Regenerative Medicine: Platelet Rich Plasma Injections and How They Work To Speed Healing

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Objectives:

• Define platelet rich plasma (PRP).
• Create an framework of understanding as to how PRP is used within sports medicine.
• Review current research related to PRP.
• Discuss how PRP may fit within the non-surgical options for patients and what subgroup appears to be the best population to respond.
What is the main pain generator?

Sites of Running Injuries
Wilder and O’Conner Running Medicine 2000
Risk Factors for Running Injuries

- **Extrinsic Factors**
  - training errors
  - running surfaces
  - environment
  - technique
  - equipment
  - nutrition

- **Intrinsic Factors**
  - inflexibility
  - muscle weakness
  - malalignment
  - muscle imbalance
  - instability

Arthrokinematics
Sagittal Plane

Frontal Plane
Transverse Plane

Realities of Exercise
Common Pain Patterns

Tendinopathy

- Tendinopathy is a condition in which tendons become inflamed (tendonitis) or have microscopic tears in the tissue as a result of overuse (tendinosis).

- The term tendinosis is used rather than tendinitis because this condition represents a degenerative process without acute inflammatory cells.

- Typical treatment for tendinopathy can include modalities such as ice, physical therapy, NSAIDS, and steroid injections.
How Can We Prevent This?
Evaluating the Athlete

OMT for the Runner
Tiers of Non-Surgical Treatment

1. Conservative management
   – Activity Modifications
   – Nutrition
   – Bracing
   – Osteopathic Manipulation
   – Physical Therapy (Graston, ART, Iontophoresis)
   – Home Exercises
   – Medications (Tylenol, NSAIDs, Narcotics)
   – Steroid Injection
   – Viscosupplementation

2. Regenerative Medicine

Clinical Gray Zones

• Chronic symptoms but “not a surgical candidate.”
• Unable to perform desired activities due to pain.
• Examples:
  – Partial thickness rotator cuff tear
  – Degenerative meniscus injury

  “Come back when it’s bad enough for surgery”
What is Regenerative Biomedicine?

• The injection of the body’s own growth factors into injured or degenerating tissue, accelerating the healing process of the musculoskeletal system.

• Techniques and products have evolved over the last few decades, as scientific research has focused on the different modalities and their benefits.

Regenerative Medicine Treatments

1. Prolotherapy
2. Autologous blood injection (ABI)
3. Platelet rich plasma (PRP)
4. Mesenchymal Stem Cells
   • Bone marrow aspirate concentrate (BMAC)
   • Adipocytes
   • Amnion
What is PRP?

- Platelet rich plasma (PRP) is obtained by centrifuging whole blood into its different components
- Has been shown to repair meniscus, ligaments, tendons, muscles, cartilage, & bone[2]
- Allow for increased collagen & matrix synthesis[1]
- Works by directly injecting platelets that contain PDGF, PDEGF, PDAF, IGF-1, TGF-β, & platelet factor 4[1]

Healing Cascade

[Diagram of the healing cascade process]
Important Growth Factors in PRP

<table>
<thead>
<tr>
<th>Growth Factor</th>
<th>Phase in Which Most Active</th>
<th>Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-1</td>
<td>Inflammation, proliferation</td>
<td>Promotes proliferation and migration of cells, stimulates matrix production</td>
</tr>
<tr>
<td>TGF-β</td>
<td>Inflammation</td>
<td>Regulates cell migration, proteinase expression, fibronectin binding interactions, termination of cell proliferation, stimulation of collagen production</td>
</tr>
<tr>
<td>VEGF</td>
<td>Proliferation, remodeling</td>
<td>Promotes angiogenesis</td>
</tr>
<tr>
<td>PDGF</td>
<td>Proliferation, remodeling</td>
<td>Regulates protein and DNA synthesis at injury site, regulates expression of other growth factors</td>
</tr>
<tr>
<td>bFGF</td>
<td>Proliferation, remodeling</td>
<td>Promotes cellular migration, angiogenesis</td>
</tr>
<tr>
<td>EGF</td>
<td>Proliferation, remodeling</td>
<td>Stimulates proliferation and differentiation of epidermal cells, stimulates angiogenesis</td>
</tr>
</tbody>
</table>

Tendinopathy Results When Normal Healing Fails
Meniscal Injuries

PRP-Before and After

Patella

"Jumper's Knee"

Pre-procedure

9 months post-procedure

Patellar Tendon

Healthier tendon after PRP
Quality of life

• Quality of life measures are determined by a person’s ability to be active
• If patients are unable to do the things they enjoy,
  – Reactive depression
  – Overeating
  – Addictive tendencies

The Use of PRP in Injection Therapy


Study:
20 patients that failed non-operative treatment for chronic epicondylar pain were randomized to evaluate effectiveness of PRP – At 1, 2, and 6 months all PRP patients had lower pain and greater ROM than control (bupivacaine). Treatment of chronic epicondylar pain with PRP should be considered prior to surgical intervention.


