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Comparative Analysis of Bone Marrow Aspirate Concentrate, Adipose-Derived Mesenchymal Stromal Cells, and Combined Therapy (PRP + BMAC + Adipose MSCs) for Knee Osteoarthritis: A 250-Patient Randomized Controlled Trial with 24-Month Follow-Up

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Abstract

Background: Intra-articular orthobiologics are widely used for knee osteoarthritis (OA), but platelet-rich plasma (PRP), bone marrow aspirate concentrate (BMAC) and adipose-derived mesenchymal stromal cells (ADSCs) have rarely been compared head to head, and the value of combining them has not been tested in a controlled setting.

Objective: To compare the efficacy, durability, structural effect, safety and cost profile of PRP, BMAC, ADSCs, a triple-combination protocol (PRP + BMAC + ADSCs) and saline placebo over 24 months.

Methods: Two hundred and fifty adults with Kellgren–Lawrence grade II–IV knee OA were randomized 1:1:1:1:1 (n = 50 per arm) to a single intra-articular treatment with saline, PRP, BMAC, ADSCs, or the combined protocol. Outcomes were assessed at baseline and at 3, 6, 12 and 24 months: visual analogue scale (VAS) pain, WOMAC, KOOS, 3-T MRI (cartilage thickness, WORMS), responder rate (VAS reduction ≥ 2 points) and adverse events. Between-group differences were analysed by one-way ANOVA with Tukey correction and by repeated-measures mixed models; categorical outcomes by chi-square test.

Results: At 24 months, mean VAS was 5.8 ± 1.4 with saline, 4.9 ± 1.5 with PRP, 2.9 ± 1.3 with BMAC, 2.5 ± 1.2 with ADSCs and 1.7 ± 1.1 with combined therapy ($F(4,245) = 86.5$, $p < 0.001$), corresponding to relative improvements of 19%, 31%, 60%, 65% and 76%. WOMAC and KOOS followed the same ordering (both $p < 0.001$). PRP peaked at 6–12 months and then regressed, whereas all cell-based arms sustained their benefit to 24 months. BMAC and ADSCs did not differ significantly from one another for any endpoint (all $p > 0.5$), while combined therapy exceeded both (vs BMAC $p < 0.001$; vs ADSCs $p = 0.021$ for VAS). MRI showed net cartilage gain only in the cell-based arms (combined +0.16 ± 0.14 mm vs saline −0.21 ± 0.18 mm, $p < 0.001$). Responder rates were 18%, 42%, 74%, 80% and 88% ($p < 0.001$). Any adverse event occurred in 12%, 28%, 46%, 42% and 58% of patients respectively; all were minor and self-limiting, with no serious adverse events. Cost per point of sustained VAS reduction was lowest for PRP (386 USD) and highest for combined therapy (891 USD).

Conclusion: Combined PRP + BMAC + ADSC therapy produced the largest and most durable clinical and structural benefit in knee OA, but at the highest procedural burden and cost. BMAC and ADSCs alone were statistically indistinguishable from each other and delivered most of the achievable benefit at roughly half the cost, making them the pragmatic default for most patients. PRP remains a reasonable low-cost option when a 6–12-month window of relief is acceptable.

Keywords

Knee osteoarthritis; Bone marrow aspirate concentrate; Adipose-derived mesenchymal stromal cells; Platelet-rich plasma; combination therapy; orthobiologics; randomized controlled trial.

Abbreviations

ADSC, adipose-derived mesenchymal stromal cell; AE, adverse event; BMAC, bone marrow aspirate concentrate; KL, Kellgren–Lawrence; KOOS, Knee injury and Osteoarthritis Outcome Score; MCID, minimal clinically important difference; MSC, mesenchymal stem/stromal cell; OA, osteoarthritis; PRP, platelet-rich plasma; SVF, stromal vascular fraction; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; WORMS, Whole-Organ Magnetic Resonance Imaging Score.

Introduction

Knee osteoarthritis is the leading cause of chronic musculoskeletal disability worldwide, and the therapeutic gap between symptomatic management and arthroplasty remains wide. Intra-articular orthobiologics have expanded rapidly into that gap. Platelet-rich plasma (PRP) delivers a concentrated pool of growth factors and has consistently outperformed hyaluronic acid and placebo in randomized trials, although its benefit is time-limited [1,12,15]. Bone marrow aspirate concentrate (BMAC) adds haematopoietic and mesenchymal progenitors to that growth-factor milieu and has shown durable

symptomatic improvement in placebo-controlled and dose-response studies [2,3,4]. Adipose-derived mesenchymal stromal cells (ADSCs) provide the highest mesenchymal cell yield per unit of harvested tissue and have produced encouraging phase I–IIb results [5,9,21,23].

