Hyaluronic Acid Versus Platelet-Rich Plasma

A Prospective, Double-Blind Randomized Controlled Trial Comparing Clinical Outcomes and Effects on Intra-articular Biology for the Treatment of Knee Osteoarthritis

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Background: The use of platelet-rich plasma (PRP) for the treatment of osteoarthritis (OA) has demonstrated mixed clinical outcomes in randomized controlled trials when compared with hyaluronic acid (HA), an accepted nonsurgical treatment for symptomatic OA. Biological analysis of PRP has demonstrated an anti-inflammatory effect on the intra-articular environment.

Purpose: To compare the clinical and biological effects of an intra-articular injection of PRP with those of an intra-articular injection of HA in patients with mild to moderate knee OA.

Study Design: Randomized controlled trial; Level of evidence, 1.

Methods: A total of 111 patients with symptomatic unilateral knee OA received a series of either leukocyte-poor PRP or HA injections under ultrasound guidance. Clinical data were collected before treatment and at 4 time points across a 1-year period. Synovial fluid was also collected for analysis of proinflammatory and anti-inflammatory markers before treatment and at 12 and 24 weeks after treatment. Several measures were used to assess results: (1) Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale; (2) International Knee Documentation Committee (IKDC) subjective knee evaluation, visual analog scale (VAS) for pain, and Lysholm knee score; and (3) difference in intra-articular biochemical marker concentrations.

Results: There were 49 patients randomized to treatment with PRP and 50 randomized to treatment with HA. No difference was seen between the groups in the primary outcome measure (WOMAC pain score). In the secondary outcome measure, linear contrasts identified a significantly higher IKDC score in the PRP group compared with the HA group at 24 weeks (mean ± standard error [SE], 65.5 ± 3.6 vs 55.8 ± 3.8, respectively; $P = .013$) and at final follow-up (52 weeks) (57.6 ± 3.37 vs 46.6 ± 3.76, respectively; $P = .003$). Linear contrasts also identified a statistically lower VAS score in the PRP group versus the HA group at 24 weeks (mean ± SE, 34.6 ± 3.24 vs 48.6 ± 3.7, respectively; $P = .0096$) and 52 weeks (44 ± 4.6 vs 57.3 ± 3.8, respectively; $P = .0039$). An examination of fixed effects showed that patients with mild OA and a lower body mass index had a statistically significant improvement in outcomes. In the biochemical analysis, differences between groups approached significance for interleukin-1β (mean ± SE, 0.14 ± 0.05 pg/mL [PRP] vs 0.34 ± 0.16 pg/mL [HA]; $P = .06$) and tumor necrosis factor α (0.08 ± 0.01 pg/mL [PRP] vs 0.2 ± 0.18 pg/mL [HA]; $P = .068$) at 12-week follow-up.

Conclusion: We found no difference between HA and PRP at any time point in the primary outcome measure: the patient-reported WOMAC pain score. Significant improvements were seen in other patient-reported outcome measures, with results favoring PRP over HA. Preceding a significant difference in subjective outcomes favoring PRP, there was a trend toward a decrease in 2 proinflammatory cytokines, which suggest that the anti-inflammatory properties of PRP may contribute to an improvement of symptoms.

Registration: ClinicalTrials.gov (Identifier: NCT02588872).

Keywords: platelet-rich plasma; hyaluronic acid; biomarkers; inflammation

Osteoarthritis (OA) is a debilitating disease that, in some form, affects up to 47 million Americans each year and is estimated to affect 67 million by 2030.[8] The increasing incidence of OA is matched by increased patient expectations for sustained symptomatic relief and a return to desired levels of activity.

The current standard of care for patients with symptomatic OA includes oral anti-inflammatory drugs, physical therapy, topical anti-inflammatory gels, and intra-articular

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injections.[1,21,26] The latter is often the last treatment option preceding surgical intervention and includes the intra-articular administration of a corticosteroid or platelet-rich plasma (PRP) or viscosupplementation (hyaluronic acid [HA]).

