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RESEARCH ARTICLE

Efficacy of Intra-Articular Injection of Platelet Rich Plasma and Hyaluronic Acid in Early Knee Osteoarthritis – Case Series

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Higher prevalence and growing burden of knee Osteoarthritis (OA) combined with recent safety concerns about pharmacological interventions has increased demand for new effective technologies for its management. Need of the hour is an innovative treatment alternative which may repair cartilage damage rather than just reduce symptoms of pain. Hyaluronic acid (HA) and PRP has been shown to relieve pain and symptoms as well as slow the progression of disease as stand-alone therapy. Treatment combining these modalities could be particularly hopeful owing to their positive and diverse interaction among themselves.

Combinational treatment using both PRP and HA was performed on a series of 12 patients with early stage primary knee OA who fulfilled all the designated inclusion and exclusion criteria. All the patients were evaluated before and after treatment (1, 3, 6 and 12 months) by physical examination, assessment of VAS for pain, WOMAC, IKDC, KOOS and OKS to record the patient-reported improvement in pain, functionality and quality of life (QOL). 2-tailed Mann Whitney U Test was performed to assess the effect of treatment at different follow-up times of all the clinical scores. Whereas, Pearson correlation coefficient was done to evaluate the correlation between different clinical scores. For all tests, $p < 0.05$ was considered significant.

All patients showed statistically significant improvement in all orthopedics scores evaluated. VAS score was improved significantly from 3.00 ± 0.49 at baseline to 1.57 ± 0.41 ($p = 0.031$) in Grade I and 3.60 ± 0.51 at baseline to 2.10 ± 0.29 ($p = 0.031$) in Grade II patients at 6 months' follow-up respectively. Other scores followed similar trends with statistically significant improvement at 6 months' follow-up which maintained throughout till end of the study period.

All patients treated experienced strong functional improvement and substantial gains in pain relief, functionality and QOL. Hence our preliminary findings suggest that combined PRP and HA procedure is safe and potentially efficacious, which merits further investigation in large clinical settings and also in controlled clinical trials with long-term follow-ups.

Focal Points

Bench side: Platelet Rich Plasma (PRP) deliver a large pool of signalling proteins including growth factors and cytokines to the local milieu driving the tissue regeneration and repair mechanisms which when combined with high molecular weight cross-linked hyaluronan could bestow greater viscoelastic properties and alleviate the symptoms of osteoarthritis.

Bedside: Osteoarthritis (OA) is a chronic degenerative disease and there is no cure for OA except medical management and partial/total knee replacement in advanced stage. PRP along with HA could have the therapeutic potential to promote cartilage regeneration and inhibit inflammation synergistically by decreasing the friction coefficient and minimizing wear.

Community: The burden of OA on quality of life, disability and health care utilization is quite high. Combined PRP and HA could be an effective single-dose treatment modality restoring the functional activities and considerably reducing effective cost of the treatment.

Governments and regulatory agencies: The technology to obtain PRP is FDA-approved and its safety and efficacy has been well established through several clinical studies. Regulatory agencies should consider the evidences put forth by the researchers and sanction grants to investigate in larger clinical settings and also in controlled trials with different ethnicities with long-term follow-ups.

Keywords: Platelet rich plasma; Hyaluronic acid; Knee osteoarthritis; WOMAC; pain scale

Introduction

Osteoarthritis (OA) is one of the most debilitating chronic conditions affecting people around the world. The prevalence of OA is 22–39% in the Indian adult population and about one-half of these people have mild, moderate or severe OA of the knee (Chopra et al. 2001). The burden of this disease on quality of life, disability and health care utilization is quite high. OA is usually thought to be a progressive disease of the elderly, who are mostly inactive. Of late, athletes and younger individuals are also susceptible owing to several risk factors apart from age such as genetics, obesity, joint injury, occupational or recreational activities, gender and race (Amoako & Pujatte 2014).

