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Analytical-Systematic Review—CME

# Systematic Review and Meta-Analysis of Nonoperative Platelet-Rich Plasma Shoulder Injections for Rotator Cuff Pathology

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**Abstract**

**Background:** Platelet-rich plasma (PRP) injections have been introduced to augment the recovery of patients with shoulder pathology. Although multiple studies have been published, no large-scale trials or meta-analyses have assessed the efficacy of nonoperative shoulder PRP injection.
**Objective:** To assess the efficacy of nonoperative PRP shoulder injection in rotator cuff pathology for pain as measured by the visual analog scale (VAS) and range of motion (ROM).
**Design:** Two authors independently screened the Medline and Cochrane databases to include prospective studies that reported VAS and ROM outcomes for nonoperative shoulder PRP injections for rotator cuff pathology. Study quality was assessed using the revised Cochrane Collaboration risk-of-bias tool and modified Downs and Black checklist. Subsequent meta-analysis was performed to determine the effect of nonoperative PRP injections on pain and ROM 3 to 12 months after intervention.
**Results:** Six studies met systematic review criteria. The included studies used different PRP formulations (concentration, leukocyte count), injection protocols (approach, injection number), and varied study designs. Three studies concluded that PRP provided no significant benefit for pain and ROM when compared to physical therapy. Within-group meta-analysis of six fairly heterogeneous studies ($I^2$ 77.8%) demonstrated a statistically significant ($P < .001$) improvement in pain 3 to 12 months after PRP injection. Within-group meta-analysis for four studies for shoulder flexion and abduction was found to be too heterogeneous to derive meaningful results.
**Conclusion:** There is a limited quantity of high-quality studies that assess the efficacy of nonoperative PRP shoulder injection for pain and ROM. Systematic review of PRP injections did not demonstrate an improvement in pain or ROM compared to physical therapy. Although within-group meta-analysis of nonoperative PRP statistically showed that nonoperative PRP improved pain, the lack of adequate negative controls precludes the ability to conclude whether improvements were due to natural recovery or nonoperative PRP.

## Introduction

Sub-acute and chronic rotator cuff shoulder injuries remain challenging conditions to treat. Traditional nonoperative musculoskeletal medicine, including the use of anti-inflammatories and targeted exercises, often fall short.[1] In recent years there has been a rapid increase in the use of biologics, such as platelet-rich plasma (PRP) injections, for a variety of musculoskeletal injures, including those attributed to rotator cuff injuries.[2] This interest in PRP is expected to continue, as the global market for PRP was valued at $195.2 million in 2017 and is projected to expand at a compound annual growth rate of 12% yearly reaching $543.5 million by 2026.[3]

PRP is an autologous concentration of platelets, growth factors, and cellular signaling factors that have the potential to improve tissue healing.[4] Peptides in PRP include epidermal growth factor, platelet-derived growth factor, transforming growth factor-B, vascular endothelial growth factor, fibrin, fibronectin, and vitronectin. When injected, the combination of these factors stimulates collagen synthesis and tissue healing. PRP-mediated matrix reinforcement is hypothesized to be due to angiogenesis, cellular movement, and reconstruction. PRP is thought to improve pain by spurring macrophage-activating antibacterial and anti-inflammatory influences.[5-7] Despite the recent popularity of PRP injections no large-scale trials

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or meta-analyses have evaluated the efficacy of nonoperative shoulder PRP injections.

## Objective

To assess the efficacy of nonoperative PRP shoulder injections in rotator cuff pathology for pain, as measured by the visual analog scale (VAS) and range of motion (ROM).

## Methods

A systematic search across multiple databases was performed for clinical trials that involved nonoperative PRP shoulder injections for the treatment of shoulder rotator cuff pathology. Medline search with meSH Terms "platelet-rich plasma," "shoulder," and "injection" along with a Cochrane library database search using key terms including "platelet-rich plasma," "PRP," "shoulder," and "injection." Two authors independently reviewed abstracts to include all studies that met the inclusion and exclusion criteria for systematic review and meta-analysis. Inclusion criteria consisted of the following: (1) nonoperative shoulder PRP injection for the treatment of rotator cuff pathology; (2) original prospective studies with both reported average pain outcomes in VAS on a 10- or 100-point scale and average mean ROM pre- and post-PRP intervention, mean and SD; and (3) study published in English. Exclusion criteria included the following: (1) PRP shoulder injection used as adjunctive therapy in a surgical procedure; (2) non-peer-reviewed publications; (3) review article; and (4) non-English publications. The risk of bias was assessed using two separate tools, the revised Cochrane Collaboration risk-of-bias tool (RoB2) for the included randomized studies and the modified Downs and Black checklist for included nonrandomized studies.[8,9] The RoB2 tool assesses risk-of-bias in five domains occurring in different stages of a clinal trial.[9] Domains included are the following: (1) bias arising from the randomization process; (2) bias from deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in the measurement of the outcome; and (5) bias in the selection of reported results.[9] The overall risk-of-bias judgment is then classified as "low risk of bias," defined as low risk of bias in all domains; "some concerns," defined as the study has some concerns in at least one domain but not a high risk of bias for any domains; and finally "high risk of bias" judged to be a high risk of bias in at least one domain or to have some concerns for multiple domains.[9] The Downs and Black checklist contains 27 items with a maximum score of 32.[8] The modified checklist has a maximum score of 28, due to a simplified scoring for item 27, where the 5-point scale is converted to a binary system with 1 point assigned for an adequate power calculation and 0 points assigned for inadequate power calculation.[10] The modified Downs and Black score ranges were given the following quality levels: excellent (26-28); good (20-25); fair (15-19); and poor (≤14).[11] Meta-analysis was completed to assess the pooled effect that PRP has on pain as measured by the VAS and shoulder ROM. Given the different end points of each study, pre-injection VAS and ROM were compared to the end of study VAS and ROM, which was between 3 and 12 months after injection. Effect size Cohen's $d_z$ for within-subjects analysis for VAS, shoulder flexion, and abduction was determined using G*power.[12,13] Correlation between pre- and post-injection has not been reported in the literature. As such, a moderate effect of 0.5 was chosen to represent *r* as the correlation between pre- and post-injection to be used for within-subject analysis.[14] The STATA12 metan function was used to compile random effects meta-analysis for VAS and ROM.

