Microfragmented Adipose Tissue Is Equivalent to Platelet-Rich Plasma for Knee Osteoarthritis at 12 Months Posttreatment

A Randomized Controlled Trial

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Background: Platelet-rich plasma (PRP) is an effective treatment for knee osteoarthritis (OA). Microfragmented adipose tissue (MFAT) is another orthobiologic that holds promise, but data supporting its use are limited. Previous studies showed that MFAT created using the Lipogems device was equivalent to PRP created via noncommercial laboratory-based processes.

Purpose: To perform a comparison of commercially available MFAT and PRP systems for treatment of knee OA.

Study Design: Randomized controlled trial; Level of evidence, 2.

Methods: A total of 71 patients with symptomatic knee OA (Kellgren-Lawrence grades 1-4) were randomized to receive a single injection of either leukocyte-rich PRP (Angel; Arthrex) or MFAT (Lipogems) under ultrasound guidance. Patient-reported outcomes (Knee injury and Osteoarthritis Outcome Score [KOOS], visual analog scale for pain with activities of daily living [VAS pain], and Tegner activity level) were recorded at baseline and at 1, 3, 6, and 12 months after injection. The primary outcome was the KOOS-Pain subscale score at 12 months after injection.

Results: Overall, 49 patients completed their 12-month follow-up (PRP group, n = 23; MFAT group, n = 26). All demographic features were similar between groups, except that more men were randomized to the PRP group and more women to the MFAT group. At 12 months posttreatment, KOOS-Pain scores improved in both groups, with no significant group difference (PRP, 78 $\pm$ 17.9 vs MFAT, 77.8 $\pm$ 19.3; P = .69). Similarly, other KOOS subscales, VAS pain scores, and Tegner scores improved at 12 months, with no differences between treatment groups.

Conclusion: Both PRP and MFAT injections for knee OA resulted in improved patient-reported outcomes at 12 months posttreatment, with no differences found between treatments.

Registration: NCT04351087 (ClinicalTrials.gov identifier).

Keywords: platelet-rich plasma; osteoarthritis; microfragmented adipose tissue; clinical trial

A growing body of literature has demonstrated the efficacy of platelet-rich plasma (PRP) for treating knee osteoarthritis (OA). The quality of data has progressed from uncontrolled cohort studies to randomized controlled trials (RCTs) demonstrating superiority over placebo, steroid, and viscosupplement. These studies include RCTs sanctioned by the US Food and Drug Administration (FDA), as well as meta-analyses of studies with Level 1 evidence.[5,9,12,14,23,25,28]

As the data supporting the use of PRP have grown and strengthened its role in OA treatment, other cell therapy options have been introduced. These alternative sources

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for autologous cells include bone marrow aspirate concentrate (BMAC) and adipose tissue. The anabolic profile of BMAC is promising, but conclusions from Level 1 evidence studies are mixed. No studies have shown BMAC to be superior to placebo or PRP, but there are data suggesting it could be better than viscosupplementation.[2,7,24] Adipose tissue is often prepared in the form of microfragmented adipose tissue (MFAT), in which the adipose tissue is harvested from the patient and processed at the point of care by mechanical resizing and rinsing (with saline).[11] Two studies have compared PRP (created independently in a laboratory) to MFAT, and neither study found a difference between treatment arms.[20,29]

Previously, we published early (6-month) posttreatment outcomes comparing PRP created with a commercial system versus MFAT.[4] The goal of publishing the early outcomes was to provide real-time clinical outcomes data on new biologics, given the speed with which these devices have been introduced to the market. In the current work, we present 12-month outcomes to report on the durability of these products. We hypothesized that there would be no difference in patient-reported outcomes between treatment groups at 12 months.

METHODS

The protocol for this study received institutional review board approval, and the study was registered at ClinicalTrials.gov. This was aRCT comparing a single injection of PRP versus MFAT for unilateral knee OA. Patients seen for knee OA treatment at a single institution between June 2020 and July 2021 were screened for study inclusion.

Patient Selection

Patients who met the inclusion and exclusion criteria (Table 1), elected to enroll, and provided written informed consent were assigned to a treatment group (PRP or MFAT) according to a computer-generated block randomization scheme in a 1:1 ratio. Given the significant and readily observable differences in cell harvest technique (venipuncture for PRP vs lipoaspiration for MFAT), neither patients nor the investigational team were blinded to treatment allocation.

