
Design: Meta-analysis of randomized and nonrandomized clinical trials

Study question: In patients with knee osteoarthritis (OA), does injection of platelet-rich plasma (PRP) improve knee function in comparison with control injections of hyaluronic acid (HA) or normal saline (NS)?

PICOS:

- Patient population: adults with osteoarthritis of the knee of any severity
- Intervention: At least two PRP injections
  - Data from one study in which one of the PRP groups had only one injection were excluded
- Comparison: Intra-articular HA or NS injections
  - One study had two HA control groups: a low molecular weight and a high molecular weight group; in this study, the high molecular weight group was selected for analysis
- Outcomes: Principal outcome was function assessed by the Western Ontario and McMaster Universities Arthritis Index (WOMAC) at 24 or more weeks
  - Secondary outcomes were pain VAS, the International Knee Documentation Committee (IKDC) form, patient-reported satisfaction, and occurrence of adverse events
- Study types: Randomized clinical trials (RCTs) and prospective cohort studies

Study selection:

- Databases included PubMed, MEDLINE, EMBASE, and the Cochrane Register through week 6 of 2013
- Two authors independently reviewed titles and abstracts for inclusion criteria and rated methodological quality with the Detsky Scale, resolving discrepancies through discussion with the senior author
  - The Detsky scale is an older quality analysis tool which has been mostly replaced by the Cochrane risk of bias tool; it resembles the Cochrane scale in most essentials
  - A Detsky scale score of 75% or greater was required for inclusion

Results:
- 157 abstracts were reviewed; after exclusion for insufficient followup, low level evidence, or inadequate data reporting, 6 studies, with 577 patients (625 knees) were included in a meta-analysis, five written in English and one in Chinese
  - Four were RCTs and two were prospective cohort studies with comparable control groups
- The mean age of the PRP patients was 56, and 51.5% were men; the mean age of the control patients was 57, and 49.5% were men
- Five studies used the Kellgren-Lawrence Grading (KLG) scale and one used the Ahlback scale to grade OA severity
  - Among the 5 studies using the KLG, 62 were grade 0, 123 were grade I, 127 were grade II, 63 were grade III, and 33 were grade IV
  - In the one study using the Ahlback scale, 61 were grade 1, 28 were grade 2, and 5 were grade 3
- In 5 studies, the control injection was HA; in one study, it was NS
- Followup intervals varied among studies, but all reported functional outcomes at 24 weeks
  - At 24 weeks, the overall WOMAC score from 4 studies with 318 patients favored PRP, with a mean difference of 18 points (95% CI from 8.3 to 27.75)
  - The IKDC score also favored PRP in 3 studies with 289 patients, with a mean difference of 7.9 (95% CI from 3.72 to 12.08)
- At 24 weeks, the pain VAS from 2 studies with 198 patients did not differ between PRP and control injections
- At 24 weeks, there was no difference in perceived patient satisfaction in 2 studies with 198 patients
- Reporting of adverse events was uneven
  - 2 studies reported no adverse events
  - 1 study reported 19 adverse events with PRP but none with NS
  - Another study reported 31 adverse events in the PRP group and 30 in the HA group
  - 1 study lacked reporting of adverse events
  - 1 study reported worsening of pain with PRP in 6 patients, resolving within two days
  - Overall, more adverse events were reported with PRP than with control (8.4% vs 3.8%)

Authors’ conclusions:

- Multiple sequential intra-articular PRP injections improve functional outcomes of WOMAC and IKDC at a minimum of 24 weeks in comparison with HA or NS
- However, pain VAS and patient satisfaction scores did not differ with PRP compared to control injection
- There may be more nonspecific adverse events with PRP than with control injection.

- The review had some limitations:
  - Both RCTs and cohort studies were pooled, which could increase the risk of selection bias; however, only high quality studies using established outcome measures were included.
  - Small sample sizes could limit the power of the pooled analysis to detect treatment effects.
  - PRP preparation techniques are among the many potential sources of heterogeneity between studies.

Comments:

- The pooling of randomized with cohort studies can be somewhat remedied by removing the latter from the analysis.
  - Figure 2 displays the forest plots for the major outcomes.
  - For the WOMAC, Spakova 2012 is a cohort study, and its removal does not affect the estimate of treatment effect; a pooled effect size of 20.4 points is not different from one of 18 points.
  - For the IKDC, Filardo 2015 also analyzed the effect of PRP on knee OA, and when it is included in a meta-analysis, the effect size for this outcome is only 6.22 points.
  - Part C of Figure 2 combines Kon’s cohort study with Patel’s RCT; it does contain a significant error in reporting the PRP group’s pain VAS as 4.6 rather than 2.54; when this is corrected, Kon is removed, and Patel is allowed to stand alone, an effect size of 2.06 points is the result in favor of PRP.

- The authors do not show their quality assessments for the included studies, and there is no information about how they arrived at the evaluation that they were of high quality.

