Randomized controlled trial comparing hyaluronic acid, platelet-rich plasma and the combination of both in the treatment of mild and moderate osteoarthritis of the knee


Platelet Rich Plasma vs Hyaluronic acid : an RCT

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Knee Osteoarthritis (OA)

• Impact on physical performance

• One of the ten major causes of disability in the world

• Conservative treatment: weight loss, physical exercises, use of non-steroid anti-inflammatory agents, analgesics, injection of glucocorticoids

• Orthobiologic injections have emerged as a potential and effective safe treatment option

Improvement with limitations – side effects

Conaghan et al., 2008; Hinton et al., 2002; Michael et al., 2010
Hyaluronic acid (HA)

• Widely used injectable treatment for degenerative joint pathology

• **Glycosaminoglycan** that acts as a backbone for proteoglycans of the extracellular matrix

• HA has positive efficacy for moderate knee OA with initial efficacy at 4 weeks, peak of 8 weeks (lasts for up to 6 months)

• HA has comparable, if not greater, therapeutic effects on knee OA, with a better safety profile than with the use anti-inflammatory

Gigante et al., 2011; Bannuru et al., 2011; Bannuru et al., 2014
Platelet Rich Plasma (PRP)

• A new great alternative as an injectable treatment for OA

• Potent cellular autologous product containing:
  - platelet concentrations above baseline
  - mixture of anti and pro-inflammatory molecules
  - anabolic and catabolic mediators to stimulate a supra-physiologic response

• Currently, most PRP studies are focused on PRP versus HA but not combined.

• RCT – superior efficacy in areas such as tendinopathies and knee OA

Mihra et al., 2014; Hinton et al., 2002; Patel et al., 2013
Platelet Rich Plasma (PRP)

- PRP and HA have potential to enhance the cartilage healing process and slow down the progression of OA.
- Comparative trials have shown that PRP can be superior to HA in knee OA treatment.
- PRP is a potent mixture of growth factors and cytokines and it has also been shown to increase the production of HA from native synoviocytes.

Filardo et al., 2012; Spaková et al., 2012; Lubowitz et al., 2013; Kon et al., 2011; Spaková et al., 2012; Anitua et al., 2007
OBJECTIVE

- Evaluate the effectiveness of HA and PRP as monotherapies for mild to moderate knee OA
- Compare the results to the combination of PRP + HA

MATERIALS AND METHODS

- Multicenter, double-blind, randomized controlled prospective study
- One year follow up
- Evaluations at: baseline, 30, 90, 180 and 360 days after the first application
- Scores/Scales: WOMAC and VAS
Patients enrolled

• January 2011 – April 2014

120 patients

HA

PRP + HA

PRP

Randomized
**Criteria**

**Inclusion**
- 40-70 years old
- History of chronic pain for at least 4 months
- Joint edema and radiographic evidence of mild to moderate Knee OA (Kelgreen-Lawrence classification)

CRP levels measures in 30, 90, 180 and 360 days In order to evaluate systemic inflammation

**Exclusion**
- Axial deviation of lower limb larger than 5º for valgus or varus
- Present: severe cardiovascular diseases, diabetes mellitus, immunosuppressive status, auto-immune diseases
- Use of anticoagulants, antithrombotic, anti-platelet drugs, steroid and non-steroid anti-inflammatory
- Hemoglobin less than 11 mg/dL
- Platelets < 150.000 mm³
- History of previous surgery in the affected joint
- Knee OA grade IV according to KL
- CRP and Uric Acid in abnormal levels
EVALUATION:
WOMAC - VAS - CRP

3 applications every fifteen days

N=105

HA
N=36

PRP
N=36

HA+PRP
N=33
**Intervention procedure**

- Without anti-inflammatory drugs two weeks before the injections until the follow up date.
- Room clinic setting – US guidance
- Application in medial compartment in 30º degree of flexion
- Lidocaine 2% with epinephrine (just for skin), buffering with sodium bicarbonate (local anestesia)

**PRP**
- 5 mL
- RBC poor
- Autologous serum activated

**HA**
- 2.0 mL of HMWH HA (Euflexxa)

**PRP + HA**
- 2.0 mL HA
- 5 mL of PRP
PRP preparation

300 x g
5 min

700 x g
17 min

Perez et al., 2013
Statistical Analyses

• Chi-square tests were used to compare binary outcomes

• Kruskall-Wallis and Wilcoxon tests were applied to compare distributions of continuous data.

