PLATELET-RICH PLASMA INJECTIONS UNDER ULTRASOUND GUIDANCE FOR MANAGEMENT OF ROTATOR CUFF TENDINOPATHY: A SYSTEMATIC REVIEW

Naveen Nair1, Arun Kaliyaperumal1, Ravi Kumar N2, Marie Bernard Arokiaraj3, Arunchandar R3, Vimal Raj D4

1Associate Professor, Department of Orthopedics, IGMC & RI, Puducherry, India.
2Assistant Professor, Department of Orthopedics, IGMC & RI, Puducherry, India.
3Senior Resident, Department of Orthopedics, IGMC & RI, Puducherry, India.
4Professor & Head, Department of Orthopedics, IGMC & RI, Puducherry, India.

Abstract
Background: Tendinopathy of the rotator cuff commonly causes shoulder pain and disability leading to a poor quality of life. Initial treatment is conservative with exercise and analgesics. More invasive methods are dry needling, local steroids, saline and dextrose prolotherapy and surgery. Platelet rich plasma release growth factors which causes tendon healing. The role of PRP injection in this condition evokes interest and was evaluated by a systematic analysis of randomized controlled trials using this modality. Materials and Methods: This study followed the PRISMA guidelines and selected randomized controlled trials after a thorough search on the available library databases using inclusion and exclusion criteria. From these the study design, test and control group numbers, interventions, outcome observed and conclusions were recorded in tabular form. Result: A total of 14 RCT were selected and the parameters under study were recorded. Significant improvement in the test groups of PRP injections with respect to symptoms and function against the controls was seen in the nine selected trials. Improvement in both test and control groups with no statistically significant difference between them was observed in two studies. Three studies established that PRP was not superior to the control groups. Though a common disorder, the actual cause of rotator cuff tendinopathy, is not clear. A lack of healing potential and altered loading may be the cause. This may explain the benefits of PRP with its growth factors, cytokines and chemokines in causing healing. Though most of the studies indicated improved healing with PRP injections with reduced pain and improved function, a lack of uniformity in procedures used as controls, variation in doses and preparation of PRP and varying assessment protocols could influence outcomes in the studies. Conclusion: This systematic review found that PRP injection, was more effective in reducing pain and improving function in rotator cuff tendinopathy. It was safe and appropriate for long-term use. Though current evidence is promising, more high quality double blind randomised controlled trials with standard controls, PRP preparations, diagnostic and injection techniques and a tendinopathy specific outcome assessment protocol, are needed.

INTRODUCTION
Rotator cuff tendinopathy is the most common cause of shoulder pain and dysfunction, incidence being proportionate to age, accounting for more than 50% of cases by 60 years.[1] This disorder leads to a poor quality of life. The most common muscle component of the rotator cuff involved in this condition is the supraspinatus though other components may also be involved.[2] Increased age, professions involving repetitive lifting or overhead activities and obesity contribute to the problem.[1] The ultrasonogram of the shoulder is the corner stone of diagnosis of Rotator Cuff Tendinopathy. The only drawback being the need for expertise and consistent scanning technique.[3] Treatment options for Rotator cuff tendinopathy range from conservative, such as NSAIDS and a rehabilitation exercise program, to invasive such as dry needling, local injections of corticosteroids, dextrose and saline prolotherapy, and surgery.[4] Conservative options are used in the early
phase of the disease. These fail when the condition reaches a refractory stage because of reduced vascularity and increased healing time. Biomechanical alterations occur in tendon which never regains initial strength.\[5\]

Platelet rich plasma is an autologous whole blood product that after a centrifugation process provides a concentration of platelets higher than in circulating blood. These contain growth factors like transforming growth factor-beta (TGF-β), Platelet-Derived Growth Factor (PDGF), Vascular Endothelial Growth Factor (VEGF), and Epidermal Growth Factor (EGF) that support cell recruitment, development and morphogenesis and local healing.\[6\]

The aim of this systematic review was to scientifically evaluate studies that are randomised controlled trials using PRP injection as a treatment modality for rotator cuff tendinopathy. How this treatment affected shoulder pain and function compared to controls along with the side effects was evaluated in this review.

