Gormeli G, Gormeli CA, et al. Multiple PRP injections are more effective than single injections and hyaluronic acid in knees with early osteoarthritis: a randomized, double‐blind, placebo‐controlled trial. Knee Surg Sports Traumatol Arthrosc 2015; DOI 10.1007/s00167-015-3705-6, in press.

Design: randomized clinical trial

Purpose of study: in patients with osteoarthritis of the knee, to compare the clinical effectiveness of three injections of PRP with different doses of PRP, hyaluronic acid injection, and saline injection

Population/sample size/setting:

- 162 patients (90 women, 72 men, mean age 53.5) who completed a RCT for knee osteoarthritis at a university setting in Turkey
- All patients had an initial AP and lateral radiograph to assess the Kellgren-Lawrence classification of the tibiofemoral joint, and patients with K-L grade 0 underwent an MRI to assess the presence of chondral degeneration
- Inclusion criteria were at least 4 months of pain or swelling with either (1) radiographically documented grades I to IV tibiofemoral osteoarthritis on the K-L classification, or (2) if the K-L classification was grade 0, the MRI showed chondral damage; if the grade 0 knees had no chondral damage, they were excluded
- Exclusion criteria were previous lower extremity surgery, systemic disorders such as diabetes, connective tissue, cardiovascular, or hematologic disorders, generalized OA, use of NSAIDS in the 5 days before injection, hemoglobin levels less than 11 g/dL, and platelet counts less than 150,000

Interventions:

- The original randomization cohort had 182 patients, who were randomized to one of four groups: 3 PRP injections (PRP3, n=46), 1 PRP injection and 2 saline injections (PRP1, n=45), 3 injections of hyaluronic acid (HA, n=46), and control with 3 saline injections (n=45)
- All patients had 3 weekly injections whose composition depended on the group to which they were randomly allocated; the patients were blinded but the injecting physician was not blinded
- All patients had antecubital venipuncture with collection of 150 ml of venous blood into a bag with 21 ml sodium citrate
    - To collect 20 ml of PRP, two centrifugations were done; the first at 1500 RPM for 6 min followed by a second at 3500 RPM for 12 min

    - The PRP was divided into 4 small units of 5 ml each: 1 for platelet count/concentration, 1 for immediate administration for the PRP groups, and 2 for storage at -30° C for future use in the PRP3 group
- HA injection was 30 mg of high molecular weight HA in 2 ml of fluid

Outcomes:

- Followup was done at 6 weeks, at 3 months, and finally at 6 months
- The 6 month followup was when the primary outcomes were assessed
    - The two outcomes were the EuroQol visual analogue scale (EQ-VAS) and the International Knee Documentation Committee (IKDC) scores
- All active injection groups improved between baseline and the 6 month followup, but the saline control group did not improve; therefore, all three active injection groups had better outcomes than the control group
- The PRP3 group had significantly better results than the PRP1 group and the HA group, and all groups were equal at baseline (between 50.2 and 50.5 for the EQ-VAS and between 40.4 and 41.2 on the IKDC)
- While the PRP3 group did better than the PRP1 and HA groups, the PRP1 and HA groups did not significantly differ on the 6 month outcomes
    - The PRP3 group 6 month score for EQ-VAS was 710.4 and the IKDC was 60.8
    - The PRP1 group 6 month score for EQ-VAS was 62.0 and the IKDC was 50.2
    - The HA group 6 month score for EQ-VAS was 60.8 and the IKDC was 48.4
    - The control group 6 month score for EQ-VAS was 48.0 and the IKDC was 36.5
- A subgroup analysis was done, where the intervention groups were divided into early OA and advanced OA
    - Early OA was Kellgren-Lawrence grade I to III or grade 0 with chondral damage on MRI (n=108)
    - Advanced OA was K-L grade IV (n=54)
    - As was the case with the full analysis of the 6 month outcomes, the early OA group showed that all the active injection groups had better scores than the control group, the PRP3 group had better scores than the PRP1 or HA groups, and there were no differences between the PRP1 and HA groups
    - However, for the advanced OA group, the PRP3, PRP1, and HA groups did not differ from one another, although all three groups had better scores than the control group

Authors' conclusions :

- Multiple PRP injections are superior to a single PRP injection and are also superior to three HA injections, and are also superior to three saline injections for patients with knee OA
- A single PRP injection and three HA injections are of equal benefit for patients with knee OA, and are superior to three saline injections
- These differences are most apparent in early OA, and in advanced OA, the difference between multiple PRP and single PRP injection is not apparent

Comments:

- The differences between group outcomes are statistically tested with analysis of variance, which rejects the null hypothesis that the mean outcomes are equal between the intervention groups
- However, the differences in mean outcome scores are not presented with confidence intervals, and there is not a comparison of the outcomes scores with respect to a clinically meaningful standard
- The point estimate of the difference between PRP3 (78.2) vs. PRP1 (64.7) for the EE-VAS from Table 3 is 14.5 points, which could be meaningful on a 100 point scale
- The study used three injections for all four arms, which is likely to be due to the fact that HA was one of the interventions being tested; since this is commonly done under a protocol calling for three injections, the number of injections may have been arranged in order to maintain a blinded comparison
    - As a result, there is no reason to assume that three injections are superior to two injections
- The composition of the "early OA" group is heterogeneous, consisting of K-L grade I to III patients and K-L grade 0 patients with evidence of chondral degeneration on MRI
    - While this is probably done in order to have adequate sample sizes for the early group, it is not clear whether the benefit is equal between grade I and grade III OA
- The study does appear to be adequate to support more than one PRP injection for knee OA, and to support high molecular weight HA for knee OA

Assessment: Adequate for some evidence that in patients with knee OA, a single PRP injection is more beneficial than a saline injection, and that more than one PRP injection is likely to be more beneficial than a single PRP injection when the Kellgren-Lawrence grade is less than Grade IV. Adequate for some evidence that three injections of high molecular weight hyaluronic acid is more beneficial than three saline injections for knee OA. Adequate for some evidence that a single PRP injection is as beneficial as three hyaluronic acid injections for knee OA.