Original Article

Treatment of knee osteoarthritis with platelet-rich plasma plus hyaluronic acid in comparison with platelet-rich plasma only

Yanqing Guo1,2*, Hongbo Yu2*, Lin Yuan1, Shusheng Yao2, Hong Yu2, Peng Wang2, Huili Lv2, Wei Li1, Shui Sun1

1Department of Orthopedics, Provincial Hospital Affiliated to Shandong University, No. 324 Jingwu Weiqi Road, Jinan 250000, China; 2Department of Orthopedics, Weihai Municipal Hospital, Weihai, China. *Equal contributors and co-first authors.

Received January 6, 2016; Accepted March 21, 2016; Epub June 15, 2016; Published June 30, 2016

Abstract: Background: The exact outcome of the combined use of hyaluronic acid (HA) and platelet-rich plasma (PRP) in the treatment for osteoarthritis remains unclear. The goal of this paper was to compare the efficacy of PRP + HA with those of a cohort of patients treated with platelet-rich plasma only. Materials and methods: A total of 126 Subjects with knee osteoarthritis were enrolled: 63 cases in PRP plus HA group and 63 cases in PRP group. After clinical and radiographic evaluation, patients received a weekly intra-articular injection of HA added with PRP or of only PRP for 3 weeks. Follow-up was carried out at 1, 3, 6, and 12 months. Results: In the participants treated with PRP plus HA and with PRP only, VAS scores decreased significantly, and accordingly, knee function (WOMAC) improved, compared to the status of patients prior to treatment. Regarding to VAS and WOMAC, no significant difference were observed between the two groups; however, there is a trend that could obtain better functional scores in PRP plus HA group (VAS, P = 0.392; WOMAC, P = 0.082). Six failures occurred in the PRP plus HA group and 11 in PRP group. No major adverse events or complications were observed in both groups. Conclusions: The association of PRP and HA is effective and safe in the management of patients suffering from mild to moderate KOA. Although no differences in functional outcomes were shown between the groups, there is a trend that PRP plus HA could obtain relatively better functional scores.

Keywords: Hyaluronic acid (HA), platelet-rich plasma (PRP), osteoarthritis, outcome

Introduction

Knee osteoarthritis (KOA) is a degenerative joint disease characterized by biochemical and biomechanical alterations of articular cartilage, which is very common in the elderly population [1-3]. It is the more common cause of chronic pain and the loss of mobility, which can undermine overall health and quality of life of the affected patients [4, 5]. Currently, available drugs including analgesics, nonsteroid and steroidal anti-inflammatory drugs (NSAIDs), glucosamine, chondroitin sulphate, and hyaluronic acid (HA), were applied for the treatment of KOA to release pain and inflammation, and to improve knee function and quality of life [6]. Unfortunately, none of managements above can halt OA progression and reverse any existing damage.

In view of the above reasons, the use several novel drugs, including platelet-rich plasma (PRP) and HA injections, which is able not only to manage clinical symptoms but also to provide an instructional environment for stimulating joint repair, was managed for KOA patients [7, 8]. The injections of platelet-rich plasma (PRP) and HA have been extensively applied to regulate the complex spatiotemporal signaling within and between the joint tissues and to improve lubrication and modulate inflammation, which can restore a natural healing micro-environment [8, 9]. Several studies [10-14] have shown superior results of intra-articular PRP injections than HA. A meta-analysis has also showed that PRP injection is more efficacious than HA injection and placebo in reducing symptoms and improving function and quality of life [15]. However, the exact efficacy of the
Platelet rich plasma combined with Hyaluronic acid for knee osteoarthritis

combination of the two therapeutic agents—PRP and HA, remains unclear.

Up to now, only one study by Abate et al [1] has been performed to investigate the association of these two therapeutic agents in patients suffering from KOA. In their study, they demonstrated that the association of PRP plus HA has the same efficacy of platelet-rich plasma only, administered in higher volume. However, there were several limitations in it, including small sample size and short follow-up period. Therefore, it is necessary to perform more studies to confirm this result.

The purpose of this study was to investigate and compare the clinical response to PRP plus HA and PRP treatment in 2 groups of patients affected by KOA.

Materials and methods

This study was approved by the Institutional Board Review of Provincial Hospital Affiliated to Shandong University. Each subject provided his or her written informed consent.