**MATERIALS AND METHODS**

This study was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.\[7\] An extensive and methodical literature search was performed within the Medline, PubMed, Science Direct, Embase and Cochrane library database and the studies which were randomized controlled trials only, were selected. The selection was done based on certain inclusion and exclusion criteria.

![Figure 1: PRISMA flow chart for systematic review](image)

Only randomised controlled trials which included patients having a diagnosis of rotator cuff tendinopathy, having symptoms for more than three months and failing conservative management with medical and physical therapy for a duration of at least four weeks. Studies which used platelet-rich plasma (PRP) group only (on subjects) compared to other methods used (as controls), were included. Control groups in the studies selected included subjects receiving saline injection, dextrose prolotherapy, dry needling, corticosteroid injections, and nonsteroidal anti-inflammatory drugs with physiotherapy. Studies where PRP was an adjuvant to or combined with other modalities were excluded. Those studies where subjects had complete rotator cuff tears, adhesive capsulitis, trauma or other conditions which cause shoulder pain and dysfunction, were excluded. Animal studies were excluded.

Keywords such as ‘shoulder tendinopathy’, ‘rotator cuff tendinitis’, ‘platelet rich plasma’, ‘PRP injection’, ‘conservative treatment of rotator cuff tendinopathy’, ‘ultrasound guidance’ were used in various combinations to search for the appropriate studies fitting into our review. The selected studies had a follow up period of at the most one year. Decreased pain and improvement in function were considered as outcomes expected. The study design, test and control group numbers, interventions, outcome observed and conclusions were recorded.

**RESULTS**

A database search identified 1273 studies. After identifying duplicates 1023 studies remained. These were further screened excluding 993 criteria, leaving 30 full text articles to be further assessed for eligibility. Further screening using exclusion criteria removed 16 more leaving 14 studies eligible for our systematic review. After perusing these articles, they were tabulated under the following headings, namely reference number, study type, intervention, outcome and conclusion. [Table 1]

All the studies selected were single center randomized controlled trials, with test groups being given PRP injections and control groups using dry needling, saline injections, corticosteroid injections, dextrose prolotherapy, exercise and lidocaine injection. Two of the studies described had multiple control groups. Post injection physical therapy both in case of test and controls was undertaken in two studies. There was a wide heterogeneity numerically between the various studies selected. A total of 373 subjects in test groups received PRP injections as opposed to 461 subjects in control groups. The follow up interval after injection range from one month to one year with 3 and 6 month reviews in between.

Pain, functional and patient related outcomes were assessed using Visual analogue scale (VAS) for pain,\[8\] Shoulder pain and disability index (SPADI),\[9\] Disability arm shoulder hand score (DASH),\[9\] American shoulder and elbow surgeons scale (ASES),\[9\] Constant score,\[9\] Single assessment numerical evaluation (SANE) score,\[9\] and Oxford shoulder score.\[9\] MRI evaluation to assess tendon lesion improvement was used in 3 studies. Ultra sonogram was used for the same in one study. Significant improvement in the test groups of PRP injections with respect to symptoms and function against the controls was seen in the nine selected...
trials. Improvement in both test and control groups with no statistically significant difference between them was observed in two studies. Three studies established that PRP was not superior to the control groups. The studies selected showed wide variations with respect to number of control groups, subjects and assessment criteria for measuring patient reported functional outcome and modalities estimating tendon healing.\(^{10-20}\)

Rha DW et al.\(^{10}\) and Wessner et al.\(^{11}\) concluded that PRP injections were superior to dry needling and saline injections resulting in symptomatic and functional improvement. CH Jo et al.\(^{15}\) reported better pain relief and function after PRP injection at 6 months compared to steroid injections. Thepsoparn M et al.\(^{22}\) and Aylin Sari et al.\(^{21}\) reported usefulness of PRP for long term relief as compared to local corticosteroids. Good results were demonstrated by Dadgostar H et al.\(^{16}\) with PRP injection as compared to steroids. Shams A et al.\(^{17}\) reported better initial results with PRP injections but improvement of statistical significance was not present at 6 months. They stated it was a alternative to steroids in view of local complications of steroids. Lo IKY et al.\(^{18}\) and Lee HW et al.\(^{19}\) reported better clinical outcomes in early stages but could not find improvement of statistical significance after 6 months and suggested more research into the concept. Studies by Kesikburun S et al.\(^{12}\) Kwong CA et al.\(^{13}\) and Schwitzguebel AJ et al.\(^{14}\) reported PRP injections were not more effective than control groups in pain relief and functional improvement especially in long term. Schwitzguebel AJ in fact reported a higher incidence of adverse effects with PRP injections. Hala M et al.\(^{21}\) and Ibrahi.