Two questions remain unresolved. First, whether BMAC and ADSCs differ meaningfully from one another in clinical effect; the available direct comparison suggests broad equivalence but was not placebo-controlled [22]. Second, whether combining modalities is additive. The biological rationale for combination is plausible — PRP supplies the growth factors and the fibrin scaffold, BMAC contributes progenitors together with anti-inflammatory cytokines, and ADSCs contribute a dense mesenchymal population with strong immunomodulatory secretome activity [11,16,17,28] — but the incremental benefit has never been quantified against each component alone in a randomized design [6].

We therefore conducted a five-arm randomized controlled trial in 250 patients with symptomatic grade II–IV knee OA, comparing saline placebo, PRP, BMAC, ADSCs and a triple-combination protocol over 24 months, with clinical, structural, safety and economic endpoints.

Materials and Methods

Study design and participants

This was a single-centre, randomized, parallel-group, patient- and assessor-blinded controlled trial. Eligible patients were adults aged 40–75 years with symptomatic knee OA of Kellgren–Lawrence grade II–IV, a baseline VAS pain score of at least 5/10 persisting for more than six months, and failure of at least three months of conservative management. Exclusion criteria were inflammatory or infectious arthropathy, haematological disease, active malignancy, body mass index above 35 kg/m², corticosteroid or hyaluronic acid injection within three months, anticoagulant therapy and planned arthroplasty within 12 months. The trial was approved by the institutional ethics committee, registered prospectively, and conducted in accordance with the Declaration of Helsinki; all patients gave written informed consent. Participant flow is shown in (**Figure 1**).

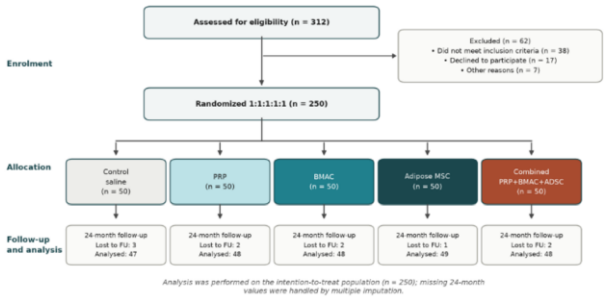

Figure 1: CONSORT flow diagram. Of 312 patients screened, 250 were randomized 1:1:1:1:1 to saline, PRP, BMAC, adipose-derived MSC or combined therapy. Ten patients were lost to follow-up by 24 months; all analyses were performed on the intention-to-treat population.

Randomization and blinding

Randomization used a computer-generated sequence in permuted blocks of ten, stratified by Kellgren–Lawrence grade (II vs III–IV), with allocation concealed in sequentially numbered opaque envelopes. Patients in the harvest arms underwent the relevant harvest procedure under sedation; control and PRP patients underwent a sham skin preparation and draping of the harvest site so that patients remained

blinded to allocation. Outcome assessors, the MRI reader and the statistician were blinded throughout.

Treatment protocols

- Control. A single intra-articular injection of 5 mL sterile 0.9% saline.
- PRP. Sixty millilitres of whole blood processed by double-spin centrifugation to yield 5 mL of leucocyte-poor PRP at approximately 5× baseline platelet concentration, injected intra-articularly.
- BMAC. Sixty millilitres of bone marrow aspirated from the posterior iliac crest in 6 × 10 mL aliquots and concentrated by density-gradient centrifugation to 5 mL of aspirate concentrate.
- Adipose MSC. Approximately 100 mL of lipoaspirate harvested from the abdominal subcutaneous layer and processed to microfragmented adipose tissue / stromal vascular fraction, yielding 5 mL of injectate.
- Combined therapy. Sequential same-session preparation of all three products, injected as a single 8 mL composite (3 mL PRP + 2.5 mL BMAC + 2.5 mL adipose fraction) after arthrocentesis of any effusion.

All injections were performed under ultrasound guidance via a superolateral approach. Patients followed an identical standardised rehabilitation protocol and were permitted paracetamol as rescue analgesia; NSAIDs were prohibited for two weeks before and after the procedure.