The patient were included if he or she met with the following diagnostic criteria: patients suffering for more than 3 months from KOA (Kellgren-Lawrence [16] 0 to III at X-ray evaluation or MRI findings of degenerative changes in patients presenting with no OA X-ray findings). Exclusion criteria were the following: patients older than 80 years; Kellgren-Lawrence score > III; systemic diseases (diabetes, renal, hepatic, cardiac, infections, endocrinopathies, malignancies); immunodepression; anticoagulant or antiaggregant therapies; use of NSAIDs in the 5 days before blood donation; and patients with Hb values < 11 g/dl and/or platelet values < 150,000/mm³. Based on the criteria above, a total of 63 cases who received PRP plus HA injections for the treatment of KOA at Provincial Hospital Affiliated to Shandong University from January 2012 to July 2014 and the same number of cases who received only PRP injections were enrolled.

All demographic and anthropometric data, including age, gender, body mass index (BMI), visual analogue scale (VAS), and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), were collected from hospital records.

The procedure for preparing PRP that is described by Abate et al. [1]. Patients received a weekly intra-articular injection (lateral approach) of the compound PRP plus HA or only PRP for 3 weeks. At the time of injection the syringe was appropriately covered to prevent patients from discovering the substance they were receiving. After each injection, the patients were kept under observation for approximately 30 min (monitoring early side effects) and then sent home with instructions to restrict the use of the leg for at least 24 hours. And all patients were suggested to use cold therapy/ice on the affected area to relieve pain. During this period, the use of NSAIDs was forbidden. Moreover, patients were permitted to take rest or mild activities (such as using an exercise bike or mild exercise in a pool), and were allowed to participate in a gradual resumption of normal sport or recreational activities as tolerated. Evaluation was repeated after 1, 3, 6, and 12 months. In order to compare the outcomes obtained in the PRP plus HA group, the same clinical and functional parameters were retrospectively employed from a group of patients who received PRP only for the treatment of KOA and the same standard assessment protocol.

### Table 1. Patient Demographic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>PRP + HA</th>
<th>PRP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size (n)</td>
<td>63</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>61.2 ± 9.6</td>
<td>60.7 ± 10.1</td>
<td>.834</td>
</tr>
<tr>
<td>Gender (f/m)</td>
<td>45/18</td>
<td>51/12</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.2 ± 4.2</td>
<td>24.6 ± 3.9</td>
<td>.755</td>
</tr>
<tr>
<td>Side, No. left/right</td>
<td>25/38</td>
<td>29/34</td>
<td></td>
</tr>
<tr>
<td>Kellgren-Lawrence, No (n, %)</td>
<td>17 (27.0)</td>
<td>15 (23.8)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>28 (44.4)</td>
<td>31 (49.2)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>18 (28.6)</td>
<td>17 (27.0)</td>
<td></td>
</tr>
<tr>
<td>Symptoms (months)</td>
<td>26</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>VAS</td>
<td>7.2 ± 3.2</td>
<td>6.9 ± 3.8</td>
<td>.517</td>
</tr>
<tr>
<td>WOMAC</td>
<td>39.9 ± 13.50</td>
<td>41.1 ± 12.7</td>
<td>.439</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>14.2</td>
<td>15.7</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: PRP, platelet-rich plasma; HA, hyaluronic acid; f, female; m, male; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
Platelet rich plasma combined with Hyaluronic acid for knee osteroarthritis

All statistical analyses were carried out with the Statistical Package for the Social Sciences (SPSS) software version 19.0 (SPSS Inc., Chicago, USA). All continuous data were reported as mean ± standard deviation (SD). Dichotomous data are expressed as frequencies and percentage. The two-sample Student’s t test was used to compare continuous variables, when the distribution of data was normal; the Wilcoxon’s rank sum test was used otherwise. The $\chi^2$ test was used to evaluate associations between categorical data. For all tests, $P < 0.05$ was considered significant.

Results

All demographic characteristics of the subjects are listed in Table 1. There were no significant difference between the two groups, in term of age, gender, and BMI. At baseline, no significant demographic and clinical differences were observed among groups, with regarding to VAS and WOMAC.

In the participants treated with PRP plus HA and PRP only (Table 2), VAS scores decreased significantly, and accordingly, knee function (WOMAC) improved, compared to the status of patients prior to treatment. Regarding to VAS and WOMAC, no significant difference were observed between the two groups; however, there is a trend that could obtain better functional scores in PRP plus HA group (VAS, $P = 0.392$; WOMAC, $P = 0.082$).

Six failures occurred in the PRP plus HA group and 11 in PRP group: in eight cases with suspected intolerance to some components of PRP and HA, and so the injective treatment was stopped after the first administration. Nine patients were still complaining of intense pain and functional deficit and sought other treatment in another medical center. No major adverse events or complications were observed in both groups. We documented temporary mild worsening of pain in the knee joint after application of PRP in six cases, which was spontaneously resolved after 2 days.