Outcome Measures

Upon enrollment, patient demographic data were collected (including age, sex, body mass index, and Kellgren-Lawrence OA grade). Knee injury and Osteoarthritis Outcome Score (KOOS) subscales (Pain, Symptoms, Activities of Daily Living, Sports and Recreation, and Quality of Life), visual analog scale for pain with activities of daily living (VAS pain), and Tegner activity level were recorded at baseline and at 1, 3, 6, and 12 months after treatment. The primary outcome measure was the KOOS-Pain score at 12-month follow-up.

Procedural Details

Before the PRP or MFAT procedure, patients were instructed to avoid nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin for 1 week before the procedure and to avoid exercise the day before and the day of the procedure.

Platelet-Rich Plasma. For the PRP group, 156 mL of whole blood was harvested by venipuncture from the antecubital fossa and mixed with 24 mL of Anticoagulant Citrate Dextrose Solution–Solution A (ACD-A; Citra Labs), which was then processed using double-spin centrifugation (Angel cPRP system using the 2% hematocrit setting; Arthrex). Whole blood (0.5 mL) and the final PRP underwent complete blood count (CBC) analysis using a Sysmex XN-350 hemoanalyzer. The PRP was injected using an ultrasound-guided superolateral approach through a 25-gauge, 1.5-inch (3.8-cm) needle by a board-certified sports medicine physician (M.B.).

Microfragmented Adipose Tissue. Adipose tissue was aspirated from the subcutaneous tissue of the abdomen or flank (depending on the ease of harvest determined by the patient's body habitus) for the MFAT procedure. Under sterile precautions, the aspiration site was injected with 10 mL of 1.0% lidocaine. A small incision was made with a No. 11 scalpel, and 120 mL of Klein solution was injected into the adipose layer bilaterally. After 15 minutes, 30 mL of adipose tissue was aspirated (15 mL from each side) using

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Ethical approval for this study was obtained from The Ohio State University (ref No. 2019H0448).

TABLE 1
Study Inclusion and Exclusion Criteria[a]

Inclusion Criteria
1. Age 25-75 years
2. Body mass index <40
3. Symptomatic knee OA (primary or posttraumatic)
4. Radiographic evidence of OA of the target knee (Kellgren-Lawrence grades 1-4)
5. Continued pain in the target knee despite at least 6 weeks of 1 of the following nonoperative treatments: activity modification, weight loss, physical therapy, or NSAID/acetaminophen
6. KOOS-Pain subscale score between 20 and 65
7. Working knowledge of English language (to be able to complete all outcome scores)
8. Ability to attend all follow-up appointments
Exclusion Criteria
1. Isolated patellofemoral OA
2. Grade 3 or higher effusion of the target knee (stroke test grading system)
3. Valgus or varus deformities >10°
4. Steroid injection in the target knee in the past 3 months
5. Viscosupplementation in the target knee in the past 6 months
6. PRP in the target knee in the past 1 year
7. Other cellular/orthobiologic treatments in the index knee (bone marrow, amniotic suspensions, etc) at any previous time
8. Participation in any experimental device or drug study within 1 year before the screening visit
9. Oral or intramuscular steroids for the past 3 months
10. Medical condition that could affect outcomes of the procedure, including anemia, thrombocytopenia, bleeding disorders, systemic inflammatory disorders (rheumatoid arthritis, lupus, etc), diabetes, history of cancer (other than nonmelanoma skin malignancies), anticoagulant therapy (that could not be held 1 week before the procedure), immunosuppression
11. Previous cartilage repair procedure on the injured cartilage surface
12. Previous surgery at the target knee within the past 1 year
13. Any degree of cognitive impairment
14. Symptomatic OA of either hip
15. Symptomatic OA of the contralateral knee
16. Pregnant, lactating, or intending to become pregnant during the treatment period
17. History of gout
18. History of infection or current infection at the affected joint
19. Smoking

[a]KOOS, Knee injury and Osteoarthritis Outcome Score; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; PRP, platelet-rich plasma.

a 13-gauge cannula. The lipoaspirate was processed with the Lipogems system according to manufacturer guidelines.[11] The MFAT injection was performed with the same approach and by the same physician as the PRP group, except that a 21-gauge needle was used due to increased injectate viscosity. Total nucleated cell count (TNC) was determined from 1.0 mL of MFAT.