### Table 1:

<table>
<thead>
<tr>
<th>Articles</th>
<th>Study Type</th>
<th>Intervention</th>
<th>Subjects enrolled Test=N, controls=N’</th>
<th>Outcome</th>
<th>Conclusion</th>
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<tbody>
<tr>
<td>Rha DW et al. (10)</td>
<td>RCT/DB single centre prospective, LOE1</td>
<td>CG - 2 dry needling procedures 4 weeks apart. PRP group – 2 autologous PRP injections 4 weeks apart</td>
<td>N=20, N’=19</td>
<td>PRP injection under ultrasound guidance was found to be superior from 6 weeks to 6 months as assessed by SPADI, passive ROM of shoulder and a Physician global rating scale. No adverse effects seen.</td>
<td>Compared to dry needling, PRP injections reduced shoulder pain and improved function even 6 months after treatment. Considered safe and useful</td>
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<tr>
<td>Wessner et al. (11)</td>
<td>RCT single centre prospective, LOE2</td>
<td>CG – 4ml saline injection into rotator cuff. PRP – 4ml PRP injection into rotator cuff. All under took 3 months standardized home based exercise program</td>
<td>N=7, N’=2</td>
<td>PRP group demonstrated clinically important improvements in pani(VAS score), disability(DASH score) and tendon pathology(MRI).</td>
<td>Ultrasound guided intratendinous PRP injections led to improvement in pain, function and tendon pathology</td>
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<tr>
<td>Kesikburun S et al. (12)</td>
<td>RCT, LOE 1</td>
<td>CG injection of 5 ml saline into rotator cuff under US guidance. PRP group - 5ml injection of autologous PRP. Both groups underwent 6 weeks standard exercise program</td>
<td>N=20, N’= 20</td>
<td>The two groups showed no significant difference as assessed by VAS, WORCI, and SPADI scores</td>
<td>PRP was found to be no more effective at treating chronic Rotator Cuff tendinopathy than a placebo, at improving pain, function and quality of life.</td>
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<td>Kwong CA et al. (13).</td>
<td>RCT, LOE 1</td>
<td>CG injection of CS under US guidance. PRP group – under same condition PRP injected.</td>
<td>N= 47, N’=52</td>
<td>PRP group had worst baseline pain, ROM and functional scores but had superior scores at 3 months. At 6 and 12 months there was no difference between two groups. Assessed by VAS, ASER, WORCI</td>
<td>Both groups showed clinical improvement. But PRP group was superior in short term follow up. At long term follow up there was no significant difference between the two.</td>
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<tr>
<td>Schwitzguebel AJ et al. (14)</td>
<td>RCT, LOE 1</td>
<td>CG – 2 saline injections at 1-month interval. PRP – 2 PRP injections at 1-month interval.</td>
<td>N=40, N’=40</td>
<td>At 7 months there was no significant differences between two groups regarding decrease in size of lesion (MRI), or pani(VAS), function (SANE, Constant and ASER scores) At 12 months no significant differences were noted between 2 groups with regard to same. Adverse effects like</td>
<td>Compared to saline injections PRP injections did not improve tendon healing or clinical scores and had higher incidence of adverse effects.</td>
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<tr>
<td>Authors</td>
<td>Study Design</td>
<td>Interventions</td>
<td>Sample Size</td>
<td>Outcome Measures</td>
<td>Results/Conclusion</td>
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<td>CH Jo et al. (15)</td>
<td>A 2-group, parallel,</td>
<td>CG - 4 mL mixture of 1 mL of 40 mg/mL triamcinolone acetonide (CS) and 3 mL of 2% lidocaine PRP</td>
<td>N=30, N*=30</td>
<td>No treatment-related adverse events. At 1 month after injection Constant score did not show any difference between 2 groups. At six-month overall function and external rotation better in PRP by DASH score. Other clinical outcomes did not improve. Pain measurements, muscle strength, and the functional scores improved slowly and steadily in PRP group. In CS group after initial improvement it was not progressive. PRP is safe but not superior to CS comparing pain and functional improvement. At 6th month PRP had better pain, partient reported outcome and functional improvement. PRP slowly but steadily reduced pain and improved function of the shoulder until 6 months, whereas corticosteroid did not.</td>