Discussion

The conservative treatment of KOA has been well documented in the literature over the past 5 decades. Treatment with PRP restores the natural rheologic and metabolic homeostasis of the joints affected by the arthritic process. The biochemical modifications induced by PRP treatment improve the protective, lubricating, and shock-absorbing effect of the synovial fluid. This therapeutic approach does not cause side effects such as inflammatory and pseudoseptic reactions, a great advantage. Moreover, improved centrifugation techniques have led to the ability to concentrate platelets as PRP, with the goal of delivering these concentrates as sources of growth factors to accelerate and support the healing of hard and soft tissue injuries naturally without subjecting the patient to significant risk.

PRP was first used in cardiac surgery by Ferrari et al. [17] in 1987 as an autologous transfusion component after open-heart surgery to reduce blood loss. PRP is a concentrate derived from peripheral blood, and it is now frequently used in different fields of medicine, including orthopedics, sports medicine, dentistry, dermatology, and ophthalmology, as well as in plastic, maxillofacial, and cosmetic surgery [18-20]. It is hypothesized to have regenerative, anti-inflammatory, analgesic, and antimicrobial properties [21]. As a result, PRP has been studied as an adjunct for healing of several structures, including bone healing [22-24], cartilage healing [25], and chronic tendinopathy [26, 27] and in the setting of surgical procedures such as rotator cuff repair [28], Achilles tendon repair [29], and anterior cruciate ligament reconstruction [30-32]. One potential advantage of platelet-rich preparations is that they are easily obtained from the patient’s blood after a simple centrifugation process.

From previous systematic reviews [33-35], it has been concluded that PRP reduces pain and improves the osteoarthritis indices (WOMAC score, IKDC score, and adverse events) of PRP injection versus HA injection or placebo. In a recent study of Sampson et al. [36] including 14 patients with primary and secondary knee OA, treatment with PRP injections significantly

<table>
<thead>
<tr>
<th>Table 2. Clinical outcomes</th>
<th>PRP + HA</th>
<th>PRP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS</td>
<td>1.3 ± 1.1</td>
<td>1.6 ± 1.9</td>
<td>.392</td>
</tr>
<tr>
<td>WOMAC</td>
<td>14.6 ± 6.9</td>
<td>15.7 ± 8.5</td>
<td>.082</td>
</tr>
<tr>
<td>Satisfaction</td>
<td></td>
<td></td>
<td>.192</td>
</tr>
<tr>
<td>Excellent/good</td>
<td>57 (90%)</td>
<td>52 (83%)</td>
<td>-</td>
</tr>
<tr>
<td>Fair/poor</td>
<td>6 (10%)</td>
<td>11 (17%)</td>
<td>-</td>
</tr>
</tbody>
</table>
improved function and reduced pain. The study by Sanchez et al. [37] presented the preliminary results of the effectiveness of intra-articular injections of PRP in retrospective cohort study of 30 patients treated with PRP and 30 patients treated with HA. Few studies have evaluated the effectiveness of PRP plus HA in KOA. To our knowledge only one recent clinical trial [1] compared the effectiveness of PRP and HA. This trial showed that the association of PRP plus HA is effective and safe in the treatment for patients suffering from mild-to-moderate KOA. Similar findings have been observed also in our study. This current study showed that PRP plus HA injections could offer a significant clinical improvement.

In the present study, there are several limitations that need to be considered. First, it should be noted that this study was a retrospective analysis that might lower the evidence of the study. Second, the follow-up period was relatively too short to find out long-term effect of the two surgical managements. Third, relatively small sample size may affect the power in statistical analysis. Finally, some bias may have existed in the selection of the technique due to the choice of medications depending on the therapist’s preference.

Conclusion

In conclusion, the association of PRP and HA is effective and safe in the management of patients suffering from mild to moderate KOA. Although no differences in functional outcomes were shown between the groups, there is a trend that PRP plus HA could obtain relatively better functional scores. A well-designed randomized controlled trial is urgently needed to identify an optimal treatment protocol.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Shui Sun, Department of Orthopedics, Provincial Hospital Affiliated to Shandong University, No. 324 Jingwu Weiqi Road, Jinan 250000, China. Tel: +86 0531-6877-8352; E-mail: shuissdjn@163.com

References


Platelet rich plasma combined with Hyaluronic acid for knee osteoarthritis


Platelet rich plasma combined with Hyaluronic acid for knee osteoarthritis


