Use of PRP, Stem Cell and Autologous Injections

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I have no conflicts of interest to disclose
Objectives

Distinguish between available evidence and popular belief regarding the efficacy of autologous blood, platelet-rich plasma, and stem cell injections

Describe practical and realistic use of these injection therapies
The forces driving use of these agents

- Athletes
- Media
- Industry (Stem cells, PRP, ABI?)
- Physicians
The Preface...


“It is astonishing but understandable that the most influential stimulus for PRP therapy in the USA, years after the method had been popularized in Europe, was a February 2009 article in the lay press.” (NY Times, 2/16/09)
A Promising Treatment for Athletes, in Blood

By ALAN SCHWARTZ
Published: February 18, 2009

Two of the Pittsburgh Steelers’ biggest stars, Hines Ward and Troy Polamalu, used their own blood in an innovative injury treatment before winning the Super Bowl. At least one major league pitcher, about 20 professional soccer players and perhaps hundreds of recreational athletes have also undergone the procedure, commonly called platelet-rich plasma therapy.

Experts in sports medicine say that if the technique’s early promise is fulfilled, it could eventually improve the treatment of stubborn injuries like tennis elbow and knee tendinitis for athletes of all types.

The method, which is strikingly straightforward and easy to perform, centers on injecting portions of a patient’s blood directly into the injured area, which catalyzes the body’s instincts to repair muscle, bone and other tissue. Most enticing, many doctors said, is that the technique appears to help regenerate ligament and tendon fibers, which could shorten rehabilitation time and possibly obviate surgery.

Research into the effects of platelet-rich plasma therapy...
PRP kit

- 8ml
- 10ml
- 12ml
- 15ml

Sports Medicine

Stem Cell Therapy
- Skin rejuvenation using Stem cell
- Fat Graft using Stem cell

Human Stem cell Conditioned Media (Growth factor)

PRP (Platelet-rich plasma) Therapy
- Skin rejuvenation using PRP
- Fat Graft using PRP
### TABLE 3. Representative Quotations

<table>
<thead>
<tr>
<th>Patient Testimonials</th>
<th>Physician Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>In a last ditch effort to avoid surgery, she tried PRP. Now, she is</td>
<td>I consider PRP about five times as potent as regular prolotherapy.</td>
</tr>
<tr>
<td>“pain-free” after 15-20 years of suffering.</td>
<td>A lot of things are fadish. I don’t think PRP will fall into that</td>
</tr>
<tr>
<td>A “one-shot cure” of degenerative joint disease is pretty darn impressive!</td>
<td>category, because the scientific evidence supporting it is so</td>
</tr>
<tr>
<td>PRP is the proverbial fountain of youth.</td>
<td>strong.</td>
</tr>
<tr>
<td>PRP allowed me as a patient to have “freedom.” I had ruptured my</td>
<td>Need for surgery can be greatly reduced by treating injured</td>
</tr>
<tr>
<td>Achilles tendon and was unable to drive. Because of PRP, I was able to speed up my</td>
<td>tissues with PRP before damage progresses and is irreversible.</td>
</tr>
<tr>
<td>recovery and NOT be a burden to family and friends.</td>
<td>Growth factors can dramatically enhance tissue recovery … the</td>
</tr>
<tr>
<td>A professional football player left the game with a sprained medial</td>
<td>components are extracted from a person’s own body. This makes</td>
</tr>
<tr>
<td>collateral ligament and was injected with PRP. He recovered enough to make two</td>
<td>the procedure entirely safe.</td>
</tr>
<tr>
<td>catches in the Super Bowl.</td>
<td>Platelet-rich plasma is helping to shorten rehabilitation time</td>
</tr>
<tr>
<td></td>
<td>and often eliminates the needs for surgery.</td>
</tr>
</tbody>
</table>
Tendon truths?

- Healing results from anything that will produce a triphasic response (inflammation, proliferation, remodeling)
- Poor relationship between structure and pain (pathological tendons are not always painful and vice versa)
- A severed tendon is not tendinosis, a stretched tendon is not tendinosis
- Tendons react to needles – substance may be irrelevant
### Theoretical rationale for use