## Results

### *Systematic Review*

A systematic search across multiple databases was completed in September 2018. A literature search identified 702 total studies. Database filters were utilized to filter for clinical trials, which resulted in 72 remaining studies. These 72 abstracts were screened and 58 studies were excluded for use of PRP injections in an operative setting. The remaining 14 full-text studies were reviewed.[7,15-27] Shams et al[25] was found to be a reanalysis of published data, Kothari et al[17] used PRP in periarthritis, Kesikburun et al[21] reported ROM as medians, and five other studies did not include both VAS and ROM data, and thus these studies did not meet inclusion criteria.[22-24,26,27] As seen in Figure 1, Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)[28] guidelines were used to summarize the process of study selection. Ultimately, the six publications that met the criteria for review were by Nejati et al,[15] Ilhanli et al,[16] Say et al,[7] Zafarani et al,[18] Cai et al,[19] and Sengodan et al.[20] The risk of bias analysis for the three including randomized controlled publications using the RoB2 tool was considered low for two studies and some concerns for one study.[9] The three included nonrandomized publications were determined to be of fair quality using the modified Downs and Black checklist.[8,10,11] All three nonrandomized studies showed some concern regarding performance and selection bias. The individualized risk-of-bias for each study are summarized in Figure 2 for the randomized control studies and Table 1 for the nonrandomized studies.

Nejati et al conducted a single-blind randomized control trial with 62 subjects comparing PRP injection therapy to exercise therapy for subacromial impingement syndrome over 6 months. Of the 62 subjects randomized, only 42 completed the study and were included in their analysis. Subacromial impingement syndrome was defined as a positive result in at least three of the following tests: empty can test, Speed's test, Jobe's test, Neer

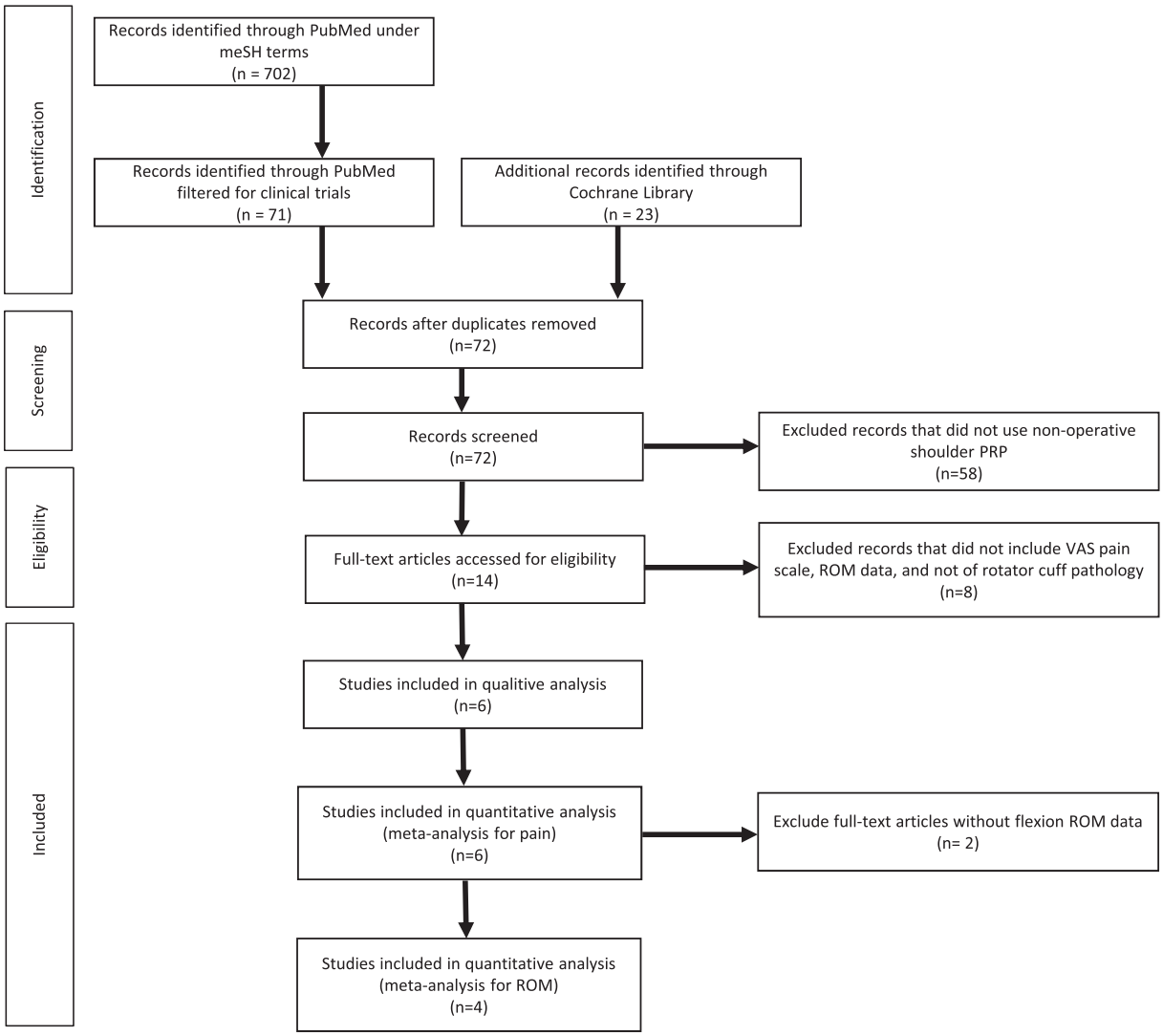


**Figure 1.** PRISMA flowchart.

impingement sign, and Hawkins-Kennedy test. Magnetic resonance imaging (MRI) was used to evaluate rotator cuff pathology. Baseline MRI findings were reported only for the 42 subjects who completed the study, which included the following: 5 patients with supraspinatus tendinopathy in the PRP treatment group and 6 in the exercise treatment group; 16 patients with partial supraspinatus tear in the PRP group and 14 in the exercise group; and one patient with a partial subscapularis tear in the PRP group with none in the exercise group. No details were reported regarding the specifics of the rotator cuff tears except that complete rotator cuff tears were excluded. The study population included eight patients with MRI findings of biceps tendinopathy, three in the PRP group and five in the exercise group. In recognition of biceps pathology as a potential confounder in the study, Nejati et al reported that post-intervention MRI resulted in no change to biceps tendinopathy from baseline in either group. The PRP group received 4 mL of PRP twice at three times the baseline concentration of platelet leukocyte poor injections 1 month apart. The PRP was injected into the injured tendons under ultrasound guidance. The PRP group did not participate in exercise therapy. The exercise group participated in once a week supervised group exercise along with a home exercise program (HEP) for the other days of the week for 3 months; they were asked to continue HEP until the remainder of the study. Outcomes compared were VAS, ROM, the Disabilities of the Arm, Shoulder, and Hand (DASH) score, and the Western Ontario Rotator Cuff Index (WORC). At 6 months, the authors concluded that there was a significant improvement in both the PRP group and the exercise group in pain and function from baseline, both groups in VAS ($P < .01$), WORC ($P < .01$), and DASH ($P < .01$). However, there was no significant difference in improvement of pain with PRP injection compared to exercise, VAS ($P = .65$), WORC ($P = .02$), and DASH ($P = .22$). In addition, exercise therapy performed better for abduction ROM and functional outcomes when measured by WORC compared to the PRP group.[15]