• P< 0.05 was considered statistically significant.

• SPSS software was used to carry out the analysis.
RESULTS

<table>
<thead>
<tr>
<th>Sex, F:M, (%)</th>
<th>HA group (n= 36)</th>
<th>PRP group (n= 36)</th>
<th>HA+PRP group (n= 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD (range)</td>
<td>60 ± 6.6 (45-70)</td>
<td>60.9 ± 7(48-70)</td>
<td>62 ± 6.1(48-70)</td>
</tr>
<tr>
<td>Limb, R:L:both (%)</td>
<td>17(47.2):13(61.6):9(16.7)</td>
<td>14(39):16(44):5(15)</td>
<td>21(64):7(21.5):5(15)</td>
</tr>
<tr>
<td>BMI</td>
<td>28.24 ± 8.77</td>
<td>27.42 ± 6.89</td>
<td>29.15 ± 7.31</td>
</tr>
<tr>
<td>Caucasian</td>
<td>14 (38.9%)</td>
<td>8 (22.2%)</td>
<td>4 (12.1%)</td>
</tr>
<tr>
<td>Brown</td>
<td>19 (52.8%)</td>
<td>27 (75%)</td>
<td>21 (63.6%)</td>
</tr>
<tr>
<td>Black</td>
<td>3 (8.3%)</td>
<td>1 (2.8%)</td>
<td>8 (24.2%)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>4 (11.1%)</td>
<td>3 (8.3%)</td>
<td>6 (18.2%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>12 (33.3%)</td>
<td>12 (33.3%)</td>
<td>8 (24.2%)</td>
</tr>
<tr>
<td>HT</td>
<td>15 (41.7%)</td>
<td>11 (30.6%)</td>
<td>19 (57.6%)</td>
</tr>
<tr>
<td>Physical Activity (walk or aquatic activity without axial impact, up until 3x per week)</td>
<td>16 (44.4%)</td>
<td>23 (63.8%)</td>
<td>17 (51.5%)</td>
</tr>
</tbody>
</table>

* P statistically significant in race (p=0.0076) and comorbidities (p=0.0266).
Baseline

✓ Only WOMAC were significant (HA-PRP p=0.0073; HA+PRP – PRP p=0.0165)
✓ Evidenced that the group of HA present more pain than the other two groups.
30 days
✓ HA group continued with more significant pain than the other groups.
✓ Significant WOMAC improvement in the HA+PRP group when compared to the other groups.
Groups treated with PRP alone or in combination showed significant less pain than HA.
Also a WOMAC improvement was observed in HA+PRP group when compared with the other groups.
180 days

✓ Significantly less pain was observed in groups treated with PRP alone or in the combination

✓ WOMAC improvement was observed only for HA+PRP group in comparison with HA

**Table 5: Median change from base (pre) to 180 days. Median (range) reported.**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HA</th>
<th>PRP</th>
<th>HA+PRP</th>
<th>HA vs PRP</th>
<th>HA vs HA+PRP</th>
<th>PRP vs HA+PRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS</td>
<td>-3.0 (-7, 4)</td>
<td>-5.0 (-9, -1)</td>
<td>-5.0 (-9, -1)</td>
<td>0.0001</td>
<td>0.0000</td>
<td>0.2235</td>
</tr>
<tr>
<td>n</td>
<td>36</td>
<td>35</td>
<td>33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WOMAC Pain</td>
<td>-162.5 (-450, 250)</td>
<td>-225.0 (-450, 0)</td>
<td>-200 (-450, -25)</td>
<td>0.1555</td>
<td>0.3029</td>
<td>0.5579</td>
</tr>
<tr>
<td>n</td>
<td>36</td>
<td>34</td>
<td>33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WOMAC</td>
<td>-62.5 (-125, 0)</td>
<td>-62.5 (-125, 0)</td>
<td>-100 (-150, 25)</td>
<td>0.9226</td>
<td>0.0953</td>
<td>0.0698</td>
</tr>
<tr>
<td>Stiffness</td>
<td>14</td>
<td>18</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WOMAC PA</td>
<td>-462.5 (-1350, 600)</td>
<td>-625.0 (-1400, 0)</td>
<td>-675.0 (-1300, -250)</td>
<td>0.0909</td>
<td><strong>0.0262</strong></td>
<td>0.1629</td>
</tr>
<tr>
<td>n</td>
<td>36</td>
<td>36</td>
<td>33</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
360 days
✓ Groups treated with PRP alone or in combination showed significant less pain in comparison to HA according to VAS.
✓ Also, these groups showed a significant WOMAC improvement in comparison to HA
In summary – VAS Scale