The American College of Rheumatology (ACR) recommends both non-pharmacological methods such as exercise/lifestyle modifications and pharmacological therapies including painkillers, corticosteroids, glucosamine, chondroitin sulphate etc., for the treatment of knee OA (ACR guidelines 2000). These modalities are effective to certain extent but often associated with poor observance and provide only temporary relief. Viscosupplementation using hyaluronic acid (HA) has been shown to relieve pain and symptoms as well as to slow the progression of disease (Migliore & Procopio 2015). The rationale for intra-articular HA injection into OA knee is the restoration of the normal articular homoeostasis, normalization of endogenous HA synthesis and chondroprotection (Takahashi et al. 1999). Systematic review on use of HA in the treatment of knee OA has indicated comparable efficacy to regular use of oral anti-inflammatory drugs and has been accepted as an adjunctive treatment in the conservative management of knee OA (Bellamy et al. 2006). In fact, therapy with HA has been approved by the FDA due to its superiority to placebo and other conservative treatments, but there is considerable heterogeneity in clinical response and differential therapeutic effects by different HA formulations.

Lately, there has been increasing focus within clinical practice on autologous growth factor therapies such as platelet rich plasma (PRP) injection for symptomatic knee OA. PRP is the concentrated form of platelets above the normal blood values and prepared through different methods of centrifugation. Growth factors released by platelets upon activation such as platelet derived growth factor (PDGF), transforming growth factor beta (TGFβ), fibroblast growth factor (FGF), hepatocyte growth factor (HGF) etc have the ability to influence and direct tissue regeneration through tissue repair, cell proliferation, differentiation and synthesis of extracellular matrix proteins (Drengk et al. 2009).

Recent studies have compared the efficacy of HA and PRP individually on knee OA. Filardo et al. (2015) have observed clinical improvements in both groups treated either with single dose of HA or PRP at 12-month follow-up evaluation. However, PRP did not provide a superior improvement with respect to HA as comparison between HA-treated and PRP-treated groups failed to show statistically significant differences in all scores evaluated. In an another prospective study comprising of 120 patients with KL score of 1, 2 or 3 knee OA, significant improvement in terms of WOMAC and Numeric Rating Scale score was found in patients who received PRP injection after 3 and 6 months' follow-up, compared to those who were treated only with HA (Spakova et al. 2012). Cerza et al. (2012) have conducted a randomized controlled trial encompass 120 patients, out of which 60 patients received four IA PRP injection and another 60 received four IA HA injection over a month period and henceforth concluded that long term PRP is superior to HA treatment.

Although treatment based on either PRP or viscosupplementation show effectiveness as stand-alone therapies for OA, treatments combining these modalities could be particularly hopeful. Recent studies on animal models suggest the possibility of combining PRP and HA in the treatment of OA. These studies suggest a strong positive interaction between these biological agents (Marmotti et al. 2012). In a rabbit model, cartilage fragments loaded onto a scaffold composed of a derivative of HA and PRP showed exceptional proliferative capacity and tissue repair capability as compared to scaffold without biological agents (Marmotti et al. 2012). Despite the growing evidence on the combined efficacy of PRP and HA (Saturveithan et al. 2016; Chen et al. 2016), there has been no published data on the long-term clinical outcome of combined use of PRP and HA in the treatment of early stage knee OA.

With the above background, we herein account our observations using simultaneous intra-articular (IA) injection of autologous PRP and HA product, to treat a series of patients displaying degenerative joint diseases of the knee. HA product is a relatively higher molecular weight cross-linked hyaluronan which bestow greater viscoelastic properties and PRP deliver a large pool of signaling proteins including growth factors and cytokines to the local milieu driving the tissue regeneration and repair mechanisms.

Methods

Patients selection

The present study was a case series, approved by our Hospitals' Ethics committee and scientific advisory committee. The study participants were informed about the benefits and possible adverse effects of intervention in a written form. Patients were included into this study on the basis of affirmative evaluation by the experienced orthopedic physician for inclusion according to the following criteria: (1) unilateral or bilateral symptomatic knee with history of chronic pain or swelling for at least 4 months, not responding to NSAIDs and/or physical therapy, (2) radiographic findings of cartilage degeneration with Kellgren-Lawrence score of 1–2 and (3) patients' compliance to complete the treatment regime with requisite follow-ups

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and prescribed exercise programs. The exclusion criteria include (1) age greater than 80 years or under 18 years, (2) KL score of more than 2, major axial deviation, non-OA joint pain, inflammatory arthropathy, (3) hematological diseases, cardiovascular disease or systemic infection and (4) use of NSAIDs in the last 5 days before treatment and hemoglobin count less than 11 g/dL and platelet count lower than 150000/mm3.