Posttreatment Care. After treatment, patients were allowed ice, acetaminophen, and NSAIDs as needed and weightbearing as tolerated. Patients were instructed to avoid high-impact exercise (eg, jogging and plyometrics) and sports for 1 week after treatment and then resume activities as tolerated thereafter. Patients allocated to PRP were scheduled for a 1-month follow-up, and those allocated to MFAT were scheduled for an additional 2-week wound check. The remaining follow-up visits were performed at the same intervals (1, 3, 6, and 12 months posttreatment).

Cellular Analysis

The PRP samples underwent routine CBC analysis by means of the hemoanalyzer. The MFAT samples were processed for stromal vascular fraction (SVF) isolation to ensure accurate TNC quantification as previously described.[1,6] In brief, the samples were washed with phosphate-buffered saline (PBS). The liquid phases were removed between washes. The MFAT samples were digested in collagenase A. The collagenase digest was neutralized by the addition of Dulbecco's modified Eagle medium (DMEM) containing 10% fetal bovine serum (FBS) and centrifuged at 800*g* for 5 minutes to separate the SVF pellet from the adipocytes. The SVF was washed twice with PBS and centrifuged at 800*g* for 5 minutes after each wash. The cell suspension was filtered through a 40-μm cell strainer. The supernatant was discarded, and the cell pellet (SVF) was resuspended in 5 mL of DMEM containing 10% FBS. Cell viability was determined via Trypan blue dye exclusion. The TNC was calculated by counting an aliquot of the resulting suspension using a hemocytometer and an inverted light microscope.

Statistical Analysis

Continuous variables were summarized as means with standard deviations, and categorical variables were reported as frequencies and percentages. The KOOS subscale and VAS pain scores were summarized by treatment group at baseline and follow-up time points, and scores were compared between the treatment groups with unpaired *t* tests. Repeated-measures analysis of variance was performed to detect the effect of treatment and/or time on the VAS pain and KOOS subscale values.

An a priori power analysis was undertaken based on the minimal clinically important difference (MCID) between baseline and final follow-up of 9 points for the KOOS-Pain subscale.[8] With an alpha error of .05 and an anticipated standard deviation of 15 points for KOOS-Pain, a total of 88 patients (44 per treatment group) would be required to detect a 9-point difference between treatment groups with 80% power. The initial study design was to enroll 110 patients (55 per group) to account for up to 20% loss to follow-up. Due to a change in regulatory requirements during the course of the study, enrollment was halted at 71 patients (before achieving the targeted accrual). A repeated power calculation demonstrated that

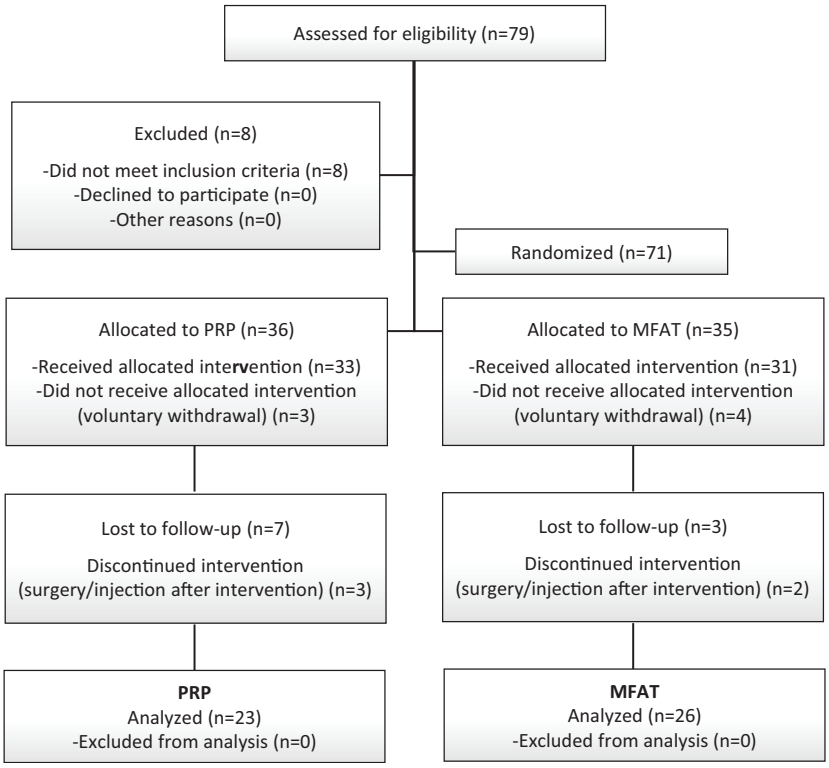

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram of participant enrollment in the study. MFAT, microfragmented adipose tissue; PRP, platelet-rich plasma.

this study achieved 56% power to detect a group difference in excess of the 9-point MCID for KOOS-Pain.

