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COMPARING HYALURONIC ACID, PLATELET-RICH PLASMA AND THE COMBINATION OF BOTH IN THE TREATMENT OF MILD AND MODERATE OSTEOARTHRITIS OF KNEE JOINT.

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ABSTRACT **Objective:** This study aims at evaluating the clinical effects of Platelet Rich Plasma (PRP) and Hyaluronic Acid (HA) as individual treatments for mild to moderate Osteoarthritis (OA) and it also examines the potential synergistic effects of PRP in combination with HA. **Design:** In this multi-center, randomized, controlled, double blind, prospective trial, 105 patients with mild to moderate knee osteoarthritis, who met the study criteria, were randomly allocated to one of three interventions: HA (n=36), PRP (n=36), or HA+PRP (n=33). Each patient received 3 intra-articular knee injections of their assigned substance, with 2-weeks intervals between each injection. Clinical outcomes were evaluated using the Arthritis Index (WOMAC) and Visual Analogue Scale (VAS) questionnaire at baseline and after 1,3,6 and 12 months. **Results:** The study showed that the PRP group have significant reduction in VAS scores at 1 (p= 0.003), 3 (p= 0.0001), 6 (p= 0.0001) and 12 (p= 0.000) months when compared to HA. In addition, the PRP group illustrated greater improvement in WOMAC physical activity scale at 12 months (p= 0.008) when compared to the HA group. Combining HA and PRP resulted in a significant decrease in pain (p=0.0001) and functional limitation (p=0.0001) when compared to HA alone at 1 year post treatment; and significantly increased physical function at 1 (p=0.0004) and 3 (p=0.011) months when compared to PRP alone. **Conclusion:** The findings of the study support the use of autologous PRP as an effective treatment of mild to moderate knee osteoarthritis. It also shows that the combination of HA and PRP resulted to better outcomes than HA alone up to 1 year and PRP alone up to 3 months. Furthermore, the results suggest that combination of PRP and HA could potentially provide better functional outcomes in the first 30 days after treatment with both PRP and HA alone.

KEYWORDS :

INTRODUCTION:

Osteoarthritis of the knee joint has a great impact on physical performance and is considered one of the ten major causes of disability in the world. Standard conservative treatments for knee osteoarthritis include: weight loss, physical exercises, use of non- steroid anti-inflammatory agents, analgesics, injection of hyaluronic acid (HA) and injection of glucocorticoids [1,2]. Although, standard conservative measures can provide symptomatic improvements, they are not without their limitations. Steroid injections are common practice among practitioners, including orthopedic surgeons, however, prolonged use of such pharmacological treatments may have adverse effects on existing cartilage[3]. Also, chronic use of anti- inflammatory medications may cause nephrotoxicity and gastrointestinal side effects [3]. However, recently, Ortho biologic injections have emerged as a potentially safe and efficacious option for joint Osteoarthritis.

Hyaluronic Acid (HA) is currently a widely used injectable treatment for degenerative joint pathology. It is a glycosaminoglycan that acts as a backbone for proteoglycans of the extracellular matrix[4], providing increased joint lubrication. Studies have demonstrated that HA has positive therapeutic efficacy for knee osteoarthritis with initial efficacy at 4 weeks, and peak effectiveness at 8 weeks which lasts for up to 6 months[5]. When compared to continuous oral NSAIDS or other anti-inflammatory medications, HA has illustrated comparable, if not greater, therapeutic effects on knee OA with a better safety profile[5,6].

Autologous platelet rich plasma (PRP) has also emerged as an alternative in the context of injectable treatment for OA. PRP is comprised of a potent cellular milieu containing platelet concentrations above baseline. However, larger randomized controlled trials have demonstrated superior efficacy in areas such as tendinopathies[7] and knee osteoarthritis[8].

Although many studies have suggested both HA and PRP have potential to enhance the cartilage healing process and slow down the progression of OA[9, 10, 11], comparative trials have shown that PRP can be superior to HA in treating knee OA[12, 13]. Furthermore, PRP with its potent mixture of growth factors and cytokines has also been shown to increase the production of HA from native synoviocytes[14]. These findings suggest a potential additive effect of combining PRP with HA in treating OA. However, there is not much research examining such synergistic effects. The main objective of our study was to evaluate the effectiveness of HA and PRP as monotherapies for mild to moderate OA and compare the results to the combination of PRP+HA.

Patients and Sampling:

The study was conducted in our college opd. 105 (87.5%) were ultimately included. The local committee of college approved the study and participants signed informed consent and were randomly allocated to one of the three groups of intervention. The following inclusion criteria for patient selection were used: age between 40 to 70 years, history of chronic pain for at least four months and/or joint edema and radiographic evidence of mild to moderate OA. The exclusion criteria were considered to be: coagulopathies, axial deviation of lower limb larger than 5° for valgus and varus knee, severe cardiovascular diseases, diabetes mellitus and, immunosuppressive status, patients on anticoagulants, antithrombotic and anti-platelet drugs and non-steroid anti-inflammatory medication.

