Hyaluronic Acid and Platelet-rich Plasma in the Treatment of Knee Osteoarthritis: A Systematic Review

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ABSTRACT

Introduction: Due to loss of function and intolerable pain associated with Osteoarthritis (OA), this condition is regarded as one of the major causes of disability, worldwide. Aging and obesity are regarded as two fundamental causes of knee OA. The aim of this study was to review the literature on the efficacy of hyaluronic acid in compression in patients with knee OA.

Materials and Methods: A systematic web-based search was conducted in Cochrane Library and MEDLINE to identify articles published before December 2014. English articles with available abstracts, relevant to the subject of the study, were retrieved. Moreover, manual search was performed in reference lists of the articles. Two commentators independently reviewed and assessed the inclusion criteria, evaluated the quality of articles and extracted the data.

Results: The evaluated articles were published during 2011-2014. All studies were conducted on adult patients with knee OA. Overall, 745 patients were evaluated in five studies. More than 100 participants were enrolled in four studies and 90 patients were included in only one study.

Conclusion: Based on the findings, the application of single-dose platelet-rich plasma is safe, useful and cost-effective in patients with knee OA.

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Introduction

Osteoarthritis (OA) is a degenerative joint disease with a multifactorial etiology. OA might present with articular cartilage damage, bone remodeling, osteophyte formation and inflammation (1). Knee OA might occur in various parts of the knee such as the patellofemoral joint, tibiofemoral joint or both.

There is some evidence on the role of patellofemoral joint damage in causing pain in the anterior part of the knee and inducing pain while performing activities which require knee flexion (2, 3).

Degenerative knee OA is a major source of knee pain, affecting 35% of individuals older than 65 years of age (4). Non-invasive treatment is commonly indicated in the early radiological phases of OA by means of relative rests, oral anti-inflammatory drugs, oral analgesics and physical therapy. In case of pain persistence, intra-articular injection of a number of agents may be indicated before surgical treatment.

These drugs typically include Hyaluronic Acid (HA), corticosteroids and Platelet-Rich Plasma (PRP) (5, 6).

Due to the loss of function and intolerable pain associated with OA, this condition is regarded as one of the main causes of disability, worldwide. Aging and obesity have been introduced as two fundamental causes of knee OA (7). Various conservative treatment modalities have been proposed for the treatment of knee OA (5). Exercise, weight management programs, walking support and braces, local cooling/heating, acupuncture and electromagnetic therapy are some of the non-pharmacological modalities (6-8).

Pharmacological approaches for OA are categorized into orally administered drugs and intra-articular injections. Analgesics such as non-steroidal, anti-inflammatory drugs and opioids are extensively used by OA patients.

Corticosteroids, HA, viscosupplements and blood-derived agents such as PRP have been used for intra-articular injections (9, 10). Intra-articular injection is contraindicated in septic arthritis and is associated with iatrogenic damage (11). The aim of this study was to
review the literature on the efficacy of HA in compression in patients with knee OA.

Materials and Methods

Articles were retrieved by searching the Cochrane Library and MEDLINE to identify articles published before December 2014. The used keywords and Medical Subject Headings (MESH) included broad terms such as "hyaluronic acid" AND "platelet-rich plasma" AND "knee osteoarthritis". The studies were assessed to identify additional relevant articles from the reference lists of the articles. English articles with available abstracts and full texts, designed as human clinical trials, were included in our analysis. Moreover, manual search was conducted in the reference lists of the articles.

Critical appraisal

Firstly, the retrieved abstracts were reviewed by two independent researchers. Finally, 33 abstracts were assessed twice in terms of relevance. Overall, 19 articles were excluded from our evaluation, based on the type of the article (11 reviews and 8 case reports). Moreover, eight full text articles were excluded due to irrelevance. The remaining six full-text articles were fully assessed by our two reviewers. We used the Consolidated Standards of Reporting Trials (CONSORT) quality appraisal from reference (12) to assess the quality of the included studies. Two reviewers independently scored the quality criteria for each included study and a third reviewer resolved the discrepancies. We used a structural data extraction tool. However, due to heterogeneity in the main outcomes, no meta-analysis was performed.

Results

The flow diagram of literature search is shown in Figure 1.

![Figure 1: Flow diagram of the literature search and study selection.](image)

The oldest study was published in 2011 and the most recent one in 2014. All studies have been conducted on adult patients with knee OA. Table 1 shows the general characteristics of the included studies. 745 patients were evaluated in 5 studies. 4 studies had participants more than 100 and only one study was enrolled on 90 patients.