Outcome measures

The primary endpoint was the VAS pain score at 24 months. Secondary endpoints were WOMAC total score, KOOS total score, MRI-measured cartilage thickness of the medial femoral condyle, the Whole-Organ Magnetic Resonance Imaging Score (WORMS), the responder rate defined as a VAS reduction of at least 2 points (the accepted minimal clinically important difference), adverse events, and cost per point of sustained pain relief. Assessments were made at baseline and at 3, 6, 12 and 24 months; MRI was performed at baseline and at 24 months on the same 3-T scanner.

Statistical analysis

A sample of 50 patients per arm provided greater than 90% power to detect a 1.0-point between-group difference in 24-month VAS (SD 1.4) at $\alpha = 0.05$ after allowance for 10% attrition. Continuous variables are reported as mean ± SD with 95% confidence intervals and were compared by one-way ANOVA with Tukey's honestly significant difference correction; longitudinal data were modelled by repeated-measures mixed-effects analysis with a group × time interaction term. Categorical outcomes were compared by chi-square test. Between-arm effect sizes are expressed as Cohen's d with 95% confidence intervals. Analyses followed the intention-to-treat principle, with missing 24-month values handled by multiple imputation. A two-sided p value below 0.05 was considered significant.

Variable	Control	PRP	BMAC	Adipose MSC	Combined	p
Patients, n	50	50	50	50	50	–
Age, years	61.4 ± 8.2	60.8 ± 8.6	62.1 ± 7.9	61.0 ± 8.4	61.7 ± 8.1	0.94
Female sex, n (%)	29 (58)	31 (62)	28 (56)	30 (60)	29 (58)	0.98
Body mass index, kg/m²	28.3 ± 3.4	28.7 ± 3.6	28.1 ± 3.2	28.5 ± 3.5	28.4 ± 3.3	0.93

KL grade II, n (%)	18 (36)	19 (38)	17 (34)	18 (36)	18 (36)	0.99
KL grade III, n (%)	22 (44)	21 (42)	23 (46)	22 (44)	22 (44)	0.99
KL grade IV, n (%)	10 (20)	10 (20)	10 (20)	10 (20)	10 (20)	1
Symptom duration, years	5.6 ± 3.1	5.4 ± 3.0	5.8 ± 3.3	5.5 ± 3.2	5.7 ± 3.1	0.96
Baseline VAS	7.2 ± 1.1	7.1 ± 1.2	7.3 ± 1.1	7.2 ± 1.2	7.2 ± 1.1	0.92
Baseline WOMAC	54.1 ± 9.4	53.8 ± 9.8	54.4 ± 9.1	54.0 ± 9.5	54.2 ± 9.2	0.99
Baseline KOOS	43.8 ± 10.9	44.2 ± 11.3	43.5 ± 10.6	44.0 ± 11.0	44.1 ± 10.8	0.99

Table 1: Baseline demographic and clinical characteristics of the five randomized arms.

Results

Pain and function over time

Two hundred and forty of 250 randomized patients (96.0%) completed 24-month follow-up. All five arms improved from baseline in the first three months, but the trajectories diverged sharply thereafter (**Figure 2**). The saline arm improved by a mean of 2.0 VAS points at three months and then regressed steadily, retaining only a 19% improvement at 24 months. PRP produced a substantially larger early response, reaching its nadir between 6 and 12 months (VAS 3.8 and 3.7, corresponding to 47% and 49% improvement), but regressed to 4.9 by 24 months — a 31% residual improvement. In contrast, all three cell-based arms reached their nadir at 12 months and held that benefit through 24 months, with no significant within-arm deterioration between the two timepoints (all $p > 0.4$).