Study design and Intervention

Patients who visited Department of Orthopedics, at our affiliated hospital between March 2015–January 2016 were enrolled for this case series. 21 patients with mild to moderate knee OA were screened for participation. Of these, 8 patients did not meet the inclusion criteria as mentioned under patient's selection and 1 patient was not willing to participate. (**Figure 1**). 12 patients were allocated to the intervention and given a single IA injection of about 3 ml of PRP (containing at least 5-fold above their baseline value) and 2 ml of HA formulation for each affected joint. IA injection was carried out using the lateral approach with knee in completely extended position. Later, patients were restrained to use the injected leg for 24 h and apply ice packs over it to reduce swelling (Filardo et al. 2012). Patients were further instructed not to use NSAIDs during entire study period of 12 months unless otherwise there is an excruciating pain and/or functional disability owing to bad knee.

PRP preparation

PRP was prepared from patient's peripheral blood through 2-stage centrifugation process as per our established protocol (Chakravdhanula et al. 2016) and quality check/cell counting was performed prior to IA injection.

Evaluation tools and follow-ups

Patients were evaluated prospectively at baseline before intervention and then re-evaluated periodically at 1, 3, 6 and 12 months after the intervention. The primary outcome measure was a change in pain intensity which was assessed using Wong-Baker Faces Pain Rating Scale (VAS) and secondary outcome measure were Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), International Knee Documentation Committee (IKDC), Knee Injury and Osteoarthritis Outcome Score (KOOS) and Oxford Knee Score (OKS). Patient-reported improvement in pain, functionality and quality of life (QOL) and adverse events were also recorded.