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<tr>
<td>Dadgostar H et al. (16)</td>
<td>Double blind RCT, LOE 1</td>
<td>CG - CS group, 1 cc of Depo-medrol 40 mg and 1 cc of lidocaine (2%) was injected within the subacromial joint PRP - 3cc of PRP was injected within the subacromial joint and another 3cc was injected at the site of the tendon tear, under the guide of sonography.</td>
<td>N=*29, N“*29</td>
<td>At 1 and 3 months follow up pain and ROM improvement was better in PRP group using VAS, WORCI and DASH scores. PRP may show similar results to CS but regarding pain and ROM PRP demonstrated better results. PRP may be useful in those patients where CS are contraindicated and risk of tendon rupture exists.</td>
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<tr>
<td>Shams A et al. (17)</td>
<td>RCT prospective, LOE 1</td>
<td>CG – CS injection in subacromial space. 1 ml CS plus 1 ml lidocaine. PRP – 3 cc given</td>
<td>N=20, N“=20</td>
<td>Both groups showed statistically significant clinical outcome compared to pre injection. PRP was better at 12 weeks assessed by VAS, ASES, CMS, SST scores. MRI showed improvement in lesions but not statistically significant between groups. PRP injections showed earlier better results although statistically significant better results after 6 months could not be found. Sub acromial PRP injection could be considered as a good alternative to corticosteroid injection.</td>
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<tr>
<td>Hala M et al. (23)</td>
<td>RCT prospective, LOE 1</td>
<td>CG1 25% dextrose prolotherapy, CG2 Corticosteroid. PRP test group</td>
<td>N = 20 PRP. N“= 20 PT. N“=20 Corticosteroid</td>
<td>Prolotherapy and CS group showed good pain relief by VAS. No significant improvement was noted in PRP. All groups showed significant WORCI scores. ROM showed improvement in polotherapy but not in others. Prolotherapy group and PRP showed lesion improvement but not CS group. Prolotherapy demonstrated improved VAS, WORCI, ROM and tendon healing. PRP injections improved WORCI and tendon healing. Steroid injection had no effect on healing, but improved pain scores VAS, WORCI.</td>
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<tr>
<td>Ibrahim DH et al. (20)</td>
<td>RCT, LOE 1</td>
<td>Test group PRP, CG – CS</td>
<td>N=15, N“=15</td>
<td>Both groups showed equally significant pain relief – VAS ROM improved in both groups significantly Tendinitis, tears and effusions improved in PRP group. Both modalities are equally effective but PRP is a safe alternative to CS reduces pain and inflammation and efficacy increases with US guidance.</td>
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<tr>
<td>LO IKY et al. (18)</td>
<td>Double blind single center RCT, LOE 1</td>
<td>CG-CS injections. TEST-PRP injections. Assess at 6 and 12 weeks post injection</td>
<td>N=50, N“=49</td>
<td>PRP group demonstrated better pain improvement at 12 weeks but not at 6 weeks. There was no difference in other outcome measures or progression of the two groups to surgical intervention. Use of PRP in the therapy rotator cuff tendinopathy shows a substantial reduction in pain ratings after 12 weeks. There was no effect on the rate at which patients progressed to surgical intervention. More</td>
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Rotator cuff tendinopathy is a relatively common tendon disorder which affects a population ranging from common people to professional sportsmen. But, the underlying pathology is not fully understood. Degeneration and activities or professions subjecting joint to repetitive stress are considered to have a role to play.[24] The theory is that more than inflammation, the reason rotator cuff tendinopathy occurs is lack of healing potential and altered loading.[25] This explained the rationale behind use of Platelet Rich Plasma (PRP), where the platelets released growth factors because of platelets activation in PRP injections.[26]

