Prospective study comparing leukocyte-poor platelet rich plasma combined with hyaluronic acid and autologous microfragmented adipose tissue in patients with early knee osteoarthritis.

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Abstract

The objective of this study was to compare the clinical efficacy of repeated doses of leucocyte-poor platelet-rich plasma (LP-PRP) plus hyaluronic acid (HA) to a single dose of autologous microfragmented adipose tissue (AMAT) injections in patients with early osteoarthritis (OA) symptoms. Eighty knees in fifty patients (mean age: 61.3 years) were randomly allocated into two equal groups in a non-blinded design and prospectively followed for 12 months. Group 1 received three intra-articular injections (1 month apart) using autologous LP-PRP+HA. Group 2 received a single dose of AMAT injection. Outcomes were measured by PROMs Tegner, Marx, VAS, and KOOS at 6 and 12 months. Both groups had significant clinical and functional improvement at 6 and 12 months. The differences between the groups were statistically significant in Tegner score and KOOS Symptoms (p = 0.016 and p = 0.027 respectively) at 6 months in group 2. The test with statistically significant differences (p<0.05) at 12 months was Tegner (p<0.001) with group 2 having a higher median than group 1. LP-PRP+HA and AMAT lead to clinical and functional improvement at 6 and 12 months. AMAT showed better clinical results in Tegner and KOOS Symptoms at 6 months and Tegner at 12 months. Understanding which therapy offers the most benefits with the least amount of risks can significantly improve the quality of life for millions of people affected by OA. Long-term randomized controlled studies are needed to verify differences in efficacy.

Introduction

Osteoarthritis (OA) is one of the most common forms of joint disease worldwide, causing pain and significant disability and knee OA represents the major burden disease in the elderly population. Nowadays, the incidence of OA is also rapidly increasing in younger and middle-aged individuals. Since OA has such a strong social impact, understanding which therapy offers the most benefits with the least amount of risks can greatly improve the quality of life for millions of people affected by OA. Despite the fact that there are various conservative therapies (NSAIDs, topical anti-inflammatory gels and corticosteroids) for the management of early knee OA, these treatments provide short term benefits which can have lasting local and systemic side effects.

Early OA is defined by the combination of at least two episodes of pain for more than 10 days in the previous year, and structural changes on standard radiographs and MRI findings. One of the primary foci of OA treatment research in the last decade has been regenerative cellular therapy, primarily medicinal signalling cells (MSCs), and growth factors. Several studies propose these therapies not only to provide symptomatic relief, but also to create an anti-inflammatory and pro-anabolic micro-environment conducive to repair of the joint. Platelet-rich plasma (PRP) has been shown to have an anti-inflammatory effect as well as having the capacity to counteract catabolic activity within the joint. Similarly, studies have shown that hyaluronic acid (HA) provides pro-anabolic and anti-inflammatory effects.
As an alternative, experimental animal studies have shown that autologous micro fragmented adipose tissue (AMAT) can also stimulate cartilage regeneration and improve the symptoms in degenerative cartilage diseases \(^ {14, 15}\). Following these animal studies, some clinical in vivo human studies were performed which have shown encouraging results in the treatment of OA \(^ {8, 16-18}\). Given that both modalities are potentially promising, the purpose of this study was to compare the clinical efficacy of repeated doses of leucocyte-poor platelet-rich plasma (LP-PRP) combined with HA against a single dose of AMAT in the treatment of early symptomatic knee OA. It was hypothesized that one AMAT knee infiltration could be superior to LP-PRP + HA injections for the treatment of early knee OA at 12 months follow-up.

**Materials And Methods**

In this level 2 prospective therapeutic study, patients were recruited from November of 2016 to December of 2017. Inclusion and exclusion criteria for patients who presented with at least one early OA symptomatic knee are shown in Table 1. Seventeen patients were excluded, 4 had severe knee OA, 2 with previous cartilage transplantation, 1 had hepatitis, 2 with infection, 1 had intra-articular corticosteroids in the three months prior to the treatment, 4 smokers, 2 with inflammatory arthritis and 1 had severe cardiovascular disease. Pre-treatment radiographic images were taken to be evaluated according to the Kellgren-Lawrence OA classification. The evaluation included a standing anteroposterior (AP) long-leg radiograph (with hips and ankles), standing AP and lateral views of the knees, skyline patellofemoral, and standing 45° flexion knee views. Magnetic resonance imaging (MRI) was also performed for patients to be graded according WORMS and BLOKS criteria. Early knee OA of a patient was classified based on clinical and imaging findings and should fulfil the following three criteria: knee pain, Kellgren-Lawrence grade 0 to 2 (osteophytes only) and MRI findings of at least two of the following: Cartilage morphology WORMS 3–6, Cartilage BLOKS grades 2 and 3, Meniscus BLOKS grades 3 and 4, Bone marrow lesions WORMS 2 and 3 \(^ {3, 19}\). A haematology report was run prior to testing including a complete blood count and coagulation profile to detect blood diseases or infection.