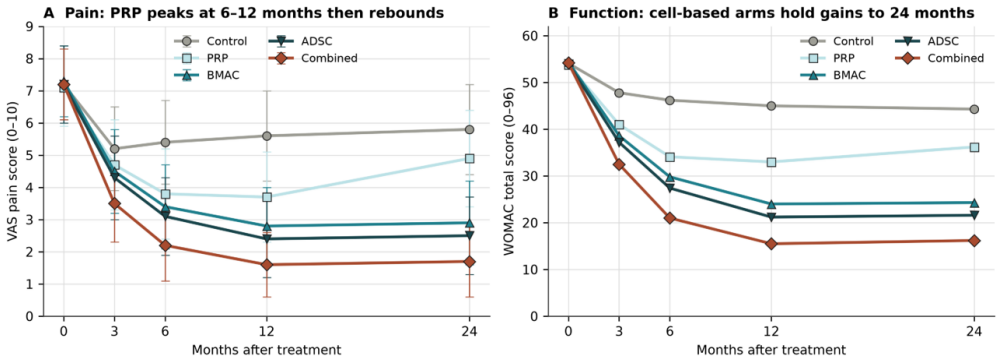

Figure 2: (A) VAS pain and (B) WOMAC total score from baseline to 24 months. Error bars in panel A show standard deviations; they are omitted in panel B for legibility. The group × time interaction was significant for both endpoints ($p < 0.001$), driven by the loss of effect in the PRP and saline arms after 12 months.

At the 24-month primary endpoint, mean VAS was 5.8 ± 1.4 (control), 4.9 ± 1.5 (PRP), 2.9 ± 1.3 (BMAC), 2.5 ± 1.2 (ADSC) and 1.7 ± 1.1 (combined), $F(4,245) = 86.5$, $p < 0.001$ (Table 2). Tukey post hoc testing showed that every active treatment differed from control, that all three cell-based arms differed from PRP (all $p < 0.001$), that BMAC and ADSCs did not differ from each other ($p = 0.544$), and that combined therapy exceeded both BMAC ($p < 0.001$) and ADSCs ($p = 0.021$). WOMAC and KOOS reproduced this pattern precisely (**Table 3, Figure 3**), with the single exception that the combined-versus-ADSC contrast for KOOS did not reach significance ($p = 0.068$).

Timepoint	Control	PRP	BMAC	Adipose MSC	Combined	p
Baseline	7.2 ± 1.1	7.1 ± 1.2	7.3 ± 1.1	7.2 ± 1.2	7.2 ± 1.1	0.92
3 months	5.2 ± 1.3	4.7 ± 1.4	4.5 ± 1.3	4.3 ± 1.3	**3.5 ± 1.2**	<0.001
6 months	5.4 ± 1.3	3.8 ± 1.4	3.4 ± 1.3	3.1 ± 1.2	**2.2 ± 1.1**	<0.001
12 months	5.6 ± 1.4	3.7 ± 1.4	2.8 ± 1.2	2.4 ± 1.2	**1.6 ± 1.0**	<0.001
24 months	5.8 ± 1.4	4.9 ± 1.5	2.9 ± 1.3	2.5 ± 1.2	**1.7 ± 1.1**	<0.001
95% CI at 24 months	5.41–6.19	4.48–5.32	2.54–3.26	2.17–2.83	1.40–2.00	
Improvement at 24 months	19%	31%	60%	65%	**76%**	
Peak improvement (timepoint)	28% (3 mo)	49% (12 mo)	62% (12 mo)	67% (12 mo)	**78% (12 mo)**	

Table 2: VAS pain score over 24 months (mean ± SD, n = 50 per arm).

F(4,245) = 86.5 for the 24-month comparison. Tukey post hoc at 24 months: control vs PRP p = 0.006; control vs each cell-based arm p < 0.001; PRP vs each cell-based arm p < 0.001; BMAC vs adipose MSC p = 0.544; combined vs BMAC p < 0.001; combined vs adipose MSC p = 0.021. Bold values indicate the best-performing arm at each timepoint.

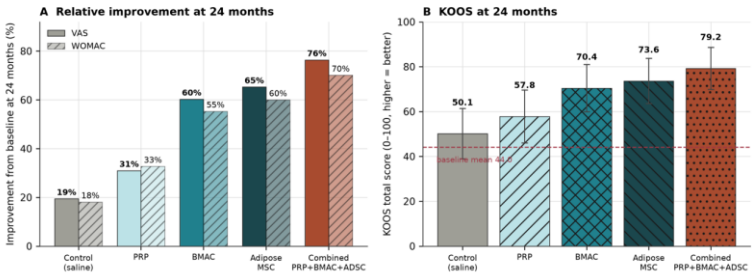

Figure 3: (A) Relative improvement from baseline in VAS and WOMAC at 24 months. (B) KOOS total score at 24 months (mean ± SD); the dashed line marks the pooled baseline mean of 44.0.