<table>
<thead>
<tr>
<th>Growth factor</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet-derived growth factor</td>
<td>Angiogenesis, macrophage activation</td>
</tr>
<tr>
<td></td>
<td>Fibroblasts: proliferation, chemotaxis, collagen synthesis</td>
</tr>
<tr>
<td></td>
<td>Enhances the proliferation of bone cells</td>
</tr>
<tr>
<td>Transforming growth factor-β</td>
<td>Fibroblasts proliferation</td>
</tr>
<tr>
<td></td>
<td>Synthesis of type I collagen and fibronectin</td>
</tr>
<tr>
<td></td>
<td>Induce deposition of bone matrix, inhibits bone resorption</td>
</tr>
<tr>
<td>Platelet-derived epidermal</td>
<td>Stimulates epidermal regeneration</td>
</tr>
<tr>
<td>growth factor</td>
<td>Promotes wound healing by stimulating the proliferation of keratinocytes</td>
</tr>
<tr>
<td></td>
<td>and dermal fibroblasts</td>
</tr>
<tr>
<td></td>
<td>Enhances the production and effects of other growth factors</td>
</tr>
<tr>
<td>Vascular endothelial growth</td>
<td>Vascularisation by stimulating vascular endothelial cells</td>
</tr>
<tr>
<td>factor</td>
<td></td>
</tr>
<tr>
<td>Insulin-like growth factor 1</td>
<td>Chemotactic for fibroblasts and stimulates protein synthesis</td>
</tr>
<tr>
<td>Platelet factor 4</td>
<td>Enhances bone formation</td>
</tr>
<tr>
<td>Epidermal growth factor</td>
<td>Stimulate the initial influx of neutrophils into wounds</td>
</tr>
<tr>
<td></td>
<td>Chemoattractant for fibroblasts</td>
</tr>
<tr>
<td></td>
<td>Cellular proliferation and differentiation</td>
</tr>
</tbody>
</table>

Mei-Dan O, et al. BJSM 2010;44(9)
What are the issues?

• What is the best platelet concentration?
• pH of local anesthetic?
• What is the optimal pH for platelet activity?
• Optimal dose?
• Number of injections?
• Interval between injections?
• What is the role of the RBC? WBC?
• Early use in 1990’s, maxillofacial surgery to augment reconstructions
• Later, used in ortho surgery to augment tendon reconstruction, articular cartilage surgery
• Even later, used for tendinoses
• Rationale: introduce biologically active factors to area of tendinosis to “jump start” the healing process
Tendinopathy treatment, one technique

- Technique
  - 3-5 mL whole blood or...
  - 15-50 mL whole blood to centrifuge to obtain about 5-6 mL platelet rich plasma
- Either landmark-based or US guided injection
- “Peppering” with the needle is frequently employed creating fenestrations in injured tissue
- NSAID “washout” prior to injection.
- No NSAID’s for ?
- RTP/workouts ?
Biological therapies

- “...aim to deliver a ‘blunderbuss’ of bioactive substances to the site of pathology and thereby stimulate a healing process.”

- Use normal physiological pathways rather than noxious stimuli to trigger the healing process
Comparisons


• Reviewed treatment of patellar tendinosis comparing results of dry needling, autologous blood, high volume PRP, corticosteroids, sclerosis, aprotinin
  – 4 RCT’s, 1 non RCT, 4 prospective cohort studies, 2 retrospective cohort studies
• All substances “showed promise”
• Corticosteroids showed relapse of symptoms
Lateral Epicondylosis
Systematic review


5 prospective case series and 4 controlled trials (3 prolotherapy, 2 polidocanol, 3 autologous whole blood, and 1 platelet-rich plasma) suggest each of the 4 therapies is effective for LE in follow-up periods ranging from 9 to 108 weeks (strong pilot-level evidence)
Lateral Epicondylosis

• Mishra AK, Skrepnik NV, Edwards SG, et al: 2013 online
  – N=116 (PRP); N=114 (“needling” control)
  – Success rate PRP 83.9%; Control, 68.3%

  N=15 vs 5 controls
  60% improvement at 8 weeks
  81% improvement at 6 months
  93% pain reduction at average of 25.6 months (range 12-38 months)

  – Results at 3 months: Pain reduction in all 3 (PRP, ABI, Corticosteroids) groups (no statistically significant difference)

“Injection therapy of PRP is effective for the treatment of patellar tendinopathy and has the promising potential to restore patients to their activities of daily living, work, and sports. However, through the present research, it is hard to draw a clear conclusion for the effectiveness of PRP treatment on patellar tendinopathy. More precise clinical researches are required.”

N=20 PRP treatment

6 month f/u

Results: Tegner, VAS, SPF-36 showed improvement


Compared PRP injection to ECSWT.

Outcomes measured at 2, 6, 12 months

Results 12 month f/u: PRP better than ECSWT
Acute Muscle Injury

Cugat (unpublished data)

– 14 professional athletes injected with PRP at site of injury.
– Results suggested earlier return to play
– Problems
  • Retrospective
  • Professionals
  • Comparisons based on other published data about return to play (muscle severity?)