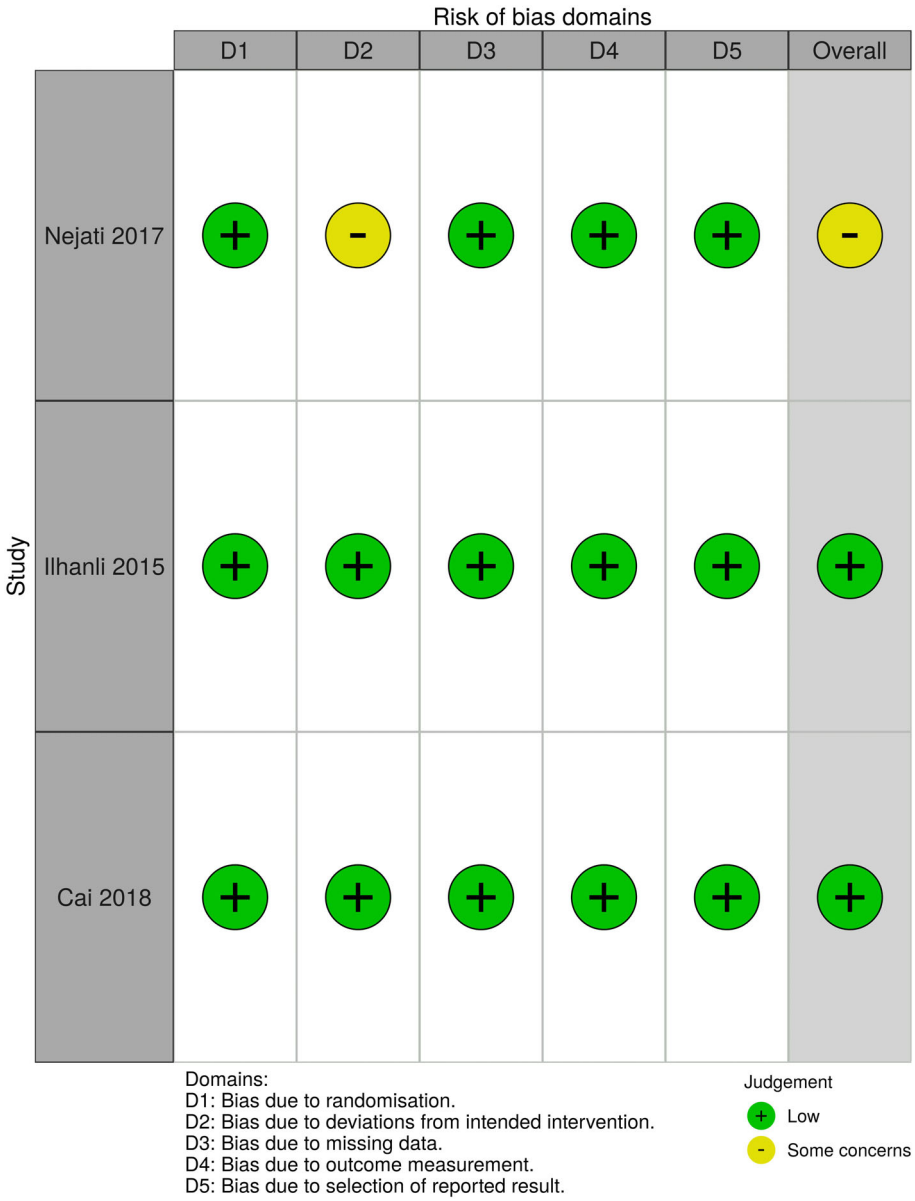


**Figure 2.** Risk of bias.

Ilhanli et al conducted a single-blind randomized control trial with 70 subjects, comparing PRP injection to physical therapy (PT) for partial supraspinatus tears over 12 months. The PRP group received 6 mL of PRP three times at 2.1 to 2.5 times the baseline platelet concentration via intra-articular shoulder injection 1 week apart. Ilhanli et al did not report what approach was used for the injection or used any image guidance technology. The PRP group received only ROM exercises before starting PT strengthening exercises 1 month after the last PRP injection. The PT group completed 15 PT sessions, 5 sessions a week for 3 weeks, then continued with a HEP for the remainder of the study. Outcomes were VAS, ROM, and the DASH score. At 12 months the authors concluded that PRP could be as effective as PT, citing both groups improved from baseline, both VAS ($P < .05$), and DASH ($P < .05$). There was no significant difference in improvement between groups, with VAS ($P = .798$) and DASH ($P = .790$). However, ROM improvement was greater in the PT group compared to the PRP group, with a comparison of means ($P < .05$).[16]

Zafarani et al conducted a nonrandomized pre-post study of 19 subjects with partial rotator cuff tears treated with a single injection of PRP. Partial rotator cuff tear diagnosis was confirmed with MRI. Subjects with grade 1 to 3 Ellman criteria qualified for inclusion. PRP was injected into the intra-articular space and subacromial bursa. The injection approach was not reported and was not guided via imaging. All patients participated in HEP consisting of shoulder stretching. Outcomes consisted of VAS, ROM, the DASH score, and the Short Form-12 (SF-12) health survey. Assessments were made pre-injection and every month post-injection for 3 months. At the end of the study, the authors reported that patients made significant improvements, including 66% less pain, 53%