Study:
20 patient prospective muscle injury pilot study with 6 month follow-up – Ultrasound guided injection of PRP within the injured muscle enhanced healing (echo-graphic images) and functional capacities 50% faster than the control group.


Study:
9 patients with hypoechoic and thickened plantar fascia were injected with PRP to evaluate the efficacy of PRP with 1 week, 2 week and 1, 3, 6, and 12 month follow-up – All patients had improvement that was noted on diagnostic ultrasound and 9 patients had complete resolution after 2 months. At 1 year, 1 of 9 patients were completely healed.
Platelet-rich Plasma vs Hyaluronic Acid to Treat Knee Degenerative Pathology

Giuseppe Filardo; Elizaveta Kon; Alessandro Di Martino; Berardo Di Matteo; Maria L Merli; Annarita Cenacchi; Pier M Fornasari; Maurilio Marcacci  BMC Musculoskelet Disord. 2012;13(239)

- **Background** Platelet Rich Plasma (PRP), a blood-derived product rich in growth factors, is a promising treatment for cartilage defects but there is still a lack of clinical evidence. The aim of this study is to show, through a randomized double blind prospective trial, the efficacy of this procedure, by comparing PRP to Hyaluronic Acid (HA) injections for the treatment of knee chondropathy or osteoarthritis (OA).

- **Methods** 109 patients (55 treated with HA and 54 with PRP) were treated and evaluated at 12 months of follow-up. The patients were enrolled according to the following inclusion criteria: age>18 years, history of chronic (at least 4 months) pain or swelling of the knee and imaging findings of degenerative changes of the joint (Kellgren-Lawrence Score up to 3). A cycle of 3 weekly injections was administered blindly. All patients were prospectively evaluated before and at 2, 6, and 12 months after the treatment by: IKDC, EQ-VAS, TEGNER, and KOOS scores. Range of motion and knee circumference changes were measured over time. Adverse events and patient satisfaction were also recorded.

- **Results** Only minor adverse events were detected in some patients, such as mild pain and effusion after the injections, in particular in the PRP group, where a significantly higher post-injection pain reaction was observed (p=0.039). At the follow-up evaluations, both groups presented a clinical improvement but the comparison between the two groups showed a not statistically significant difference in all scores evaluated. A trend favorable for the PRP group was only found in patients with low grade articular degeneration (Kellgren-Lawrence score up to 2).

- **Conclusions** Results suggest that PRP injections offer a significant clinical improvement up to one year of follow-up. However, conversely to what was shown by the current literature, for middle-aged patients with moderate signs of OA, PRP results were not better than those obtained with HA injections, and thus it should not be considered as first line treatment. More promising results are shown for its use in low grade degeneration, but they still have to be confirmed.

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How Can We Prevent This?

Evaluating the Runner
OMT for the Runner

Anti-inflammatory Agents:

- Ice
- Low protein-plant based diets.
- Garlic
- Cinnamon
- Unsweetened Cocoa Powder
- Turmeric
- Ginger
- Tart Cherry Juice
- Vitamin D and Omega 3 fatty acids
Turmeric

- Contains more than two dozen anti-inflammatory compounds, including six different COX-2-inhibitors.
- The yellow hue is from curcumin.
- Dosage: 400-600mg BID
- Also consider Turmeric tea.

Zyflamend

Supplement Facts

<table>
<thead>
<tr>
<th>Serving Size: 500 mg</th>
<th>Servings per container: 30.00</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amount Per Serving</strong></td>
<td><strong>% Daily Value</strong></td>
</tr>
<tr>
<td>Extract (root) 100mg standardized extract and 50 mg curcumin (2% total phenolic antioxidants, TRC)</td>
<td>150.00 mg</td>
</tr>
<tr>
<td>Turmeric (Curcuma) Longa standardized extract (95% turmericin-95mg) and 10mg curcumin extract (7% curcuminoids-7mg)</td>
<td>110.00 mg</td>
</tr>
<tr>
<td>Ginger (Zingiber) Longa standardized extract, organic (70% gingerol, 4% shogaol, 5% zingerone, 1% paradol, 0.5% germacrone, 1.5% zingerone-1.5mg)</td>
<td>100.00 mg</td>
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<tr>
<td>Hael Bael Extract (50% bael juice and 50%)</td>
<td>100.00 mg</td>
</tr>
<tr>
<td>Green Tea Extract (95% polyphenols-9mg)</td>
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<tr>
<td>Hua Zhang Extract (Polygonum cuspidatum-root &amp; rhizome)-9% rehmannia-9mg</td>
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<tr>
<td>Clerodendrum Bicolor Extract (5% berberine-5mg)</td>
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</tr>
<tr>
<td>Barbarea Extract (root)-4% barberry-4mg</td>
<td>40.00 mg</td>
</tr>
<tr>
<td>Oriental (Biloba) standardized extract (90.6% TPGS-0.05mg)</td>
<td>40.00 mg</td>
</tr>
<tr>
<td>Radix (Shikonia) Sponge Extract (root)-17% spongistatin, 35% saponins, and 30% greenol-30mg</td>
<td>30.00 mg</td>
</tr>
</tbody>
</table>

