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Authors

Lum, Zachary

Guntupalli, Lohitha

Huish, Eric

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Outcomes of platelet rich plasma injections in the adhesive capsulitis of the shoulder

Zachary C. Lum [a,*], Lohitha Guntupalli [a], Eric G. Huish [b]

[a] Nova Southeastern University, Kiran C. Patel School of Osteopathic Medicine, Davie, FL, 33028, USA
[b] San Joaquin General Hospital, French Camp, CA, USA

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ABSTRACT

Background: Platelet rich plasma (PRP) injections have been utilized in an attempt to provide improved pain and functional outcomes to patients with a variety of orthopaedic ailments. Adhesive capsulitis, also known as frozen shoulder is a common debilitating condition that carries significant morbidity due to the painful and prolonged course. Various studies have investigated intra-articular PRP administration with different methodologies and outcomes.
Hypothesis/purpose: We sought to perform a meta-analysis on outcomes of adhesive capsulitis after PRP injection, determine effectiveness compared to corticosteroid, and compare adverse events.
Study design: Meta analysis.
Methods: EMBASE, EBSCO, Pubmed and Google Scholar were used to extract titles and abstracts using keywords "adhesive capsulitis", "frozen shoulder", "PRP", "platelet rich plasma". 41 articles were found and after duplicates removed and full-text review, 7 studies investigating 385 patients undergoing PRP or corticosteroid injections were found. Age, gender, body mass index (BMI), and ASA scores were obtained. Patient reported outcomes (PROs) were obtained and all reported range of motion (ROM) were recorded and compared after PRP and steroid injections using random effects meta-regression pre-injection and post-injection.
Results: Both intra-articular PRP and steroid injections resulted in improved outcomes for treatment of adhesive capsulitis at 3 months. PRP injections had significantly better range of motion in passive forward flexion (151° vs 144.1°, $p = 0.024$) and had improved Shoulder Pain and Disability Index (SPADI) scores (14.6° vs 18.6°, $p = 0.009$) compared to steroid, however these may not reach minimum clinical thresholds. PRP had significantly better active (60° vs 43. 5°, $p = 0.038$) and passive internal rotation (69.6° vs 52.7°, $p = 0.017$) compared to steroid which did reach minimum clinical thresholds. There were no differences detected between VAS pain, active forward flexion, extension, abduction, external rotation nor difference in adverse events.
Discussion: Both injections decreased pain and improved range of motion in patients. Intra-articular PRP injections may result in improved internal rotation compared to corticosteroid. Improvement in SPADI and passive forward flexion may be statistically significantly but may not be clinically relevant.
Level of evidence: 3, Therapeutic.

Clinical relevance

PRP injections are a safe and effective treatment in adhesive capsulitis.

What is known about the subject

Adhesive capsulitis of the shoulder can be a prolonged and morbid disease. Options for treatment include physical therapy, injection therapies, manipulation and surgery. Platelet rich plasma injection therapy for adhesive capsulitis is a relatively new treatment with sample sizes small compared to other treatment therapies.

What this study adds to existing knowledge

PRP injection therapy was equal to, if not better than comparison corticosteroid injections. Interestingly, posterior based injections resulted in better internal rotation than corticosteroid injection. Further

* Corresponding author.
E-mail address: zlum@ucdavis.edu (Z.C. Lum).

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studies may need to explore if anterior based PRP injections may result in improved external rotation, a key problem in adhesive capsulitis pathogenesis.

1. Introduction

Adhesive capsulitis, also known as frozen shoulder is a common debilitating condition that carries significant morbidity due to the painful and prolonged course. Management is usually conservative consisting of gentle stretching, physiotherapy and intra-articular corticosteroid injections (CS).[5] For recalcitrant cases, manipulation under anesthesia with or without arthroscopic shoulder surgery may be indicated.[7]

Platelet rich plasma (PRP) injections are suggested to provide improved pain and functional outcomes to patients with a variety of orthopaedic ailments. PRP injection for adhesive capsulitis is a novel and emerging treatment for patients who have failed conservative measures, but do not wish or may not qualify to undergo surgery.

Various studies have investigated intra-articular PRP administration with varying results. We sought to perform a meta-analysis on outcomes of adhesive capsulitis after PRP injection, to determine effectiveness compared to corticosteroid, and compare adverse events.