Physiological impact of bolus infiltration of unknown concentration of platelets is scientifically unknown. Theoretical risks have not been quantified

Use of PRP has no clinical evidence base
Ligament injury

Mandelbaum BR et al: Unpublished study

- N=22. PRP administered 72 hours after acute ligamentous injury
- RTP time decrease by 27% compared to controls
  (retrospective, small numbers)


- N=34 athletes with partial UCL tears of elbow
- Single US guided PRP injection to UCL
- Results: F/U average 70 weeks (11-117 weeks)
- 30/34 returned same level of play
- Ave time of RTP 12 weeks (10-15)
Achilles tendinopathy

N=54, 27 PRP, 27 saline, both eccentric program
US exam at baseline. VISA-Achilles outcome measure

Results:
59% of both groups were satisfied
Both groups had similar US improvement

N=14 (15 Achilles tendons)
Results at 18 months
AOFAS scale 55 to 96
VISA-A 24 to 96
Imaging reported as improved.
Rotator cuff tendinopathy


N=40 (18-70 years old). + MRI findings.

20 PRP, 20 controls. 5 mL PRP or 5 mL saline injected into subacromial space by US guidance

Outcomes (WORC, SPADI, VAS scores) measured start, 3, 6, 12, 24 months, 1 year

Results:

At one year **no difference** in outcomes.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Patients, n.</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gani</td>
<td>2007</td>
<td>26</td>
<td>1-2 ABI</td>
<td>Nirshl 3.3 to 1.2; pain score 5.5 to 3/10</td>
</tr>
<tr>
<td>Edwards et al.</td>
<td>2003</td>
<td>28</td>
<td>1-3 ABI</td>
<td>22/28 complete pain relief</td>
</tr>
<tr>
<td>Conell</td>
<td>2006</td>
<td>35</td>
<td>One ABI with needling under guidance</td>
<td>All improved</td>
</tr>
<tr>
<td>Saldana</td>
<td>2003</td>
<td>39</td>
<td>One ABI</td>
<td>10 healed</td>
</tr>
<tr>
<td>Delghani</td>
<td>2009</td>
<td>22</td>
<td>One ABI</td>
<td>Pain score 44 to 9</td>
</tr>
<tr>
<td>Bharti</td>
<td>2010</td>
<td>25</td>
<td>One ABI</td>
<td>23 good or excellent results</td>
</tr>
<tr>
<td>Present study</td>
<td>2007-2011</td>
<td>130</td>
<td>1-2 ABI</td>
<td>85% satisfied</td>
</tr>
</tbody>
</table>

ABI, autologous blood injection.
Figure 4 Mean (±sd) of PPT score in PRP and Autologous Whole Blood (AWB) groups at baseline, 4, 8 weeks, 6 and 12 months after therapy.
Figure 2 Mean (±sd) of VAS score in PRP and Autologous Whole Blood (AWB) groups at baseline, 4, 8 weeks, 6 and 12 months after therapy.
Figure 3 Mean (±sd) of Mayo score in PRP and Autologous Whole Blood (AWB) groups at baseline, 4, 8 weeks, 6 and 12 months after therapy.
PRP vs ABI


- N = 28 (14 per group)
- Randomized to either 3 mL ABI or 3 mL PRP, both groups given eccentric strengthening program for wrist extensors.
- Outcome measures VAS score and Liverpool elbow score at 6 weeks, 3 months, and 6 months
- Results
  - At 6 weeks, VAS scores statistically significant for PRP outcomes
  - No statistically significant differences at 3 and 6 months

**No difference in Liverpool elbow score at 6 weeks, 3 months, and 6 months**
PRP vs ABI

• “...in a difficult group of patients in whom non-operative therapy fails, ABI/PRP can be used as effective second-line therapy, preventing surgery in a majority of patients who would previously have had no other option.”

• “Our findings raise important questions about how much growth factor needs to be delivered to an injury site in order to stimulate healing, because a normal concentration of platelets appeared to be as efficacious as a higher concentration.”
  – ‘Less’ may in fact be ‘more’ in terms of $$$ vs. benefit
• Growth factor-based therapies provide additional benefit beyond physical therapy in resistant elbow tendinopathy: a prospective, single-blind, randomised trial of autologous blood injections versus platelet-rich plasma injections.
  – Creaney, L., Wallace, A., Curtis, M., Connell, D.

• Elbow tendinopathy that had failed non-operative treatment
  – Given 2 injections each (at 0 and 1 month)
  – N = 80 PRP, N = 70 ABI

• Patient-related tennis elbow evaluation (PRTEE) scores
  – Recorded at 0, 1, 3 and 6 months
  – Validated composite outcome for pain, ADL and physical function
  – “Clinically significant improvement” = 25/100-point difference

• Results - Identical

The efficacy of PRP was similar to whole blood injection at 12 month follow up in relieving pain and improving function. It can be concluded from our study that there might be no need to platelets in higher concentration than whole blood to get therapeutic effects.
“Traditional”
Soft tissue injections
Corticosteroids


– Dose dependent decrease in tenocyte proliferation and decrease in collagen production.
– Tendon ruptures.
– Plantar fascia ruptures.
– No study has shown any reparative mechanisms.
– “There is no conclusive evidence for the efficacy of glucocorticosteroid injections in the treatment of the human musculoskeletal structures.”
Soft tissue injections
Corticosteroids


- Corticosteroid injection vs sham injection for tennis elbow.