**Table 1**
Quality assessment of the included non randomized studies using the modified Downs and Black checklist

| | Say et al[7] | Zafarani et al[18] | Sengodan et al[20] |
|---|---|---|---|
| Reporting | | | |
| Q1: Aim clearly described? | Yes | Yes | Yes |
| Q2: Outcomes clearly described? | Yes | Yes | Yes |
| Q3: Patients' characteristics clearly described? | Yes | Yes | Yes |
| Q4: Interventions clearly described? | Yes | Yes | Yes |
| Q5: Principal confounders clearly described? | Partially | Partially | No |
| Q6: Main findings clearly described? | Yes | Yes | Yes |
| Q7: Random variability for main outcome provided? | Yes | Yes | Yes |
| Q8: Adverse events reported? | No | No | Yes |
| Q9: Loss to follow-up reported? | Yes | Yes | Yes |
| Q10: Actual *P* value reported? | Yes | Yes | Yes |
| External Validity | | | |
| Q11: Sample asked to participate representative of the population? | Yes | Yes | Yes |
| Q12: Sample agreed to participate representative of the population? | Yes | Yes | Yes |
| Q13: Staff participating representative of the patients' environment? | Yes | Yes | Yes |
| Internal Validity—Performance Bias | | | |
| Q14: Attempt to blind participants? | No | No | No |
| Q15: Attempt to blind assessors? | No | No | No |
| Q16: Data dredging results stated clearly? | Yes | Yes | Yes |
| Q17: Analysis adjusted for length of follow-up? | Yes | Yes | Yes |
| Q18: Appropriate statistics? | Yes | Yes | Yes |
| Q19: Reliable compliance? | Unable to determine | Unable to determine | Unable to determine |
| Q20: Accurate outcome measures? | Yes | Yes | Yes |
| Internal Validity—Selection Bias | | | |
| Q21: Same population? | Yes | Yes | Yes |
| Q22: Participants recruited at the same time? | Yes | No | Yes |
| Q23: Randomized? | No | No | No |
| Q24: Adequate allocation concealment? | No | No | No |
| Q25: Adequate adjustment for confounders? | No | No | No |
| Q26: Loss of follow-up reported? | Yes | Yes | Yes |
| Power | | | |
| Q27: Power calculation? | No | No | No |
| Total score (quality level) | 19 (Fair) | 18 (Fair) | 19 (Fair) |

improved in ROM, 76% improved in DASH scores, and 84% improved in SF-12 from baseline ($P < .001$) in all outcome measures.[18] Significant confounders exist with this study including the lack of PRP injectate cytology and the lack of an adequate placebo comparison group. Without cytology, it is not known if the same PRP concentration of PRP injectate was used for all subjects. Without a placebo comparison, it is not possible to determine if the results were due to PRP or the natural progression of partial rotator cuff tear recovery over 3 months.

Cai et al conducted a double-blind randomized control trial in 184 subjects comparing PRP to saline placebo to sodium hyaluronate (SH) to SH + PRP combination for partial rotator cuff tears over 12 months of follow-up. All injection groups received a total of four injections each 4 mL in volume, whereas the SH + PRP group received a 4 mL mixture of 2 mL SH and 2 mL PRP once a week over 4 weeks. PRP preparation reached $1 \times 10^{12}$/L and was leukocyte poor in concentration. The injectate was injected into the subacromial space via ultrasound guidance. The presence or absence of a formal or informal exercise program was not documented. Outcomes compared were radiological anterior-posterior tear size, VAS, ROM, the American Shoulder and Elbow Surgeons (ASES) score, and the Constant score. Results compared baseline to 12-month post-intervention for each group. With regard

**Table 2**
Baseline characteristics

| Study author | n | Male | Age* | Age SD | Chronicity of shoulder complaints |
|---|---|---|---|---|---|
| Nejati | 22 | 9 | 52.50 | 7.30 | At least 3 mo |
| Ilhanli | 30 | 9 | 59.16 | 10.76 | Male 8.23 ± 4.10 mo, female 6.86 ± 3.67 mo |
| Say | 30 | 10 | 49.20 | 7.00 | At least 3 mo |
| Zafarani | 19 | 8 | 56.00 | 4.10 | More than 3 mo |
| Cai | 45 | 22 | 40.56 | 7.85 | Average of 3 mo |
| Sengodan | 20 | 12 | 55.00 | 6.40 | 2 to 18 mo |

*Reported as mean.
SD = standard deviation.

**Table 3**
Summary of publications

| Author | Study type | Year | Journal | Sample size in PRP group | Study length | Shoulder pathology | PRP injection #/interval/ volume/platelet concentration/activation | Ultrasound guidance/Injection approach/target | Exercise therapy after PRP | Comparison | Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Nejati | Randomized controlled trial Single blind | 2017 | The Orthopedic Journal of Sports Medicine | n = 22 | 6 mo | Supraspinatus tendinopathy or partial tear or subscapularis partial tear by MRI | 2/1 mo/4 mL/3×/No | Yes/posterolateral/ center of lesion | No | Exercise therapy | PRP and exercise improved pain, VAS ($P$ < .01) and function, WORC ($P$ < .01), DASH ($P$ < .01). No difference between PRP and exercise, VAS ($P$ = .65), WORC ($P$ = .02) and DASH ($P$ = .22) |
| Ilhanli | Randomized controlled trial Single blind | 2015 | Iran Red Crescent Med Journal | n = 30 | 12 mo | Chronic supraspinatus tear by MRI | 3/1 wk/6 mL/2.1-2.5×/ Yes, calcium chloride | No/Unknown/ Intraarticular | Yes | Physical therapy and home exercise program | PRP and physical therapy improved pain, VAS ($P$ < .05) and function, DASH ($P$ < .05). No significant difference between either, VAS ($P$ = .798), and DASH ($P$ = .790) |
| Say | Quasi experiment | 2016 | Journal of Orthopedic Surgery | n = 30 | 6 mo | Subacromial impingement syndrome >3 mo | 1/Not applicable/2.5 mL/4×/ Yes, calcium chloride | No/posterolateral/ subacromial space | Yes | Steroid injection | Steroid injection was more effective than PRP for pain, VAS ($P$ < .001) and function, Constant score ($P$ < .001) |
| Zafarani | Case series | 2017 | The Archives of Bone and Joint Surgery | n = 19 | 3 mo | Partial rotator cuff tear by MRI | 1/Not applicable/ Unknown/Unknown/No | No/unknown/ subacromial bursa and intra-articular space | Yes | None | PRP showed positive recovery effects on partial rotator cuff related pain, VAS ($P$ < .001) and function, range of motion ($P$ < .001), DASH ($P$ < .001) and the Short form-12 ($P$ < .001) |
| Cai | Randomized controlled trial Double blind | 2018 | Medicine & Science in Sports & Exercise | n = 45 | 12 mo | Partial supraspinatus bursal sided tears by MRI | 4/1 wk/4 mL/1 × $10^{12}$/L/ No | Yes/unknown/ subacromial space | No reported exercise program in any group | Saline placebo, SH, SH + PRP Combination | SH + PRP combination and PRP is superior to saline placebo for pain, function (no statistical analysis done between groups) and healing of partial bursal sided rotator cuff tears when compared to baseline |
| Sengodan | Case series | 2017 | Journal of Clinical Imaging Science | n = 20 | 3 mo | Partial rotator cuff tear by MRI and ultrasound | 1/not applicable/ 2-3 mL/Unknown/No | Yes/unknown/ center of lesion | No reported exercise program | None | Ultrasound guided PRP injections are effective in reducing pain, VAS ($P$ < .001) and improving shoulder function, Constant ($P$ < .001), UCLA ($P$ < .001) in partial rotator cuff tears |

PRP = Platelet-rich plasma, MRI = magnetic resonance imaging, SH = sodium hyaluronate, VAS = Visual analog scale, WORC = Western Ontario Rotator Cuff Index, DASH = Disabilities of the arm, shoulder and hand score, UCLA = University of California Los Angeles shoulder score.