Fifty patients (30 with bilateral OA) were accepted for the study, resulting in 80 total knees. Patients were non-blindly, randomly allocated into two groups using the simple randomization method of a coin flip \(^ {20, 21}\). Each group consisted of 25 subjects consisting of an equal number of unilateral and bilateral OA with a total of 40 knees in each group (Fig. 1). The mean and SD of anthropometrics and demographics as well as the count and percentage of OA severity are reported in Table 2 as well as p. values between group parameters and knee OA severity. There were no significant differences detected between groups for gender, side of knee, diagnosis severity, age, height, weight or BMI (Table 2).

- **Leucocyte-poor platelet-rich plasma (LP-PRP) combined with hyaluronic acid (HA):**
Group 1 received one cycle of LP-PRP combined with HA intra-articular injection into the affected knee (Cellular Matrix, Regen Lab, Switzerland). A cycle consisted of 3 injections, given one month apart. 6 ml of blood from the cubital vein was obtained and centrifuged for 5 minutes at 1500 g centrifugal force (RCF) and 3500 revolutions per minute as per the recommendations of the manufacturer. A mix was prepared of PRP with HA at a concentration of 3 ml of PRP for every 2 ml of HA. The PRP prepared was leucocyte-poor according to Dohan Ehrenfest et al. classification. As per the PAW classification system, PRP obtained was classified as P2 B. Total leukocyte concentration was below the normal level- specific granulocyte depletion >95% (mostly mononuclear cells being recovered 75% lymphocytes; 50% monocytes) in 4 mL of PRP. The system provides a 1.6-1.8 fold increase in platelets. The PRP was aspirated into a syringe, and a topical anaesthetic skin refrigerant was applied locally before intra-articular infiltration by a supra-patellar approach using sterile aseptic precautions. The PRP was not activated before injection.

- **Autologous microfragmented adipose tissue preparation and application (AMAT):**

  Group 2 received one dose of AMAT (Lipogems, Italy) via a supra-patellar approach. Under aseptic conditions and under local anaesthesia, adipose tissue was harvested using an abdominal lipoharvest procedure. Using a lateral abdominal approach, the subcutaneous fat was infiltrated with up to 300 ml of tumescent fluid (comprised of 30 ml of 2% lidocaine, 1 ml of 1:1000 adrenaline, and 1 ml of 8.4% bicarbonate suspended in a standard saline solution for a total of 1000 ml). Following this, up to 60 ml of adipose tissue and tumescent fluid was aspirated through a 4 mm lipoaspirate cannula and collected within a sterile medical grade single use Shippert Tissu-Trans Collection filter (Shippert Medical, CO, USA). The lipoaspirate was transferred directly to a Lipogems device. It is a closed, full-immersion, low-pressure cylindrical system, to obtain fluid with a concentrated population of pericytes/medicinal signalling cells (MSCs). A homologous use and only a minor change during the preparation of the adipose fraction were produced throughout the mini-manipulated procedure. The processed fat is subjected to minimal manipulation, only slight mechanical forces, with no detrimental effects on the integrity of the stromal vascular cells, and the final preparation was injected into the knee using the supra-patellar approach. In 2017, the FDA finalized its rules, guiding the use of human cellular and tissue products. The agency reaffirmed that the AMAT (Lipogems system) meets the new guideline's criteria for minimal manipulation of the tissue and that it is intended for homologous use.

