Khoshbin A, Leroux T, et al. The Efficacy of Platelet-Rich Plasma in the Treatment of Symptomatic Knee Osteoarthritis: A Systematic Review With Quantitative Synthesis. Arthroscopy 2013;29(12)2037-2048.

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%)

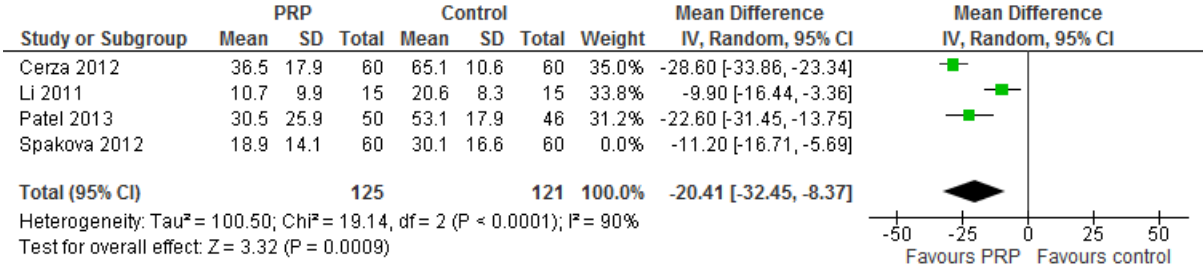
Authors' conclusions:

- 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:



Study or Subgroup	PRP Mean	PRP SD	PRP Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Cerza 2012	36.5	17.9	60	65.1	10.6	60	35.0%	-28.60 [-33.86, -23.34]
Li 2011	10.7	9.9	15	20.6	8.3	15	33.8%	-9.90 [-16.44, -3.36]
Patel 2013	30.5	25.9	50	53.1	17.9	46	31.2%	-22.60 [-31.45, -13.75]
Spakova 2012	18.9	14.1	60	30.1	16.6	60	0.0%	-11.20 [-16.71, -5.69]
Total (95% CI)			**125**			**121**	**100.0%**	**-20.41 [-32.45, -8.37]**

Heterogeneity: Tau² = 100.50; Chi² = 19.14, df = 2 (P < 0.0001); I² = 90%
Test for overall effect: Z = 3.32 (P = 0.0009)

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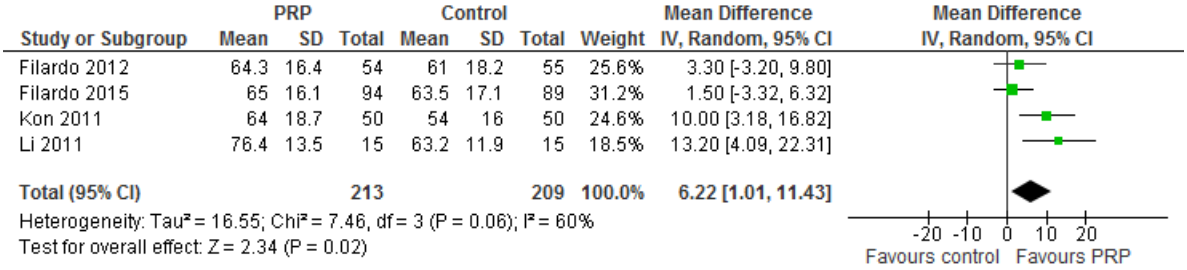
    - For the IKDC, Filardo 2015 also analyzed the effect of PRP on knee OA, and when it is included in a meta-analysis, the effect size for this outcome is only 6.22 points:



Study or Subgroup	PRP Mean	PRP SD	PRP Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Filardo 2012	64.3	16.4	54	61	18.2	55	25.6%	3.30 [-3.20, 9.80]
Filardo 2015	65	16.1	94	63.5	17.1	89	31.2%	1.50 [-3.32, 6.32]
Kon 2011	64	18.7	50	54	16	50	24.6%	10.00 [3.18, 16.82]
Li 2011	76.4	13.5	15	63.2	11.9	15	18.5%	13.20 [4.09, 22.31]
Total (95% CI)			**213**			**209**	**100.0%**	**6.22 [1.01, 11.43]**

Heterogeneity: Tau² = 16.55; Chi² = 7.46, df = 3 (P = 0.06); I² = 60%
Test for overall effect: Z = 2.34 (P = 0.02)

    - 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

- 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:

Cerza F, Carni S, et al. Comparison Between Hyaluronic Acid and Platelet-Rich Plasma, Intra-articular Infiltration in the Treatment of Gonarthrosis. Am J Sports Med 2012 40: 2822-2827.

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