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HYALURONIC ACID VERSUS PLATELET-RICH PLASMA: A PROSPECTIVE, DOUBLE-BLIND RANDOMIZED CONTROLLED TRIAL COMPARING CLINICAL OUTCOMES.

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Abstract:

Introduction: *The use of platelet-rich plasma (PRP) for treating osteoarthritis (OA) has shown mixed clinical results in randomized controlled trials as opposed to hyaluronic acid (HA), an approved non-chirurgical treatment for symptomatic OA. Anti-inflammatory effect on the intraarticular environment has been demonstrated by biological study of PRP.* ***Methods:*** *In total, 111 patients received a series of PRP leukocyte-poor injections or ultrasound guidance injections with symptomatic unilateral knee OA. Until diagnosis and at a time of 4 points over a span of 1 year, clinical data had been obtained. In addition, Synovial Fluid has been obtained before treatment and 12 and 24 weeks after treatment for proinflammatory and anti-inflammatory marker study. Multiple steps were used to evaluate outcomes: (1) WOMAC pain subscale; (2) IKDC subjective knee assessment, VAS pain visual comparison, and Lysholm knee score; and (3) difference of biochemical intraarticulary marker concentrations. In this study, the effects were assessed by several different measures.* ***Conclusion:*** *We notice no difference between HA and PRP at any time point in the primary outcome measure: the patient-reported WOMAC pain rate. Certain outcomes reported by patients have seen major changes, with PRP over HA findings favored. In the past, the propensity to decrease in two proinflammatory cytokines has been shown to indicate that the anti-inflammatory properties of PRP are able to lead to symptom improvement.*

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INTRODUCTION:

The deteriorating state is Osteoarthritis (OA) that affects up to 47 million Americans annually and in some way, it is estimated that by 2030 it will concern 67 million. **(**1) The rising incidence of OA is combined with increased patient optimism and transition to acceptable symptomatic relief and desired activity rates. Current quality of treatment covers oral anti-inflammatory medications, physical therapy, topical ant inflammatory gels and intra articular injections for patients with symptomatic OA. (2) This is also the last choice for the treatment prior to the procedure and involves a corticosteroid or platelet-rich plasma (PRP) intra-articular administered or viscosupplemented by hyaluronic acid. HA injection is costly and synthetically produced However, the intra-articular inflammatory cascade has not been shown to resolve this effectively and can cause acute reactions. (3)

The autologous blood products like PRP offers an ability to maximize health safety by providing an autologous biological alternative to HA and also by enhancing growth factors and reducing inflammatory conditions.(4) In an effort to reconcile anabolism and catabolism Several biological treatments, including PRP injections have been proposed. Biochemical study into this technique As Anabolic growth factors, including growth factor b transition (TGF-b), bone morphogenic proteins (BMP) and the insulin growth factor (IGF-1) a growth factor originating from platelet (PDGF), and their role in inhibiting inflammation and pain as well as enhancing the biosynthesis of cartilage and the bone matrix. (5) Catabolic factors such as Tumor Necrosis Factor a (TNF-a) and Interleukin (IL)–1, IL-1b and IL-6, in comparison, are pro-inflammatory and postulated to be blocked by PRP.(6) This research used the low-leukocyte autologous conditioned plasma (ACP) method (Arthrex Inc) based on growing evidence that it is the platelet-to-leukocyte ratio and not just the number of platelets that defines a PRP-type product's biological activity.(7)

A meta-analysis of the existing literature covering 1055 patients in 6 randomized controlled trials found that leukocyte-poor PRP preparations showed better outcomes as compared with HA or placebo. In comparison, there was no statistically significant difference between leukocyte-rich PRP preparations and HA or placebo. The objective is a biological study of synovial fluid and clinical outcome measures to assess the impact of PRP against HA in patients with mild or moderate OA.(8)

Our primary outcome metric was the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and we hypothesized PRP to lead at 12- and 24-weeks following diagnosis to a favourable and statistics-important difference as compared to HA. Our secondary outcome tests included the visual analogue scale (VAS) for pain (0-100), the Lysholm knee score, the IKDC (International Knee Documentation Committee, subjective knee assessment (0-100) and WOMAC stiffness and physical sub-stages (100 denoting no functional limit or high degree of activity pain). The tertiary result measurement was TNF 12 and 24 weeks in the knee, with hypothesis that the amount of PRP is substantially lower. The additional biological findings included the chemokine ligand 8 (CXCL8)/IL-8 concentrations in synovial fluid, which included IL-1B / IL-F2, IL-1R, IL-6 and C-X-C.