2. Methods

Three reviewers performed a systematic review of studies using the PubMed, EMBASE, EBSCO, Cochrane Library database and Google Scholar for studies performed from inception through March 2022, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The search strategy was developed using MeSH terms of keywords "adhesive capsulitis", "frozen shoulder", "PRP", "platelet rich plasma".

Publication types were limited studies of sample size greater than 10. The reviewers completed the searches separately and results were cross-referenced. Discrepancies were discussed and all studies were initially included if they were deemed relevant. Each study title and abstract was reviewed, full articles were then retrieved if they were deemed potentially relevant. The complete article was then critically analyzed to determine eligibility for the study based upon predefined criteria.

The inclusion criteria were: (1) patients over 18 years of age with diagnosis of adhesive capsulitis (2) patients receiving intra-articular injection of platelet rich plasma, (3) had mean follow up $>$ 1 month, (4) full-text studies published in peer-review journal and (5) written in English. Studies with systematic reviews, meta-analysis, editorials, and commentary articles were excluded.

A total of 254 records were identified. Excluding duplicates, 49 unique articles were screened with 42 removed based on failure to meet inclusion criteria. This left 7 full-text articles that met inclusion criteria for final analysis (Fig. 1). Institutional review board (IRB) approval was not obtained as the study did not require direct contact with patients or patient identifying medical record review.

3. Study characteristics

The 7 included studies for meta-analysis were published between 2018 and 2021, there were 94 males, 290 females and one unidentified gender (Table 1).[1,3,4,6,8,10,11] Relevant studies included 243 patients who were identified to receive intra-articular platelet rich plasma injection therapy. In those studies, there were 142 patients who received corticosteroid injections. The type of PRP was not identified in the studies. One study investigated allogenic PRP. The amount varied between 2 mL (2 studies) to 4 mL (3 studies) to 6 mL and 12 mL over two weeks. There were 3 studies that compared PRP to corticosteroid injection. The number of participants included in the studies ranged from 15 to 102. The mean age of the participants ranged from 50 years to 60, with pooled mean 54.9 [95 % CI 50.88–58.9]. All studies included participants of both sexes, and the follow up ranged from 1 week to 12 weeks.

4. Data extraction and quality assessment

Data was extracted from each study including first author, year of publication, type of PRP injection, injection quantity and administration amount, average patient demographics (age, sex, BMI), visual analog scale (VAS) score, and range of motion outcome measures that were reported for each study. Pretreatment and posttreatment VAS scores and outcome measures were collected from each study, for studies that reported multiple time points for follow up the final follow up was taken as the "post-injection" score respectively. Average postoperative follow up for all pooled trials was 12 weeks.

5. Outcome measures

For all studies with reported VAS scores to measure the intervention effect on pain, changes of 20 on a 100 VAS scale for pain, was defined as the minimal clinically important difference (MCID). MCID was set at 12° of forward flexion and 10 points for SPADI[2,9][Simovitch, Dabija]. Age, gender, BMI, and ASA scores were obtained. Patient reported, outcomes (PROs) were obtained and all reported range of motion (ROM) were recorded. PRP and steroid injections were compared using random effects meta-regression pre-injection and post-injection.

6. Heterogeneity

I^2 statistic was utilized to determine study heterogeneity for subsequent meta-analysis. Thresholds for analysis were based on the Cochrane group, where $<$25 % corresponds with low heterogeneity, 25–50 % moderate heterogeneity and $>$50 % indicates substantial heterogeneity. Compiled data $^{\text{illustrated}}$ I^2 value of 0 % ($p = 0.983$) for the available 7 trials, meaning low heterogeneity of data. Therefore, continuous random effects modeling was utilized for statistical analysis.

7. Statistical analysis

Meta-analysis was completed using OpenMetaAnalyst v10.12 (Brown University, Providence, RI). OpenMetaAnalyst is an open-source meta-analytical program sponsored by Agency for Healthcare Research and Quality (AHRQ grant #R01HS018574). Continuous random-effects modeling using the DerSimonian-Laird method utilizing Hedges' g was used to determine differences. All studies that included pain using a VAS score were normalized to 100, for comparison in the analysis. Outcome measures were pooled and analyzed separately for passive and active range of motion of the shoulder.

