout of a few).
Selective reporting (reporting bias)	High risk	No standardized orthopaedic upper-extremity PROM was used outside of VAS and Roles-Maudsley scores.	Low risk	Outcomes were reported at each follow-up time point.
Other bias	Low risk	—	Low risk	The study did not have a specific limitations section, but nothing otherwise suggested additional biases.

PROM, patient-reported outcome measure; VAS, visual analog scale.

Appendix Table 6. Cochrane Risk-of-Bias Assessment for Olaussen et al.[12] (2015)

	Rater 1		Rater 2	
Bias	Rater's Judgment	Support for Judgment	Rater's Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	"A computerised [*sic*] randomisation [*sic*] schedule was prepared by an independent researcher (ML), using numeric block randomisation [*sic*] with variable block size."	Low risk	"A computerised [*sic*] randomisation [*sic*] schedule was prepared by an independent researcher (ML), using numeric block randomisation [*sic*] with variable block size."
Allocation concealment (selection bias)	Low risk	"A computerised [*sic*] randomisation [*sic*] schedule was prepared by an independent researcher (ML), using numeric block randomisation [*sic*] with variable block size. Stratification of patients was not done. The patients were first assessed by one of two trial doctors. If inclusion criteriae [*sic*] were met, the patient was enrolled in the study. Only then was an independent research assistant contacted, who, by consulting the previously prepared randomisation [*sic*] schedule, allocated the patient to one of three treatments."	Low risk	The independent research assistant generating the randomization was not involved in treatment or evaluation of the patients.
Blinding of participants and personnel (performance bias)	Low risk	"A research assistant prepared the syringes used for the injection treatment and concealed its content by an opaque adhesive patch, thus blinding the content of the injection for both administering doctor and patient."	Low risk	Both the provider and the patient were blinded because the syringe body was concealed so that the contents could not be identified.
Blinding of outcome assessment (detection bias)	Unclear risk	"To ensure blinded assessment of treatment effect, in the follow-up period from week six patients saw the other trial doctor, who was blinded for treatment. Patients were cautioned at each assessment not to disclose their treatment, and the success of blinding was assessed at 52 weeks by the trial doctor guessing which treatment the patient had received."	Low risk	"To ensure blinded assessment of treatment effect, in the follow-up period from week six patients saw the other trial doctor, who was blinded for treatment. Patients were cautioned at each assessment not to disclose their treatment, and the success of blinding was assessed at 52 weeks by the trial doctor guessing which treatment the patient had received."
Incomplete outcome data (attrition bias)	Low risk	The "drop-out rate stayed near the 10% prediction [in our study design] (20 drop-outs, 11%)."	Low risk	Sufficient patient data points were recorded at all follow-up time points.
Selective reporting (reporting bias)	High risk	A nonstandardized PROM was used: "The main outcome measure was treatment success defined as patients rating themselves completely recovered or much better on a six-point scale."	Low risk	"The percentage of treatment success was presented unadjusted, calculated based on the number of patients included, assuming those lost to follow-up had no success as outcome."
Other bias	Low risk	—	Low risk	"A Chi-square test for independence indicated significant association between treatment group and correctly guessing the treatment ($P = .04$)."

PROM, patient-reported outcome measure.

Appendix Table 7. Cochrane Risk-of-Bias Assessment for Tahririan et al.[13] (2014)

	Rater 1		Rater 2	
Bias	Rater's Judgment	Support for Judgment	Rater's Judgment	Support for Judgment
Random sequence generation (selection bias)	High risk	No further information was given beyond the following: "Random numbers table was used to allocate patients between Groups 1, 2, 3 and 4."	Low risk	"Random numbers table was used to allocate patients between Groups 1, 2, 3 and 4. These assignments were then put into concealed envelopes and given to the trial clerk. Each of the trial subjects would be given a concealed envelope."
Allocation concealment (selection bias)	High risk	Allocation concealment before assignment was poorly specified.	Low risk	"The trial pharmacist also prepared a series of similar vials containing either 40 mg of Depomedrol (Aburaihan Comp., Iran) (1 cc) or 1 cc normal saline and coded them either 1, 2, 3 or 4, [and] the group assignments were not decoded until the end of the trial when the final analysis was due to take place."
Blinding of participants and personnel (performance bias)	Low risk	"Patients took their envelopes to the trial pharmacist who gave them a coded vial which they took to the orthopaedic surgeon who made the injection. Due to the color difference of depomedrol [*sic*] and normal saline, both vials and syringes were covered by stickers in order to conceal the injection solution."	Low risk	Because of injection color differences, syringes had stickers on them to cover the injection material and were labeled with unidentified numbers.
Blinding of outcome assessment (detection bias)	Low risk	An independent assessor (trial clerk) was used. "The trial subjects were then evaluated using Oxford elbow scale (OES) and visual analog scale (VAS) (OES is the gold standard for clinical evaluation of elbow complaints) by the trial clerk. The patients were evaluated at the baseline and before administration of treatment and they were also asked to come to the trial office at 2 weeks, 4 weeks and 24 weeks for follow-up evaluation which was also conducted by administration of OES and VAS by the trial clerk."	Low risk	Assessors (trial clerks) were blinded to the treatment group because they only knew the patient's allocation number (1-4), which was deidentified at the end of the study.
Incomplete outcome data (attrition bias)	Low risk	Only 1 patient was lost to follow-up (of 79) at 24 wk. No patients were excluded from PROM evaluation.	Low risk	One patient was lost to follow-up.
Selective reporting (reporting bias)	Low risk	The study used a standardized orthopaedic upper-extremity PROM (OES). In addition, it reported on early and late follow-up periods (2, 4, and 24 wk).	Low risk	The OES and VAS were the primary outcome measures and performed adequately.
Other bias	Low risk	—	Low risk	None were identified.