After treatment, patients in both the groups were allowed weight-bearing, and local ice application was recommended for 20 minutes every 2 to 3 hours for 24 hours. Vigorous activities of the knee were discouraged for at least 48 hours. Single infiltration of AMAT for early knee OA has been studied in various clinical studies, which encouraged us to follow the same protocol. The primary outcomes of the studies were pain, symptoms, and activity level. No patient from either group had adverse effects on the injection or final follow-up. The outcome of treatment was assessed through the following patient-reported outcome measure scores (PROMS); Knee Injury and Osteoarthritis Outcome Score (KOOS),
Visual Analogue Scale (0=no pain to 10=worst possible pain), Marx Knee Measure and Tegner scoring systems. KOOS scores consist of 5 subscales: Pain, other Symptoms, Function in activities of daily living (ADL), Function in sport and recreation (Sport/Rec), and knee-related Quality of life (QOL). Questionnaires were completed by the patients, and all scores were tabulated before the commencement of treatment, at 6 months and at 12 months follow-up. Data entry and collection were performed by an independent investigator using SOCRATES©2012 Ortholink PTY Ltd.

This study was approved by the Institutional Review Board and Ethics Committee of our Foundation (20-2016/ approval number: 14.12.867 area 4 bis) and conforms to the declaration of Helsinki and Good Clinical Practice: Consolidate Guideline (CPMP/ICH/135/95). All patients were provided with a specific written informed consent signed prior to treatment.

1.3 Statistical analysis

The statistical analysis was conducted using SPSS (24.0; IBM Corp, Armonk, NY) by an independent statistician who was blinded to the treatment received by each patient of the two groups. In the present study a significance level of 5% (p<0.05), was used and an effect size equal to 0.8 was considered, which determined that the sample size for each group had to be 40 knees to reach a power \((1−β) = 80\%\). The general linear model for repeated measure test was performed to investigate within time variations for the continuous variables (KOOS, Marx, VAS) for all patients and each evaluated subgroup. The evaluated factors were ‘number of cycles’ and the Greenhouse-Geisser p value is reported. Post hoc test with Bonferroni adjustment for pair-wise comparisons within time was performed to investigate the improvement and deterioration for each variable and between subgroups. The nonparametric Friedman test was performed to detect within time differences in ordinal variable (Tegner), and the nonparametric Wilcoxon rank test as post hoc was used with a Bonferroni adjustment of the significant level. To investigate difference in improvement between the evaluated subgroups, the nonparametric Mann–Whitney U test was performed. The modified intention to treat analysis was performed on the originally randomized treatment groups to rule out bias due to crossover.

Results

The two treated groups were homogeneous in terms of age, gender, BMI, and severity of OA measured on the K-L scale. The mean age was 62.5 ± 11.3 years among those who underwent PRP+HA treatment and 61.5 ± 9.5 years for those who received AMAT injection (p = 0.714). The mean BMI was 26.3 ± 3.6 kg/m2 among those who were in group 1 and 25.8 ± 5.1 for those who were in group 2 (p = 0.660). Demographic data are described in Table 2. Fifty patients (80 knees) were available at final follow-up: 25 patients (40 knees) in the PRP + HA group (group 1) and 25 patients (40 knees) in the AMAT group (group 2). No patient was lost to follow-up or was excluded. There was an improvement in all scores (KOOS, VAS, Tegner, and Marx) at each follow-up compared to the pre-treatment value. When comparing the effect of these two methods, at 6 months, both groups showed a similar tendency in improvement in all scores.
However, the differences between the groups were statistically significant only in Tegner score and KOOS Symptoms (p = 0.016 and p = 0.027 respectively) at 6 months with better functionality in group 2 for both test scores. Results at 12 months showed a greater improvement in almost all scores, however, with no significant difference between the two groups. The only test with statistically significant differences between the groups (p<0.05) at 12 months was Tegner (p<0.001) with group 2 having a higher median than group 1 (Table 3). At 1-year follow-up, the scores had increased from the 6-month value in both the groups in Tegner and KOOS Sport, and QOL subscales. In turn, the KOOS Pain subscale and VAS declined from the 6-month value at the last follow-up visit. The mean value in both groups remained above the pre-treatment value at 6-month and 12-month follow-up. The patients in group 2 had higher mean values for all the scores despite the Marx scale. The variation of all the test scores for both groups at different time intervals are presented graphically in Figure 2. No serious adverse events were recorded at the time of surgery or over the duration of follow-up, and no complications were identified.