8. Results

There was no difference between any of the pre-treatment variables (VAS pain, forward flexion, extension, abduction, external rotation, internal rotation nor Shoulder Pain and Disability Index [SPADI]) of PRP or corticosteroid injection groups. The average age of the cohort was 55 years (95 % CI 51.26–58.74), with 24.4 % males, and 385 total patients in the pooled cohort. Of those, 243 patients received PRP injection compared to 142 receiving corticosteroid in the same trials. BMI, ASA and other co-morbidities were not reported in the vast majority of the studies and were not able to be analyzed.

Both intra-articular PRP and steroid injections resulted in improved outcomes for pain, active and passive range of motion in all planes for treatment of adhesive capsulitis at 3 months (Table 2). Platelet-rich plasma injections had significant improvements over corticosteroid injections in passive forward flexion (151° vs 144.1°, $p = 0.024$), and also had better SPADI scores than the corticosteroid group (14.6 vs 18.6, $p = 0.009$). While these improvements are significant, they may not have

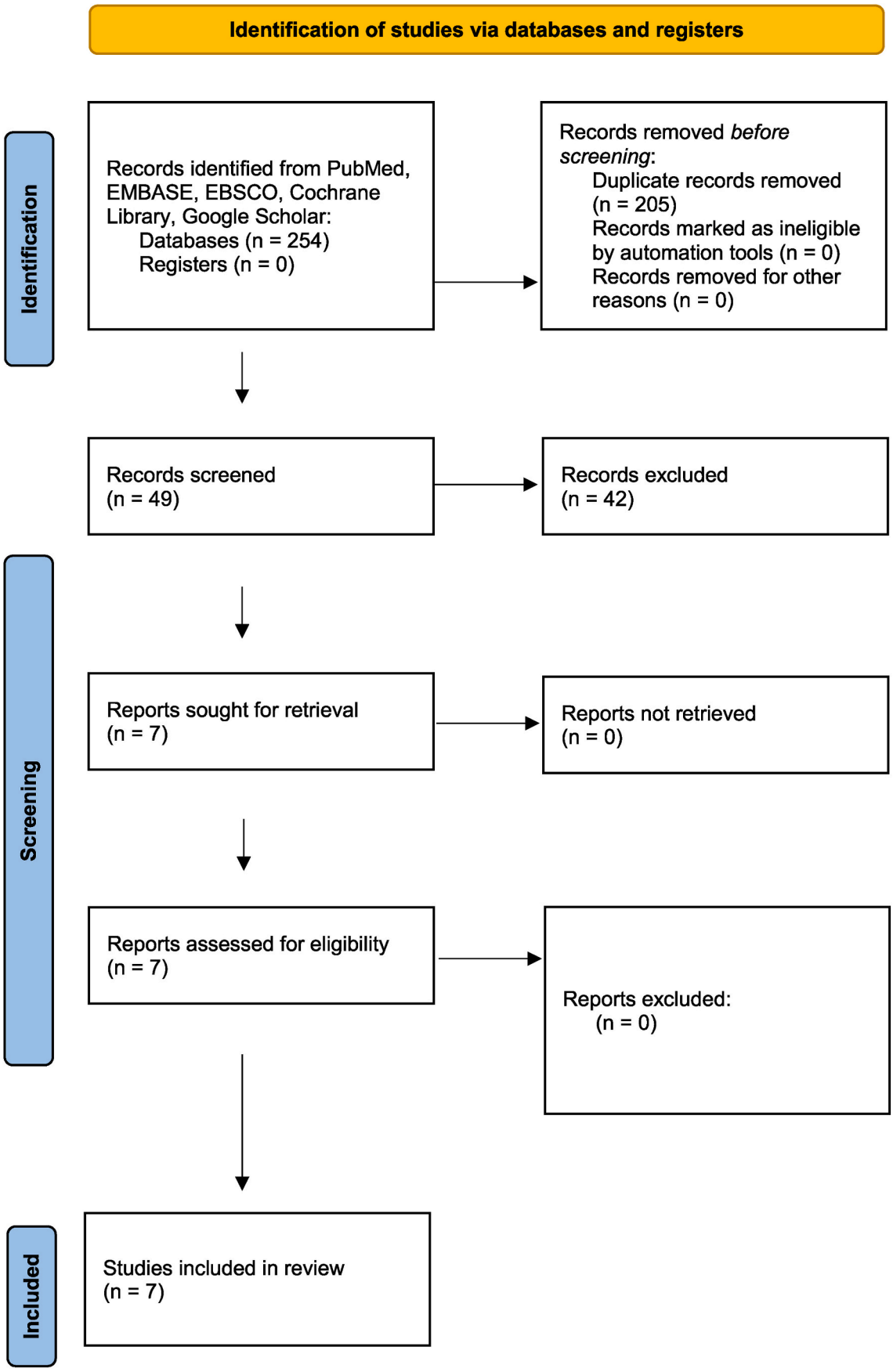
Identification of studies via databases and registers
Identification
Records identified from PubMed, EMBASE, EBSCO, Cochrane Library, Google Scholar:
Databases (n = 254)
Registers (n = 0)
Records removed *before screening*:
Duplicate records removed (n = 205)
Records marked as ineligible by automation tools (n = 0)
Records removed for other reasons (n = 0)
Records screened (n = 49)
Records excluded (n = 42)
Screening
Reports sought for retrieval (n = 7)
Reports not retrieved (n = 0)
Reports assessed for eligibility (n = 7)
Reports excluded: (n = 0)
Included
Studies included in review (n = 7)

Fig. 1. PRISMA flowchart.
From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372:n71. https://doi.org/10.1136/bmj.n71

Table 1
List of studies, PRP: platelet rich plasma, M: male.

Name	Year	N	Age	Sex	PRP dose/type
Lee[4]	2021	15	60.3	7 M	4 mL allogenic PRP, 1154 × 10^3/uL
Barman[1]	2019	28	50	12 M	4 mL of PRP
Shahzad[8]	2021	102	52.4	43 M	2 mL of PRP
Thu[10]	2020	31	52.8	4 M	4 mL of PRP
Unlu[11]	2021	17		6 M	2 mL of PRP, series of 3
Karabas[3]	2021	20		14 M	3 mL of PRP, biweekly series of 2
Lin[6]	2018	30	59.8	9 M	2 mL of PRP, 756 × 10^3/uL
Total		385		95 M	

Table 2
Outcomes for pain, function and range of motion. SPADI: Shoulder Pain and Disability Index, FF: forward flexion, ABD: abduction, Pre: pre-injection, Post: post-injection, IR: internal rotation, ER: external rotation, ext: extension.

Outcome	PRP	Steroid	Difference	P value
Pre VAS pain	64.4 (45.3–83.4)	66.8 (40.0–93.7)	−2.5 (−35.4–30.4)	0.882
Post VAS pain	13.2 (6.2–20.1)	18.7 (9.7–27.6)	−5.6 (−16.9-5.8)	0.336
Pre active FF	94.0 (77.1–110.8)	91.6 (72.5–110.7)	2.3 (−23.1–27.8)	0.858
Post active FF	145.2 (133.2–157.1)	131.9 (118.4–145.4)	13.3 (−4.8–31.3)	0.149
Pre passive FF	102.0 (98.3–105.7)	100.0 (96.1–103.9)	2.0 (−3.4–7.4)	0.462
Post passive FF	151.0 (147.0–154.9)	144.1 (139.6–148.6)	6.9 (0.9–12.9)	0.024
Pre active Ext	31.6 (20.3–43.0)	20.0 (4.5–35.5)	11.7 (−7.5–30.9)	0.234
Post active Ext	48.6 (37.6–59.5)	35.7 (20.3–51.1)	12.9 (−6.0–12.9)	0.182
Pre passive Ext	36.8 (27.3–46.3)	29.1 (15.9–42.4)	7.7 (−8.6–24.0)	0.355
Post passive Ext	52.8 (45.1–60.5)	45.8 (34.8–56.7)	7.0 (−6.3–20.4)	0.303
Pre active ABD	77.7 (61.1–94.2)	77.1 (58.2–95.9)	0.6 (−24.5–25.7)	0.963
Post active ABD	138.6 (121.0–156.2)	128.6 (109.0–148.3)	10.0 (−16.4–36.4)	0.459
Pre passive ABD	88.5 (85.1–92.0)	89.0 (84.8–93.3)	−0.5 (−6.0–5.0)	0.858
Post passive ABD	147.0 (135.3–158.8)	128.5 (113.4–143.6)	18.6 (−0.6–37.7)	0.057
Pre active ER	31.3 (22.8–39.8)	28.1 (18.5–37.7)	3.3 (−9.6–16.1)	0.619
Post active ER	60.8 (47.7–73.9)	47.1 (32.0–62.2)	13.7 (−6.2–33.7)	0.178
Pre passive ER	41.9 (29.1–54.8)	27.6 (5.8–49.5)	14.3 (−11.0–39.7)	0.269
Post passive ER	71.8 (58.7–84.9)	53.6 (35.4–71.8)	18.2 (−4.2–40.7)	0.111
Pre active IR	24.1 (16.8–31.4)	21.7 (13.2–30.3)	2.4 (−8.8–13.6)	0.679
Post active IR	60.0 (50.0–69.9)	43.5 (31.5–55.5)	16.4 (0.9–32.0)	0.038
Pre passive IR	26.2 (24.1–28.3)	26.9 (25.1–28.7)	−0.7 (−3.4-2.1)	0.627
Post passive IR	69.6 (61.4–77.7)	52.7 (41.6–63.9)	16.9 (3.0–30.7)	0.017
Pre SPADI	73.5 (56.7–90.4)	59.7 (39.0–80.3)	13.8 (−12.8–40.5)	0.308
Post SPADI	14.6 (12.8–16.4)	18.6 (16.2–20.9)	−4.0 (−7.0–−1.0)	0.009

reached minimal clinical thresholds. PRP had significantly better active (60° vs 43.5°, p = 0.038) and passive internal rotation (69.6° vs 52.7°, p = 0.017) compared to steroid *which did reach minimal clinical thresholds*.