**Table 4**
Visual Analog Scale (VAS) Cohen's $d_z$

| Study # | Study author | n | Pre | Pre-SD | Post | Post-SD | Cohen's $d_z$ | Variance |
|---|---|---|---|---|---|---|---|---|
| 1 | Nejati | 22 | 8.10 | 1.70 | 4.50 | .40 | 2.338 | .170 |
| 2 | Ilhanli | 30 | 7.80 | 1.78 | 2.70 | 1.48 | 3.090 | .192 |
| 3 | Say | 30 | 7.50 | 1.40 | 5.30 | 1.60 | 1.457 | .069 |
| 4 | Zafarani | 19 | 7.53 | .77 | 2.58 | 1.22 | 4.632 | .617 |
| 5 | Cai | 45 | 6.27 | 1.50 | 1.98 | .69 | 3.299 | .143 |
| 6 | Sengodan | 20 | 5.40 | .92 | 2.55 | .83 | 3.244 | .313 |

r = .5 assumed for moderate effect of interdependence for within-subjects analysis.
SD = Standard deviation.

to VAS at 12 months post-intervention the SH + PRP improved the most ($P < .05$), followed by the PRP group ($P < .05$), the SH group ($P < .05$), and finally the saline group ($P < .05$). Similarly, it was reported by the end of the 12-month follow-up that the PRP and SH + PRP groups demonstrated more improvement in Constant and ASES scores from baseline relative to the SH group; all reached statistical significance ($P < .05$). No improvement in function was seen in the saline group (reported $P$ value).[19] A significant concern is that there was no statistical analysis comparing the four groups using any of the outcome measures; therefore it is impossible to know if the reported differences were statistically significant.

Say et al conducted a nonrandomized cohort study of 60 subjects treated with a single-dose injection of PRP or steroid injection for subacromial impingement syndrome (SIS).[7] The diagnosis of SIS was based on the presence of shoulder pain, restricted ROM, positive Neer impingement sign, and/or Hawkins-Kennedy test. MRI was used to determine rotator cuff pathology. Baseline MRI findings included 42 patients with rotator cuff tendonitis and 18 with partial tendon tear. To qualify for the study, subjects had to be recalcitrant to conservative nonsteroidal anti-inflammatory drug (NSAID) or exercise treatment for >3 months. Outcome measures including the Constant score,[7] VAS, and shoulder ROM were assessed at 6 weeks and 6 months. Both groups underwent rotator cuff stretching and strengthening for 6 weeks. The injectates were injected into the subacromial space without image guidance using a landmark posterolateral approach. The authors concluded that the steroid injection group experienced a statistically significant Constant score ($P < .001$) and VAS ($P < .001$) at 6 weeks and 6 months compared to the PRP cohort. ROM of the shoulder was comparable between two groups: flexion ($P = .106$), abduction ($P = .699$), internal rotation ($P = .205$), and external rotation ($P = .259$). Of interest, ROM is a variable within the Constant score, which may suggest that pain had a stronger statistical contribution to the significant difference between the PRP and steroid groups than ROM.