- Results: No significant difference between corticosteroid injection and sham for improvement in pain relief first 4-8 weeks.

- At 6 months, there was no difference in outcomes.
Traditional treatment?

**Autologous blood injection** was more effective over the follow-up period than corticosteroid injection in improving pain, function, and grip strength.

Recommended as a first-line injection treatment because it is simple, cheap, and effective.

How solid is the evidence?
From CJSM in 2011

“...there is a lack of high-level evidence regarding randomized clinical trials assessing the efficacy of PRP in treating ligament and tendon injuries.

Basic science and animal studies and small case series reports on PRP injections for ligament or tendon injuries, but few randomized controlled clinical trials have assessed the efficacy of PRP injections and none have demonstrated scientific evidence of efficacy.

Scientific studies should be performed to assess clinical indications, efficacy, and safety of PRP, and this will require appropriately powered randomized controlled trials with adequate and validated clinical and functional outcome measures and sound statistical analysis.”

Cochrane review 2013

• Quality of evidence is very low
• Very weak evidence for slight benefit of PRP in pain in short term (up to three months)
• Data do not show that PRP makes a difference in function in short, medium or long term
• Low risk (weak evidence)
Lateral epicondylalgia (-osis)


Platelet-rich plasma or autologous blood injections have been found to be both more and less effective than corticosteroid injections

Existing literature fails to provide conclusive evidence that there is one preferred method of non-surgical treatment for this condition
Nonsurgical treatments included injections (corticosteroid, platelet-rich plasma, autologous blood, sodium hyaluronate, or glycosaminoglycan polysulfate), physiotherapy, shock wave therapy, laser, ultrasound, corticosteroid iontophoresis, topical NTG patches, oral naproxen.

Pooled data from RCTs indicate a lack of intermediate- to long-term clinical benefit after nonsurgical treatment of lateral epicondylitis compared with observation only or placebo.

The level of evidence remains low, as few well-designed randomized controlled trials have been published.

The available scientific evidence does not warrant the use of PRP for the first-line treatment of tendinopathy.

A key point is that the complexity of the tendon healing process cannot be replicated simply by injecting a subset of growth factors, whose effects may occur in opposite directions over time.
This study demonstrated that both the ABI and saline groups experienced a significant improvement in symptoms. However, when the results were compared, there was no statistical difference between the 2 groups.

This research showed that tendon fenestration is an alternative cost-effective treatment for recalcitrant PT.
Stem Cells

What are they?

Progenitor cells (undifferentiated cells) with capability for differentiation into specialized cells

May differentiate into specialized tissues
How do they work, in theory?

- Stem cells can support and serve as a cell reservoir for musculoskeletal tissue repair
- Stem cells obtained, prepared for use (tissue culture, activating enzymes)
- Injected into affected site
Stem Cells

Hematopoietic
- Blood products

Mesenchymal
- Other tissues
  - Tenocyte-derived
  - Adipose-derived
  - Dermal fibroblasts
  - Amniotic-derived
Adipose-Derived Stem Cells
From Wikipedia
Evidence?


Stem cell gel injected into 1 cm gap in rabbit Achilles tendon

- Results: Increased cross section, better function, improved architecture

Human studies (few) tennis elbow, patellar tendinopathy resulted in improved function, less pain
Where are stem cell injection therapies in 2015?

• Supporting evidence is sparse
• Best source of stem cells?
• Does best source vary with type of tissue being treated?
• Number of cells? Timing and frequency of injections?

Other Considerations

• Substance

• Needle

• Placebo Effect
Placebo

- Color of tablets/Expense
- Number of tablets/Expense
- Pill vs. injection
- Setting of the treatment
- Therapeutic ritual
- Power of expectations
- Belief and conviction of the person administering treatment
- Physician knowledge
- Informed consent
Thoughts about use of the “biological stew”

• Animal studies are promising, but we have no proof this is what happens in humans.

• I think we will prove these treatments will be more effective, but which biological/substance is “better” has not been established.

• Each time we develop a new biological, the expense increases.
Question 1

Which of the following best describes the state of the “science” of ABI, PRP and stem cell injections?

A. Double blind, placebo-controlled studies proving efficacy
B. Large case series demonstrating efficacy
C. Promising animal studies, but no supporting data in humans
D. Surgical results support the efficacy of tendon injections
Question 2

Based on available case series, which of the following injections has been shown to be most efficacious?

A. Autologous blood
B. Platelet-rich plasma
C. Stem cell
D. No one injection substance has been shown to be superior
Question 3

Which of the following has the most profound effect on these biological injections?

A. Substance
B. Needle
C. Placebo
D. Unknown