Plate Lysate/Platelet Releasate vs PRP in Regenerative Medicine “Blood-derived Growth Factor Concentrates” EBM update

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Clearwater Beach, FL
KISS PRINCIPLE

- Try to simplify to make things teachable and understandable
- You are only going to learn a few things from each lecture
- Make it count!
20 Minute Lecture

- Simple Topic
- 500 slides
- 2 minute lecture
- 18 minutes for Q&A
- Done on time
- No Problem!
PRP History

- Late 90s, use in implant dentistry
- Mid 2000s—the beginning of orthopedic use
- Late 2000s more widespread adoption as an orthobiologic
Platelets live in whole blood...
The good stuff lives in granules...
Types of granules...

- Alpha-GFs, clotting factors, fibrin stabilizing factors
- Dense-ATP, ADP, Ca2+, serotonin
Platelets have growth factors inside them...
How platelets augment healing...

1. Circulating, inactive platelets
   - Initiation of coagulation
   - Fibrin receptor activation

2. Activated platelets bind fibrin
   - Augmentation of clotting

3. Activated platelets spread within fibrin
   - Platelet deformation/spreading
   - Myosin-driven contraction

4. Activated platelets collapse fibrin
   - Clot contraction
Using PRP
Activation?

- Thrombin and CaCl2 will activate platelets.
- Platelets will also be activated by injecting them into an OA joint or tendon.
- Hence, it’s unlikely that manual activation carries a benefit.
Different Preps and Techniques?

- Preparation
- Classification
- Activation
- WBCs?
- RBCs?
- Concentration
WBCs?

- No evidence yet for clinical differences in knee OA between LR and LP-[Arthroscopy]. 2016 Mar;32(3):495-505
- Antibacterial effects not related to WBCs (likely cytokines)-[BMC Microbiol]. 2015 Jul 30;15:149.
LR vs. LP PRP (Leukocyte Rich vs. Poor)-Knee

LR resulted in significant synovial cell death and pro-inflammatory mediators in-vitro, whereas LP did not. 

LP caused better chondrocyte proliferation in-vitro. LP caused anabolic ECM production, LR caused catabolism-

LR vs. LP PRP (Leukocyte Rich vs. Poor)-Tendon

- LP caused less tendon inflammation, but similar cellularity-animal model-
- More on this once we review concentration
MSC Responses to LR vs. LP PRP
Representative MSC colonies for CFU counts (inversion microscopy).

MSC Colonies (CFUs)

RBC-, PRP

No growing MSCs

RBC+, PRP

RBC-, PL
The best concentration for tendons?
Animal model of tendon healing-increasing platelet concentrations from 2X to 5-7X to 15-20X, with and without WBCs

Even 2X showed good tendon healing

It was more important to eliminate WBCs than to hyper-concentrate tendons (i.e. maximizing platelet to leukocyte ratio was better)

There may be a threshold of concentration beyond which going higher could reduce expression of certain collagen types

Tendon concentration/WBC summary?

Many animal models performed in young tissues
There is likely a plateau effect
Our own data has shown that in-vitro work with high platelet concentrations can negatively impact culture conditions due to mitochondrial waste products
Is there a negative effect of going higher?
A PRP count of 2B is approximately 7X
Recommendation-For young tendons, you likely don’t need more than 2-3X, for older tendons go as high as 5-7X. Either way, best to avoid RBCs!
Knee OA (meta-analysis)

*Arthroscopy.* 2016 Mar;32(3):495-505

6 studies reviewed (n=739, 817 knees, 39% males, mean age of 59.9 years, with 38 weeks average follow-up)

PRP injection results in significant clinical improvements up to 12 months postinjection.

Clinical outcomes and WOMAC scores are significantly better after PRP versus HA at 3 to 12 months postinjection.
In general, PRP works better in less severe OA.

Sweet spot seems to be KI grade 1-2 (mild to moderate OA).

Less likely to work in severe OA.
N=111 RCT, 3 weekly US guided injections of PRP vs. PRP+HA vs. HA
LP-PRP-concentrations not listed
PRP superior to the other two tested treatments
Best Achilles tendon study to date:

- 20 Achilles tendon ruptures treated with PRP vs. saline
- They took samples of the tendon
- PRP treated tendons with better collagen 1, better cellularity, less vascularity, better GAGs
- PRP outperformed saline control on pain/function

*Lancet.* 2015 Feb 26;385 Suppl 1:S19
Best Tendonitis Study to date (lateral epicondylitis):

- DB multi-center RCT
- N=230
- LR-PRP

No significant differences were found at 12 weeks in this study. At 24 weeks, however, clinically meaningful improvements were found in patients treated with leukocyte-enriched PRP compared with an active control group.

Lysate vs releasate—what’s the difference?
Platelet Lysate

- Lyse platelets by freezing
- GF Immediately available
- More advanced techniques leave fewer platelets hanging around
- Anti-inflammatory
- Creates Neovasculogenesis around nerves
A releasate is a growth factor (gf) poor product...

- A releasate is created by overwhelming PRP with CaCl₂ or thrombin to create a clot and prompt a GF release.
- Platelets naturally release GFs over 7-10 days.
- Hence prompting early release only allows a fraction of the total GF payload to be degranulated.
perfect for epidural use

- PL injected epidural using fluoroacopically guided transforaminal route or caudal
- Same patient population who would normally benefit from ESI-radiculopathy secondary to disc protrusion, extrusion, sequestration, or stenosis
• Prospective registry data of epidural steroid patients versus platelet lysate epidurals
• Validated Functional Rating Index (FRI) used before and after at 3 and 6 months
• Patient population was lumbar radiculopathy due to HNP, bulge, or stenosis (mixed group)
• Injections were fluoro guided transforaminal and caudal (>90% TF)
• 11 patients crossed over from the ESI to the PL group
• Better FRI scores at 3 and 6 months for the PL group vs. ESI (p<0.05)
• Cases chosen based on no missing registry data

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Summary

- PRP seems to work
- WBCs/RBCs are likely an issue (red PRP)
- Going higher on concentration in joints to stimulate local MSCs may be helpful
- Going lower on concentration in tendons may be a good idea
- PL is anti-inflammatory and works for epidurals and hydrodissection of nerves