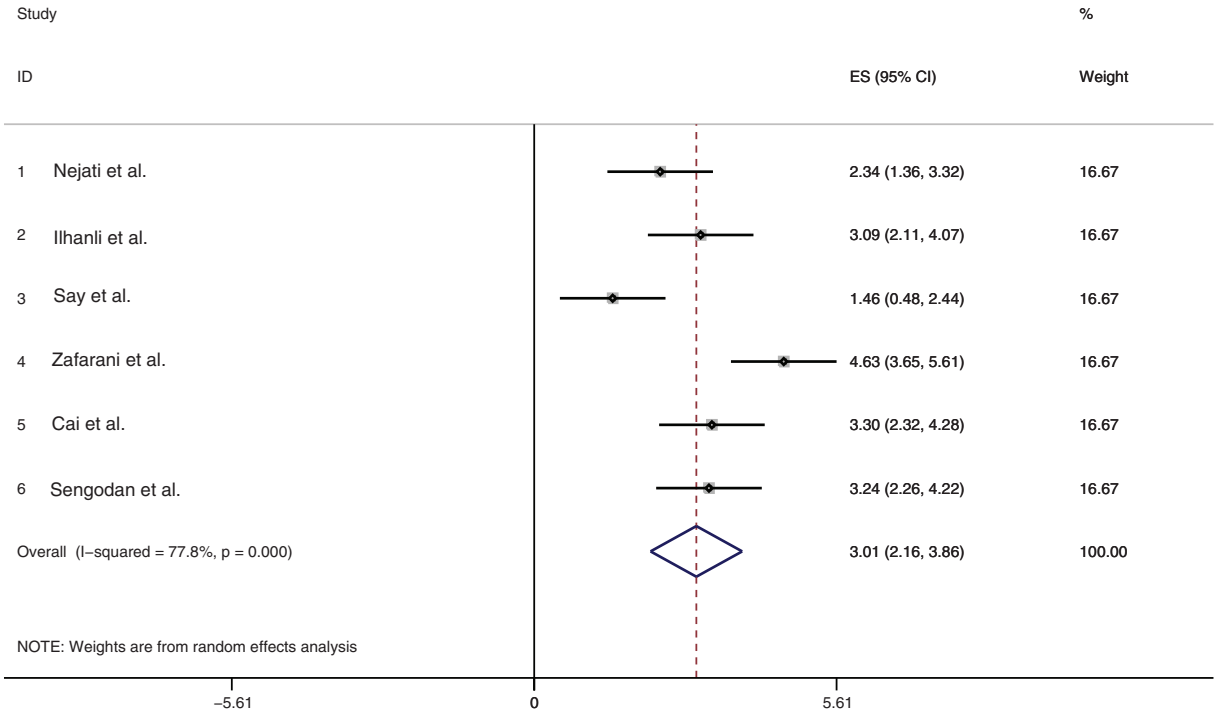


**Figure 3.** Forest plot visual analog scale.

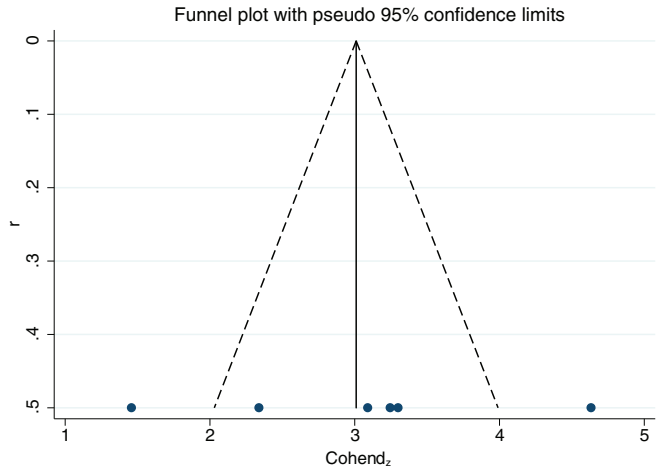


**Figure 4.** Funnel plot visual analog scale.

Sengodan et al conducted a nonrandomized pre-post study of 20 subjects treated with PRP for partial rotator cuff tears. The diagnosis of partial tear was confirmed with MRI evidence of less than 50% thickness injury. Subjects were also treated with 2 months of conservative management. PRP was injected via ultrasound guidance into the center of the rotator cuff lesion. Outcome measures including the Constant score, VAS, and University of California Los Angeles (UCLA) shoulder score[20] at the time of injection, 8 weeks, and 3 months. The authors noted that VAS ($P$ < .001), Constant ($P$ < .001), and UCLA scores ($P$ < .001) improved significantly from time zero to 8 weeks and 3 months. The absence of a placebo group in this study confounds the ability to attribute the significant improvements to natural healing, PRP, or the 2 months of conservative management. Of note, the mean Constant score difference between pre and post exceeded the minimum clinically important difference.[29]

In the review of the six selected publications, two single-blind randomized control trials by Ilhanli et al[16] and Nejati et al[15] concluded that PRP was not superior to placebo and was not significantly better than physical therapy or exercise therapy for shoulder pain or function due to rotator cuff pathology. Cai et al's[19] double-blind randomized control trial reported improvements in pain, ROM, and function in PRP + SH, PRP, and SH from baseline to 12-month follow-up compared to no improvement from baseline in the placebo group. However, no statistical analysis was performed to compare the study arms; therefore it is not possible to assess if this was a significant difference. Three other studies reported improvement in pain and ROM; however, study designs lacked randomization and control groups. A summary of all the publications reviewed is shown in Tables 2 and 3.[7,15,16,18-20]

### *Meta-Analysis*

The meta-analysis of the six qualifying publications found through systematic review was performed with VAS as the primary outcome measure. Secondary outcome measures were shoulder flexion and abduction.[7,15,16,18-20]

Six publications included VAS data, and the effect size was calculated as Cohen's $d_z$ (Table 4).12 Meta-analysis for continuous outcomes and random effects demonstrated significant ($P$ < .001) improvement in VAS at 3 to 12 months post-PRP injection series, as depicted in the forest plot in Figure 3. Because heterogeneity, as measured by $I^2$ for VAS, was 77.8%, as shown in Figure 3, it was concluded that it was fair to compare the results

