

**Moraes VY, Lenza M, et al. Platelet-rich therapies [PRT] for musculoskeletal soft tissue injuries (Review). Cochrane Database of Systematic Reviews 2013;Issue 12, Art# CD010071.**

Design: Meta-analysis of randomized clinical trials

PICOS:

- Patients: people with musculoskeletal soft tissue injuries being treated either surgically or conservatively
  - o Injuries were broadly grouped into acute traumatic injuries and tendinopathies (either acute or chronic)
  - o Studies of osteoarthritis were excluded
- Interventions: Platelet-rich therapies (PRT), either as the only treatment or as an adjunct to other treatments
- Comparisons: placebo injection, dry needling, whole blood injection
  - o Studies with active agent controls such as steroid injection were excluded
- Outcomes: functional evaluation by scales such as questionnaire-based measurements appropriate to the part of the body in which the injection is given (such as the DASH for upper extremity); pain by scales such as the VAS; local and systemic adverse effects
  - o Secondary outcomes included recovery time (return to sports or return to daily activities); quality of life, recurrence of the condition, need for surgery, or patient satisfaction with treatment
- Study types: randomized trials and quasi-randomized trials (such as allocation by hospital record number or date of birth)

Study selection:

- Databases included MEDLINE, the Cochrane Register, EMBASE, and other electronic databases through March 2013
  - o Reference lists of articles were searched; experts in the field were queried, and conference abstracts of several orthopedic associations were searched
- Two authors independently extracted study data and evaluated articles for inclusion, assessing bias with the Cochrane Risk of Bias tool
- Two subgroup analyses were planned: one grouping studies by condition (rotator cuff tear, Achilles tendon); one grouping studies by whether they used PRT as the main treatment for tendon disorders or whether PRT was a surgical augmentation procedure

Results:

- 39 studies were assessed for eligibility; 19 studies, with 1088 participants, were included in the analysis
- Most studies were published between 2005 and 2013
- 17 studies were randomized, and 2 were quasi-randomized (neither of them concerned with the shoulder)
- Studies of patients with sports injuries (tennis elbow, lower extremity injuries) enrolled mostly young patients; studies of degenerative conditions (rotator cuff tears and chronic impingement syndrome) were mostly older patients
- For rotator cuff tears, 6 studies with 291 patients were included, all of them assessing platelet-rich plasma (PRP) after arthroscopic rotator cuff repair
  - o PRP was applied through one of the portals and the position was checked by arthroscope to the suture site before closure of the surgical wounds
  - o Functional status at one year was documented in six studies, with the Constant score being used in 5 studies
    - A minimally clinically important difference of 10.4 points was assumed for rotator cuff surgery on the basis of other studies
    - The mean difference between PRP and placebo was less than this minimally important difference; the estimate was 2.47 points, with 95% confidence intervals from 0.68 to 4.26 points
  - o Pain in the short term (7 days) was reported by two studies, and the pooled treatment effect in favor of PRP was 1.4 points (95% CI, 0.36 to 2.44) on a 10 point VAS
    - Pain 30 days were heterogeneous between studies, preventing the authors from pooling the data, but at one year there were no pain differences between groups
  - o Retear rates were reported in three studies; at one year, there were fewer retears in the PRP (10/101) than in the placebo groups (19/98)
    - At 2 years, only 2 studies reported re-tear rates, and the results were more similar between PRP (19/36) and placebo (22/37)
- For shoulder impingement syndrome, one study with 40 Patients compared PRP versus no PRP; at 6 weeks, the PRP group had less pain (1.4 points, 95% CI between 0.44 and 2.36)
  - o Function measured by the Shoulder Index Score favored PRP at 6 weeks (0.90 points, 95% CI from 0.01 to 1.79)
- The authors also pooled data from different regions of the body (rotator cuff tear, elbow epicondylitis, Achilles tendinopathy, Achilles tendon rupture), using 4 different functional scores, but found no statistically significant difference between PRP and control; the heterogeneity was 35%, which was moderate by the authors' standards