RESULTS

Patient Demographics

A total of 79 patients were screened; of these patients, 71 were randomized. At the conclusion of the study, 49 patients (23 patients in the PRP group, 26 patients in the MFAT group) completed their 12-month follow-up (Figure 1). The only significant group difference in baseline demographics was that more men were allocated to PRP and more women to MFAT ($P = .01$) (Table 2). The final cellular compositions of the PRP and MFAT treatments are presented in Table 3. Note that of the 23 PRP patients, only 18 had PRP cell counts performed. The reason for this was that if the final PRP was $\leq$4 mL, the decision was made to inject the entirety of the product rather than send 0.5 mL for cell count. The rationale for this decision was that in our practice, lower volume PRP injections are less effective. Therefore, we chose to maximize the therapeutic dosing to optimize the clinical effect rather than count cells and risk a subtherapeutic outcome.

Outcomes

No major complications (including hematoma, bleeding, infection, or cosmetic defect) occurred. Regarding the primary outcome measure (KOOS-Pain), both groups surpassed the MCID by 1 month posttreatment and sustained this level for the duration of the study. However, the 12-month posttreatment KOOS-Pain score was not significantly different between the PRP and MFAT groups (78 $\pm$ 17.9 vs 77.8 $\pm$ 19.3, respectively; $P = .69$). Similar clinical improvements (defined by the MCID) were seen in the other KOOS subscales, with no significant between-group differences at 12-month follow-up. The same dynamic was observed with the VAS pain and Tegner scores: clinical improvement with no between-group differences at 12 months (Table 4 and Figure 2).

DISCUSSION

The most important finding of this study was that there was no difference between treatment groups (PRP or MFAT) at 12 months, which confirmed our hypothesis. Both treatment groups demonstrated clinical improvement by exceeding the MCID threshold on all KOOS subscales as well as the VAS pain score at 1 month after injection. This improvement was durable for the 12-month duration of this study.

This work adds to the growing body of literature comparing PRP versus MFAT. Kaszyński et al[20] performed the first randomized comparison of PRP versus MFAT. They randomized a total of 40 patients with Kellgren-Lawrence grade 1 to 3 OA to receive either a series of 3

TABLE 2
Patient Characteristics by Study Group[a]

Characteristic	PRP (n = 23)	MFAT (n = 26)	*P*
Age, y	52.8 ± 14.0	56.7 ± 7.8	.22
Body mass index, kg/m^2	31.8 ± 4.7	31.2 ± 4.8	.65
Sex			**.01**
Male (n = 24)	16	8	
Female (n = 25)	7	18	
Race			.65
White (n = 39)	17	22	
Black (n = 7)	4	3	
Asian (n = 3)	2	1	
Osteoarthritis type			.38
Primary (n = 33)	17	16	
Posttraumatic (n = 16)	6	10	
Kellgren-Lawrence grade			.14
Grade 1 (n = 8)	6	2	
Grade 2 (n = 12)	7	5	
Grade 3 (n = 17)	7	10	
Grade 4 (n = 12)	3	9	

[a]Data are reported as mean ± SD or No. of patients. Boldface *P* value indicates statistically significant difference between groups ($P < .05$). MFAT, microfragmented adipose tissue; PRP, platelet-rich plasma.

TABLE 3
Cellular Composition of Whole Blood, PRP, and MFAT[a]

	Whole Blood	PRP	MFAT
Injection volume, mL	—	5.2 ± 1.0	8.2 ± 3.9
Platelets, $10^3/\mu L$	186.1 ± 47.5	2977.1 ± 1046.3	—
White blood cells, $10^3/\mu L$	5.5 ± 1.5	27.9 ± 12.8	—
Red blood cells, $10^6/\mu L$	3.6 ± 0.7	0.2 ± 0.1	—
Neutrophils, %	54.7 ± 8.5	10.5 ± 9.4	—
Lymphocytes, %	32.9 ± 7.3	70.6 ± 9.9	—
Monocytes, %	8.9 ± 1.6	17.9 ± 4.9	—
Stromal vascular fraction, millions/mL	—	—	3.8 ± 4.8
Viability, %	—	—	98 ± 1.4

[a]Data are reported as mean ± SD. Dashes indicate areas not applicable. MFAT, microfragmented adipose tissue; PRP, platelet-rich plasma.