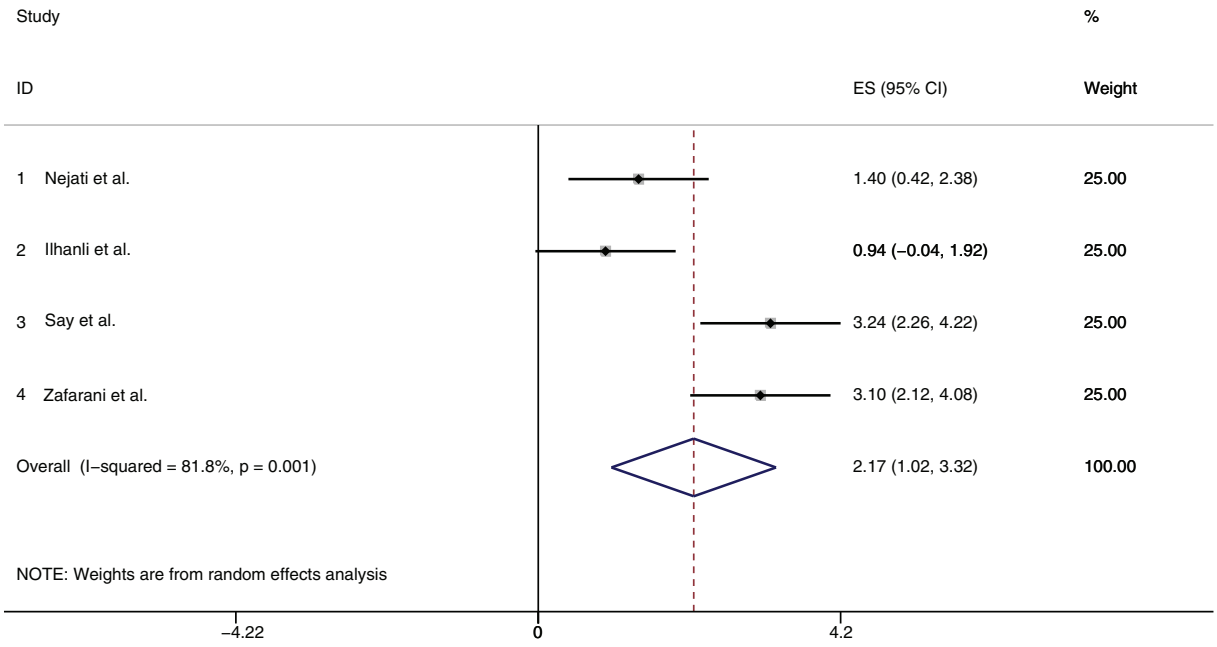


**Figure 5.** Forest plot shoulder flexion.

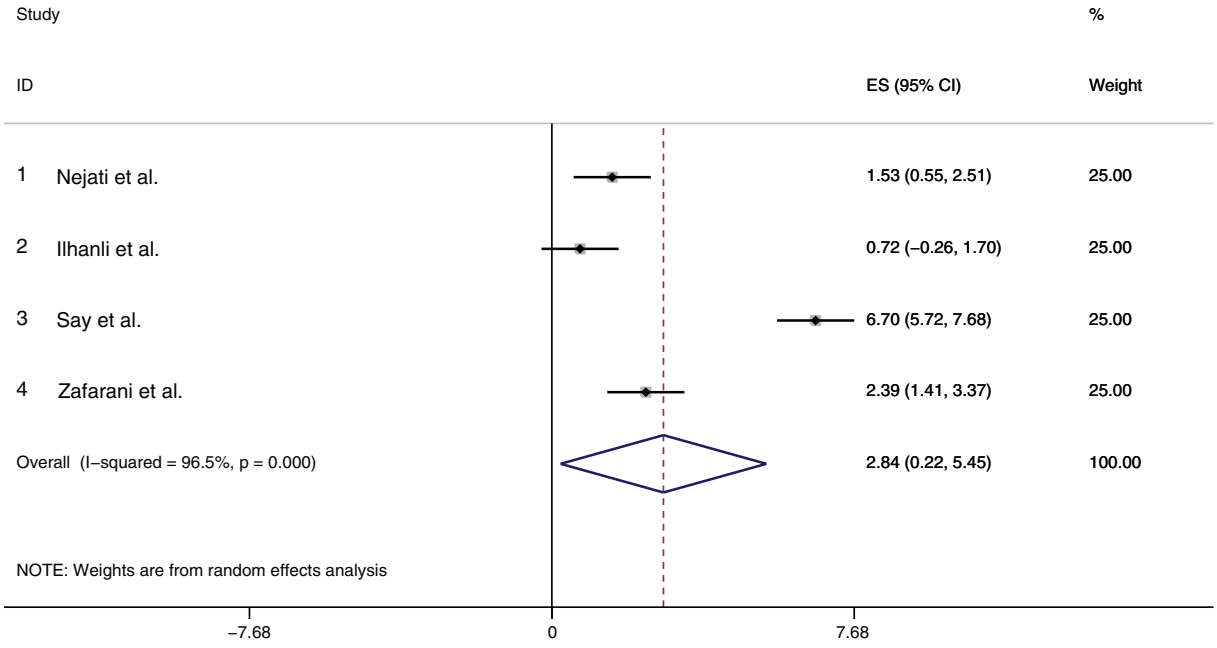


**Figure 6.** Forest plot shoulder abduction.

between the publications. The funnel plot for VAS revealed a moderate amount of asymmetry toward positive results, therefore suggesting the possibility of publication bias (Figure 4).

Four publications included ROM data for flexion and abduction. Cohen's $d_z$ was calculated for effect size, and meta-analyses for continuous outcomes and random effects were performed.[12] Shoulder flexion and abduction ROM improved significantly, both ($P < .001$) at 3- to 12-month post-injection series, as shown in the forest plot in Figures 5 and 6, respectively (Tables 5 and 6). However, it was unreasonable to compare the four studies in this situation because heterogeneity was too high as measured by $I^2$ for shoulder flexion was 81.8%, as shown in Figure 5, and for shoulder, abduction was 96.5%, as shown in Figure 6.[7,15,16,18] Funnel plots for flexion and abduction revealed a moderate amount of asymmetry toward positive results, therefore suggesting the possibility of publication bias (Figures 7 and 8).

## Discussion

This is the first systematic review with meta-analysis performed to evaluate the efficacy of nonoperative PRP injections for rotator cuff shoulder pathology. Our findings suggest a possible reduction in pain and improved shoulder flexion ROM that is unlikely superior to exercise or physical therapy. The lack of adequate placebo control abrogates a clear conclusion. Clinical application of PRP in musculoskeletal, sport, pain, and spine medicine has grown rapidly in the last few years.[2] There remains a large variability in PRP products used for regenerative therapies across multiple body parts both operatively and nonoperatively.[30-33] There is no consensus regarding the optimal method of preparation, injection number, ideal platelet or leukocyte concentration, or use of platelet-activating agents.[34] The large variation in PRP protocols used and lack of a standard for PRP formulation has made it difficult to develop discrete protocols and larger-scale studies.[35,36] Some evidence suggests that PRP results in longer-term pain relief compared to steroid injections in musculoskeletal medicine as a reported meta-analysis by Mi et al in lateral epicondylitis.[37] Recently, a systematic review without meta-analysis investigating nonoperative shoulder PRP in rotator cuff disease by Hurley et al suggested that PRP injections alone may not be beneficial.[5] Similarly, in this systematic review, limited high-quality studies were identified

**Table 5**
Shoulder flexion Cohen's $d_z$

| Study # | Study author | n | Pre | Pre-SD | Post | Post-SD | Cohen's $d_z$ | Variance |
|---|---|---|---|---|---|---|---|---|
| 1 | Nejati | 22 | 91.10 | 40.60 | 143.60 | 7.40 | 1.402 | .090 |
| 2 | Ilhanli | 30 | 94.77 | 40.83 | 129.33 | 30.47 | .940 | .048 |
| 3 | Say | 30 | 123.00 | 19.00 | 177.00 | 7.00 | 3.245 | .209 |
| 4 | Zafarani | 19 | 97.26 | 17.13 | 149.11 | 16.25 | 3.103 | .306 |

r = .5 assumed for moderate effect of interdependence for within-subject analysis.
SD = standard deviation.

**Table 6**
Shoulder abduction Cohen's $d_z$

| Study # | Study author | n | Pre | Pre-SD | Post | Post-SD | Cohen's $d_z$ | Variance |
|---|---|---|---|---|---|---|---|---|
| 1 | Nejati | 22 | 69.80 | 35.40 | 118.80 | 8.70 | 1.534 | .099 |
| 2 | Ilhanli | 30 | 84.66 | 38.41 | 109.83 | 30.32 | .718 | .042 |
| 3 | Say | 30 | 92.60 | 12.60 | 166.00 | 7.20 | 6.704 | .782 |
| 4 | Zafarani | 19 | 90.95 | 20.45 | 139.84 | 20.48 | 2.389 | .203 |

r = .5 assumed for moderate effect of interdependence for within-subject analysis.
SD = standard deviation.