*Daily value not established.

Other ingredients: Oleic acid, sorbitol, polyethylene glycol, and yellow beeswax.
Capsule: gelatin, vegetable glycerin, sodium water and soda.
Supplement Information

• The Agency for Healthcare research and Quality (AHRQ) compiles a summary of the evidence for certain supplements and herbal products: [www.ahrq.gov/clinic](http://www.ahrq.gov/clinic)

• Independent research on supplements and herbal products may be reviewed: [www.consumerlab.com](http://www.consumerlab.com)

• USP seal

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How to read the Label

1. Look at serving size

2. Add EPA + DHA Levels
Balancing the ANS
Acupuncture

– A method of treating patients by manipulating thin, solid needles that have been inserted into specific points in the skin

– Stimulating these points can correct imbalances in the flow of Qi through channels known as meridians

Iliotibial Band Syndrome

• The most common cause of lateral knee pain in runners
• Incidence as high as 12% of all running-related overuse injuries
• Results from recurrent friction of the iliotibial band sliding over the lateral femoral condyle
Graston Technique

- A form of instrument-assisted soft tissue mobilization that enables clinicians to effectively break down scar tissue and fascial restrictions. The technique utilizes specially designed stainless steel instruments to specifically detect and effectively treat areas exhibiting soft tissue fibrosis or chronic inflammation.

Active Release Technique (ART)

- ART is a soft tissue system/movement based massage technique that treats problems with muscles, tendons, ligaments, fascia and nerves.
Yoga

Runners
Cross Training

Why Cross Train?

- Helps reduce the risk of injuries.
- Cross-training allows for a tremendous volume of central circulatory training without overuse of a particular muscle group.
- Provides variety in the training regimen.
- Workouts based on time rather than distance.
- Allows for greater daily training intensity. Even though the same muscles are being utilized, they are being used differently.
- Non-weight bearing cross training activities give the legs and running muscles a well deserved break, promoting recovery.
Treatment With Platelet-Rich Plasma Is More Effective Than Placebo for Knee Osteoarthritis

Sandeep Patel, Mandeep S. Dhillon, Sameer Aggarwal, Neelam Marwaha, and Ashish Jain, MD


• **Background:** Specific growth factors have been proposed as therapeutic proteins for cartilage repair.
• **Hypothesis:** Platelet-rich plasma (PRP) provides symptomatic relief in early osteoarthritis (OA) of the knee.
• **Study Design:** Randomized controlled trial; Level of evidence, 1.
• **Methods:** A total of 78 patients (156 knees) with bilateral OA were divided randomly into 3 groups. Group A (52 knees) received a single injection of PRP, group B (50 knees) received 2 injections of PRP 3 weeks apart, and group C (46 knees) received a single injection of normal saline. White blood cell (WBC)–filtered PRP with a platelet count 3 times that of baseline (PRP type 4B) was administered in all. All the groups were homogeneous and comparable in baseline characteristics. Clinical outcome was evaluated using the Western Ontario and McMaster Universities Arthritis Index (WOMAC) questionnaire before treatment and at 6 weeks, 3 months, and 6 months after treatment. They were also evaluated for pain by a visual analog scale, and overall satisfaction with the procedure and complications were noted.

• **Results:** Statistically significant improvement in all WOMAC parameters was noted in groups A and B within 2 to 3 weeks and lasting until the final follow-up at 6 months, with slight worsening at the 6-month follow-up. The mean WOMAC scores (pain, stiffness, physical function, and total score) for group A at baseline were 10.18, 3.12, 36.56, and 49.86, respectively, and at final follow-up were 5.00, 2.10, 20.08, and 27.18, respectively, showing significant improvement. Similar improvement was noted in group B (mean WOMAC scores at baseline: 10.62, 3.50, 39.10, and 53.20, respectively; mean WOMAC scores at final follow-up: 6.18, 1.68, 22.40, and 30.48, respectively). In group C, the mean WOMAC scores deteriorated from baseline (9.04, 2.70, 33.80, and 45.54, respectively) to final follow-up (10.87, 2.76, 39.46, and 53.09, respectively). The 3 groups were compared with each other, and no improvement was noted in group C as compared with groups A and B (P<.001). There was no difference between groups A and B, and there was no influence of age, sex, weight, or body mass index on the outcome. Knees with Ahlback grade 1 fared better than those with grade 2. Mild complications such as nausea and dizziness, which were of short duration, were observed in 6 patients (22.2%) in group A and 11 patients (44%) in group B.