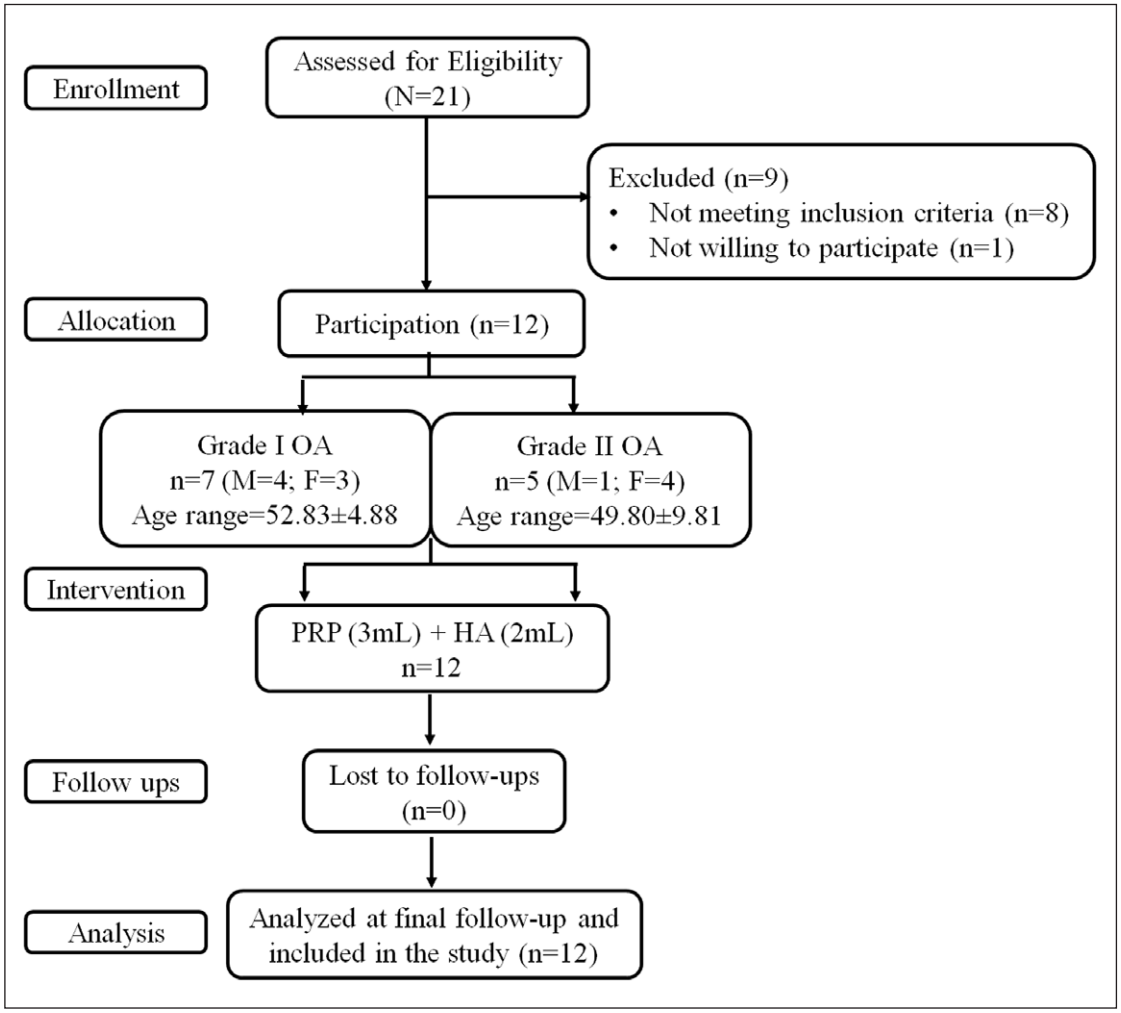

Figure 1: Flow diagram of the case series showing patients selection process. n Number of patients, M male, F female, OA osteoarthritis, PRP platelet-rich plasma, HA hyaluronic acid.

Statistical analysis

All continuous data were expressed in terms of mean and standard error of the mean. Shapiro-Wilk test was performed to check the normal distribution of the dataset. 2-tailed Mann Whitney U Test was performed to assess the effect of treatment at different follow-up times of all the clinical scores. Pearson correlation coefficient was done to assess the correlation between different clinical scores. For all tests, $p < 0.05$ was considered significant (Zhang 2016). The SPSS statistical program (Version 22.0.0.0) was used to perform statistical analyses.

Results

Twelve patients who fulfilled our inclusion and exclusion criteria were enrolled in the study. Seven patients were having Grade 1 knee OA with mean age of 52.83 ± 4.88 and five patients were having Grade II knee OA with age of 49.8 ± 9.81. Of these, six patients with bilateral knee OA and six with unilateral knee OA, totaling to eighteen knees for IA injection of PRP and HA. As shown in **Figure 2**, both grade I and II patients showed statistically significant improvement in all orthopedics scores evaluated and reported restoration of functional activities post treatment. VAS score was statistically improved from 3.00 ± 0.49 at baseline to 1.57 ± 0.41 at 6 months ($p = 0.031$) in Grade I patients and 3.60 ± 0.51 at baseline to 2.10 ± 0.29 at 6 months ($p = 0.031$) in Grade II patients respectively. However, patients reported a slight increase in pain scale at 12-months follow-up, albeit with no decline in functional activities and QOL. For other orthopedic scores, there was a statistically significant improvement ($p < 0.05$) at 6-months follow-up and thereon remained constant without any further decrement till the end of study period of 12 months. Furthermore, both grade I and grade II patients showed similar trends in terms of improvement in pain scale, functional activities and QOL post treatment.