METHODS:

It was a prospective randomized, dual-blind and comparative clinical trial with an allocation ratio of 1:1, which was accepted at the main institution by the institutional review board. A total of 2299 patients have been screened for involvement between 2011 and 2014. All knee OA patients have been screened. Among those, 156 refused to participate or ordered one of the services, and 2032 were not meeting the inclusion conditions.

Patient selection: Between 2011 and 2014 inclusive, a total of 111 patients indicated for treating symptomatic cartilage lesions and/or OA were enrolled. A previous power analysis was focused on sample size estimates from previous studies; an average of 12 weeks focused on the WOMAC pain subscale showed that a total of 37 patients would be needed for each group to define a 4-point difference between groups using an alpha value of 0.05 and a power set of 0.8. We have set our target to account for attritional losses at 50 per group. All patients were classified and recruited in a continuous fashion based on pre-established requirements for inclusion / exclusion.

PRP and HA Product description This study utilized low-leukocyte ACP Setup. This is a single-spin device that concentrates platelets and removes red blood cells from the treatment component, as well as white blood cells (WBCs). Some 10 mL of blood was drawn and spun for 5 minutes at 1500 rpm. That yielded around 4 mL of PRP for use.(9) In either case, within 30 minutes, PRP was drawn, spun, and injected into the patient's knee. The phase negated the need for anticoagulants to be used. Synvisc (Sanofi-Aventis) was used in 3 consecutive injections in 2-mL aliquots that contain 16 mg of G-F 20 hylan in the HA group. Molecular weight averaged 6 MDa. (10)

Treatment and evaluation: The patients who satisfied their integration criteria were randomised in two groups, one group receiving intra-articular RPP and the other receiving intra-articular HA, through an electronic randomization process. Randomisation was carried out by non-clinical employees, injecting was done by hospital staff and main study tests and analyses were carried out by primary research team. Tasks were blinded by patients and the main study team performing analysis techniques.

A 10-mL blood draw was carried out for all patients for PRP preparation and a 3-mL blood draw for a total blood count for differential leukocyte. It was performed on patients receiving HA for preserving patient blindness and characterizing peripheral WBCs and platelet counts. Before injections, a full blood count was performed on PRP to determine the fold rise in platelet concentrations, and to confirm the abundance of red and white blood cells. For the intra articular environment analysis of the enzyme-linked immunosorbent assay (ELISA) prior to and after treatment, an approximately 2 mL synovial fluid aspirate was performed under ultrasound guidance just before each PRP or HA injection. Patients were advised to restrict leg usage for at least 24 hours after diagnosis, and to use cold therapy / icing for pain.

Rest or moderate exertion activities (such as an exercise bicycle or aquatic therapy) were prescribed during this treatment time, accompanied by a gradual return to as tolerated sports or leisure activities. A clinician who was not involved in the outcome's evaluation conducted three weekly ultrasound-guided intra-articular injections. While the number of PRP injections for OA treatment is not a precedent, we opted for three consecutive weekly injections to keep patients and research staff blind.

Clinically, patients were assessed using subjective and objective tests at baseline, care weeks 2 and 3 and post-treatment weeks 6, 12, 24 and 52 to meet the primary goal of assessing the clinical effects of PRP and HA after diagnosis. All patients obtained demographic data from the United States Centre's Centers on Disease Control and Prevention (CDC), including patient age , sex, Kellgren Lawrence (K-L) OA grade and body mass index (BMI) for each. (11) The K-L classification describes knee OA on plain radiographs as 0 (devoid of OA), 1 (possible joint space narrowing and osteophyte formation), 2 (definite osteophyte formation and joint space narrowing), 3 (multiple osteophytes, definite joint space narrowing, sclerosis, and deformity), and 4 (large osteophytes, marked joint space narrowing, severe sclerosis, and definite bony deformity). (12) The CDC classification of BMI describes normal weight as 18.5-24.9 kg/m2 , overweight as 25.0-29.9 kg/m2 , and obese as 30 kg/m2.

Over time, clinical and biological data across the HA and PRP groups have been compared. Regression analysis has also been carried out to identify variables which affected reactions, including OA, BMI, age , sex and preoperative pain. The degree of association between outcomes measurements and biochemical changes in the synovial fluid sampled has been calculated. (13) Biochemical Assay For catabolic factors like TNF-a, IL-1B / IL-F2, IL-1ra / IL-1F3, IL-6, and CXCL8 / IL-8, aspired synovial fluid was analyzed using ELISA in duplicate with the mean registered. During the course of the ultrasound instructions before and after treatment (weeks 2 and 3), the synovial fluid was aspirated for patients, and also at the follow-ups at 6 and 24 weeks. These samples have been cataloged, centrifuged, frozen and analyzed in lots.(14)