• **Conclusion:** A single dose of WBC-filtered PRP in concentrations of 10 times the normal amount is as effective as 2 injections to alleviate symptoms in early knee OA. The results, however, deteriorate after 6 months. Both groups treated with PRP had better results than the group injected with saline only.
**Platelet-Rich Plasma Intra-articular Knee Injections Show No Superiority Versus Viscosupplementation**

Giuseppe Filardo, MD, PhD, Breando Di Matteo, MD, Alessandro Di Martino, MD, Maria Letizia Merli, MD, Anna Rita Cenacchi, MD, Pier Maria Fornasier, MD, Maurilio Marzacci, MD, Prof, and Elizaveta Kon, MD

*Am J Sports Med July 2015 vol. 43 no. 7 1575-1582*

- **Background:** Osteoarthritis (OA) is a common disease that will affect almost half the population at some point in their lives through pain and decreased functional capacity. New nonoperative options are being proposed to treat earlier stages of joint degeneration to provide symptomatic relief and delay surgical intervention.

- **Purpose:** To evaluate the benefit provided by platelet-rich plasma (PRP) injections to treat knee joint degeneration in comparison with hyaluronic acid (HA), the most common injective treatment currently adopted for this condition.

- **Study Design:** Randomized controlled trial; Level of evidence, 1.

- **Methods:** A total of 443 patients were screened, and 192 of them were enrolled in the study according to the following inclusion criteria: (1) unilateral symptomatic knee with history of chronic pain (at least 4 months) or swelling and (2) imaging findings of degenerative changes (Kellgren-Lawrence score of 0-3 at radiographs or MRI evidence of degenerative chondropathy). Patients underwent 3 weekly intra-articular injections of either PRP or HA. Patients were prospectively evaluated at baseline and then at 2, 6, and 12 months from follow-up using the International Knee Documentation Committee (IKDC) subjective score (main outcome), Knee injury and Osteoarthritis Outcome Score, EuroQol visual analog scale, and Tegner score. Range of motion, transpatellar circumference, patient satisfaction, and adverse events were also recorded.

- **Results:** Two patients reported severe pain and swelling after HA injections, while no major adverse events were noted in the PRP group. However, PRP presented overall significantly more postinjection swelling and pain. Both treatments proved to be effective in improving knee functional status and reducing symptoms: the IKDC score in the PRP group rose from 52.4 ± 14.1 to 66.2 ± 16.7 at 12 months (P < .0005), and in the HA group it rose from 49.6 ± 13.0 to 64.2 ± 18.0 at 12 months (P < .0005). A similar trend was observed for all the clinical scores used. The comparative analysis of the 2 treatments showed no significant intergroup difference at any follow-up evaluation in any of the clinical scores adopted.

- **Conclusion:** PRP does not provide a superior clinical improvement with respect to HA, and therefore it should not be preferred to viscosupplementation as injective treatment of patients affected by knee cartilage degeneration and OA.
Tiers of Non-Surgical Treatment

1. Conservative management
   – Lifestyle Modifications
   – Physical Therapy/Exercise
   – Medications (Tylenol, NSAIDs)
   – Injection Therapy
2. Viscosupplementation
3. Prolotherapy
4. Autologous blood injection (ABI)
5. Platelet rich plasma (PRP)
6. Bone marrow aspirate concentrate (BMAC)
7. Adipocytes
8. Amnion

Conclusion

• PRP is a new treatment for knee degenerative pathologies and an increasing number of studies show promising results.
• However, despite its wide application in the clinical practice and the positive findings reported, there is a lack of scientific background to guide the clinical application of PRP.
• To avoid indiscriminate and inappropriate use of PRP, it is important to determine the type of patients who will not benefit from this treatment, and therefore the authors designed a high level study to understand clearly the indication of this treatment.
• The present results suggest, conversely to what was shown by the current literature, that for middle-aged patients with moderate signs of OA, PRP did not offer better results compared to HA, and thus it should not be considered as first line treatment.
• More promising results are shown for its use in less degenerated cases, but they still need to be confirmed.
Citations


Citations

Figure Citations

• [1] www.mediworks.ca