VAS pain reduced for the PRP cohort from 64.4 cm to 13.2 cm and for the corticosteroid injection cohort from 66.8 cm to 18.7 cm. There was no difference in pain scores between PRP and corticosteroid injection at 3 months (p = 0.336). There were no differences detected between active forward flexion, abduction, external rotation nor extension between the two cohorts. No major adverse events were reported in any of the studies with respect to PRP or CS. Few studies reported mild injection site pain in both groups with no difference between the two.

9. Discussion

Adhesive capsulitis can be a challenging condition to treat. We found that PRP and corticosteroid injection decreased pain, improved disability scores and range of motion in patients with adhesive capsulitis at 3 months. Interestingly, PRP resulted in improved internal rotation of the shoulder compared to corticosteroid, although the reason for this is not clear. The majority of the studies methodology revealed injections were administered by posterior approach, which may have resulted in increased motion to that affected tight area. One study performed an anterior-based injection and had reported significantly better range of motion in all planes, compared to methylprednisolone injections.[3] In future studies, targeted injection to the anterior inferior glenohumeral ligaments and capsule may be a worthwhile investigation.

The strengths of this study are that we are the first study to our knowledge to register and report the outcomes of a meta-analysis on platelet rich plasma for adhesive capsulitis in the shoulder. Additionally, weighted analysis was able to detect a significant and clinically important difference in range of motion with platelet rich plasma injections.

The limitations of the study are the lack of standardization in the type, quantity and administration of PRP. Additionally, the follow up was short at 3 months, and further follow up is necessary to fully evaluate the long term effectiveness of the injections.

In conclusion, PRP may be an effective treatment option for patients with adhesive capsulitis. We found that PRP and CS injections decreased pain, improved disability scores and improved range of motion. We also found that PRP may result in improved internal rotation compared to CS. PRP may be a viable alternative to corticosteroid injection for adhesive capsulitis.

IRB approval

IRB is exempt as there are no human subjects nor participants in this trial. This is not a clinical trial.

Funding/sponsorship

None.

Work performed at

Nova Southeastern University.

Ethical review

No issues were brought up upon ethical board review.

Declaration of competing interest

None. Authors have no conflict of interest, nor to this body of literature.

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None.

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