Statistical Analysis Continuous outcomes measurements were analyzed using a mixed effects model for each measure with time, treatment group (HA or PRP), K-L grade (1, 2 , or 3), age, BMI, preoperative pain level, and sex, all treated as fixed effects. (15) For the time point and treatment group an interaction concept has been added. The identity of the patients was treated as a random effect, and the time point was eventually treated as a categorical variable to allow for nonlinear effects. Post hoc tests of Tukey and linear comparisons have been used as appropriate. All data have been analyzed via JMP 10 (SAS Institute Inc). Significance was overall set as P\.05. (16)

RESULTS:

For the initial 111 patients, there were an average age for 56.26.10.2; 53 men and 58 women. During the follow-up period 2011-2014, (11%) patients missed their follow-up or failed to complete the study. There were 49 patients within the PRP and 50 in the HA group in the final study population. The 2 groups of age, gender, and K-L did not differ substantially or laterality for OA. The BMI had a slight but significant disparity. The BMI in patients of the HA and PRP Group fell within the "overweight" classification based on the weight assessment of the CDC. This difference was considered clinically insignificant.

DISCUSSION:

To our knowledge, this is the first prospective randomized controlled trial to compare ultrasonic injections with folding increases in WBC and platelet preparations for the administration of HA and PRP in two groups of patients with subjective outcomes as well as intra articulate catabolic

markers over 52 weeks. (17) PRP must have a concentrations of more than 13 platelet levels than whole blood, according to Marx18 in a 2001 defining PRP concentration study. Those are backed by our clinical findings in the latest paper, treatment indicates a clinically significant pain and work recovery from both HA and PRP pre-treatment periods.(18)

Despite the disappointment of WOMAC 's primary clinical tests, our secondary tests measurements revealed that the IKDC score between PRP and HA groups was not only statistical but therapeutic in value in the weeks 24 and 52. For order to reach therapeutic relevance, a patient must have an actual improvement at least 6.3 at 24 weeks and 16.7 at 52 weeks, according to Greco et al. (19)
Due to the existence of the IKDC score as a role predictor for the knee of athletes, it is assumed that only the IKDC score for Lysholm and WOMAC score, focussing on a lower degree of action, will understand a therapeutic distinction between groups that receive PRP versus HA.(20)

Relative to HA, the VAS result favoured PRP for 24 and 52 weeks, with a gap of more than 10 points on follow-up visits for 24 and 52 weeks. Again, both PRP and HA reported increasing pain levels between 24 and 52 weeks, which represent the literature suggesting a potential drop in effectiveness. In the experiment, a major effect was accomplished by fixed effects, including K-L grade and BMI. (21) The disparity is valid even on the formula for fixed-effects, with the groups having a low, but substantially different BMI. This discovery fits with the literature and indicates that patients can be graded as "responders," "non-respondents" to care. We now find that intraarticular therapy is more easily responded by patients with K-L level 1 (doubtable joint restriction and possible osteophyte lipping) than by patients of K-L grade 2 or 3. This is compatible with K and others who observed that PRP over HA shows superior results in patients suffering from cartilage lesions and early OA.

Our results did not indicate any difference in PRP compared with HA with a fixed effect of K-L classification. The fixed effect of BMI revealed, in contrast to a large BMI, that a lower BMI has a substantial influence on the findings reported by patients. An intermediate BMI did not have a major impact.

The lack of a placebo test group and a contrast with corticosteroids was a limitation of this study. This is of great importance to perform a large randomized and controlled trial involving placebo treatment, injection of Corticosteroids, HA and PRP. In comparison, the BMI by 2 points in the treatment categories was slightly higher. Given this disparity, they were described by the CDC classification as "overweight." In a model for combined results that included BMI, K-L, age, pre-operative pain, and sex, both statistical analyses were also conducted. Eventually, the power study was based on patient-reported findings only because of the absence, over time, of evidence on intraarticular biology changes. The use of the data presented in this report for a power analysis based on biological results is warranted for future study.

CONCLUSION:

The study's results lead to major pain reductions up to 24 weeks with a resulting reduction in PRP and HA in the management of OA. At 24 and 52 weeks after diagnosis PRP demonstrated a statistically significant gain over HA. While our results show that both HA and PRP may be a superior therapy for patients with moderate OA and low BMI. In addition, this is the first study in combination with patient-reported results to discuss the intra-articular inflammatory milieu. Finally, despite a substantial difference in PRP-friendly subjective results, there was a trend towards a decline in IL-1b and TNF-a, 2 proinflammatory cytokines in the knee. This finding suggests that PRP's anti-inflammatory properties can contribute to an OA symptom improvement. More work would be needed to delineate the clinical utility of PRP in the treatment of symptomatic OA and determine the optimum number of injections and timing between those injections.

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