An HA injection is expensive and is a synthetically manufactured product.[6,16] In addition, HA has not been shown to reliably address the intra-articular inflammatory cascade and can cause acute reactions in some patients.[6,14,20] The use of autologous blood products, such as PRP, provides an opportunity to improve patient outcomes using an autologous biological alternative to HA while also addressing the underlying inflammation through the stimulation of growth factors and the suppression of inflammatory cytokines.

In an effort to balance anabolism and catabolism in an affected joint, several biological treatments such as intra-articular PRP injections have been proposed.[5,9,15,16,24] This strategy stems from biochemical research on anabolic growth factors, such as transforming growth factor β (TGF-β), insulin-like growth factor 1 (IGF-1), bone morphogenetic proteins (BMPs), and platelet-derived growth factor (PDGF), and their role in inhibiting inflammation and pain as well as enhancing the biosynthesis of cartilage and the bone matrix.[4,7] In contrast, catabolic factors such as tumor necrosis factor α (TNF-α) and interleukin (IL)–1, IL-1β, and IL-6 are proinflammatory and have nociceptive properties, which are postulated to be inhibited by PRP.[2,7,11,13,17,23]

This study utilized the low-leukocyte autologous conditioned plasma (ACP) system (Arthrex Inc) based on increasing evidence that it is the ratio of platelets to leukocytes and not only the number of platelets that determines the biological activity of a PRP-type product.[3] A meta-analysis of the current literature spanning 1055 patients in 6 randomized controlled trials concluded that leukocyte-poor PRP preparations demonstrated improved outcomes when compared with HA or placebo.[22] In contrast, no statistically significant difference was found between leukocyte-rich PRP preparations and HA or placebo.

The objective of this study was to compare the effects of PRP to HA in patients with mild to moderate OA using a biological analysis of synovial fluid and clinical outcome measures. Our primary outcome measure was the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale, and we hypothesized that PRP would lead to a favorable, statistically significant difference when compared with HA at 12 and 24 weeks after treatment. Our secondary outcome measures included the visual analog scale (VAS) for pain (0-100, with 100 denoting worst possible pain), Lysholm knee score, International Knee Documentation Committee (IKDC) subjective knee evaluation (0-100, with 100 denoting no functional limitation or pain with high-level activity), and WOMAC stiffness and physical function subscales. The tertiary outcome measure was TNF-α within the knee at 12 and 24 weeks; we hypothesized that a significantly lower concentration would be found in the PRP group. Additional biological outcomes included IL-1B/IL-F2, IL-1ra/IL-1F3, IL-6, and C-X-C motif chemokine ligand 8 (CXCL8)/IL-8 concentrations in synovial fluid.

METHODS

This was a prospective, randomized, double-blind, comparative clinical trial with an allocation ratio of 1:1 that received institutional review board approval at the principal institution. Between 2011 and 2014, a total of 2299 patients were screened for participation (registered at ClinicalTrials.gov: NCT02588872). All patients with a diagnosis of knee OA were screened. Of these, 2032 patients did not meet the inclusion criteria (Table 1), and 156 patients declined to participate or specifically requested one of the treatments (Figure 1).

Patient Selection

A total of 111 patients indicated for the treatment of symptomatic cartilage lesions and/or OA were enrolled between 2011 and 2014 inclusive. An a priori power analysis was based on sample size calculations from prior studies; a mean of 12 weeks based on the WOMAC pain subscale demonstrated that to identify a 4-point difference between groups using an alpha value of .05 and power set at 0.8, a minimum of 37 patients would be required for each group. We set our goal at 50 per group to account for attritional losses. All patients were identified and recruited on the basis of pre-established inclusion/exclusion criteria in a continuous fashion.

Description of PRP and HA Products

This study utilized a low-leukocyte ACP system. This is a single-spin system that concentrates platelets and separates red blood cells as well as white blood cells (WBCs) from the treatment product. Approximately 10 mL of blood

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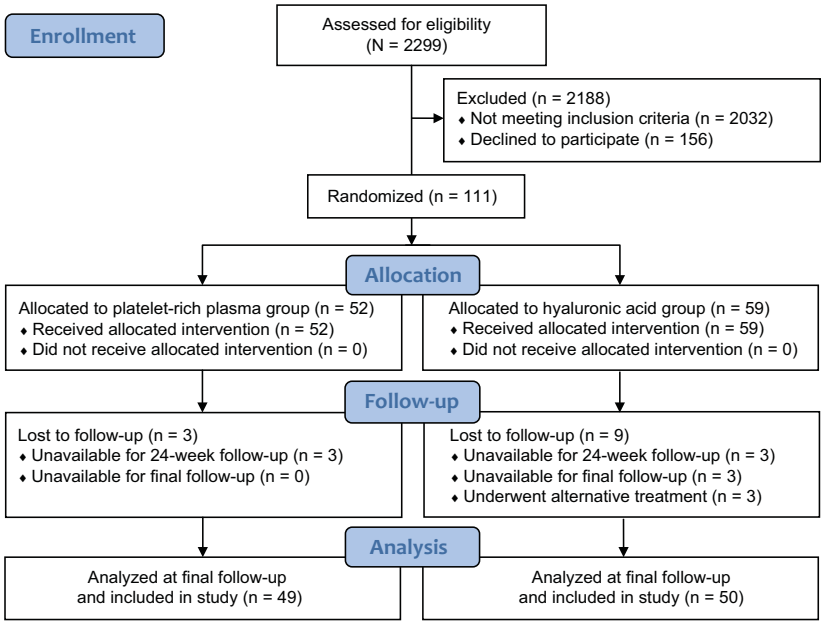

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram used in the design of the trial.

TABLE 1
Patient Screening Criteria[a]

Inclusion Criteria
- Age between 18 and 80 years
- Ability to provide informed consent
- Mean VAS pain score of >40 of 100 (worst possible pain) over the course of 7 days during the previous month
- OA diagnosed by radiographic imaging
- Grade 1-4 radiographic OA as defined by the K-L classification
- Unilateral symptoms

Exclusion Criteria
- Knee instability
- Pretreatment VAS pain score of <40 of 100
- Major axial deviation (>5° valgus or varus deviation)
- Bilateral symptomatic lesions
- Systemic disorders such as diabetes, rheumatoid arthritis, hematological diseases (coagulopathies), severe cardiovascular diseases, infections, or immunodeficiencies
- Current use of anticoagulant medications or NSAIDs used in the 5 days before blood donation
- History of known anemia
- Recent intra-articular injection of corticosteroids (within 30 days) and prior treatment with HA in past 6 months
- Pregnancy or possible pregnancy

[a]Consecutive patients were screened before enrollment using the above criteria at the clinic of the senior author (B.J.C.). HA, hyaluronic acid; K-L, Kellgren-Lawrence; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; VAS, visual analog scale.

was drawn and spun at 1500 rpm for 5 minutes. This yielded approximately 4 mL of PRP for use. In all cases, PRP was drawn, spun, and injected into the patient's knee within 30 minutes. This process negated the need for the use of anticoagulants.

In the HA group, Synvisc (Sanofi-Aventis) was used in 3 consecutive injections in 2-mL aliquots containing 16 mg of hylan G-F 20. The average molecular weight was 6 MDa.

Treatment and Evaluation

Patients who met the inclusion criteria were randomized via an electronic randomization process into 2 groups: one group received intra-articular PRP, and the other received intra-articular HA. Nonclinical staff performed the randomization, clinical staff performed the injections, and results and analyses were performed by the primary research team. Patients and the primary research team performing analyses were blinded to assignments. All patients underwent a 10-mL blood draw for the PRP preparation and a 3-mL peripheral blood draw for a complete blood count with a leukocyte differential. This was performed on patients who received HA to maintain patient blinding and to characterize the peripheral WBCs and platelet counts. A complete blood count was performed on PRP before injections to evaluate the fold increase in platelet concentrations and to confirm the rarity of red and white blood cells. For enzyme-linked immunosorbent assay (ELISA) analysis of the intra-articular environment before and after treatment, a synovial fluid aspirate of approximately 2 mL was performed under ultrasound guidance just before each PRP or HA injection. After treatment, patients were instructed to limit the use of the leg for at least 24 hours and use cold therapy/icing for discomfort. During this treatment period, rest or mild exertion activities (such as an exercise bicycle or aquatic therapy) were recommended, followed by a gradual return to sports or recreational activities as tolerated.