✓ PRP significantly decrease the pain in comparison with HA in all the period of follow-up
In summary – WOMAC Score

✓ PRP significantly improve the function of the knee in comparison with HA in all the period of follow-up
**PRP**

- Platelets, leukocytes and fibrinogen, with small residue of red blood cells

- Platelet concentration 800,000 – 1,600,000 cells/μL -5-8 folds basal number.
PRP (alone or in combination) → increase in the CRP levels after 90 days and a decrease at the end of the follow-up.

On the other hand, the group treated with HA showed an increase in 30 days with a posterior decrease in 90 days, but at the end of the follow-up the levels of CRP were higher than baseline.
DISCUSSION

L-PRP

• Antimicrobial and immune-regulatory activity due to leukocytes and an increase in the platelet number

• Controversies in the literature, especially in the use of neutrophils that liberate metalloproteins which cause degradation to the extracellular matrix and release of free radicals

• Macrophages are responsible for the removal of the debris, phagocytic function and role in the balance of pro and anti-inflammatory aspects of healing

Cieslik-Bielecka et al., 2007; Moojen et al., 2008; Dohan et al., 2006; El-Sharkaw et al., 2007; Weibrich et al., 2005
L-PRP

• The increase of CRP levels in the first 90 days of treatment in the PRP groups can be explained due to the increase of inflammatory activity because of the WBC.

• Polymerization and final architecture of fibrin network are considerable influences on growth factors, and the presence of leukocytes maintains a fundamental role in the development of this network.

Dohan et al., 2012
**PRP activation**

- Chemical activators – instability in the fibrin network and fast growth factor release

- A physiological release - a stable tetramolecular network and it has influences on the speed and amount of the growth factors.

Dohan et al., 2012
In comparison to HA, PRP - improvement in VAS at 30, 90, 180 and 360 days, greater WOMAC PA at 360 days

Supports the findings of others studies that PRP is superior to HA in treatment of knee OA
• Many studies suggested that the application of HA and PRP may have potential positive effects on cartilage repair and retard the progression of knee OA

• Lack of studies in the literature that examined the combination

• According to the literature, PRP+HA may benefit from their different biological mechanisms.

• PRP+HA showed synergic effects in their regenerative and anti-inflammatory potential in comparison to HA or PRP alone

Filardo et al., 2012; Spaková et al., 2012; Lubowitz et al., 2013; Andia et al., 2014; Chen et al., 2014
The lubrication and support to extracellular matrix provided by the HA seemed to enable an earlier functional benefit to the PRP injection.

This combination may result in a better rehabilitation and an earlier return to the daily activities.

No significant statistical differences were verified in WOMAC pain and stiffness at anytime.
STUDY LIMITATIONS

• Self reported Scores (WOMAC and VAS)

• MRI – a more objective response to the treatment

• Absence of a gold standard or true control group using saline
CONCLUSIONS

• The combination of PRP+HA is a safe and effective method for treatment of mild to moderate OA

• The association resulted in significant less pain and less functional limitation compared to HA alone until 1 year of follow-up

• Also, there was a significant improvement in physical function in comparison to PRP alone

• More RCT with a large number of patients are needed to confirm these findings.
Thank you

Dr José Fábio Lana