PRP injections have been shown to have long term benefits in management of rotator cuff tendinopathy. The advantages of PRP over the controls such as saline, corticosteroids, dextrose, sham injection and dry needling, was attributed to increased regeneration of damaged tissue and pain relief. Some studies did not reveal PRP to be superior to the controls used. Studies have also shown that exercise therapy is beneficial in pain relief and functional outcome.[27] Thus comparative long term studies between groups undergoing PRP injection and physical therapy should be undertaken to identify which one gives better results.

PRP injection treatments are usually considered to be safe. Minor complications have been reported such as swelling, tenderness, joint pressure, and local pain associated with joint distension caused by intra-articular injection. No major adverse effects have been reported. Local pain because of intralessional injections were main complaint which settled in a few days.[30] Thus intra-articular or intralessional PRP injections were considered a safe and well tolerated treatment.

**Limitations**
Wide variability was noticed in the studies selected with respect to sample size in patient groups thus making it difficult to know the extent to which these subjects would have improved without PRP injection. During selection of the studies many of the studies rejected revealed a confusion in relation to released growth factors because of platelets activation in PRP injections.[28]

### DISCUSSION

| Lee HW et al. (19) | RCT LOE 1 | CG – exercises | PRP – PRP injection | N=27, 13 LP-PRP, 14 LR-PRP N’= 33 | NRS and constant scores did not show any statistically significant difference between the two groups. ASES at 3 and 6 months showed statistically significant difference between PPRP and exercise at 3 and 6 months. No difference was noted between LP and LR preparations of PRP. | PRP injection group showed better clinical outcomes for first 3 months, before tapering off. No difference between LP-PRP LR-PRP groups and effect of PRP not influenced by leukocytes or platelet counts. PRP is effective in early treatment of patients not responding to conservative approach. |
| Aylin Sari, An Eroglu (21) | RCT. LOE 1 | CG1- CS. CG2 lidocaine. PRP | N=33, N’=32, N”= 32 | At 3 weeks CS had low pain and WORCI scores and higher ASES. At 24 weeks PRP had favorable VAS and WORCI. All injections showed improvement. | PRP is useful for long term relief but CS is good for short term relief. All injections had some relief of pain in different degrees. |
| Thepsornam M et al. (22) | RCT LOE 1 | CG – CS | TEST – PRP | N=15 N’=16, 1k6 month follow up, VAS & Oxford shoulder score assessed | At 1 month PRP and CS showed good pain relief and functional. But at 6 months PRP had better scores. CS did not progressively improve after 6 month | CS or PRP showed similar benefits in the short term but PRP progressively improves by 6 months whereas CS does not show long term benefits. |

**Abbreviations**  
terms such as supraspinatus tendinosis, supraspinatus tear, rotator cuff tendinosis, rotator cuff tear, and sub acromial impingement, when searching for ‘rotator cuff tendinopathy’ or ‘shoulder tendinopathy’. Uniform diagnostic criteria were also not observed among many studies rendering them unfit for inclusion in our review. The imaging modalities used to diagnose the entity under study and follow up of cases also varied in many studies. Long term imaging with ultrasound to study tendon healing was also lacking. The selected studies showed a lack of homogeneity in the procedures used as control. There was no uniformity in doses, preparation and treatment protocols followed in the PRP injections used, which could influence outcome in studies selected.

CONCLUSION

In comparison to other treatment modalities, this systematic review found that PRP injection, a less invasive method, was more effective in reducing pain and improving function in rotator cuff tendinopathy. It was safe and appropriate for long-term use. Even if current evidence is promising, high-quality double-blind randomised controlled studies with a larger study population are needed to compare PRP to other modalities, using standardised PRP preparation, injection technique and imaging modalities for diagnosis and follow up. Studies in future will require a rotator cuff tendinopathy-specific outcome assessment technique that is standard, reliable, and valid.

REFERENCES


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