Three weekly ultrasound-guided intra-articular injections were performed by a clinician not involved with the

TABLE 2
Demographic Data Before Treatment[a]

	PRP Group (n = 49)	HA Group (n = 50)	*P* Value
Age, y, mean ± SD	55.9 ± 10.4	56.8 ± 10.5	.46
Sex, male:female, n	28:21	20:30	.087
BMI, kg/m^2, mean ± SD	27.4 ± 3.9	29.0 ± 6.4	.05
K-L classification, n			.13
Grade 1	3	0	
Grade 2	26	27	
Grade 3	20	22	
Unknown	0	1	
VAS pain score (0-100), mean	57.2	62.9	.44

[a]BMI, body mass index; HA, hyaluronic acid; K-L, Kellgren-Lawrence; PRP, platelet-rich plasma; VAS, visual analog scale.

outcome assessment. Although no precedent exists on the number of PRP injections for the treatment of OA, we chose 3 consecutive weekly injections to maintain the blinding of patients and research staff. Patients were clinically evaluated using subjective and objective assessments at baseline, treatment weeks 2 and 3, and posttreatment weeks 6, 12, 24, and 52 to address the primary aim of evaluating the clinical outcomes of PRP and HA after treatment.

Demographic data including patient age, sex, OA grade according to the Kellgren-Lawrence (K-L) classification, and body mass index (BMI) according to the United States Centers for Disease Control and Prevention (CDC) were collected on all patients. 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). The CDC classification of BMI describes normal weight as 18.5-24.9 kg/m^2, overweight as 25.0-29.9 kg/m^2, and obese as $\geq$30 kg/m^2.

Clinical and biological data were compared across the HA and PRP groups over time. Regression analysis was also performed to identify variables that affected responses including the degree of OA, BMI, age, sex, and preoperative pain. Finally, the degree of correlation between outcome measures and biochemical changes within the sampled synovial fluid was calculated.

Biochemical Assay

Aspirated synovial fluid was analyzed using ELISA, in duplicate with the mean reported, for catabolic factors including TNF-α, IL-1B/IL-F2, IL-1ra/IL-1F3, IL-6, and CXCL8/IL-8. Patients' synovial fluid was aspirated under ultrasound guidance before treatment and at each treatment visit (weeks 2 and 3) as well as at the 6- and 24-week follow-ups. These specimens were cataloged, centrifuged, frozen, and subsequently evaluated in batches.

Statistical Analysis

Continuous outcome measures were assessed 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 score, and sex, all of which were treated as fixed effects. An interaction term was added for the time point and treatment group. The patients' identity was treated as a random effect, and finally, the time point was treated as a categorical variable to allow for nonlinear effects. Tukey post hoc tests and linear contrasts were used as appropriate. All data were analyzed using JMP 10 (SAS Institute Inc). Significance was set as $P < .05$ throughout.

RESULTS

The mean age of the 111 initial study patients was 56.2 ± 10.2 years; there were 53 male and 58 female participants. During the follow-up period between 2011 and 2014, 12 (11%) patients were lost to follow-up or were unwilling to complete the study. The final study population contained 49 patients in the PRP group and 50 patients in the HA group. There were no significant differences between the 2 groups across age, sex, K-L grade for OA, or laterality. There was a small but significant difference in the BMI. This difference was not deemed clinically meaningful, as the BMI of patients in the HA group (29.0 ± 6.4 kg/m^2) and PRP group (27.4 ± 3.9 kg/m^2) fell within the "overweight" classification based on the weight assessment of the CDC. This information is delineated in Table 2.

Clinical Results

For all outcome scores, there was a significant interaction between pretreatment and posttreatment results up to the 24-week follow-up ($P < .05$) (Figure 2). An improvement was seen in both the HA and PRP groups and then a decline to the 52-week follow-up.

The primary clinical outcome measure, the WOMAC pain score, was not found to be significant between the PRP and HA groups at any time point ($P > .05$) (Table 3). The secondary clinical outcome measures demonstrated statistically significant between-group findings at several time points as well as significant effects of fixed variables including the K-L grade and BMI at the time of enrollment.