PRP injections or a single injection of MFAT. The PRP was created independently (without the use of commercial kits). The injections consisted of 3.0 mL of platelets concentrated 8 times over baseline, whereas leukocyte concentrations were not presented. For the MFAT group, 100 mL of adipose tissue was harvested under general anesthesia and processed in the Lipogems device, and a total of 10 mL of MFAT was injected. Partial weightbearing precautions using crutches were implemented for 2 weeks.

TABLE 4
Patient-Reported Outcomes[a]

		Posttreatment			
Outcome Measure	Baseline	1 Month	3 Months	6 Months	12 Months
KOOS-Pain					
PRP	51.7 ± 10.8	79.1 ± 12.9	83.6 ± 12.6	85.5 ± 11.6	78 ± 17.9
MFAT	51.1 ± 10.2	73.1 ± 12.2	83.3 ± 12.1	82.2 ± 17.1	77.8 ± 19.3
KOOS-Symptoms					
PRP	56.7 ± 17.1	77.2 ± 13.8	82.6 ± 12.1	83.2 ± 11.9	76.4 ± 20.2
MFAT	49.7 ± 17.5	63.3 ± 2.5	75.6 ± 16.67	76.5 ± 19.4	71.8 ± 20.5
KOOS-ADL					
PRP	59 ± 14.4	85.6 ± 14.1	89.5 ± 9.3	91.1 ± 10	84.5 ± 17.1
MFAT	61.1 ± 18	79.6 ± 12.7	89.4 ± 10.7	89.2 ± 15.8	83.7 ± 18.4
KOOS-Sports/Rec					
PRP	29.4 ± 19.9	65 ± 24.4	70.9 ± 19.9	72.8 ± 22.5	65.4 ± 27.8
MFAT	27.9 ± 20	52.1 ± 19.9	66.7 ± 21.6	66.4 ± 26.7	57.7 ± 31.1
KOOS-QOL					
PRP	31.5 ± 13	64.1 ± 20.4	65.2 ± 19.8	69.3 ± 19.2	65 ± 26.3
MFAT	30.1 ± 17.4	50.2 ± 15.4	66.4 ± 18.5	69.2 ± 22.2	61.1 ± 27.6
VAS pain					
PRP	50 ± 22	20.67 ± 20.1	15.8 ± 17.9	16.4 ± 19.3	18.3 ± 21.1
MFAT	49.8 ± 23.8	23.6 ± 18.5	15.4 ± 16.4	14.8 ± 21	23.4 ± 25.1
Tegner					
PRP	2.8 ± 1.3	4.1 ± 1.9	4 ± 1.2	3.9 ± 1.5	3.8 ± 2.1
MFAT	3 ± 1.5	3.7 ± 1.4	4.2 ± 1.4	4.3 ± 1.5	4.2 ± 1.7

[a]Data are reported as mean ± SD. Patients in both study groups saw clinical improvement throughout the study, with no significant difference between groups. ADL, Activities of Daily Living; KOOS, Knee injury and Osteoarthritis Outcome Score; MFAT, microfragmented adipose tissue; QOL, Quality of Life; Sports/Rec, Sports and Recreation; PRP, platelet-rich plasma; VAS, visual analog scale.