OES, Oxford Elbow Score; PROM, patient-reported outcome measure; VAS, visual analog scale.

Appendix Table 8. Cochrane Risk-of-Bias Assessment for Krogh et al.[14] (2013)

	Rater 1		Rater 2	
Bias	Rater's Judgment	Support for Judgment	Rater's Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	A medium to large block size was used. "Eligible participants were randomly assigned in permuted blocks of 6, using a simple 'shuffling envelopes' procedure to undergo PRP, glucocorticoid, or saline injection."	Low risk	"Eligible participants were randomly assigned in permuted blocks of 6, using a simple 'shuffling envelopes' procedure to undergo PRP, glucocorticoid, or saline injection."
Allocation concealment (selection bias)	Low risk	"To ensure concealment of the assigned intervention, the treating rheumatologist obtained the sequentially numbered, opaque, sealed envelope containing the participant's assigned intervention from the study nurse."	Low risk	"To ensure concealment of the assigned intervention, the treating rheumatologist obtained the sequentially numbered, opaque, sealed envelope containing the participant's assigned intervention from the study nurse."
Blinding of participants and personnel (performance bias)	High risk	The treating rheumatologist was not blinded. "The patient and outcome assessor were blinded to the treatment, but the treating physician was not."	Low risk	"Preparation of the 3 injectants took place out of sight of the patient." "The patient and outcome assessor were blinded to the treatment, but the treating physician was not." "In both the PRP and saline treatment groups, the injection technique included making 5 to 7 perforations into the common tendon origin. Thus, it is not certain that the saline injection serves as an innate placebo control for the PRP injection."
Blinding of outcome assessment (detection bias)	Low risk	"The patient and outcome assessor were blinded to the treatment."	Low risk	The evaluator was not involved in the injection process and was thus blinded to which solute the patients received.
Incomplete outcome data (attrition bias)	Low risk	"During the study, there were no patients lost to follow-up. All patients were assessed at 1 month and at primary outcome at 3 months."	High risk	It appears that there were indeed quite a few dropouts at 12 mo, but the authors simply redefined their follow-up period to a shorter follow-up: They reported a "huge dropout rate with very few participants left after 3 months." "Our a priori sample size calculation did not take into account the huge dropout after 3 months. Because of this, data are presented as 3-month data (no attrition)." "During the study, there were no patients lost to follow-up." Only 40%, 25% and 15% of patients completed the full 12 mo in each arm.
Selective reporting (reporting bias)	Low risk	A standardized orthopaedic PROM was used (PRTEE).	Low risk	The authors mentioned that they found no significance in their pain data at 3 mo; the disability scores also did not show a significant difference. They also mentioned, "Our results do not match the promising results observed in previous studies with PRP," but this study is important to have in the literature because their results counter other trends in results.
Other bias	Low risk	—	Low risk	The provider was not blinded.

PROM, patient-reported outcome measure; PRP, platelet-rich plasma; PRTEE, Patient-Rated Tennis Elbow Evaluation.

Appendix Table 9. Cochrane Risk-of-Bias Assessment for Wolf et al.[15] (2011)