Assessment and Outcomes:

Patients were assessed baseline assessment. Patients were followed for over one year and were submitted to four more follow-up evaluations: +30 (one month), +90 (3 months), +180 (6 months) and 360 days (1 year), where they completed VAS and WOMAC questionnaires. Arthritis Index (WOMAC) used in the study was translated. The primary analysis is the median change in VAS and WOMAC scores from pre-treatment baseline to 360 days across the three groups. Since VAS and WOMAC outcomes did not follow normal distribution, median values were used. Intervention Patients were asked to discontinue the use of any anti-inflammatory drugs two weeks before initiation of treatment until trial completion. The procedure was performed in a procedure room at a clinic setting. Injections were given three times in the affected knee(s), with interval of two weeks between them. The injections were administered using the lateral mid-patellar approach using strict sterile technique. Lidocaine 2% was used for local anesthesia. The PRP group received 5 ml of platelet rich plasma (white blood cells (WBC) rich, red blood cells (RBC) poor, activated with serum), while the HA group received 2.0 ml (20 mg of HA) of

high molecular weight (2.4 - 3.6 million Dalton's). The PRP+HA group received both treatments, with the 2.0 ml injection of HA first, followed by the 5 ml of PRP. After the injections, patients were instructed to apply local icepack, three times a day for 30 minutes each in the first 2 days after injection and switch to hot packs in the third and fourth days after injection. Patients took tramadol + paracetamol twice a day for the first two days after procedure.

RESULTS:

The mean age was 60.9 years (45-70), 90 patients (84.8%) were female. In all of the 105 patients, a mild adverse reaction in the form of a knee swelling was reported 3-5 days after the application. It was not a reported as a major complication by any patient. Also, it was observed that the patients were overweight through BMI in all the groups of treatment. The majority of the population had comorbidities such as hypothyroidism, dyslipidemia and hypertension. Half of the patients in all the groups were physically active, practicing walking or aquatic activities, without axial impact.

It was found that statistical differences in the groups related to comorbidities (p=0.0266). In regard to the comorbidities, a significant difference was observed between the groups that were treated with HA+PRP and PRP (p=0.0031). In the baseline only WOMAC pain 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.

Three days after the treatment, it was verified through VAS that the HA groups continued with significant more pain than the other groups (HA-PRP p=0.0034; HA+PRP-PRP p=0.0113). It was also observed that there was a significant improvement on the WOMAC physical in the group treated with HA+PRP when compared to the other groups (HA+PRP-HA p=0.0001; HA+PRP-PRP p=0.0004).

According to the VAS, in 90 days, it was verified that the groups treated with PRP alone (p=0.0001) or in combination (p=0.0000) showed significant less pain than HA. Also, an improvement in WOMAC physical was observed in the group HA+PRP when compared with the other groups (HA- HA+PRP p=0.0052; PRP-HA+PRP P=0.0110).

At the 180-day mark, significantly less pain was observed in the groups treated with PRP alone or in the combination and an improvement in the WOMAC physical was observed only for the group HA+PRP in comparison with HA (p=0.0262).

This tendency was verified at 360 days. It was verified that the groups treated with PRP alone (p=0.0000) or in combination (p=0.0000) showed significant less pain in comparison to HA according to VAS.

Also, these groups showed a significant improvement in WOMAC physical in comparison to HA (HA+PRP HA p=0.0001; PRP-HA p=0.0089). In summary, the PRP group had significantly greater median VAS improvement at 30, 90, 180, 360 days and significantly greater WOMAC PA improvement at 360 days when compared to the HA group.

When comparing HA + PRP group to PRP alone, the combination resulted in a statistically significant improvement in median WOMAC PA values at 30 and 90 days only.

The median changes from day 0 baseline in WOMAC pain and WOMAC stiffness were not statistically different among the three groups at any time. Relative to PRP, our final PRP product consisted of platelets, leukocytes and circulating fibrinogen, with a small residue of red cells.

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 follow-up the levels of CRP were higher than baseline.

DISCUSSION:

Most of the patients expressed favorable outcome at 12 months after treatment. Kon *et al*[15] published a study involving 100 patients with chronic degenerative condition of the knees treated with intraarticular knee injections and followed at 6 and 12 months. They showed statistically significant improvement in all clinical scores and concluded that their preliminary results indicate that treatment with PRP injections is safe and has the potential to reduce pain and improve knee function and quality of life in younger patients with low degree of articular degeneration.

In our study, the patients enrolled have some significant differences between the groups when evaluated for comorbidities. When PRP was compared to HA, the PRP group had significantly greater median VAS improvement at 30, 90, 180, 360 days and significantly greater WOMAC PA improvement at 360 days compared to the HA group. This supports the findings of other studies that showed PRP having superior results versus HA in the treatment of knee OA.

Many studies have suggested that the application of hyaluronic acid and PRP may have potentially positive effects on cartilage repair and slow down the progression of OA[9-11]. The results of our study showed that the HA + PRP group had statistically significant decrease from baseline of the median VAS and WOMAC PA when compared to the HA group. Thus, combining HA and PRP resulted to less pain and less functional limitation compared to HA alone at 30, 90, 180 and 360 days.

The median changes from day 0 baseline in WOMAC pain and WOMAC stiffness were not statistically different among the three groups (HA, PRP and HA+PRP) at any time.

When the inflammation was evaluated, it was verified that the groups that treated with PRP alone or in combination presented lower levels of CPR at the end of follow-up in comparison to HA.

CONCLUSION:

Our results suggest that the use of autologous PRP and its combination with HA are safe and effective methods for treatment of mild to moderate osteoarthritis of the knee. The PRP group had significantly greater reduction in VAS scores at 30, 90, 180 and 360 days and significantly greater WOMAC physical activity improvement at 360 days compared to the HA group. Combining HA and PRP resulted to significantly less pain and less functional limitation compared to HA alone up to 1 year after treatment. HA+ PRP combination also resulted to significantly more physical function early in the treatment (1 month and 3 months) as compared to PRP alone.

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Patient 1 : Only Platelet Rich Plasma
Patient 2 : Only Hyaluronic Acid

Patient 3 : Both Prp & Ha
Clinical Picture

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