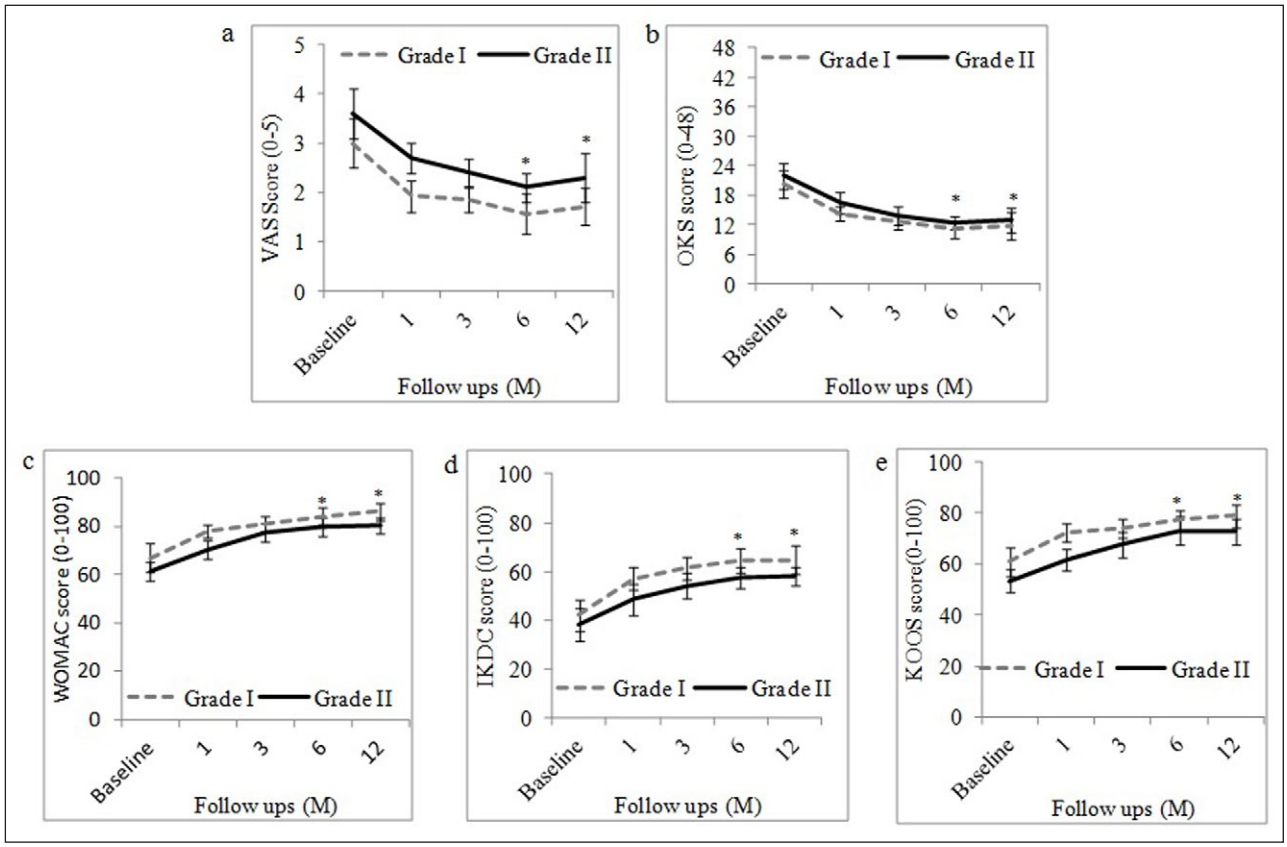

Figure 2: a) Mean visual analog scale (VAS) score over the course of 12-months. *Statistically significant difference between treatment at 6-month ($p = 0.0037$; $p = 0.0301$) and 12-month ($p = 0.0047$; $p = 0.0499$) for Grade I and Grade II patients respectively. Error bars demonstrate the standard error. **b)** Mean oxford knee score (OKS) score over the course of 12-months. *Statistically significant difference between treatment at 6-month ($p = 0.0179$; $p = 0.0214$) and 12-month ($p = 0.0324$; $p = 0.0310$) for Grade I and Grade II patients respectively. Error bars demonstrate the standard error. **c)** Mean Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score over the course of 12-months. *Statistically significant difference between treatment at 6-month ($p = 0.0476$; $p = 0.0121$) and 12-month ($p = 0.0408$; $p = 0.0121$) for Grade I and Grade II patients respectively. Error bars demonstrate the standard error. **d)** Mean International Knee Documentation Committee (IKDC) score over the course of 12-months. *Statistically significant difference between treatment at 6-month ($p = 0.05$) and 12-month ($p = 0.0492$; $p = 0.0499$) for Grade I and Grade II patients respectively. Error bars demonstrate the standard error. **e)** Mean Knee Injury and Osteoarthritis Outcome Score (KOOS) score over the course of 12-months. *Statistically significant difference between treatment at 6-month ($p = 0.0476$; $p = 0.0301$) and 12-month ($p = 0.05$; $p = 0.0493$) for Grade I and Grade II patients respectively. Error bars demonstrate the standard error.