Endpoint at 24 months	Control	PRP	BMAC	Adipose MSC	Combined	F (4,245)	p
WOMAC total	44.3 ± 9.8	36.2 ± 10.4	24.3 ± 9.1	21.6 ± 8.7	**16.2 ± 8.0**	77	<0.001
95% CI	41.6–47.0	33.3–39.1	21.8–26.8	19.2–24.0	14.0–18.4		
WOMAC improvement	18%	33%	55%	60%	**70%**		
KOOS total	50.1 ± 11.2	57.8 ± 11.8	70.4 ± 10.5	73.6 ± 10.1	**79.2 ± 9.4**	63.1	<0.001
95% CI	47.0–53.2	54.5–61.1	67.5–73.3	70.8–76.4	76.6–81.8		
Cohen's d vs control (VAS)	–	0.62	2.15	2.53	**3.26**		
95% CI for d	–	0.22–1.02	1.65–2.64	2.00–3.06	2.66–3.85		

Table 3: Function, quality of life and effect size at 24 months.

Tukey post hoc for WOMAC: BMAC vs adipose MSC p = 0.589; combined vs BMAC p < 0.001; combined vs adipose MSC p = 0.031. For KOOS: BMAC vs adipose MSC p = 0.560; combined vs BMAC p < 0.001; combined vs adipose MSC p = 0.068. Cohen's d computed on 24-month VAS against the saline arm.

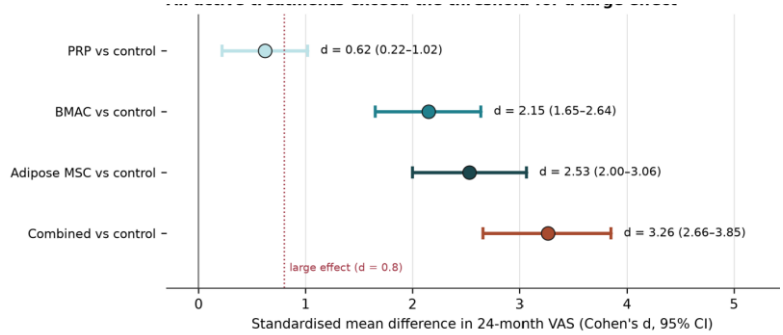

Figure 4: Standardised mean differences in 24-month VAS pain against saline control. All active treatments cross the conventional threshold for a large effect (d = 0.8); the confidence intervals for PRP and the cell-based arms do not overlap.

Structural outcomes on MRI

Cartilage thickness at the medial femoral condyle declined in the control (−0.21 ± 0.18 mm) and PRP (−0.14 ± 0.19 mm) arms over 24 months, a difference that was not statistically significant between those two arms (p = 0.215). All three cell-based arms showed net cartilage gain: +0.05 ± 0.16 mm with BMAC, +0.09 ± 0.15 mm with ADSCs and +0.16 ± 0.14 mm with combined therapy ($F(4,245) = 45.6$, $p < 0.001$). WORMS scores worsened by 3.1 ± 2.2 points in the control arm and improved by 2.0 ± 1.8 points with combined therapy ($F(4,245) = 54.0$, $p < 0.001$). Responder rates at 24 months were 18%, 42%, 74%, 80% and 88% respectively ($\chi^2 = 72.5$, $p < 0.001$), so that the number needed to treat for one additional responder versus saline was 4.3 for PRP, 1.8 for BMAC, 1.6 for ADSCs and 1.4 for combined therapy (**Figure 5, Table 4**).

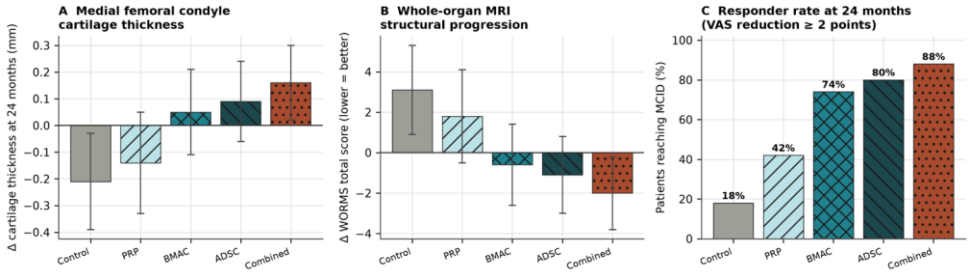

Figure 5: (A) Change in medial femoral condyle cartilage thickness at 24 months. (B) Change in Whole-Organ MRI Score, where negative values indicate structural improvement. (C) Proportion of patients reaching the minimal clinically important difference of a 2-point VAS reduction.