Examining the fixed effects, and controlling for other factors in the model, there was a significant effect of the

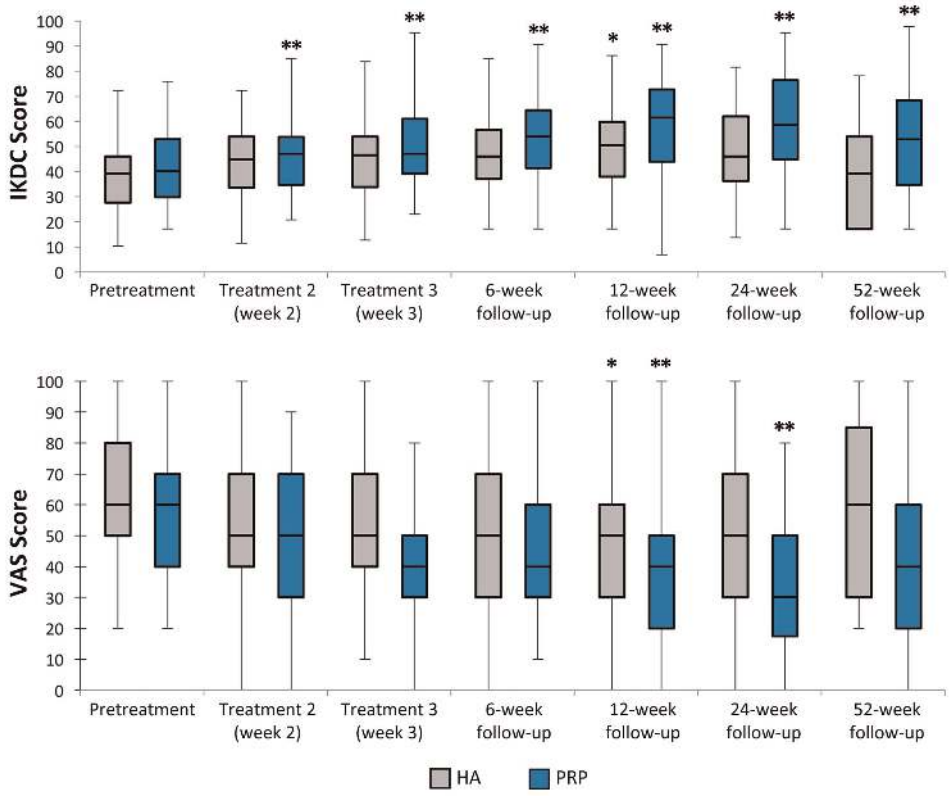

Figure 2. Box-and-whisker plot showing the treatment effect of hyaluronic acid (HA) and platelet-rich plasma (PRP) over time. There was a significant improvement in the International Knee Documentation Committee (IKDC) and visual analog scale (VAS) scores from before treatment to after treatment. Statistically significant difference between pre- and posttreatment score at a given time point for *HA and **PRP. The solid line delineates the median value.

TABLE 3
WOMAC Pain Score at Study Time Points[a]

	PRP Group	HA Group
Before treatment	7.00 ± 0.53	7.52 ± 0.58
Treatment visit 2 (week 2)	6.15 ± 0.54	6.32 ± 0.55
Treatment visit 3 (week 3)	5.06 ± 0.48	5.53 ± 0.51
Follow-up		
6 weeks	4.57 ± 0.48	4.66 ± 0.47
12 weeks	3.98 ± 0.63	5.00 ± 0.60
24 weeks	4.11 ± 0.56	5.00 ± 0.50
52 weeks	3.02 ± 0.48	4.00 ± 0.60

[a]Data are presented as mean ± standard error. The mixed-effects model demonstrated no significant difference between the groups at any time point (P = .93). HA, hyaluronic acid; PRP, platelet-rich plasma; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

K-L grade (mean ± standard error [SE], 69.2 ± 8.0 [grade 1], 49.2 ± 1.8 [grade 2], and 43.6 ± 2.08 [grade 3]; P = .005) and BMI (57.74 ± 3.02 [normal weight, 18.5-24.9 kg/m^2] and 41.5 ± 4.8 [obese, >30 kg/m^2]; P = .0046) on the IKDC score. There were no significant effects of age or sex (P > .05). Overall, the model fit was good (adjusted R^2 = 0.59). Patients with OA classified as K-L grade 1 had a statistically significant improvement in the IKDC score when compared with those with grade 3 changes. There were no significant differences in the IKDC score between grade 1 and 2 or grade 2 and 3 changes.