- Data was pooled from four studies covering three conditions (rotator cuff tear, shoulder impingement syndrome, elbow epicondylitis), showing a small but homogeneous effect of PRP on short-term pain (0.95 points on a 10 point scale)
- Anterior cruciate ligament reconstruction was also included in the analysis; PRP as an augmentation procedure found no treatment effects for PRP

#### Authors' conclusions:

- There is very low quality evidence, from a diverse collection of small trials, for a marginal short-term pain relief effect of PRT in a variety of musculoskeletal soft tissue injuries
- There is very low quality evidence that the use of PRT does not have a clinically relevant effect on short-term or long-term function
- Many trials were not registered, raising the possibility of bias from selective outcome reporting, since the original study protocol cannot be compared with what was published in the journals where the studies appeared
- Platelets can be prepared in a variety of ways, with wide variations in the platelet dose, the methods of platelet activation, and the mix of white blood cells in the preparation which is administered to the patient
  - o A standardized methodology for platelet preparation should be a priority for research, if there is to be confidence in the generalizability of study findings
- There is currently insufficient evidence to support the use of PRT in the treatment of these injuries

#### Comments:

- The authors grouped a heterogeneous group of conditions together for some analyses, which can raise issues about the comparability of the results
  - o However, the pooled data for short term pain from rotator cuff tear, shoulder impingement, and elbow epicondylitis, were statistically homogeneous
  - o A minimal effect of platelet therapies was observed in both upper and lower extremity soft tissue injuries
  - o The authors achieved some control over heterogeneity by grouping the platelet interventions into the two categories of treatment as an adjunct to arthroscopic surgery and treatment as a primary intervention
- As the authors mention, there are multiple issues involved in platelet preparation and administration, resulting in a wide variety of bioactive factors with different systems; the same individual may have a successful platelet concentration in a system from one manufacturer and a failure to concentrate platelets in a system from a different manufacturer (Boswell et al 2012)
  - o Boswell 2012 also mentions that there are differences in concentrations of plasma proteins between different patients; some of these, such as clotting

factors and cell adhesion molecules, have been shown to influence migration of fibroblasts and other tissue-regenerating cells

- Leukocyte concentrations may also affect the biological activity of platelet preparations; it is possible that a high number of neutrophils have a deleterious effect on scar formation (DeLong et al 2012)
- Since this meta-analysis was published, an additional study of PRP in arthroscopic rotator cuff repair has been published (Ruiz-Moneo et al 2013); it reported on 69 patients with full-thickness tears who had all undergone debridement and repair with a double-row suture technique, and were randomized to PRP or no PRP at the time of the operation
  - o This study reported no significant difference between groups after surgery; both improved their UCLA shoulder scores equally, and were equally satisfied with the results of surgery
- The rotator cuff studies had participants who were older adults (mean age in studies in the mid-fifties to mid-sixties); it does not appear that patients taking antiplatelet drugs were excluded from these studies, but these drugs are frequently used in that age demographic, and could create an additional source of variation in platelet effects
- The authors were right to be very cautious about any conclusions about the effects of platelet therapies; the sources of variation in biological activity have a strong possibility of masking the therapeutic effects of the treatments

Assessment: High quality meta-analysis. It supports a statement that current evidence does not show a clinically important treatment effect for shoulder pain or function when given as an adjunct to arthroscopic rotator cuff repair. However, at present, there is also a lack of standardization of platelet preparation methods, which precludes clear conclusions about the effect of platelet-rich therapies for musculoskeletal soft tissue injuries

#### References:

Boswell SG, Cole BJ, et al. Platelet-Rich Plasma: A Milieu of Bioactive Factors. *Arthroscopy* 2012; 28(3): 429-439

DeLong JM, Russell RP, Mazzocca AD. Platelet-Rich Plasma: The PAW Classification System. *Arthroscopy* 2012;28(7): 998-1009

Ruiz-Moneo P, Molano-Muniz J, et al. Plasma Rich in Growth Factors in Arthroscopic Rotator Cuff Repair: A Randomized, Double-Blind, Controlled Clinical Trial. *Arthroscopy* 2013;29(1): 2-9