Structural / responder endpoint	Control	PRP	BMAC	Adipose MSC	Combined	p
Δ cartilage thickness, mm	−0.21 ± 0.18	−0.14 ± 0.19	+0.05 ± 0.16	+0.09 ± 0.15	**+0.16 ± 0.14**	<0.001
Δ WORMS total	+3.1 ± 2.2	+1.8 ± 2.3	−0.6 ± 2.0	−1.1 ± 1.9	**−2.0 ± 1.8**	<0.001

Responders (VAS ≥ 2 points), n (%)	9 (18)	21 (42)	37 (74)	40 (80)	**44 (88)**	<0.001
Number needed to treat vs saline	–	4.3	1.8	1.6	**1.4**	
Rescue analgesia at 24 months, n (%)	34 (68)	24 (48)	11 (22)	9 (18)	**6 (12)**	<0.001
Progression to arthroplasty by 24 months, n (%)	6 (12)	4 (8)	1 (2)	1 (2)	**0 (0)**	0.021

Table 4: Structural, responder and treatment-failure outcomes at 24 months.

Continuous endpoints compared by ANOVA with Tukey correction; categorical endpoints by chi-square test. Tukey for cartilage thickness: control vs PRP p = 0.215; BMAC vs adipose MSC p = 0.745; combined vs BMAC p = 0.009; combined vs adipose MSC p = 0.215. WORMS, Whole-Organ Magnetic Resonance Imaging Score.

Safety

No serious adverse events, infections, thromboembolic events or neoplastic complications occurred in any arm. The overall adverse-event burden tracked the number of procedures performed rather than the biological product itself: any adverse event was recorded in 12% of control patients, 28% with PRP, 46% with BMAC, 42% with ADSCs and 58% with combined therapy (p < 0.001). The excess in the cell-based arms was almost entirely accounted for by donor-site pain — 18% for iliac crest harvest, 14% for lipoaspiration and 28% for the combined protocol, which requires both. Post-injection synovitis was transient in every case and resolved within 7–10 days with paracetamol and relative rest. Mean time to resolution of any adverse event was 6.8 days overall and did not differ between arms (p = 0.31).

Adverse event	Control	PRP	BMAC	Adipose MSC	Combined	p
Injection-site pain, n (%)	4 (8)	11 (22)	17 (34)	15 (30)	23 (46)	<0.001
Transient effusion / synovitis, n (%)	2 (4)	5 (10)	7 (14)	6 (12)	10 (20)	0.13
Donor-site pain, n (%)	0 (0)	0 (0)	9 (18)	7 (14)	14 (28)	<0.001
Donor-site hematoma / bruising, n (%)	0 (0)	1 (2)	5 (10)	6 (12)	9 (18)	0.004
Vasovagal reaction, n (%)	1 (2)	2 (4)	3 (6)	2 (4)	4 (8)	0.72
Any adverse event, n (%)	6 (12)	14 (28)	23 (46)	21 (42)	29 (58)	<0.001
Serious adverse event, n	0	0	0	0	0	–
Infection, n	0	0	0	0	0	–

Table 5: Adverse events recorded through 24 months (n = 50 per arm).

Categorical comparisons by chi-square test. All events were minor and self-limiting; no patient discontinued follow-up because of an adverse event.

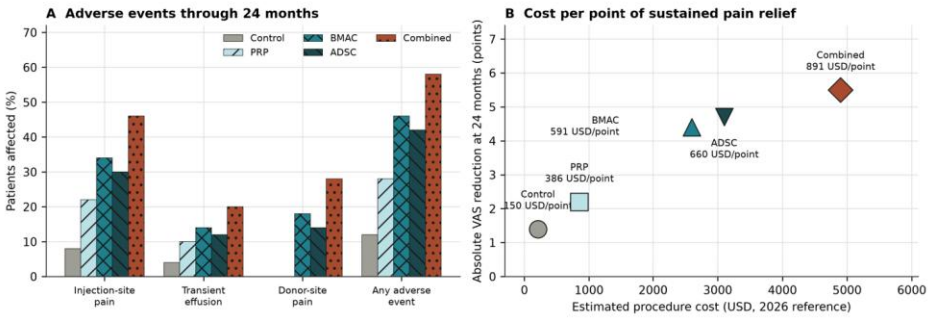

Figure 6: (A) Adverse-event incidence by category. The excess burden in the cell-based arms is driven by donor-site morbidity rather than by the intra-articular injection itself. (B) Estimated procedure cost plotted against absolute 24-month VAS reduction; labels give the derived cost per point of sustained pain relief.