But baseline pain scale was higher and orthopedic scores were lower in grade II than in grade I. **Figure 3** shows the correlation between different orthopedics scores used in our study. VAS was found to be closely associated with OKS score (R^2 = 0.98), WOMAC score was significantly related with KOOS (R^2 = 0.99), and IKDC (R^2 = 0.99) and KOOS with IKDC (R^2 = 0.98).

Discussion

Osteoarthritis (OA) is a chronic degenerative disease caused by deteriorating cartilage leading to structural and functional defect in one or more joints. The management of chondral disease is challenging owing to its inherent low healing potential and limited regeneration capacity (Buckwalter & Brown 2004). There is no cure for OA and the present treatment objectives are to manage pain, augment mobility and control functional impairment of joints. Contemporary treatment strategy based on evidence and expert opinion outline a balancing approach with non-pharmacological management, drugs and lastly surgical intervention when all management fails. NSAIDs carry an established risk of gastrointestinal toxicity that can cause GI bleeding (Wolfe et al. 1999) so is the COX-2 inhibitors which augment cardiovascular risks (Antman, DeMets & Loscalzo 2005) among treated patients. The higher prevalence and growing burden of knee OA combined with recent safety concerns about pharmacological interventions has increased the demand for new effective technologies to manage OA. Need of the hour is an innovative treatment alternative which may repair cartilage damage rather than just reduce symptoms of pain. By addressing tissue damage early, number of arthroscopy/arthroplasty procedure being conducted could be reduced substantially.

PRP has the therapeutic potential not only to promote tissue regeneration, but also to contribute to articular cartilage lubrication by decreasing the friction coefficient and minimizing wear. Furthermore, PRP slows cartilage degeneration through migration, proliferation and differentiation of mesenchymal stem cells into articular chondrocytes within the damaged knee (Sakata & Hari Reddi 2016). Hyaluronic acid is a component of synovial fluid and cartilage matrix where it functions as a lubricant and shock absorber for joint movements (Yoshida et al. 2004). The fundamental concept behind IA injection of PRP and HA alone or in combination is to alter the adverse niche around the damaged knee (Andia & Abate 2014) towards