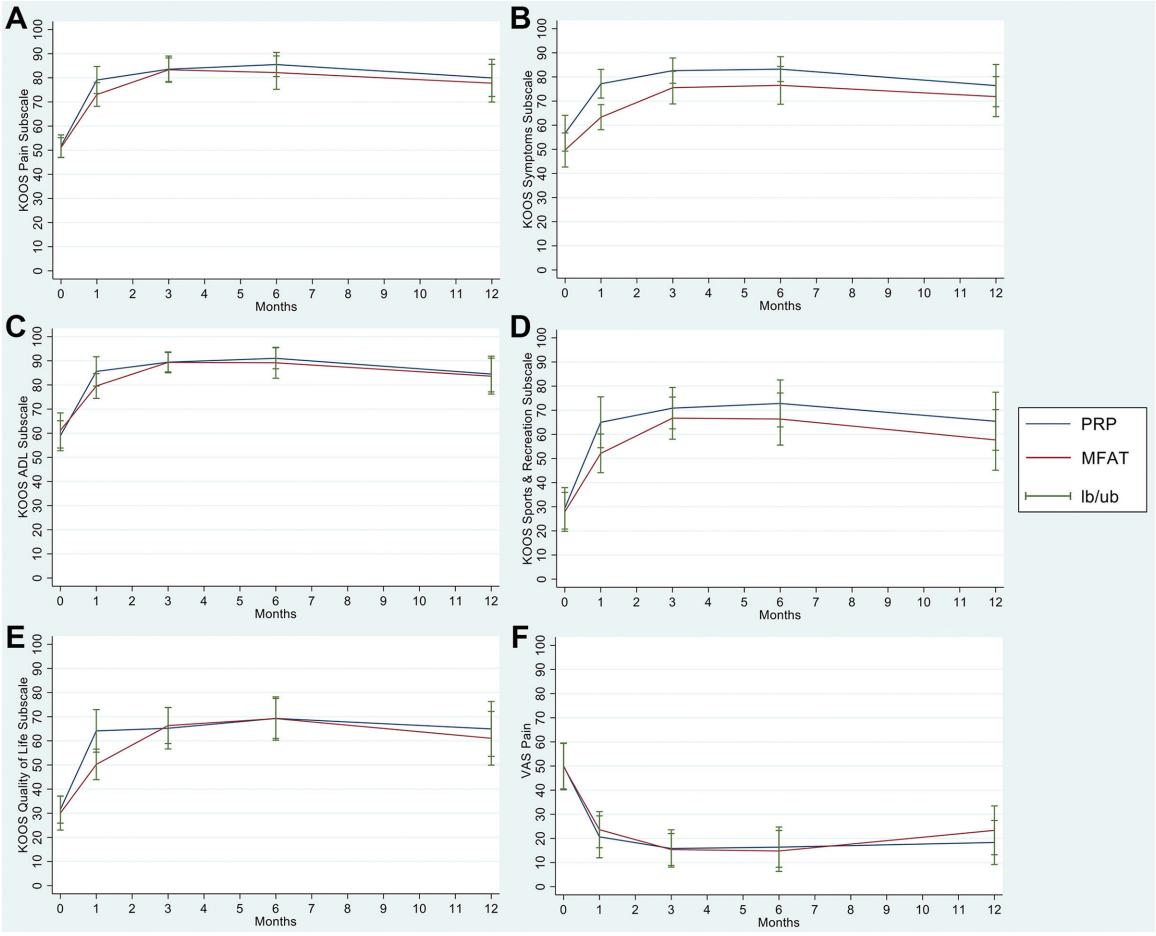

Figure 2. Outcome scores by group from 0 to 12 months posttreatment. (A) KOOS-Pain, (B) KOOS-Symptoms, (C) KOOS-ADL, (D) KOOS-Sports/Rec, (E) KOOS-QOL, and (F) VAS pain. ADL, Activities of Daily Living; KOOS, Knee injury and Osteoarthritis Outcome Score; lb/ub, lower bound/upper bound; MFAT, microfragmented adipose tissue; QOL, Quality of Life; Sports/Rec, Sports and Recreation; PRP, platelet-rich plasma; VAS, visual analog scale.

At 12 months, patient-reported outcomes (including KOOS and VAS pain scores) improved, but there was no difference between groups.

Zaffagnini et al[29] randomized 118 patients to a single injection of either PRP or MFAT. The PRP was prepared in the laboratory, without commercial kits, to create 5 mL of PRP with platelet concentrations 5 times over baseline and leukocyte concentration 1.5 times over baseline. The PRP was activated by freeze-thawing and adding 1 mL of calcium gluconate. The MFAT was also prepared using the Lipogems device; the final injection volume was 10 mL, but harvest technique details were not provided. Patients in the MFAT group were given crutches to aid in weightbearing for 2 weeks. At the final follow-up of 2 years, there was no difference in clinical outcomes (including KOOS and International Knee Documentation Committee [IKDC] score) between treatments. A subgroup analysis found that patients with severe OA who received MFAT had better IKDC scores (but not KOOS) at 6 months compared with the PRP group, but that difference was not present at 12 or 24 months.