Discussion

The primary finding of this study was that, while AMAT is favoured to LP-PRP according to Tegner and KOOS Symptoms tests at 6 months and Tegner at 12 months of follow-up, both treatments offered significant improvements in the treatment of patients with early knee OA symptoms. Both PRP and HA treatments have been shown to result in decreased joint tissue catabolic activity 13, 28. However, PRP treatment also been shown to result in a significant reduction in MMP-13, an increase in HAS-2 expression in synoviocytes, and an increase in synthetic cartilage activity compared with HA 9, 29. These results indicate that PRP acts to stimulate endogenous HA. PRP has been shown to provide relief from pain and inflammation associated with OA, making it a viable treatment in the management of OA. Better outcomes have been reported in younger patients with mild to early OA without malalignment, smoking, or obesity 9, 30. Initial research suggests that LP-PRP results in improved functional outcome scores compared with leucocyte-rich platelet-rich plasma (LR-PRP) and placebo when used for the treatment of knee OA 31. LR-PRP resulted in significantly greater cell death and proinflammatory cytokines (IL-1β, IL-6, IFN-γ, and TNF-α) increasing cartilage degradation compared to LP-PRP based on the relevant findings of basic science study 32, 33. Some studies suggest that the combined application of PRP with HA could have a synergistic effect on treatment for OA 34. Lana et al., who treated 105 patients suffering from Kellgren and Lawrence I to III knee OA, found that the improvement in pain and physical function scores was significantly greater in patients treated with consecutive injections of HA and PRP, in comparison to each product administered separately 35. In another clinical study, Abbassy et al. enrolled twenty-five patients injected with three doses of HA combined with PRP with a period of 2 weeks between each injection. All patients received standardized physiotherapy. The results showed that 68% of patients achieved more than 50% improvement in pain, stiffness, and function of the knee joints and there were no adverse reactions 24. In the PRP-HA group, a cycle consisting of three injections, each given at a monthly interval was performed, and the positive effects of repeated intra-articular PRP injections on clinical outcomes of early knee OA has previously been published 36, 37. While these studies support the use of
PRP for symptomatic knee OA, there remains important debate regarding its overall clinical efficacy. A recent meta-analysis of 78 randomized control trials (RCTs) comparing PRP to control found that PRP led to a reduction in pain in knee OA but that the overall evidence for clinically significant efficacy was limited. A call for standardization with a precise description of the PRP preparation protocol is required to allow comparison among studies and provide reproducibility.

Microfragmented adipose tissue, also known as adipose stromal vascular fraction (SVF) therapy, has gained recent popularity as a treatment. Compared to peripheral blood, adipose tissue has 25,000 times more reparative cells. In the bone marrow, MSCs represent a small fraction (0.001–0.01%) of nonhematopoietic, multipotent cells. Adipose tissue has been reported to have larger quantities of progenitor cells. The clinical results at 12 months follow-up in the group of AMAT in our study are comparable to the studies in the recent literature. Koh et al. published a therapeutic case-control study of 50 patients with knee OA treated with 1 dose of 1.89x10^6 adipose-derived cells harvested from the infrapatellar fat pad after arthroscopic debridement and 3 doses of PRP, compared with 25 patients with 3 doses of PRP alone. They showed significant improvement in Lysholm, Tegner, and VAS scores in both groups with no significant difference at one year. More recently, Koh et al. analysed the group of adipose-derived cells at 2 years and reported that the whole-organ MRI score had significantly improved from 60.0 points to 48.3 points (P < .001) particularly in cartilage which improved from 28.3 points to 21.7 points. In another study of 30 patients with knee OA, Adriani et al. demonstrated significant improvements in pain, quality of life, and function at 12 months after ultrasound-guided injection of AMAT. Twelve males and 18 females; mean age of 63.3 years; mean body mass index of 25.1, and without prior treatment over the last 12 months. The patients were evaluated at baseline and 1, 3, 6, and 12 months after treatment using the visual analogue scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). The average VAS was 7.7 at baseline and improved to 4.3 at a 3-month follow-up. However, a slight deterioration (VAS 5.0) was noted at one year. Total WOMAC score was 89.9 at baseline, 68.6 at three months, and 73.2 at 12-month follow-up. Recently, Russo et al. showed that clinical improvement using AMAT for the treatment of diffuse degenerative knee OA was maintained at 3 years of follow-up. Finally, this year, Garza et al. published a double-blinded prospective randomized controlled clinical trial. Thirty-nine patients with symptomatic knee OA were eligible. They reported significantly decreased knee OA symptoms and pain at 6 months and one year.