regarding the use of nonoperative PRP in shoulder rotator cuff pathology. Only three randomized controlled trials, one double-blinded and two single-blinded, which included a placebo, exercise, or therapy comparison group, and three nonrandomized noncontrolled studies, were found through systematic search across multiple databases. All the studies had relatively limited sample sizes of between 40 to 184 participants. All qualifying trials had different PRP injection protocols including three trials that utilized multiple serial PRP injections with varying intervals. The injection approach, use of image guidance, and injection targets varied. In addition, all studies used different PRP preparations, different platelet concentrations, and different leukocyte counts. Two studies included an activating agent in their PRP injectate. Despite the reported heterogeneity in PRP preparation and injection protocols, ultimately two of the three randomized controlled studies concluded that nonoperative PRP shoulder injections provided no additional benefit compared to exercise-based rehabilitation for shoulder pathology.[15,16,19] Unfortunately, the single randomized double-blind controlled trial that compared PRP shoulder injections to three other injection formulations did not document any formal or informal exercise program utilized throughout the trial.[19] Because rehabilitative exercises have shown benefit in treating patients with shoulder pathology, this omission represents a potential confounding factor. In addition, no statistical analysis was performed to compare the intervention and placebo groups; therefore, it is unknown if the positive effect found with PRP + SH, PRP, and SH injectate compared to placebo was of true statistical significance. The three identified studies that were nonrandomized without comparison groups reported potential benefits after PRP to pain, ROM, and function from baseline.[7,18,20] The lack of a control is a significant confounding factor, as it is not possible to know if the improvements seen are superior to what is seen in the natural recovery course of shoulder rotator cuff pathology. Therefore, it cannot be concluded that nonoperative shoulder PRP injections alone provides more benefit than exercise therapy over the course of a 6- to 12-month period. To further study the effect of nonoperative PRP shoulder injections on pain alone over the course of a 3- to 12-month period post-injection, a meta-analysis was performed pooling the reported result across six qualifying studies. Meta-analysis yielded significantly improved pain scores as reported with reduction in VAS. Despite the varied PRP formulations and protocols, the mathematical $I^2$ heterogeneity between studies was acceptable. However, the results of this meta-analysis have to be interpreted with caution as the analysis was done without use of a comparison group, and therefore it cannot be determined whether reduction in pain and improvement in function was due to the intervention or was due to the natural progression seen in rotator cuff pathology. It can be concluded that the PRP injection does not increase VAS in shoulder rotator cuff pathology between 3 and 12 months. Caution is advised,

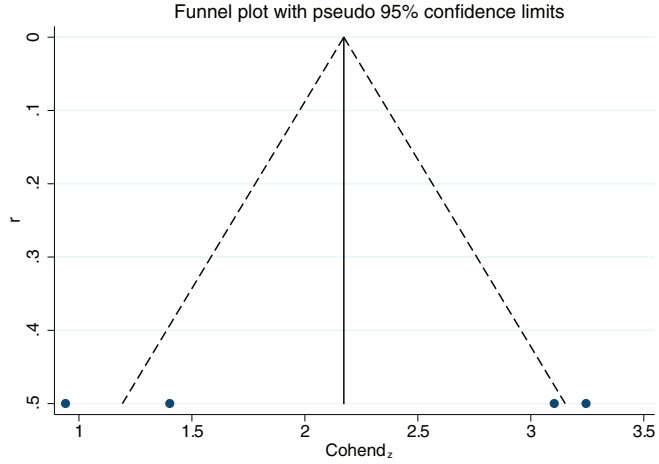


**Figure 7.** Funnel plot shoulder flexion.

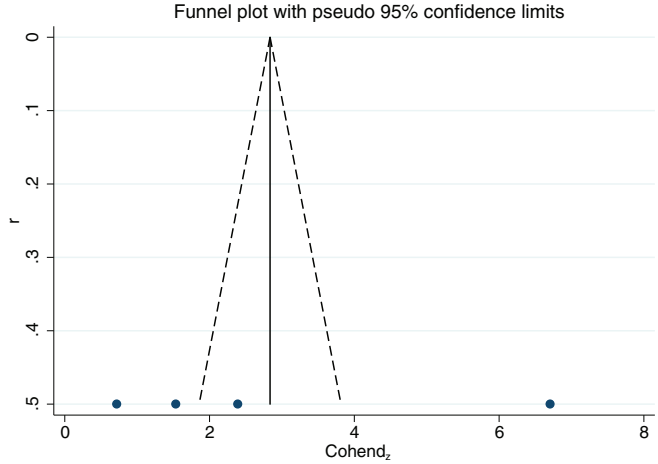


**Figure 8.** Funnel plot shoulder abduction.

as the inherent different time period end points in the studies included can be a confounding variable, potentially masking the longer-term effects of PRP. The analysis of pooled studies also revealed a modest publication bias toward positive results.

The conclusions from this systematic review and meta-analysis are limited because of the limited number of clinical trials, the lack of a control group in many studies, and the different protocols used in PRP preparation and administration. Analysis of the results of future trials will be facilitated when a standard reporting method for PRP preparation and concentration becomes accepted. It appears that PRP shoulder injections in combination with other compounds may provide some benefit over placebo injection.

## Conclusion

There is limited high-quality evidence for the use of nonoperative platelet-rich plasma injections in the treatment of rotator cuff shoulder pathology. The meta-analysis including noncontrolled available research showed statistically significant benefits including improved pain, as measured by VAS over 3 to 12 months. However, without an adequate comparison group, it cannot be determined whether these results are simply the result of the natural progression of rotator cuff disease. There is also a moderate amount of publication bias. When non-operative PRP injections are compared to standard of care, physical therapy, or exercise therapy there was no additional benefit. This research is confounded by the lack of standard reporting protocols for non-operative PRP shoulder injections including PRP formation, the protocol for number and frequency of injections, injection approach, or use of image guidance. Further confounding factors include studies that include several different shoulder pathologies or a lack of adequate comparison groups to PRP injections.

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## Author Contributions

The following co-authors Mickey Lui, Majid Ashfaq, and Duc Tran provided equal contributions to conception, design, data acquisition, analysis, and interpretation. Author Wendy Shih provided statistical consultation for design, data acquisition, analysis, and interpretation. The following co-authors Mickey Lui, Nicole Yim, Majid Ashfaq, Murray Brandstater, and Duc Tran contributed equally in the drafting and revision of the article for critically important intellectual content. All co-authors gave final approval of the version of the article to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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## Disclosure

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## CME Question

In comparison to physical therapy, this systematic review demonstrated which of the following regarding PRP shoulder injections for rotator cuff pathology?

a. Improvement in pain and ROM
b. No improvement in pain or ROM
c. Improvement in pain only
d. Improvement in ROM only

**Answer online at** https://onlinelearning.aapmr.org/