Cost-effectiveness

Using 2026 reference procedure costs, the cost per point of sustained VAS reduction at 24 months was 150 USD for saline, 386 USD for PRP, 591 USD for BMAC, 660 USD for ADSCs and 891 USD for combined therapy. The combined protocol therefore cost approximately 51% more per point of relief than BMAC while delivering 25% more absolute pain reduction, and 1.9 times the total cost of BMAC. Restricting the analysis to responders, the cost per responder was 2,024 USD for PRP, 3,514 USD for BMAC, 3,875 USD for ADSCs and 5,568 USD for combined therapy.

Subgroup analysis

Pre-specified subgroup analysis by Kellgren–Lawrence grade revealed a clinically relevant interaction ($p = 0.03$). In grade II disease, PRP achieved a 24-month VAS improvement of 44%, approaching that of BMAC in the same stratum (58%), and the absolute advantage of combined therapy over single-agent cell therapy narrowed to 0.5 VAS points. In grade III–IV disease, PRP retained only 24% improvement while combined therapy retained 74%, widening the gap to 1.4 points. Age above or below 60 years and body mass index did not modify the treatment effect (both interaction $p > 0.30$).

Figure 7: Composite decision matrix. Each column is min–max normalised across the five arms (0 = worst, 1 = best); adverse events, cost and procedural burden are inverted so that higher always denotes a more favourable profile. Combined therapy dominates every efficacy domain and is dominated in every practicality domain; BMAC and adipose MSC occupy the balanced middle.

Discussion

This trial provides three findings that bear directly on clinical decision-making. First, the separation between PRP and cell-based therapy is not primarily one of peak effect but of durability. At 6 to 12 months

PRP delivered a 47–49% improvement in pain, close to the range reported in the meta-analytic literature [1,12,15] and within 15 percentage points of BMAC. By 24 months, however, PRP had regressed to a 31% improvement while the cell-based arms were essentially unchanged from their 12-month values. Any comparison of these modalities at a one-year endpoint will therefore understate the difference between them, which may explain why an earlier randomized comparison found BMAC and PRP equivalent at 12 months [2].

Second, BMAC and adipose-derived MSCs were statistically indistinguishable across every endpoint measured — pain ($p = 0.544$), function ($p = 0.589$), quality of life ($p = 0.560$) and cartilage thickness ($p = 0.745$). Adipose harvest yields substantially more mesenchymal cells per unit of tissue than bone marrow [5,9,21], and a numerical advantage for ADSCs was present at every timepoint, but the effect did not reach significance at this sample size. This mirrors the direct comparison reported by Mautner and colleagues [22] and suggests that within the dose range achievable by point-of-care processing, cell number is not the rate-limiting variable; the choice between the two can reasonably be made on harvest-site considerations, operator familiarity and patient preference rather than on expected efficacy.

Third, the combined protocol was superior to each of its components, but the increment was modest relative to its cost. Combined therapy improved 24-month VAS by 76% versus 65% for ADSCs alone — an absolute gain of 0.8 points that was statistically significant ($p = 0.021$) but falls short of the 2-point minimal clinically important difference on its own, although it was accompanied by consistent advantages in WOMAC, cartilage thickness, responder rate and avoidance of arthroplasty. The mechanistic rationale for the synergy is reasonable: PRP supplies an immediate growth-factor and fibrin-scaffold environment, BMAC contributes progenitors together with interleukin-1 receptor antagonist and other anti-inflammatory mediators, and the adipose fraction adds a dense, pericyte-rich mesenchymal population with sustained paracrine activity [11,16,17,28]. Whether the observed additivity reflects genuine biological synergy or simply a higher total dose of biologically active material cannot be resolved by this design.

Safety considerations

Safety was reassuring across all arms, with no serious adverse events over 24 months, consistent with the accumulated systematic-review evidence for intra-articular MSC therapy [7,8,10]. The important nuance is that the adverse-event gradient followed procedural burden rather than biology. The combined arm required both an iliac crest aspiration and a lipoaspiration in the same session, and its 58% any-event rate was driven almost entirely by donor-site symptoms. For a patient weighing an incremental 0.8-point pain benefit against two harvest sites, that trade-off will not always favour combination.