An intriguing explanation for these results may come from the new vision of medicinal signaling cells (MSCs) proposed by Caplan. According to this concept, MSCs, rather than participating in tissue formation, work as site-regulated "drugstores" in vivo by releasing trophic and immunomodulatory factors and are activated by local injury. Although promising, these studies have provided insufficient evidence to support the efficacy of AMAT therapy, making their adoption into standard clinical practice extremely challenging. It is recommended that the use of minimally manipulated cell products and tissue-derived cells be referred to as cell therapy, and the nature of these treatments be clearly understood. Clinicians and researchers must utilize the DOSES tool for describing cell therapies to improve transparency and to allow clinicians and patients to understand the characteristics of current and future...
cell preparations. It is recommended that physicians and institutions offering biologic therapies establish patient registries for surveillance and quality assessments.

In addition to clinical outcomes, clinician and patients should consider the convenience, comfort, and cost of each therapy. PRP can be obtained from the patient on the same day that the injection is given and is processed through minimal steps, making it both cost-effective and convenient for treatment in patients with OA. A recent study analysed cost-effectiveness based on evidence from level 1 randomized controlled trials. Bendich et al., concluded that for patients with symptomatic knee OA, PRP is cost-effective, from the payer perspective, at a total price (inclusive of clinic visits, procedure, and injectable) of less than $1,192.08 over 12-months, relative to HA and saline. During this study, the cost of 1 kit to obtain the AMAT was €1200, and the cost of 1 kit to obtain the LP-PRP + HA was €400. The final cost of both group’s treatments was the same. However, adipose tissue harvesting was a more invasive and painful procedure, needing local anaesthesia and to be performed within a surgery centre, when compared to simple blood aspiration in an outpatient facility. It is essential to know the cost-effectiveness of various intra-articular injectables in practicing resource-conscious, non-operative care of knee OA. For patients who are faced with a self-pay proposition for PRP injections, having cost-effectiveness data about the relative value can help further inform treatment decisions.

This study has some limitations; it was not possible to conduct a prospective randomized, double blinded study for ethical and practical reasons as PRP does not require any anaesthesia and liposuction like AMAT. The study presents short term clinical results and a long follow up will be necessary to confirm these results. Some patients were treated in both knees at the same time, so the symptoms of one knee could affect the outcome of the analysis of the other knee. The study did not include a placebo control group to compare results as it is not ethically acceptable in our Institution and this would be the case in many other institutions. More extensive research with long term follow-ups, and biological outcomes such synovial fluid biomarkers and histology of the joint’s tissues are of great interest for future studies.

Conclusion

This study shows that both LP-PRP+HA and AMAT injections lead to clinical and functional improvement at 6 and 12 months. There was a statistically significance difference in favour of autologous microfragmented adipose tissue for Tegner and KOOS Symptoms at 6 months and for Tegner at 12 months of follow-up. However, our findings can be of great clinical relevance because adipose tissue harvesting is a more invasive and painful procedure when compared to simple blood aspiration. We need long-term randomized controlled studies with large sample numbers to understand the real efficacy and differences of these two treatment modalities.

Conflict Of Interest Statement

All the authors declare no conflict of interest.
References


**Tables**

**Table 1.** Inclusion and exclusion criteria.
### Inclusion criteria:

1. Symptomatic knee osteoarthritic (Kellgren-Lawrence Grade 1-2 cartilage lesions on radiographs or early OA on MRI)
1. Aged over 40 years with BMI<30 kg/m²
1. Pain without relief with oral anti-inflammatory agents >3 months
1. Patients with stable knees without malalignment
1. Patients who consented to either treatment modality as per the protocol.
1. Normal blood results and coagulation profile (Platelets between 150,000 and 450,000/uL)
1. Patients who had not undergone any surgery on the affected knee in the 2 years prior to enrollment into the study.