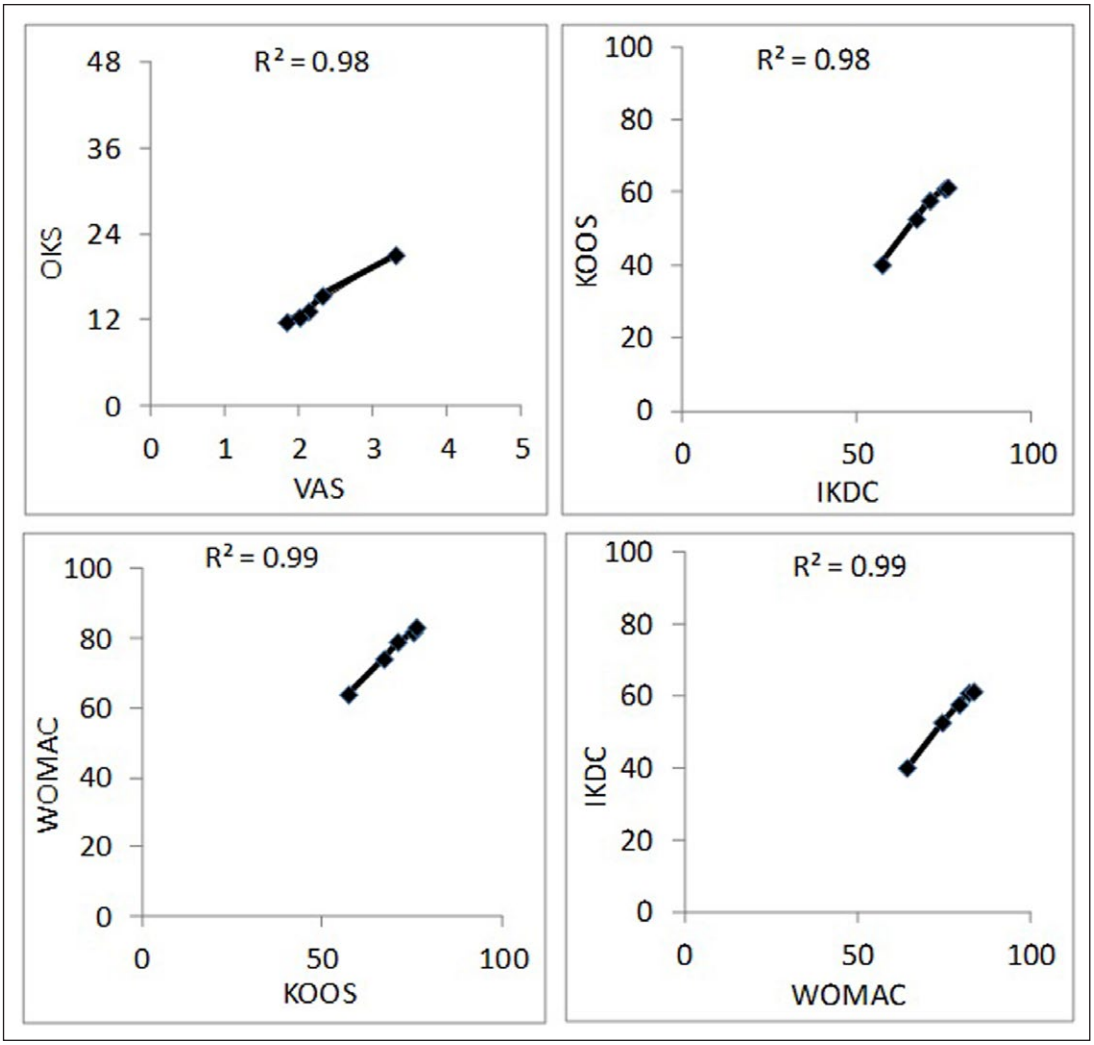

Figure 3: Correlation analysis between different orthopedics scores, VAS correlation with OKS score (R^2 = 0.98), WOMAC with KOOS (R^2 = 0.99), WOMAC with IKDC (R^2 = 0.99) and KOOS with IKDC (R^2 = 0.98).

remission. Several prospective and retrospective studies asserted that PRP performed better in alleviating the symptoms of OA patients, as compared to HA (Cerza et al. 2012; Abate, Andia & Salini 2015). Nevertheless, combining PRP and HA could derive benefit from their dissimilar biological mechanisms and help in controlling delivery and presentation of signaling molecules. However, there are no current clinical studies supporting this basic notion in long-term management of early stage knee OA, though there are studies that assert functional improvement in advanced knee OA in elderly patients (Saturveithan et al. 2016; Chen et al. 2016). Nevertheless, there are reports which claim excellent results of PRP and HA association in the healing of pressure ulcers and surgical wounds (Cervelli et al. 2010a; Cervelli et al. 2010b).

In this study, we have explored PRP injection in combination with HA formulation as a potential approach for the treatment of knee OA. Recent basis research supports the notion that PRP and HA treatment could be advantageous to OA without altering the original relevant characteristics of both products. In vitro study proves that PRP improve the biological properties of HA and conversely, HA facilitates the molecular pool released from PRP to reach the target cells by creating a pericellular bioactive scaffold around the cells thereby synergistically promoting cartilage regeneration and inhibiting OA inflammation and results in improved outcome in the long run (Cervelli et al. 2010b). Combined efficacy of PRP and HA was apparent in our study as most of the patients showed steady and stable improvement in terms of pain control, functionality and QOL during 12 months' evaluation period.

Conclusion

Our initial experience has been encouraging as all our patients' experienced significant gain in treatment without adverse events. All the patients treated experienced strong functional improvement and near-complete pain relief. Patients uniformly expressed satisfaction with outcomes during their follow-up evaluation. Hence our preliminary findings suggest that combined PRP and HA procedure is safe, potentially efficacious and provides long-term functional benefit. Single treatment course and follow-up period of 12 months are associated with substantial gains in pain relief and functionality and merits further investigation in larger clinical settings and also in controlled clinical trials with long-term follow-ups.

Competing Interests

The authors have no competing interests to declare.

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