	Rater 1		Rater 2	
Bias	Rater's Judgment	Support for Judgment	Rater's Judgment	Support for Judgment
Random sequence generation (selection bias)	High risk	No further information was given beyond the following: "At both centers, patients were randomized into 3 treatment groups by sealed envelopes generated centrally by a random numbers table."	Low risk	Patients were "randomized into 3 treatment groups by sealed envelopes generated centrally by a random numbers table."
Allocation concealment (selection bias)	High risk	No effort to conceal allocation before assignment was explicitly stated.	Unclear risk	Envelopes were sealed, and patients were not told to which group they belonged. It is unclear whether there was foreknowledge of forthcoming allocations.
Blinding of participants and personnel (performance bias)	High risk	Although patients were blinded, treating physicians were not blinded. "To keep study participants effectively unaware of the study protocol, each patient had 3 mL blood drawn before the injection was prepared. Each injection was mixed by the physician, who stayed behind a curtain or screen and then covered the syringe with aluminum foil."	Low risk	"To keep study participants effectively unaware of the study protocol, each patient had 3 mL blood drawn before the injection was prepared. Each injection was mixed by the physician, who stayed behind a curtain or screen and then covered the syringe with aluminum foil." Personnel were not blinded, but they were not the individuals conducting outcome analyses.
Blinding of outcome assessment (detection bias)	Unclear risk	The study does not explicitly state who instructed the patients during the PROM assessment. It also does not explicitly state who completed the aggregated PROM analysis.	Low risk	The blinded patients determined their own outcomes with self-administered surveys.
Incomplete outcome data (attrition bias)	Low risk	A minimal loss to follow-up occurred. No patients were excluded from analysis outside of those lost to follow-up. "A total of 34 subjects were enrolled in the study at 2 centers. Three subjects dropped out of the study after 2 weeks, and another 3 did not follow up after initial injection, leaving 28 subjects with data for analysis."	Low risk	Only 3 patients dropped out, and only 3 did not undergo follow-up.
Selective reporting (reporting bias)	Low risk	A standardized orthopaedic PROM was used (DASH).	Low risk	There was no expected selective reporting because patients were not able to discern their treatment group.
Other bias	Low risk	—	Low risk	None were identified other than the sample size.

DASH, Disabilities of the Arm, Shoulder and Hand; PROM, patient-reported outcome measure.

Appendix Table 10. Cochrane Risk-of-Bias Assessment for Espandar et al.[16] (2010)

	Rater 1		Rater 2	
Bias	Rater's Judgment	Support for Judgment	Rater's Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	"A computer-generated sequence with a block size of four patients was used for randomization. The patients were assigned consecutive numbers based on the order of enrollment in the study."	Low risk	"A computer-generated sequence with a block size of four patients was used."
Allocation concealment (selection bias)	Low risk	Although a pre-generated randomized sequence list was created and patients were assigned to treatments through this list based on their order of enrollment, the only person with access to the randomized sequence was independent of the enrollment process. There did not appear to be any foreknowledge of forthcoming allocations. "A computer-generated sequence with a block size of four patients was used for randomization. The patients were assigned consecutive numbers based on the order of enrollment in the study. A session for a pre-injection evaluation and injection was scheduled with the patients, and their assigned numbers were sent to a research assistant whose only role in this study was to prepare the solutions for the injection date. The research assistant was the only one with access to the randomization list."	Low risk	The only person who had the patients' assigned numbers was the research assistant, whose only study role was in preparing the injections. There did not appear to be any foreknowledge of forthcoming allocations.
Blinding of participants and personnel (performance bias)	High risk	"We could not ensure that participants were blinded to the drug they received because of the high rate of extensor lag in the botulinum toxin group."	Low risk	Adequate precautions were taken to blind patients and personnel. Solutions were covered in tape to prevent the provider or patient from guessing the contents, but even if the solutions were seen, both were colorless. The same syringe was given in both groups, in addition to the same number of injections and amount of fluid. However, the authors did state, "As for the limitations of our study, we could not ensure that participants were blinded to the drug they received because of the high rate of extensor lag in the botulinum toxin group." This extensor lag was unavoidable.
Blinding of outcome assessment (detection bias)	Low risk	"To preserve blinding of the physician who gave the injections and assessed pain and grip strength, extensor lag was assessed by a research assistant who was not aware of the study design. Also, the patients were asked to hold the dynamometer before the physician entered the room so he would not realize the existence of extensor lag."	Low risk	The research assistant working through the outcome measures with the patients was not aware of the study design and "was not involved in recording of other major and minor outcome measures of the study in order to preserve blinding."
Incomplete outcome data (attrition bias)	High risk	"None of the patients were lost during follow-up."	Low risk	"None of the patients were lost during follow-up."

(continued)

Appendix Table 10. Continued

Bias	Rater 1		Rater 2	
	Rater's Judgment	Support for Judgment	Rater's Judgment	Support for Judgment
Selective reporting (reporting bias)	High risk	No standardized orthopaedic outcome reporting was used outside of a VAS.	Low risk	The authors reported both results that were and results that were not statistically significant, suggesting that no selective reporting occurred. For example, "the difference was not statistically significant and grip strength returned to its baseline level at week 16."
Other bias	High risk	"More than 90% of the participants were women. Most of the male participants did not meet the inclusion criteria, had at least one of the exclusion criteria or did not consent to participate in the study because they thought that development of extensor lag would affect their ability to work." Fifteen patients were excluded before analysis based on the exclusion criteria, which included the following: "having a hobby or job that requires extension of fingers or wrist." Persons who find themselves with lateral epicondylitis often have such hobbies or jobs, and excluding them may bias the results of this study such that the studied patients had better outcomes.	Low risk	None were identified.

VAS, visual analog scale.