Evaluating the IDKC score for comparison between groups, there was a significant interaction between time and treatment (P = .0054). Linear contrasts identified a significantly higher IKDC score in the PRP group compared with the HA group at 24-week follow-up (mean ± SE, 65.5 ± 3.6 vs 55.8 ± 3.8, respectively; P = .013). A similar effect was observed at the final 52-week follow-up, with a significantly higher IKDC score for the PRP group versus the HA group (57.6 ± 3.37 vs 46.6 ± 3.76, respectively; P = .003) (Figure 3). No between-group differences were observed at other time points.

Examining for fixed effects, there were no significant effects of age, BMI, sex, or K-L grade on the VAS score (P > .05). Evaluating the VAS score for comparison between groups, there was a significant interaction between time and treatment (P < .001). Linear contrasts identified a statistically lower VAS score in the PRP group versus the HA group at 24 weeks (mean ± SE, 34.6 ± 3.24 vs 48.6 ± 3.7, respectively; P = .0096) as well as at 52 weeks (44 ± 4.6 vs 57.3 ± 3.8, respectively; P = .0039) (Figure 4).

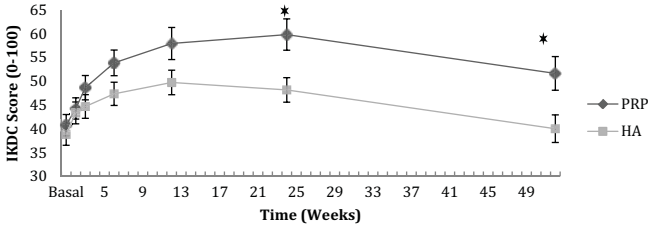

Figure 3. Mean International Knee Documentation Committee (IKDC) score in the hyaluronic acid (HA) and platelet-rich plasma (PRP) groups over the course of 52 weeks. *Statistically significant difference (P = .013) between treatment groups at 24 weeks. Error bars demonstrate the standard error.

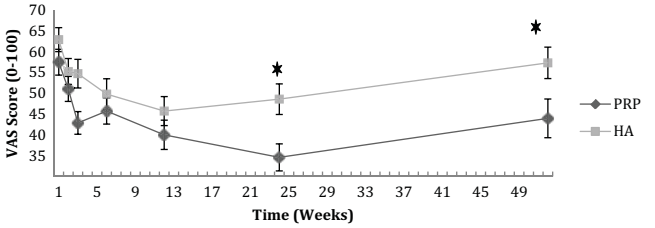

Figure 4. Mean visual analog scale (VAS) score in the hyaluronic acid (HA) and platelet-rich plasma (PRP) groups over the course of 52 weeks. *Statistically significant difference between treatment groups at 24 (P = .0096) and 52 weeks (P = .0039). Error bars demonstrate the standard error.

The remainder of the outcome measures (Lysholm, WOMAC) demonstrated trends toward greater improvement in the PRP group but did not demonstrate statistical significance ($P > .05$).

PRP Preparations

PRP preparations and peripheral blood were analyzed at each of the 3 treatment visits (weeks 1-3) on patients who were randomized to the PRP group (n = 49). A total of 125 PRP preparations were available for laboratory testing. A PRP preparation was not sent for laboratory testing if there was less than 4 mL available for an injection. The collected PRP contained a mean (±SE) of 790 ± 0.11 WBCs/μL, confirming a leukocyte-poor preparation. The mean (±SE) PRP-to–peripheral blood ratio of the platelets was 1.73 ± 0.05 (Table 4). The fold increase in PRP did not correlate with clinical outcomes at any time point.

TABLE 4
Ratio of PRP to Peripheral Blood[a]

	Mean ± Standard Error
Treatment 1	1.71 ± 0.08
Treatment 2	1.68 ± 0.08
Treatment 3	1.79 ± 0.09
All	1.73 ± 0.05

[a]Ratio of platelets in platelet-rich plasma (PRP) and platelets in peripheral blood at each treatment and finally as a whole across the study (all).

ELISA Results

Synovial fluid samples were collected from both the PRP (n = 49) and HA (n = 50) groups and sent for ELISA testing to evaluate for proinflammatory and anti-inflammatory cytokines (IL-1β, IL-1ra, IL-6, IL-8, TNF-α). Evaluating for comparison between groups, there was not a significant interaction between time and treatment ($P > .05$), nor was there a significant interaction between treatment groups ($P > .05$). Linear contrasts did demonstrate a significance for IL-1β (mean ± SE, 0.14 ± 0.05 pg/mL [PRP] vs 0.34 ± 0.16 pg/mL [HA]; P = .06) as well as for TNFα (0.08 ± 0.01 pg/mL [PRP] vs 0.2 ± 0.18 pg/mL [HA]; P = .068) at 12-week follow-up (Figure 5).

DISCUSSION

To our knowledge, this is the first prospective randomized controlled trial to compare the administration of HA and PRP in 2 groups of patients with subjective outcomes as well as catabolic intra-articular markers over the course of 52 weeks using ultrasound-guided injections in addition to quantification of the fold increase in WBC and platelet concentrations of the PRP preparation. According to Marx[18] in a defining 2001 study on PRP concentrations, PRP must have greater than 1× the concentration of platelets than whole blood. The preparation used in the current study had a mean 1.73 ± 0.05× concentration when compared with whole blood. This is comparable with the recent literature on single-spin PRP preparations.[3,22]

Our clinical results corroborate those in the recent literature[5,9,16,19] in that treatment demonstrates a statistically significant improvement in pain and function from the pretreatment time point with both HA and PRP. Despite the failure of our primary clinical outcome measure, the WOMAC pain score, to show statistical significance, our secondary outcome measures demonstrated not only a statistical but also a clinically meaningful difference in the IKDC score between the PRP and HA groups at 24 and 52 weeks. According to Greco et al,[12] a patient must have, at minimum, an absolute change of 6.3 at 24 weeks and 16.7 at 52 weeks on the IKDC score to achieve clinical significance. Our observed change of 10 (mean ± SE, 65.5 ± 3.6 [PRP] and 55.8 ± 3.8 [HA]; P = .013) reached clinical significance at 24 weeks and approached clinical significance at 52 weeks, with an absolute difference of 11 (57.6 ± 3.37 [PRP] and 46.6 ± 3.76 [HA]; P = .003). Because of the nature of the IKDC score as an indicator of function in the athlete's knee, we hypothesize that a clinical difference was only appreciated between groups receiving PRP versus HA with the use of the IKDC score because Lysholm and WOMAC scores that focus on lower activity levels

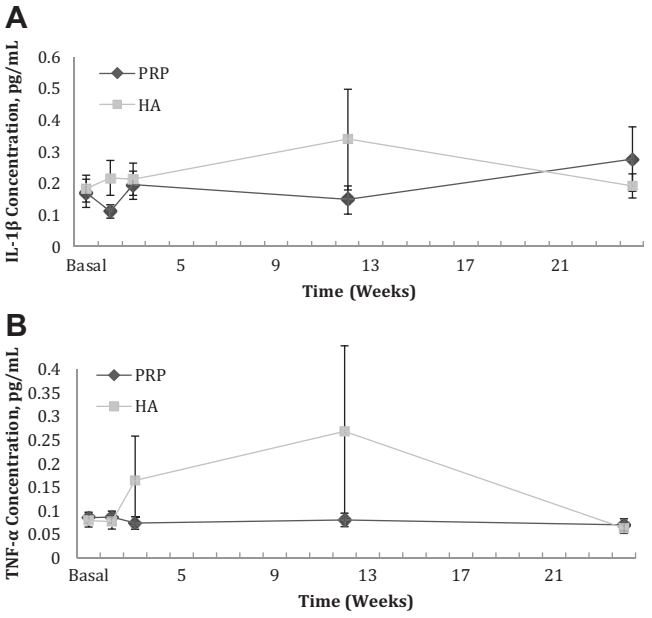

Figure 5. Mean values of intra-articular (A) IL-1β and (B) TNF-α before treatment, at the second and third treatment visits (weeks 2 and 3), and at 12- and 24-week aspiration time points, demonstrating a trend toward decreased IL-1β and TNF-α at 12 weeks. Error bars demonstrate the standard error.

could not discern a difference in this younger, more active patient cohort.[26]

The VAS score also favored PRP as compared with HA at 24 and 52 weeks, with a greater than 10-point difference at the 24- and 52-week follow-up visits. Again, both PRP and HA showed increasing pain scores from 24 to 52 weeks, which is consistent with the literature that demonstrates an eventual decline in efficacy.[10,19]

Fixed effects including the K-L grade and BMI did have a significant effect within the model. Despite the groups having a small but significantly different BMI, this difference holds true based on the fixed-effects model employed. This finding coincides with the literature and demonstrates that certain intrinsic characteristics may categorize patients as "responders" or "nonresponders" to treatment.[16,25] At present, we find that patients with K-L grade 1 (doubtful joint space narrowing and possible osteophyte lipping) respond more readily to intra-articular therapy than patients with K-L grades 2 or 3. This result coincides with results from Kon et al,[16] who also found that patients with cartilage lesions and early OA showed superior results when treated with PRP over HA. Our results showed no difference in response to PRP versus HA with the K-L grade as a fixed effect. The fixed effect of BMI also demonstrated that a low BMI (<24 kg/m^2) had a significant effect on patient-reported outcomes when compared with a high BMI (>34 kg/m^2). We found no significant effect of an intermediate BMI (>24 or <34 kg/m^2). The current literature is mixed on BMI as a fixed effect on patient outcomes after HA or PRP injections, with some studies showing superior treatment effects in patients with a low BMI[15] and others showing no difference.[19] This may be because of the heterogeneous PRP preparations and treatment schedules used in the various studies.

ELISA analysis of patients included in this study demonstrated a trend toward greater concentrations of IL-1β and TNF-α in the synovial fluid of patients treated with HA at 12-week follow-up. This in vivo trend precedes the clinical difference found with the IKDC score at 24 weeks and may suggest a lag time between a decrease in inflammatory cytokines in the knee and subsequent improvement in patient-reported outcomes. Although there was no statistical difference reported, this in vivo direct comparison of the intra-articular inflammatory state of the knee after treatment with HA or PRP yielded new insight on the nature of inflammation after injections.

A limitation of this study is the lack of a sham control group and a comparison with corticosteroids. A large randomized controlled trial including a sham control, corticosteroid injection, HA injection, and PRP injection is of great interest. In addition, there was a significant difference in the BMI of 2 points in the patient groups. Despite this difference, both groups were characterized as "overweight" according to the CDC classification (BMI, 25.0-29.9 kg/m^2). In addition, all statistical analyses were conducted in a mixed-effects model that included BMI, K-L grade, age, preoperative pain, and sex as fixed effects. A final limitation is that the power analysis was based on patient-reported outcomes only because of the paucity of data on changes in intra-articular biology over time with treatment. Future study is warranted with the use of data presented herein for a power analysis based on biological outcomes.

CONCLUSION

The findings of this study support a significant improvement in pain and function up to 24 weeks with a decline thereafter with the use of PRP as well as HA for the treatment of OA. PRP demonstrated a statistically significant improvement over HA at 24 and 52 weeks after treatment. Our findings further suggest that both HA and PRP may be a superior treatment for patients with mild OA and a low BMI. Additionally, this is the first study to address the intra-articular inflammatory milieu in conjunction with patient-reported outcomes. Finally, preceding a significant difference in subjective outcomes favoring PRP, there was a trend toward a decrease in IL-1β and TNF-α, which are 2 proinflammatory cytokines within the knee. This finding suggests that the anti-inflammatory properties of PRP may contribute to an improvement in OA symptoms. Further research to determine the optimal number of injections and timing between these injections will be important to delineate the clinical utility of PRP in the treatment of symptomatic OA.

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