<table>
<thead>
<tr>
<th>Reference NO.</th>
<th>year</th>
<th>Target population</th>
<th>Drugs</th>
<th>Sample size</th>
<th>The main microbiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>2013</td>
<td>Adults</td>
<td>HA/ (PRP)</td>
<td>90</td>
<td>PRP is more effective than HA</td>
</tr>
<tr>
<td>14</td>
<td>2013</td>
<td>Adults</td>
<td>HA/ (PRP)</td>
<td>100</td>
<td>PRP is more effective than HA</td>
</tr>
<tr>
<td>15</td>
<td>2012</td>
<td>Adults</td>
<td>HA/ (PRP)</td>
<td>109</td>
<td>PRP is more effective than HA</td>
</tr>
<tr>
<td>16</td>
<td>2012</td>
<td>Adults</td>
<td>HA/ (PRP)</td>
<td>176</td>
<td>PRP is more effective than HA</td>
</tr>
<tr>
<td>17</td>
<td>2012</td>
<td>Adults</td>
<td>HA/ (PRP)</td>
<td>120</td>
<td>PRP is more effective than HA</td>
</tr>
<tr>
<td>18</td>
<td>2011</td>
<td>Adults</td>
<td>HA/ (PRP)</td>
<td>150</td>
<td>PRP is more effective than HA</td>
</tr>
</tbody>
</table>

The results of these studies have shown the application of single dose PRP is safe, effective and low-cost in patients with knee OA (13-18). Current research is investigating new methods for stimulating repair or replacing damaged cartilage. In particular, the most recent knowledge about tissue biology concerns a complex regulation of Growth Factors (GFs) for the normal tissue structure and its reaction to damage. The influence of GFs on cartilage repair has been investigated in vitro and in vivo (9), and Platelet Rich Plasma (PRP) is a simple, low-cost and minimally-invasive method that provides a natural concentrate of autologous GFs from the blood (14). This method is now being increasingly applied in clinical practice to treat knee degenerative pathology, such as chondropathy and early OA (7-10).

In OA, a deleterious fluidic microenvironment is established, with presence of HA fragments, catabolic enzymes and inflammatory molecules. The central concept underlying intra-articular injection is to modify deleterious fluidic microenvironments. PRP administration has shown pain remission and function improvement, but less than half of the patients showed clinically significant improvement. PRP exceeds HA, the comparator used in PRP clinical trials, albeit both HA and PRP alleviate symptoms in mild-to-moderate OA patients. Combining PRP and HA may benefit from their dissimilar biological mechanisms and help in
controlling delivery and presentation of signaling molecules. Three armed randomized studies, using both HA and PRP as comparators, will provide information about the impact of this approach (19-21). Although beneficial effects on pain, function and patient global assessment have been documented, the real entity of improvement and which of the many available HA products can offer the best results is not clear (17).

Discussion & Conclusion

Osteoarthritis (OA) is the most common type of arthritis found in the United States population and is also the most common disease of joints in adults throughout the world (3). The knee joint is the most frequently affected of all joints in epidemiological studies with estimates of 37% of United States’ adults ≥ 60 years of age having radiographic evidence of knee OA and 12% having symptoms related to knee OA accompanying radiographic findings (5). Symptomatic knee OA has also been highly associated with self-reported activity limitations, need for assistive walking devices, and increased use of prescription medications for pain relief (7). While the synovium, bone, and cartilage are recognized as the main structures being destroyed during disease progression, further research in the field is revealing that OA is not simply a biomechanical process placing excess load on the affected joint but contributions from catabolic cytokine cascades and production of inflammatory mediators also play a significant role and should be targets for intervention (9-11).

In conclusion, despite PRP widespread application, there is a lack of high level studies in the literature to demonstrate the real efficacy of PRP. We believe that it is important to have scientifically robust studies to clearly prove the real potential of this biological approach in order to guide its clinical use and avoid an indiscriminate clinical application, and therefore a high level study was designed. Due to similarity in the current treatment indications and the widespread use of viscosupplementation, this was chosen as a control group, whereas for ethical reasons a placebo group was avoided. Viscosupplementation involves the use of intra-articular injections of hyaluronic acid (HA), a glycosaminoglycan that provides joint lubrication, shock absorbency, and acts as the backbone for the proteoglycans of the extracellular matrix.

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References


