Vavken P, Sadoghi P, Murray MM. The effect of platelet concentrates on graft maturation and graft-bone interface healing in ACL reconstruction in human patients: A systematic review of controlled trials. Arthroscopy. 2011; 27(11): 1573–1583.

Design: Systematic review of controlled trials

Study question: When anterior cruciate ligament reconstruction is performed, does the application of platelet concentrates improve outcomes?

PICOS:

- Patient population: humans undergoing ACL reconstruction
- Interventions: Platelet concentrates applied intraoperatively as a liquid or gel, with or without a carrier scaffold to the graft or tunnel
    - Studies of postoperative application of platelets, repeated applications of platelets, or combination of platelets with other bioactive reagents (growth factors, cytokines) were excluded
- Comparison : ACL reconstruction without application of platelet concentrates
- Outcomes: graft maturation, graft-bone interface healing, and clinical outcomes
    - Graft maturation was assessed by MRI, wherein a low intensity signal with T2 or Proton Density (PD), similar to native ligaments, was judged to show that the graft had matured
    - Graft-bone interface healing was assessed by histology, MRI, or CT
    - Clinical outcomes were assessed with Knee injury and Osteoarthritis Outcome Score (KOOS), the KT-1000 knee arthrometer, the Lysholm score, the Tegner score, or the International Knee Documentation Committee Score (IKDC)
- Study types: both randomized and nonrandomized studies

Study selection:

- Databases were PubMed, CINAHL, EMBASE, and the Cochrane Central Register of Controlled trials
- Risk of bias was assessed with three of the Jadad criteria, giving one point each for randomization, concealment of allocation, and reporting of sample size/attrition, with 0 points as the worst score and 3 points as the best score
- Quantitative data analysis was not undertaken because of the clinical heterogeneity of platelet concentration systems, different platelet concentrations, and different ACL reconstruction techniques

Results:

- 8 articles reporting on 380 patients (198 with platelets, 182 without platelets) were selected
- All reports used bone-tendon-bone or hamstring autografts
- Four studies were both randomized and had blinded outcome assessment
- These four studies reported on graft maturation
    - One study found 100% low intensity signal in the 26 platelet patients and low intensity signal in 21 of 27 control patients (p=0.036)
    - A second study reported low intensity signal in 19 of 30 platelet patients and in "42.11%" of 20 control patients (p=.316)
    - A third study reported a 21% lower intensity with PD in the platelet group than with the control group (p=0.454) and 23% lower intensity with T2 (p=0.100)
    - The fourth study reported no difference with and without platelet treatment
- Three of the randomized, blinded studies reported on graft-bone interface healing
    - Two found no significant difference between groups
    - The third reported significantly better vascularization in the platelet group (0.33 ± 0.09) than in the control group at the osteoligamentous interface (0.16 ± 0.09, $p < 0.001$), but no revascularization in the intra-articular part of the graft
- Three studies reported clinical outcomes, two of them randomized and blinded
    - One randomized, blinded study reported no difference in Lysholm or IKDC scores, even though it had found a difference in graft maturation
    - The other randomized, blinded study reported no difference in range of motion, VAS, KT-1000, or IKDC scores, not had it reported a difference in radiographic outcomes
    - A randomized but unblinded study reported no difference in KOOS or KT-1000 scores

Authors' conclusions:

- There is limited evidence that platelet concentrates may improve the rate at which ACL grafts achieve a low T2 signal intensity and histologic evidence of graft remodeling, but little to no effect on tunnel healing
- Graft-bone interface healing was not convincingly shown
- Clinical outcomes were not different, but this should be interpreted cautiously, since the goal of platelet concentrates is to improve the speed of graft maturation, which is not necessarily visible in clinical scores of pain and function; in addition, the studies would be underpowered to detect clinical outcome differences
- Platelet concentrates have a biologically plausible mechanism for improving graft healing, but also have the potential to over-stimulate cells leading to a poorly

differentiated scar, while some growth factors may have adverse effects such as suppression of osteoclast generation

Comments:

- Pooling of outcome data would have been impractical because of clinical heterogeneity and some unclear reporting of outcomes
- The MRI outcomes which showed a platelet effect are surrogate measures of clinical outcome differences, and may not reflect true differences in final function of the knee
- The Jadad risk of bias criteria of randomization, blinding, and accounting for dropouts did not include concealment of allocation, which is one of the Cochrane risk of bias criteria and is a potential source of bias not addressed in the review
    - Even with inadequate control of biases which could inflate the treatment effect of platelets, the reported results remain unimpressive, suggesting that the generally null results are likely to be approximately accurate
- Overall, the data do not support an important role of platelet concentrates in improving the outcomes of ACL reconstruction

Assessment: Although the review is generally weak and does not adequately assess all sources of potential bias, it does support a statement that there is no evidence of a beneficial effect of platelet concentrates during ACL reconstruction