### Table: Treatment Effect Sizes

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PRP Mean</th>
<th>PRP SD</th>
<th>PRP Total</th>
<th>Control Mean</th>
<th>Control SD</th>
<th>Control Total</th>
<th>Mean Difference</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerza 2012</td>
<td>36.5</td>
<td>17.9</td>
<td>60</td>
<td>65.1</td>
<td>10.6</td>
<td>60</td>
<td>-28.6 (-33.88, -23.34)</td>
<td></td>
</tr>
<tr>
<td>Li 2011</td>
<td>10.7</td>
<td>9.9</td>
<td>15</td>
<td>20.6</td>
<td>8.3</td>
<td>15</td>
<td>-9.9 (-18.44, -0.36)</td>
<td></td>
</tr>
<tr>
<td>Patel 2013</td>
<td>20.5</td>
<td>25.9</td>
<td>50</td>
<td>53.1</td>
<td>17.9</td>
<td>46</td>
<td>-31.2 (-31.45, -13.75)</td>
<td></td>
</tr>
<tr>
<td>Spakova 2012</td>
<td>18.9</td>
<td>14.1</td>
<td>60</td>
<td>30.1</td>
<td>16.6</td>
<td>60</td>
<td>-11.2 (-15.71, -6.69)</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI): 125 (121) 100.0% -20.41 (-32.45, -8.37)

Heterogeneity: $I^2 = 100.00$; $H^2 = 19.14$, $df = 2$ ($P = 0.0001$); $P = 90$

Test for overall effect: $Z = 3.32$ ($P = 0.0009$)

- Figure 2 displays the forest plots for the major outcomes.
  - For the WOMAC, Spakova 2012 is a cohort study, and its removal does not affect the estimate of treatment effect; a pooled effect size of 20.4 points is not different from one of 18 points.
  - For the IKDC, Filardo 2015 also analyzed the effect of PRP on knee OA, and when it is included in a meta-analysis, the effect size for this outcome is only 6.22 points.
  - Part C of Figure 2 combines Kon’s cohort study with Patel’s RCT; it does contain a significant error in reporting the PRP group’s pain VAS as 4.6 rather than 2.54; when this is corrected, Kon is removed, and Patel is allowed to stand alone, an effect size of 2.06 points is the result in favor of PRP.

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</tr>
</thead>
<tbody>
<tr>
<td>Filardo 2012</td>
<td>84.5</td>
<td>16.4</td>
<td>54</td>
<td>61</td>
<td>18.2</td>
<td>55</td>
<td>25.5%</td>
<td>3.30 (3.20, 3.40)</td>
</tr>
<tr>
<td>Filardo 2015</td>
<td>65</td>
<td>16.1</td>
<td>94</td>
<td>63.5</td>
<td>17.1</td>
<td>89</td>
<td>21.2%</td>
<td>1.50 (1.32, 1.68)</td>
</tr>
<tr>
<td>Kon 2011</td>
<td>64</td>
<td>18.7</td>
<td>50</td>
<td>54</td>
<td>15</td>
<td>50</td>
<td>24.6%</td>
<td>6.00 (5.10, 6.90)</td>
</tr>
<tr>
<td>Li 2011</td>
<td>76.6</td>
<td>13.6</td>
<td>15</td>
<td>63.2</td>
<td>11.9</td>
<td>15</td>
<td>18.3%</td>
<td>13.20 (10.08, 22.31)</td>
</tr>
</tbody>
</table>

Total (95% CI): 213 (209) 100.0% 6.22 (1.01, 11.43)

Heterogeneity: $I^2 = 18.55$; $H^2 = 7.46$, $df = 3$ ($P = 0.06$); $P = 60$

Test for overall effect: $Z = 2.34$ ($P = 0.02$)
The omission of detail about the quality rankings casts considerable doubt on the strength of the meta-analysis, since one of the included studies (Cerza 2012) was probably not adequately randomized

- Cerza “randomized” consecutive patients by admission to the hospital, and only did platelet counts on those allocated to PRP; this may prevent selection bias but the allocation is considered quasi-randomized rather than randomized
  - Because only the PRP group had blood drawn for concentrating the platelets, the study cannot have been adequately blinded
- Patel probably randomized adequately by “computer-derived random charts,” which is likely to mean that a random process was implemented; Patel also drew blood from both groups to maintain blinding
- Filardo 2012, one of the included studies, was adequately randomized and blinded; it favored PRP but the confidence interval included the null value for knee function

- Patel randomized patients into three groups: Group A had one PRP injection, Group B had two PRP injections, and Group C had a single NS injection; only Group B was included in the analysis of results
  - Groups A and B had very nearly identical outcomes, and the comparison with NS does not greatly suffer from the choice of comparison group

- Different studies included patients with different grades of OA pathology
  - Patel graded OA with the Ahlback system, while the other studies used KLG
  - Patel’s Table 1 shows 61 knees as grade 1, 28 as grade 2, and 5 as grade 3
  - Ahlback grade 1 is joint space narrowing of less than 3 mm, and is about equivalent to KLG grade III; grade 2 is joint space obliteration, and is about equivalent to KLG grade IV
  - Therefore the Patel study appears to have enrolled patients with more advanced OA, many of whom would be candidates for knee replacement
  - However, nothing can be said about the potential for PRP to forestall the need for total joint replacement with advanced OA

- Patel used NS as the control while the others used HA; removing Patel from the pooled data on the WOMAC had no effect on the treatment effect; this is consistent with evidence from elsewhere that HA has little effect beyond placebo for OA
- Because of the overall uncertainty about the quality of all included studies, the level of current evidence is better rated as “some” than as “good”

Assessment: Marginally adequate meta-analysis which nevertheless supports a statement that there is some evidence that in the setting of knee OA, intra-articular injection with PRP is more effective than HA or placebo in improving knee function and pain

References:


