The American Journal of Sports Medicine
http://ajs.sagepub.com/

Intra-articular Autologous Conditioned Plasma Injections Provide Safe and Efficacious Treatment for Knee Osteoarthritis: An FDA-Sanctioned, Randomized, Double-blind, Placebo-controlled Clinical Trial

Patrick A. Smith

Am J Sports Med published online February 1, 2016
DOI: 10.1177/0363546515624678

The online version of this article can be found at:
http://ajs.sagepub.com/content/early/2016/01/29/0363546515624678

Published by:
SAGE
http://www.sagepublications.com

On behalf of:
American Orthopaedic Society for Sports Medicine
AOSSM

AJSM PreView, published on February 1, 2016 as doi:10.1177/0363546515624678

Intra-articular Autologous Conditioned Plasma Injections Provide Safe and Efficacious Treatment for Knee Osteoarthritis

An FDA-Sanctioned, Randomized, Double-blind, Placebo-controlled Clinical Trial

Patrick A. Smith,*† MD
Investigation performed at the Columbia Orthopaedic Group, Columbia, Missouri, USA

Background: Platelet-rich plasma (PRP) injections have become an intriguing treatment option for osteoarthritis (OA), particularly OA of the knee. Despite the plethora of PRP-related citations, there is a paucity of high-level evidence that is comparable, cohort specific, dose controlled, injection protocol controlled, and double-blinded.

Purpose: To determine the safety and efficacy of leukocyte-poor PRP autologous conditioned plasma (ACP) for knee OA treatment through a feasibility trial regulated by the US Food and Drug Administration (FDA).

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

Methods: In accordance with FDA protocol, patient selection was based on strict inclusion/exclusion criteria; 114 patients were screened, and 30 were ultimately included in the study. These patients were randomized to receive either ACP (n = 15) or saline placebo (n = 15) for a series of 3 weekly injections. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores served as the primary efficacy outcome measure. Patients were followed for 1 year.

Results: No adverse events were reported for ACP administration. Furthermore, the results demonstrated no statistically significant difference in baseline WOMAC scores between the 2 groups. However, in the ACP group, WOMAC scores at 1 week were significantly decreased compared with baseline scores, and the scores for this group remained significantly lower throughout the study duration. At the study conclusion (12 months), subjects in the ACP group had improved their overall WOMAC scores by 78% from their baseline score, compared with 7% for the placebo group.

Conclusion: ACP is safe and provides quantifiable benefits for pain relief and functional improvement with regard to knee OA. No adverse events were reported for ACP administration. After 1 year, WOMAC scores for the ACP subjects had improved by 78% from their baseline score, whereas scores for the placebo control group had improved by only 7%. Other joints affected with OA may also benefit from this treatment.

Keywords: FDA; autologous conditioned plasma; leukocyte-poor platelet-rich plasma; placebo; saline control; WOMAC; osteoarthritis; level 1

Osteoarthritis (OA) is one of most common adult joint diseases worldwide and a leading cause of global disability.[11,13,24,50] Although many definitions exist, OA of the knee is most commonly evaluated with the Kellgren-Lawrence (K-L) radiographic grading scheme, which has been in use for more than 40 years.[26] It has been estimated that 10% of men and 13% of women older than 60 years suffer from symptomatic knee OA.[50] For this reason, several studies have been conducted to examine the negative effect of knee OA on multiple quality-of-life measures.[2,11]

Several treatment options are available for knee OA, including intra-articular (IA) injections, oral nonsteroidal

*Address correspondence to Patrick A. Smith, MD, Columbia Orthopaedic Group, 1 South Keene Street, Columbia, MO 65201, USA (email: psmithmudoc@aol.com).
†Columbia Orthopaedic Group, Department of Orthopaedic Surgery, University of Missouri, Columbia, Missouri, USA.

The author has declared the following potential conflict of interest or source of funding: P.A.S. is a consultant for Arthrex Inc. Arthrex Inc. provided support for this study.

The American Journal of Sports Medicine, Vol. XX, No. X
DOI: 10.1177/0363546515624678

anti-inflammatory drugs (NSAIDs), and even a variety of alternative medicine techniques, all of which have been met with varying levels of success.[10,36] One of the most effective treatments for OA involves exercising and improving physical condition.[17,18,44] This is particularly effective for pain reduction in overweight and obese people with OA.[23] IA hyaluronic acid (HA) injections have been used in the United States for nearly 20 years but with varying levels of success.[9,19,31,47] IA injection of corticosteroids to treat OA is often met with controversy and contention in the medical field and therefore may not be a sustainable recovery solution for the patient.[7,20,38] While NSAID use has proven effective in pain management for OA, the potential complications associated with NSAIDs in older patients may outweigh the potential advantages in OA management.[36,43] Given the aging population and increasing rates of obesity, new methods are needed to reduce patient pain and improve mobility.

Recently, platelet-rich plasma (PRP) injections have become an intriguing treatment option for OA, particularly for treatment of OA of the knee.[4,8,29] This treatment is appealing to patients because it involves the use of their own blood product and is not an exogenous substance like steroids or HA. PRP can be either leukocyte-poor (LP-PRP) or leukocyte-rich (LR-PRP), depending on the preparation method. Several evidence level 1 studies have shown good success with use of LP-PRP.[5,15,32,40-42]

Despite the plethora of PRP-related citations, there is a paucity of high-level evidence that is comparable, cohort specific, dose controlled, injection protocol controlled, and double-blinded.[16,30] The primary objective of the current study was to characterize the safety and efficacy of autologous conditioned plasma (ACP) in patients with primary OA of the knee through a feasibility trial regulated by the US Food and Drug Administration (FDA) and based on treatment of 2 study groups, receiving 3 injections of either LP-PRP ACP or placebo (normal saline) at 1-week intervals. The hypothesis was that no differences would be present for outcomes related to patient safety, while significant improvement related to efficacy between blinded study groups would be present, and that these results would be maintained throughout the data collection period.

METHODS

FDA Oversight

This was a sanctioned FDA feasibility study (Investigational Device Exemption [IDE] #14796) as the first study designed and implemented specifically to determine the safety and efficacy of IA PRP injections for knee OA treatment. The study was performed under guidelines established by the FDA. For this trial, the main concept governing FDA approval was the safety and tolerability of ACP PRP treatment (referred to as ACP henceforth) in patients with OA who had failed nonoperative treatment for at least 6 weeks. Safety was the primary endpoint of this study. In addition, evaluation of clinical efficacy was performed as a secondary endpoint to ensure reliability of scientific data. Because this trial was a clinical study performed on human subjects to investigate a potential new drug, device, or biologic product, the FDA limited the study to 1 site with a maximum of 30 subjects. The FDA further delineated the criteria for study endpoints, administration of doses, eligibility to participate, laboratory screening criteria, and outcome score used (Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC]) to assess the potential therapeutic effects. The FDA's review of the study was focused on the safety and efficacy of the product and whether the potential benefit of the PRP injection justifies the overall risk.

Study Parameters

This was designed as a prospective, single-center, randomized, double-blind (patient and investigator), 2-arm (parallel group) study. Institutional review board approval was obtained through RCRC IRB (now Salus IRB). A certified research organization (CRO) monitored the study quarterly, and the FDA monitored it yearly (Medrio eClinical & Electronic Data Capture; Medrio Inc). These entities were separate from the research site to minimize potential bias. All had specific regulatory responsibilities in regard to conducting clinical trials; the FDA was the regulatory official overseeing the study and the subsequent reporting. Study data were captured electronically via clinical software (Medrio eClinical & Electronic Data Capture).

Subject recruitment occurred through a clinical evaluation of patients seeking treatment for knee OA from the author (primary investigator). Patient selection was based on strict inclusion/exclusion criteria (Table 1); 114 patients were screened and 30 were ultimately included (Figure 1). Each patient was then monitored by the CRO. A total of 30 patients were randomized (after inclusion) to receive 3 weekly IA injections of either ACP treatment (n = 15) or normal saline placebo (n = 15). The study was designed to evaluate the safety and efficacy of 3 IA ACP injections at 1-week intervals over a 12-month period. Patients in both treatment groups were allowed to take only acetaminophen for breakthrough pain.

All patients had a screening visit (visit 1) and 3 treatment visits 1 week apart (visit 2 at week 0, visit 3 at week 1, and visit 4 at week 2), followed by 3 follow-up visits (visit 5 at 2 months, visit 6 at 3 months, and visit 7 at 6 months) after the first treatment visit for enrollment. All patients had an end-of-study visit (visit 8) at 12 months after the first treatment visit (Figure 1).

Randomization

Once subjects were identified who met all the inclusion criteria, randomization of the subjects was conducted. The medical assistant responsible for the patients' blood draws used an automated, internet-based randomization system to ensure concealed randomization from the author and from eligible, consenting subjects. Subjects were randomized to 1 of 2 treatment groups: The ACP group (investigational arm) underwent 3 IA injections of 3 to 8 mL of ACP at 1-week intervals (n = 15), and the placebo group (control

TABLE 1
Subject Eligibility Criteria[a]

Inclusion criteria
- Age between 30 and 80 years
- Documented diagnosis of primary OA for at least 6 weeks
- Documented radiographic evidence of OA in the tibiofemoral or patellofemoral compartment of the target knee (Kellgren-Lawrence grades 2 or 3)
- Continued OA pain in the target knee despite at least 6 weeks of 1 of the following nonoperative treatments: activity modification and weight loss, physical therapy, or NSAID
- WOMAC–pain subscale score of at least 8/20 and at least moderate pain (a score of 2) for at least 2 questions on the WOMAC–physical function subscale

Exclusion criteria
- Clinically 3+ effusion of the target knee (stroke test grading system)
- Significant (>10°) valgus or varus deformities as evidenced by standard-of-care radiograph
- Viscosupplementation in any joint in the past 6 months
- Increased risk for postsurgical bleeding (eg, bleeding disorder or taking anticoagulants except low-dose aspirin) or postsurgical infection (eg, taking immunosuppressants or having a severe infection or a history of serious infection)
- Previous cartilage repair procedure on the injured cartilage surface (ie, OATS and ACI)
- Any degree of cognitive impairment.
- Previous surgery at the target knee within the past 6 months
- OA of either hip
- Symptomatic OA of the contralateral knee
- Systemic or IA injection of corticosteroids in any joint within 3 months before screening
- Underlying medical conditions that could interfere with evaluation of the outcome
- Positive pregnancy test, or lactating, or intent to become pregnant during treatment period
- Rheumatoid arthritis
- Gout
- History of infection or current infection at the affected joint
- Participation in any experimental device or drug study within 1 month before screening visit
- Cartilage repair "microfracture" in the past 5 years

[a]ACI, autologous chondrocyte implantation; IA, intra-articular; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; OATS, osteochondral autograft transfer system; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

arm) underwent 3 IA injections of 3 to 8 mL of phosphate-buffered saline at 1-week intervals (n = 15).

Demographics

Data are reported as mean ± SD. The study included a total of 19 women and 11 men, age 50.06 ± 9.35 years, with a body mass index (BMI) of 28.50 ± 5.91. Patients in the ACP group were aged 53.53 ± 8.22 years and had a BMI of 29.53 ± 6.89; there were 10 women and 5 men. The placebo group patients were aged 46.60 ± 9.37 years and had a BMI of 27.47 ± 4.78; there were 9 women and 6 men.

Blinding and Injection Protocol

A trained medical assistant completed all the blood draws on all subjects. This individual further prepared the injections and ensured the blinding of the syringes. Blinding of the syringe was performed by covering each syringe first with a black finger glove followed by a nonlatex white finger glove to securely conceal the syringe contents. This successfully established subject and investigator blinding. This single individual prepared both treatments and delivered either the ACP or saline (placebo) in a concealed, opaque syringe for administration by the author, who personally administered each injection. Each injection was done via a lateral parapatellar approach, which has been noted to be the most reliable knee injection.[22]

Preparation of ACP

A volume of 15 mL of blood was drawn into a double syringe system (Arthrex Inc) for a single spin in a centrifuge (Hettich ROTOFIX 32 A; Arthrex Inc.) at 1500 rpm for 5 minutes. The ACP was procured by pulling back on the secondary (smaller) syringe to remove the yellow leukocyte-poor PRP layer, leaving the lower leukocyte-rich red blood cell pack behind (Figure 2). The volume of available PRP produced during the ACP procedure differed per individual, ranging from 4 to 7.1 mL. Per the protocol, the minimum injection volume of ACP was 3 mL and the maximum injection volume was 8 mL. These numbers were based on the recommendations of the available literature.[14,27,28,40] All patients in both groups had their blood drawn and spun for ACP procurement during each injection visit, because the amount of saline administered to a given patient in the placebo treatment group was equal to the volume of available PRP that was produced from that patient's ACP centrifugation. Because the ACP is only spun once for 5 minutes, the total preparation time is well less than 20 minutes; therefore, treatment with an anticoagulant such as anticoagulant citrate dextrose

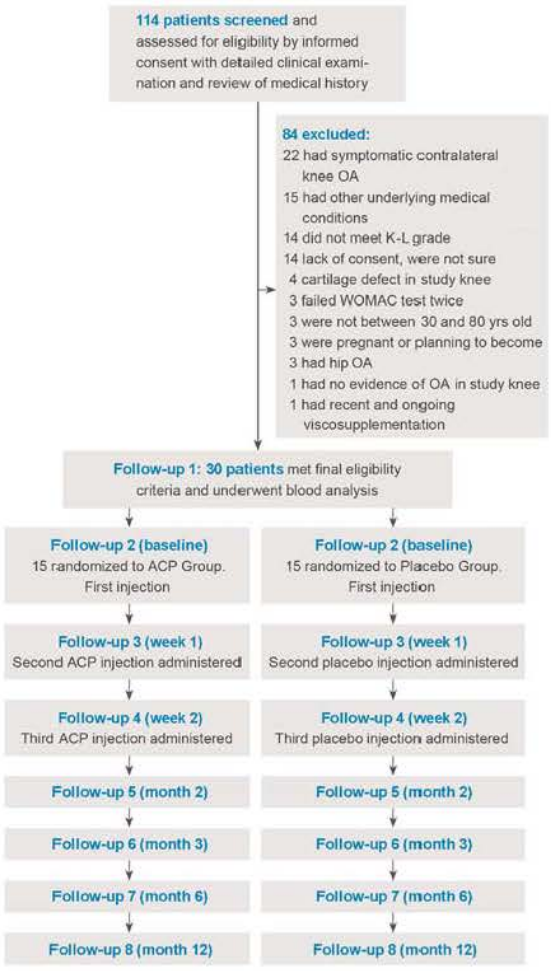

Figure 1. Flow diagram of study method. ACP, autologous conditioned plasma; K-L, Kellgren-Lawrence; OA, osteoarthritis; PRP, platelet-rich plasma; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

solution A (ACD-A) was not necessary, which further optimized the timing of the entire procedure.[37]

Radiographic Grading

Radiographs that were obtained included anteroposterior (AP) weightbearing and posteroanterior (PA) flexion weightbearing views of both knees, with a lateral view of the affected knee and a sunrise view of both knees. The author evaluated the radiographs using the Kellgren-Lawrence system for classification of knee OA knee (Table 2).[26]

Outcome Measures

In a feasibility trial, the safety of a medical product concerns the medical risk to the subject, which is usually

Figure 2. Image of syringe components with blood separated into the leukocyte-rich red blood cell pack and final injection syringe containing autologous conditioned plasma (ACP).

TABLE 2
Kellgren-Lawrence Grading Values

Kellgren-Lawrence Grade	Total Patients, n	Autologous Conditioned Plasma Group, n	Placebo Group, n
2	18	8	10
3	12	7	5

assessed in a clinical trial by laboratory tests (including clinical chemistry and hematologic tests), vital signs, clinical adverse events (diseases, signs, and symptoms), and other special safety tests. The tolerability of the medical product represents the degree to which the subject can tolerate any such adverse effects.

The requirements noted above were fulfilled through laboratory blood tests (both pre- and postinjection series), adverse event reporting, and any clinical signs that became apparent. All subjects underwent a screening visit so that baseline clinical signs were documented and thus any new adverse events could be documented. Analysis of the safety and tolerability of the product's effects occurred at 6 months, with a final analysis at 12 months.

The primary efficacy outcome was the change in pain, joint stiffness, and physical function (disability) measured using the WOMAC at baseline, 1 week, 2 weeks, 2 months, 3 months, 6 months, and 12 months during the prospective trial. This test has been validated by its use in previously completed PRP, HA, and other OA studies.[3,5,33,34,39] The WOMAC consists of 24 total items divided among 3

TABLE 3
WOMAC Osteoarthritis Index Scores for ACP and Placebo Groups[a]

WOMAC	Baseline	1 Week	2 Weeks	2 Months	3 Months	6 Months	12 Months
Overall							
ACP	47 (41-53)	35 (29-40)	22 (15-29)[b]	14 (5-23)[b]	10 (3-18)[b]	11 (3-20)[b]	10 (4-17)[b]
Δ from baseline, %	—	26[c]	53[c]	70[c]	78[c]	75[c]	78[c]
Placebo	46 (40-53)	38 (30-46)	36 (28-44)	31 (22-41)	37 (30-45)	44 (36-53)	43 (33-54)
Δ from baseline, %	—	18	22	32[c]	20	4	7
Pain							
ACP	10 (9-11)	7 (6-8)	4 (2-6)[b]	3 (1-5)[b]	2 (1-4)[b]	3 (1-4)[b]	2 (1-4)[b]
Δ from baseline, %	—	30[c]	59[c]	71[c]	79[c]	75[c]	76[c]
Placebo	11 (10-12)	8 (6-10)	8 (6-9)	7 (5-9)	8 (6-9)	9 (7-11)	9 (6-11)
Δ from baseline, %	—	24[c]	27[c]	34[c]	28[c]	13	19
Stiffness							
ACP	4 (4-5)	3 (2-4)	2 (1-3)[b]	1 (1-2)	1 (0-2)[b]	1 (0-2)[b]	1 (0-2)[b]
Δ from baseline, %	—	30[c]	55[c]	67[c]	76[c]	76[c]	77[c]
Placebo	4 (4-5)	3 (2-4)	3 (2-4)	3 (2-3)	3 (2-4)	4 (3-5)	4 (3-5)
Δ from baseline, %	—	27[c]	30[c]	43[c]	28[c]	9	6
Physical function							
ACP	32 (27-37)	24 (21-28)	16 (10-21)[b]	9 (3-16)[b]	7 (2-12)[b]	8 (2-14)[b]	7 (3-11)[b]
Δ from baseline, %	—	24[c]	51[c]	71[c]	78[c]	75[c]	78[c]
Placebo	31 (26-37)	27 (21-32)	25 (20-31)	22 (15-29)	27 (21-32)	31 (25-37)	30 (23-37)
Δ from baseline, %	—	15	19	30[c]	15	0	3

[a]Values are reported as mean (95% CI) unless otherwise indicated. ACP, autologous conditioned plasma; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
[b]Significant difference from placebo group.
[c]Significant difference from baseline within each respective group.

subscales: pain, stiffness, and physical function. The patient answers the questions and then receives a cumulative score in each of the 3 areas (pain, 0-20; stiffness, 0-8; physical function, 0-68). Higher scores are representative of greater pain and stiffness as well as worsened physical capability.

Statistical Analysis

Statistical analysis was performed by use of SigmaPlot (v12.0; Systat Software Inc). Differences in WOMAC scores from baseline within each study group were assessed via 1-way analysis of variance (ANOVA) with a Tukey test for post hoc comparison. Differences between study groups were assessed with a t test. A post hoc power analysis was performed using G*Power (Universität Düsseldorf).[12]

RESULTS

Safety

Throughout the course of this study, 1 patient in the placebo group felt that the pain was worsening in the target leg, although the patient remained in the study. No reactive effusions or acute postinjection pain flares were noted in either the ACP or the placebo group.

Efficacy

No difference in pretreatment (baseline) WOMAC scores existed between the 2 groups ($P = .952$). The lower overall WOMAC scores for the ACP group were statistically different than the WOMAC scores for the placebo group starting at 2 weeks ($P = .016$) and remained statistically different through the study duration (Figure 3 and Table 3). A statistically significant decrease in WOMAC scores when compared with baseline was seen in the ACP group starting at 1 week ($P = .005$), and the decrease remained statistically significant throughout the study duration. In fact, the results for WOMAC score improvement for the ACP group were statistically significant ($P \leq .001$) from 2 weeks until study completion at 12 months. All 15 patients who received the ACP treatment had this improvement in WOMAC scores. The WOMAC subscales (pain, stiffness, physical function) are also noted in Table 3. Notably for the placebo group, a statistically significant decrease in WOMAC score from baseline was seen at 2 months ($P = .015$), suggesting some placebo effect; however, this was the only time point that remained statistically significant with slight improvement from baseline. A post hoc power analysis revealed that the sample size was 200% greater than the required sample size of 10 (5 for each variable), and the power was calculated as 1.0. The effect size achieved was 2.78, compared with the required effect size of 1.36.

DISCUSSION

The primary objective of the current study was to determine the safety of ACP, and the secondary objective was to determine the efficacy of ACP in patients with primary OA of the knee. The results confirmed the study hypothesis that no

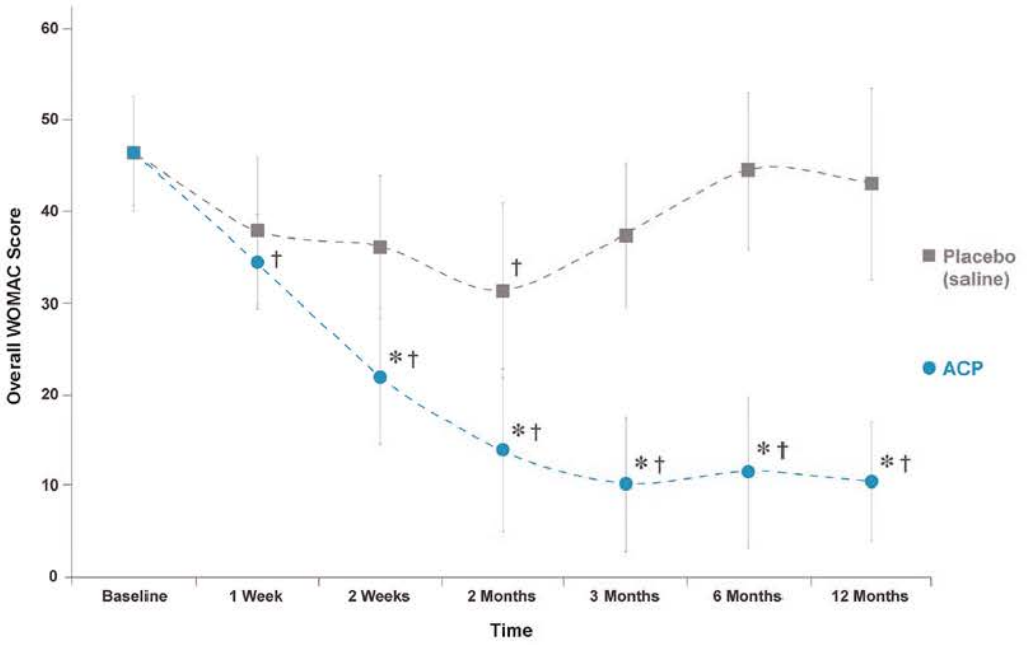

Figure 3. Overall Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores versus time for the autologous conditioned plasma (ACP) and saline placebo treatment groups. *Significant difference from saline placebo ($P < .05$); †significant difference from baseline within each respective group ($P < .05$).

differences were present for outcomes related to patient safety, while significant improvements related to efficacy between ACP and placebo groups were present throughout the study duration. Starting at week 1 and continuing through the 12-month follow-up, the ACP group showed a statistically significant improvement in WOMAC scores compared with baseline, confirming efficacy that ACP injections relieve pain and stiffness for patients with knee OA.

Similarly, the complete absence of adverse events associated with the ACP injection indicates that the injection is safe for human treatment. All 15 patients in the ACP group reported improvements in their WOMAC scores at 12 months compared with baseline scores. Furthermore, the ACP group experienced improvements in all WOMAC subscales (pain, stiffness, physical function) (Table 3).

Certainly, the fact that all 15 patients in the ACP cohort showed such significant clinical improvement is remarkable, but the outcomes were based on patient-reported WOMAC scores to avoid investigator bias. Plus, the data actually showed a statistically significant improvement from baseline for the placebo control group at one time point. This strongly suggests a positive placebo effect—a known phenomenon in scientific research—from the injections themselves, indirectly lending credence to the study method and the patient-focused outcome data collection, as the WOMAC scores were reported directly by the patients.[1] Additionally, this study was subjected to strict monitoring and frequent auditing to ensure high scientific validity. Likewise, the strict inclusion criteria successfully narrowed the selection pool for participants, further enhancing the validity of the study. Finally, all patients in this study were K-L grade 2 or 3, so their significant positive response to the ACP treatment would not relate to having "minimal" OA.

The study results are consistent with prior LP-PRP outcome studies, as the ACP injections yielded significantly improved WOMAC score results without subjecting the patients to negative adverse reactions.[5,21,32,41,42,47] Potentially, these results relate to the fact that the ACP system concentrates platelets while minimizing leukocytes, thus producing LP-PRP.[46] Sundman et al[46] ran a cellular analysis of ACP, revealing that the single-spin ACP product decreases the concentration of leukocytes compared with a double-spin buffy coat preparation as well as compared with whole blood. Furthermore, because ACP is leukocyte-poor and the preparation process takes less than 20 minutes, there is no need to add an anticoagulant such as ACD-A.[37] This results in the injection of a pure substance back into the joint space, which could account for the absence of adverse reactions during the feasibility trial.

Data from Cole et al[6] are similar to the results of this study. These authors compared 3 weekly injections of ACP versus HA and analyzed synovial fluid via enzyme-linked immunosorbent assay (ELISA). The investigators found clinically significant improvements in both International Knee Documentation Committee (IKDC) and visual analog scale (VAS) scores after ACP treatment compared with HA treatment at both 6 months (IKDC $P = .0248$; VAS $P = .0068$) and 1 year (IKDC $P = .0096$; VAS $P = .0039$) after

injection. Their analysis of the synovial fluid suggests that treatment with the ACP system produces tumor necrosis factor–α levels that are lower than the associated levels after HA treatment at 6-month follow-up.

Previous studies have shown that PRP injections are safe and can potentially reduce pain in the osteoarthritic knee.[28,42,45] The majority of these studies have compared PRP versus viscosupplementation. Kon et al[28] published the first such study in 2011, comparing LR-PRP to both low- and high-molecular-weight HA injections in 3 groups, each consisting of 50 patients. These authors noted that the PRP groups showed better performance at 6-month follow-up than the HA groups. Sánchez et al[41] found that plasma rich in growth factors (PRGF), a form of LP-PRP, is more likely to decrease pain and stiffness while improving functionality, based on WOMAC scores compared with HA. Similarly, Vaquerizo et al[49] determined that PRGF improves WOMAC scores significantly compared with HA at both 24 and 48 weeks after injection.

Cerza et al[5] specifically evaluated ACP compared with HA for the treatment of knee OA. They found that ACP provides statistically better outcomes than treatment with HA, particularly in K-L grade 3 OA. As in the current study, the ACP cohort examined by Cerza et al had K-L grades of 2 or 3, as assessed radiographically, indicative of more advanced disease, and still had significant improvement. Also similar to the current study, the Cerza et al study made no mention of adverse effects of the ACP treatment within the clinical outcomes.

Recently, Riboh et al[35] conducted a meta-analysis of the effect of PRP leukocyte concentrations on the efficacy of OA treatment in the knee. Their study accumulated 6 randomized controlled trials (level 1 evidence) and 3 prospective comparative studies (level 2 evidence) and, through transitivity, attempted to analyze the most effective PRP preparations for OA treatment. Their study concluded that there is sufficient evidence to suggest that LP-PRP has a more profound effect on functional outcomes related to OA than does LR-PRP. Riboh et al cited a trend toward a better response with younger knee OA patients treated with PRP. In contrast, in the current study, although the ACP patients on average were more than 7 years older than the patients receiving placebo, the ACP group demonstrated a remarkable treatment response, indicated by the WOMAC score improvement over the 1-year duration of the study.

One potential limitation with the current study relates to the small sample size mandated by the FDA. However, these concerns were resolved by the statistically significant outcomes for the ACP treatment group, in that all 15 patients had major improvement by an average of 78% from their baseline WOMAC score. Additionally, these concerns were alleviated after the post hoc power analysis proved adequate sample size. Another potential limitation in this study could be the use of saline as a placebo control instead of HA or steroids. The FDA, however, mandated saline placebo to create a realistic baseline for comparing the effects of ACP. Despite this requirement, it might be inferred that the use of saline would give an unfair advantage to ACP in terms of showing efficacy. In that regard, it is important to evaluate other trials using saline placebo, particularly against HA. Specifically, Karlsson et al[25] performed a study that showed no statistical differences between HA (Synvisc [Sanofi Aventis] and Supartz [Smith & Nephew]) and saline placebo. In addition, the approval summary documentation from the FDA reveals that another HA supplement (Supartz) was approved after only a 0.68 difference in Lequense scores between the saline group and HA supplement group across their multicenter (5 sites) study.[48] This stands in contrast to the wide difference seen in the current study, where the average total WOMAC score for the saline group started at 46 and ended at 43 after 12 months, compared with the ACP cohort, in which the total WOMAC score improved from 46 to 10 after a year. The amount of improvement of ACP versus saline placebo is therefore quite impressive in this study compared with other saline placebo-controlled OA studies, where the difference was much smaller.

Administration of ACP improved WOMAC scores by 78% from the baseline score versus only 7% for the placebo control group after 1 year. Furthermore, no adverse events for ACP treatment were reported. Therefore, the study conclusion is that ACP is safe and provides quantifiable benefits for pain relief and functional improvement with regard to knee OA. Other joints affected with OA may also benefit from this treatment.

ACKNOWLEDGMENT

The author thanks Jordan Bley for his assistance with final manuscript preparation.

REFERENCES

1. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. *Ann Intern Med*. 2015;162(1):46-54.
2. Bernad-Pineda M, de Las Heras-Sotos J, Garces-Puentes MV. [Quality of life in patients with knee and hip osteoarthritis]. *Rev Esp Cir Ortop Traumatol*. 2014;58(5):283-289.
3. Bodick N, Lufkin J, Willwerth C, et al. An intra-articular, extended-release formulation of triamcinolone acetonide prolongs and amplifies analgesic effect in patients with osteoarthritis of the knee: a randomized clinical trial. *J Bone Joint Surg Am*. 2015; 97(11):877-888.
4. Campbell KA, Erickson BJ, Saltzman BM, et al. Is local viscosupplementation injection clinically superior to other therapies in the treatment of osteoarthritis of the knee: a systematic review of overlapping meta-analyses. *Arthroscopy*. 2015;31(10):2036-2045.e14.
5. Cerza F, Carni S, Carcangiu A, et al. Comparison between hyaluronic acid and platelet-rich plasma, intra-articular infiltration in the treatment of gonarthrosis. *Am J Sports Med*. 2012;40(12):2822-2827.
6. Cole BJ, Fortier LA, Karas V, et al. HA vs. PRP: double-blind RCT comparing clinical outcomes and intra-articular biology for knee arthritis treatment. Poster presented at the AAOS Annual Meeting; March 24-28, 2015; Las Vegas, NV. http://aaos2015.conferencespot.org/58906-aaos-1.1965581/t002-1.1973805/f002-1.1973806/a020-1.1973978/p408-1.1974113.
7. Cole BJ, Schumacher HR Jr. Injectable corticosteroids in modern practice. *J Am Acad Orthop Surg*. 2005;13(1):37-46.
8. Cole BJ, Seroyer ST, Filardo G, Bajaj S, Fortier LA. Platelet-rich plasma: where are we now and where are we going? *Sports Health*. 2010;2(3):203-210.

9. Colen S, van den Bekerom MP, Mulier M, Haverkamp D. Hyaluronic acid in the treatment of knee osteoarthritis: a systematic review and meta-analysis with emphasis on the efficacy of different products. *BioDrugs*. 2012;26(4):257-268.
10. Creamer P. Intra-articular corticosteroid treatment in osteoarthritis. *Curr Opin Rheumatol*. 1999;11(5):417-421.
11. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis*. 2014;73(7):1323-1330.
12. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods*. 2007;39(2):175-191.
13. Felson DT. Epidemiology of hip and knee osteoarthritis. *Epidemiol Rev*. 1988;10:1-28.
14. Filardo G, Di Matteo B, Di Martino A, et al. Platelet-rich plasma intra-articular knee injections show no superiority versus viscosupplementation: a randomized controlled trial. *Am J Sports Med*. 2015;43(7):1575-1582.
15. Filardo G, Kon E, Pereira Ruiz MT, et al. Platelet-rich plasma intra-articular injections for cartilage degeneration and osteoarthritis: single- versus double-spinning approach. *Knee Surg Sports Traumatol Arthrosc*. 2012;20(10):2082-2091.
16. Foster TE, Puskas BL, Mandelbaum BR, Gerhardt MB, Rodeo SA. Platelet-rich plasma: from basic science to clinical applications. *Am J Sports Med*. 2009;37(11):2259-2272.
17. Fransen M, McConnell S. Land-based exercise for osteoarthritis of the knee: a metaanalysis of randomized controlled trials. *J Rheumatol*. 2009;36(6):1109-1117.
18. Fransen M, McConnell S, Hernandez-Molina G, Reichenbach S. Exercise for osteoarthritis of the hip. *Cochrane Database Syst Rev*. 2009;(3):CD007912.
19. Gallagher B, Tjoumakaris FP, Harwood MI, Good RP, Ciccotti MG, Freedman KB. Chondroprotection and the prevention of osteoarthritis progression of the knee: a systematic review of treatment agents. *Am J Sports Med*. 2015;43(3):734-744.
20. Gray RG, Gottlieb NL. Intra-articular corticosteroids: an updated assessment. *Clin Orthop Relat Res*. 1983;177:235-263.
21. Hart R, Safi A, Komzak M, Jajtner P, Puskeiler M, Hartova P. Platelet-rich plasma in patients with tibiofemoral cartilage degeneration. *Arch Orthop Trauma Surg*. 2013;133(9):1295-1301.
22. Jackson DW, Evans NA, Thomas BM. Accuracy of needle placement into the intra-articular space of the knee. *J Bone Joint Surg Am*. 2002;84(9):1522-1527.
23. Jamtvedt G, Dahm KT, Christie A, et al. Physical therapy interventions for patients with osteoarthritis of the knee: an overview of systematic reviews. *Phys Ther*. 2008;88(1):123-136.
24. Johnson VL, Hunter DJ. The epidemiology of osteoarthritis. *Best Pract Res Clin Rheumatol*. 2014;28(1):5-15.
25. Karlsson J, Sjogren LS, Lohmander LS. Comparison of two hyaluronan drugs and placebo in patients with knee osteoarthritis: a controlled, randomized, double-blind, parallel-design multicentre study. *Rheumatology (Oxford)*. 2002;41(11):1240-1248.
26. Kellgren JH, Lawrence J. The epidemiology of chronic rheumatism. In: *Atlas of Standard Radiographs of Arthritis, Volume II*. Oxford, UK: Blackwell Scientific; 1963.
27. Kon E, Buda R, Filardo G, et al. Platelet-rich plasma: intra-articular knee injections produced favorable results on degenerative cartilage lesions. *Knee Surg Sports Traumatol Arthrosc*. 2010;18(4):472-479.
28. Kon E, Mandelbaum B, Buda R, et al. Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: from early degeneration to osteoarthritis. *Arthroscopy*. 2011;27(11):1490-1501.
29. Lubowitz JH. Editorial commentary: autologous platelet-rich plasma. *Arthroscopy*. 2015;31(4):784.
30. Meheux CJ, McCulloch PC, Lintner DM, Varner KE, Harris JD. Efficacy of intra-articular platelet-rich plasma injections in knee osteoarthritis: a systematic review [published online September 29, 2015]. *Arthroscopy*. doi:10.1016/j.arthro.2015.08.005.
31. Migliore A, Procopio S. Effectiveness and utility of hyaluronic acid in osteoarthritis. *Clin Cases Miner Bone Metab*. 2015;12(1):31-33.
32. Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. *Am J Sports Med*. 2013;41(2):356-364.
33. Raeissadat SA, Rayegani SM, Babaee M, Ghorbani E. The effect of platelet-rich plasma on pain, function, and quality of life of patients with knee osteoarthritis. *Pain Res Treat*. 2013;2013:165967.
34. Rayegani SM, Raeissadat SA, Taheri MS, et al. Does intra articular platelet rich plasma injection improve function, pain and quality of life in patients with osteoarthritis of the knee? A randomized clinical trial. *Orthop Rev (Pavia)*. 2014;6(3):5405.
35. Riboh JC, Saltzman BM, Yanke AB, Fortier L, Cole BJ. Effect of leukocyte concentration on the efficacy of platelet-rich plasma in the treatment of knee osteoarthritis [published online April 29, 2015]. *Am J Sports Med*. pii:0363546515580787.
36. Ringdahl E, Pandit S. Treatment of knee osteoarthritis. *Am Fam Physician*. 2011;83(11):1287-1292.
37. Rock G, Tittley P, Fuller V. Effect of citrate anticoagulants on factor VIII levels in plasma. *Transfusion*. 1988;28(3):248-252.
38. Rozental TD, Sculco TP. Intra-articular corticosteroids: an updated overview. *Am J Orthop (Belle Mead NJ)*. 2000;29(1):18-23.
39. Sánchez M, Anitua E, Azofra J, Aguirre JJ, Andia I. Intra-articular injection of an autologous preparation rich in growth factors for the treatment of knee OA: a retrospective cohort study. *Clin Exp Rheumatol*. 2008;26(5):910-913.
40. Sánchez M, Delgado D, Sánchez P, et al. Platelet rich plasma and knee surgery. *Biomed Res Int*. 2014;2014:890630.
41. Sánchez M, Fiz N, Azofra J, et al. A randomized clinical trial evaluating plasma rich in growth factors (PRGF-Endoret) versus hyaluronic acid in the short-term treatment of symptomatic knee osteoarthritis. *Arthroscopy*. 2012;28(8):1070-1078.
42. Say F, Gurler D, Yener K, Bulbul M, Malkoc M. Platelet-rich plasma injection is more effective than hyaluronic acid in the treatment of knee osteoarthritis. *Acta Chir Orthop Traumatol Cech*. 2013;80(4):278-283.
43. Scarpignato C, Lanas A, Blandizzi C, et al. Safe prescribing of non-steroidal anti-inflammatory drugs in patients with osteoarthritis—an expert consensus addressing benefits as well as gastrointestinal and cardiovascular risks. *BMC Med*. 2015;13:55.
44. Silva LE, Valim V, Pessanha AP, et al. Hydrotherapy versus conventional land-based exercise for the management of patients with osteoarthritis of the knee: a randomized clinical trial. *Phys Ther*. 2008;88(1):12-21.
45. Spakova T, Rosocha J, Lacko M, Harvanova D, Gharaibeh A. Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid. *Am J Phys Med Rehabil*. 2012;91(5):411-417.
46. Sundman EA, Cole BJ, Fortier LA. Growth factor and catabolic cytokine concentrations are influenced by the cellular composition of platelet-rich plasma. *Am J Sports Med*. 2011;39(10):2135-2140.
47. Trigkilidas D, Anand A. The effectiveness of hyaluronic acid intra-articular injections in managing osteoarthritic knee pain. *Ann R Coll Surg Engl*. 2013;95(8):545-551.
48. US Food and Drug Administration. *Summary of Safety and Effectiveness—SUPARTZ (P980044)*. Arlington, VA: Quintiles, Incorporated; 2001.
49. Vaquerizo V, Plasencia MA, Arribas I, et al. Comparison of intra-articular injections of plasma rich in growth factors (PRGF-Endoret) versus Durolane hyaluronic acid in the treatment of patients with symptomatic osteoarthritis: a randomized controlled trial. *Arthroscopy*. 2013;29(10):1635-1643.
50. Zhang Y, Jordan JM. Epidemiology of osteoarthritis. *Clin Geriatr Med*. 2010;26(3):355-369.