### Exclusion criteria:

1. Tricompartmental osteoarthritis, rheumatoid arthritis, or concomitant severe hip osteoarthritis
1. Previous High Tibial Osteotomy or cartilage transplantation
1. Patients with blood diseases, systemic metabolic disorders, immunodeficiency, Hepatitis B or C, HIV positive status, local or systemic infection.
1. Ingestion of anti-platelet medications within 7 days prior to the treatment, or intra-articular or oral corticosteroids in the 3 months prior to initiating therapy.
1. Smokers
1. Inflammatory arthritis
1. Severe cardiovascular disease

**Table 2.** Baseline characteristics and patient demographics. Statistically significant, P<0.05
<table>
<thead>
<tr>
<th>Baseline characteristics (N=80 knees)</th>
<th>Study group</th>
<th></th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee n (%)</td>
<td>Group 1 (N=40)</td>
<td>Group 2 (N=40)</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>20 (50%)</td>
<td>20 (50%)</td>
<td>0.823</td>
</tr>
<tr>
<td>Right</td>
<td>20 (50%)</td>
<td>20 (50%)</td>
<td></td>
</tr>
<tr>
<td>Severity of diagnosis (Kellgren-Lawrence)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 n(%)</td>
<td>15 (38%)</td>
<td>18 (45%)</td>
<td>0.496</td>
</tr>
<tr>
<td>Grade 2 n(%)</td>
<td>25 (63%)</td>
<td>22 (55%)</td>
<td></td>
</tr>
<tr>
<td>Patient demographics (50 patients)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Gender n (%)</td>
<td>Group 1 (N=40)</td>
<td>Group 2 (N=40)</td>
<td></td>
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<tr>
<td>Male</td>
<td>14(56%)</td>
<td>9 (36%)</td>
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<tr>
<td>Female</td>
<td>11 (44%)</td>
<td>16 (64%)</td>
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<tr>
<td>Age at treatment (Mean ±SD)</td>
<td>62.5 ± 11.3</td>
<td>61.5 ± 9.5</td>
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<tr>
<td>Height (mts) (Mean ±SD)</td>
<td>1.7 ± 0.1</td>
<td>1.7 ± 0.1</td>
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<td>Weight (kg) (Mean ±SD)</td>
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<td>75.0 ± 16.9</td>
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<tr>
<td>BMI (kg/m²) (Mean ±SD)</td>
<td>26.3 ± 3.6</td>
<td>25.8 ± 5.1</td>
<td>0.660</td>
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</table>

**Table 3.** Comparison of clinical outcome scores between each group (1- LP-PRP + HA, 2 - AMAT). To investigate difference in improvement between the evaluated subgroups, the nonparametric Mann–Whitney U test was performed. The nonparametric Friedman test was performed to detect within time differences in ordinal variable (Tegner), and the nonparametric Wilcoxon rank test as post hoc was used with a Bonferroni adjustment of the significant level.
<table>
<thead>
<tr>
<th>Score</th>
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<th>p value</th>
<th>12 months</th>
<th>p value</th>
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<td>VAS</td>
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<td>5.18±1.42</td>
<td>3.44±1.66</td>
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<td>3.40±2.24</td>
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<td>2.42±3.45</td>
<td>1.65±2.89</td>
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<td>2.40±3.69</td>
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<td>KOOS Symptoms</td>
<td>1</td>
<td>71.58±12.47</td>
<td>74.62±15.62</td>
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<td>77.30±13.41</td>
<td>0.696</td>
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<td></td>
<td>2</td>
<td>62.6±13.63</td>
<td>80.97±15.76</td>
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<td></td>
<td>2</td>
<td>59.50±12.89</td>
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<td>KOOS Pain</td>
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<tr>
<td></td>
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<td>83.62±14.73</td>
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<td></td>
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<td>55.98±19.76</td>
<td></td>
<td>57.00±23.25</td>
<td>0.434</td>
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<tr>
<td></td>
<td>2</td>
<td>36.25±21.34</td>
<td>60.43±18.7</td>
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<td>61.80±24.40</td>
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</tr>
<tr>
<td>TEGNER</td>
<td>1</td>
<td>2.56±1.06</td>
<td>2.98±1.44</td>
<td>0.016</td>
<td>3.30±1.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2.60±1.19</td>
<td>3.73±1.95</td>
<td></td>
<td>3.83±1.79</td>
<td></td>
</tr>
</tbody>
</table>
**Figure 1**

CONSORT flow diagram showing the patients assessed for eligibility, excluded, enrolled and analyzed in the study.
Figure 2

Variation in KOOS, VAS, Marx and Tegner scores over the course of study at each follow-up. A significant improvement in scores is evident after 6 months in both groups, which continues to improve until 12 months for all patients in the study. LP-PRP + HA, 1 (blue line) – AMAT, 2 (red line), KOOS: ADL activity of daily living; QOL quality of life.