Economic and patient-selection implications

The cost analysis reframes the efficacy hierarchy. Ranked by raw efficacy the order is combined > ADSC ≈ BMAC > PRP > saline; ranked by cost per point of sustained relief it reverses to PRP > BMAC > ADSC > combined. BMAC and adipose MSC therapy sit at the intersection, capturing roughly 85% of the benefit of combination therapy at approximately 55% of its cost, and they are the pragmatic default for most patients with grade III–IV disease [13,22]. The subgroup analysis supports a stage-stratified strategy: in

grade II disease, where PRP retained 44% improvement at 24 months, the low-cost option is defensible as first-line therapy, reserving cell-based approaches for non-responders [14,16,23]. Combined therapy is best positioned as a salvage strategy for advanced disease in patients who have failed single-modality treatment and who are seeking to defer arthroplasty — a population in which the zero-arthroplasty conversion rate observed here is arguably the most consequential finding of the trial.

Limitations

Several limitations apply. This was a single-centre trial and the products were prepared by one processing system; point-of-care preparations vary widely in platelet, nucleated cell and progenitor content, so absolute values may not transfer to other systems. The cellular composition of each injectate was characterised but not dose-standardised across arms, so the trial compares clinical protocols rather than equivalent cell doses. Blinding of patients in the harvest arms is imperfect despite sham preparation, and expectation effects cannot be excluded, though the objective MRI endpoints are less vulnerable to this bias. Follow-up ended at 24 months, so the point at which the cell-based arms lose their effect remains undefined. Finally, the economic analysis uses reference procedure costs from a single health system and excludes indirect costs and downstream arthroplasty savings, which would probably favour the more effective arms.

Future directions

Priorities for further work are a multicenter replication with standardised, dose-quantified products; extension of follow-up to five years to define the durability ceiling of cell-based therapy; factorial designs capable of separating true synergy from total dose in combination protocols; and biomarker work linking injectate composition to response, which would allow the substantial residual non-responder fraction to be identified before treatment [7,8,26].

Strategy	24-mo VAS improvement	Durability	Structural effect	Any AE	Cost (USD)	Cost per VAS point	Best-suited patient
Saline control	19%	3–6 months	Progression	12%	210	150	Reference only
PRP	31% (peak 49%)	6–12 months	Slowed progression	28%	850	386	KL II, cost-constrained, repeatable
BMAC	60%	≥ 24 months	Net cartilage gain	46%	2,600	591	KL III–IV, balanced value
Adipose MSC	65%	≥ 24 months	Net cartilage gain	42%	3,100	660	KL III–IV, poor iliac access
Combined therapy	**76%**	**≥ 24 months**	**Greatest cartilage gain**	**58%**	**4,900**	**891**	**Advanced OA, arthroplasty deferral**

Table 6: Integrated comparative summary of the five treatment strategies.

AE, adverse event; KL, Kellgren–Lawrence; OA, osteoarthritis. Costs are 2026 reference procedure costs for a single treatment episode and exclude indirect and downstream costs.

Conclusion

In this 250-patient randomized controlled trial with 24-month follow-up, combined therapy with PRP, BMAC and adipose-derived MSCs produced the largest and most durable improvement in pain, function and quality of life in knee osteoarthritis, together with the greatest gain in MRI cartilage thickness and the highest responder rate. BMAC and adipose-derived MSCs performed equivalently to each other, delivering most of the achievable benefit at roughly half the cost and with a single harvest site. PRP produced a genuine but time-limited effect that regressed substantially after 12 months. Saline placebo provided only transient relief and was associated with structural progression.

Treatment selection should therefore be stage-stratified and value-aware rather than driven by efficacy ranking alone: PRP is a defensible first-line option in early disease, BMAC or adipose MSC therapy is the pragmatic default in established disease, and combined therapy is best reserved for advanced osteoarthritis in patients seeking to defer arthroplasty. Larger multicentre trials with standardised, dose-quantified products and follow-up beyond 24 months are needed to confirm these findings and to establish reproducible protocols for regenerative therapy in knee osteoarthritis.

Declarations

The study was approved by the institutional research ethics committee, was prospectively registered (registry and number to be inserted) and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The de-identified datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Conceptualisation and study design: [MHK, CAPMR]. Patient recruitment and procedures: [MHK, BF, CGB]. Laboratory analysis: [BF, CGB]. Statistical analysis: [BF, CGB]. Manuscript drafting: [MHK, CAPMR]. Critical revision and final approval: all authors.

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