Our study adds unique data and perspectives to the existing literature. First, this study used a commercially available PRP system, whereas the previous 2 RCTs[20,29] used laboratory-based methods. This is valuable, especially for physicians who do not have laboratories available to them for PRP processing. Many physicians rely on commercial systems, and given the known cellular variability among various PRP preparation methods, it is necessary to perform independent investigations unique to the specific PRP.[22] This study provides 12-month posttreatment outcome comparisons between 2 widely recognized commercial devices. Second, regarding the MFAT procedure, our work demonstrates that a simplified approach is safe and feasible. The aforementioned studies harvested adipose tissue in the operating room. In contrast, we used local anesthetic in a clinic-based procedure room. Our patients experienced no major complications (including hematoma, bleeding, infection, or cosmetic defect). This demonstrates that with proper training and precautions, the MFAT procedure can be safely performed in the clinic without general anesthesia. This reduces cost and the risk

of general anesthesia without compromising patient outcomes. Third, our study was less restrictive with the postinjection precautions. The previous studies[20,29] restricted weightbearing for 2 weeks, whereas our patients bore weight immediately and were allowed to resume exercise and sport in 1 week. Although there was no direct comparison between postinjection recovery approaches, patients in both groups still exceeded the MCID threshold by 1 month and for the duration of the study. Therefore, our work demonstrates that early weightbearing and activity do not have a negative impact on clinical outcomes. Additionally, the weightbearing allowance reduces mobility restrictions that could increase the risk of complications (like joint stiffness or deep venous thrombosis). Comparative studies are needed to determine whether postinjection protocols influence outcomes, but for now, early mobility does not appear to negate the therapeutic benefit of either intervention.

The collective results of the current study as well as the previous RCTs[20,29] have a significant impact for physicians using PRP. There is mounting evidence supporting the use of PRP for knee OA. This has led some experts to consider PRP a first-line injection therapy.[10] As PRP has been established in OA care, newer interventions like BMAC and MFAT have been introduced under the premise that they are "advanced" therapies because they are composed of unique cells and proteins not found in PRP. For example, both have been discussed as types of "stem cell" therapy.[19,21,26] Over time, this has been clarified, as the population of mesenchymal stem cells is minute and unlikely to be the primary source of treatment effect.[8] The emphasis on these interventions then shifted from stem cells to proteins like interleukin-1 receptor antagonist protein in BMAC and macrophage density in adipose tissue.[16,17,27] However, despite the plausible rationale for using these cells, so far neither BMAC nor MFAT has outperformed PRP for knee OA in a randomized trial.[2,3,20,29] This is important because these latter techniques are more invasive and expensive than PRP. Although BMAC and MFAT may have utility in OA care that needs elucidation, the clinical outcomes, risk, and cost all favor PRP.

Limitations

There are important limitations to this study to consider. First, the sample size is smaller than what was required to detect a difference according to our original power analysis. During continuing review with our institutional review board, it was determined that because our study was designed to evaluate the efficacy of off-label use of 2 devices (Angel cPRP and Lipogems), the trial required that 2 separate investigational device exemptions (IDEs) be filed with the FDA.[18] This was confirmed directly with the FDA through their Q-risk determination. Due to resource restriction, we decided to end enrollment. This issue is critical for all investigators in the United States to recognize. Regardless of institutional review board approval, all off-label investigations for these devices must have IDEs submitted to the FDA under current guidelines. Second, there was a significantly different allocation to treatment between sexes. Sex may play an important role in the anabolic effect of autologous therapies, so the uneven allocation may have affected the result. On review, the randomization scheme was free of error, and this distribution of patients was deemed a random occurrence. Had the study completed its target enrollment, we anticipate that this difference would not exist. A third limitation is that we used a leukocyte-rich (LR) PRP, so we cannot determine whether leukocyte-poor (LP) PRP would perform differently in comparison. However, the current state of evidence, including RCTs, shows no difference between LR-PRP and LP-PRP for knee OA.[13,15] Therefore, changing leukocyte content may have no impact on our conclusion. Another limitation is that only the TNC and viability were analyzed. There may be additional bioactive proteins not represented by the TNC count analysis performed, which may be an area of further investigation.

Finally, the study was limited by the absence of a placebo group. Placebo effect plays an important role in interventional studies, so we cannot know the extent of that effect in the present study.[30] To determine the placebo effect, patients would have to be blinded and, therefore, would need to undergo sham venipunctures and lipoaspiration, which is not practical for our study design.

CONCLUSION

In the current study, both PRP and MFAT injections for knee OA resulted in improved patient-reported outcomes at 12 months, with no significant difference between the treatment groups.

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