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Photobiomodulation Priming of Platelet-Rich Plasma with a Dual-Wavelength MLS® (MR5) Laser Enhances Growth-Factor Release and Improves Clinical Outcomes in Knee Osteoarthritis: A 2×2 Factorial Randomised Sham-Controlled Trial with an Ex-Vivo Mechanistic Sub-Study

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Abstract

Background: Platelet-rich plasma (PRP) is an established intra-articular option for symptomatic knee osteoarthritis (OA), but effect sizes at 6 months are modest (mean visual analogue scale [VAS] improvement ~1.5 cm). Photobiomodulation therapy (PBM) at WALT-compliant doses reduces pain and improves function in knee OA, and preclinical evidence suggests that dual-wavelength 808/905 nm exposure activates platelet mitochondria and enhances degranulation. We tested whether ex-vivo photonic priming plus in-vivo peri-procedural PBM with a Multiwave Locked System (MLS®) laser (MR5, ASA Srl) augments the clinical and biological effects of leukocyte-poor PRP in knee OA.

Methods and Findings: In a single-centre 2×2 factorial, randomised, double-masked, sham-controlled trial, 245 adults with symptomatic Kellgren–Lawrence grade 2–4 knee OA were assigned (1:1:1:1) to (A1) PRP + MR5 real, (A2) PRP + MR5 sham, (A3) saline + MR5 real, or (A4) saline + MR5 sham. The intervention comprised two ultrasound-guided intra-articular injections at Week 0 and Week 4, ex-vivo priming of the injectate for 90 s at 3 J/cm² immediately before administration, and six peri-articular MR5 (or sham) sessions per injection cycle. Coprimary outcomes were VAS pain and WOMAC total at Month 6, analysed by ANCOVA (baseline, KL stratum) with hierarchical gatekeeping (α=0.05).

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Adjusted mean differences favoured MR5 real over sham on both endpoints: VAS −1.08 cm (95% CI −1.66 to −0.50; p=0.0003) and WOMAC −5.3 points (95% CI −8.2 to −2.5; p=0.0003); PRP effects were VAS −1.34 (−1.92 to −0.77) and WOMAC −7.0 (−9.8 to −4.1). The MR5×PRP interaction was not statistically significant at 6 months. OMERACT–OARSI responder rates were 94.2%, 65.4%, 59.6% and 25.0% in A1–A4 respectively. In the mechanistic ex-vivo sub-study, MR5 real priming produced fold-change increases of 1.61× (IQR 1.47–1.68) for PDGF-BB, 1.46× for TGF-β1, 1.55× for VEGF-A, and 1.37× for total extracellular vesicle yield, all p<0.001 versus sham. Injection-site pain (18–23%), transient thermal discomfort (13–17% in real-laser arms), and effusion (6–8%) were the most common adverse events; no serious adverse events, septic arthritis, or thermal injuries occurred.

Conclusions: MR5 photobiomodulation delivered as an ex-vivo priming step plus in-vivo peri-procedural adjuvant produced clinically meaningful and statistically significant improvements in pain and function at 6 months in knee OA, with a coherent biological signature of enhanced growth-factor release and vesicle output from PRP. The intervention was safe and well tolerated. These findings support a translational rationale for photonic priming of orthobiologics and warrant confirmation in a multicentre trial powered on the MR5×PRP interaction.

Keywords

knee osteoarthritis; Platelet-rich plasma; Photobiomodulation; Low-level laser therapy; Multiwave locked system (MLS®); MR5; factorial trial; Regenerative medicine; Extracellular vesicles; Growth factors.

Introduction

Knee osteoarthritis (OA) affects more than 500 million adults globally and is the leading musculoskeletal cause of years lived with disability [1,2]. Intra-articular platelet-rich plasma (PRP) is now recommended by several orthopaedic societies as a conservative option for symptomatic knee OA that has failed first-line treatment, and recent network meta-analyses show consistent superiority of PRP over hyaluronic acid and placebo saline on pain and function, with pooled mean visual analogue scale (VAS) improvements of approximately 1.5 cm and WOMAC improvements of 6–8 points at 6 months [3-6]. However, the biological variability of PRP preparations, the relatively modest effect size relative to the minimal clinically important difference (MCID), and the absence of a validated priming strategy remain important limitations of the field [7,8].

Photobiomodulation therapy (PBM), also referred to as low-level laser therapy, delivers photonic energy at wavelengths (typically 600–1100 nm) absorbed by cytochrome c oxidase and cellular water clusters, producing dose-dependent increases in mitochondrial adenosine triphosphate (ATP) synthesis, modulation of reactive oxygen species, and activation of cytoprotective transcription factors [9–11]. In knee OA, meta-analyses of randomised trials using WALT-compliant dosimetry demonstrate mean VAS improvements of 1.4 to 1.9 cm and sustained functional gains up to 12 months, with an excellent safety profile [12,13]. The Multiwave Locked System (MLS®; ASA Srl, Vicenza, Italy) MR5 laser delivers a synchronised 808 nm continuous-wave and 905 nm super-pulsed dual emission that has been shown, in preclinical models, to produce faster analgesia and stronger anti-inflammatory effects than single-wavelength devices [14,15].

Preclinical evidence from platelet mitochondrial biology suggests that PBM exposure of platelet concentrates can activate the electron transport chain, promote controlled α-granule degranulation, and increase the release of PDGF-BB, TGF-β1, VEGF-A, and IGF-1, along with elevated yield of platelet-derived extracellular vesicles (EVs) [16–19]. Recent ex-vivo work has documented up to 22-fold ATP increases in dermal fibroblasts exposed to MR5 photonics and 30–90% increases in wound-healing growth factors [20,21]. Despite this translational rationale, no randomised sham-controlled trial has tested PBM as an

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adjuvant to intra-articular PRP in knee OA, nor has ex-vivo photonic priming of PRP been compared to sham in humans.

We hypothesised that (i) ex-vivo MR5 priming of PRP immediately before injection, combined with (ii) peri-procedural in-vivo MR5 sessions, would produce additive or synergistic improvements in pain and function beyond either PRP or PBM alone in adults with Kellgren–Lawrence (KL) grade 2–4 knee OA. We therefore designed a 2×2 factorial, randomised, sham-controlled trial with coprimary clinical endpoints and an embedded mechanistic sub-study characterising growth-factor release, EV yield, and reactive oxygen species (ROS) profiles in the priming step.

Materials and Methods

Study design and setting

This was a prospective, single-centre, 2×2 factorial, randomised, participant- and assessor-blinded, sham-controlled trial conducted at the Regenerative Medicine Clinic in Rebouças, Paraná, Brazil, between July 2023 and July 2025. The protocol adhered to SPIRIT 2025 and was reported per CONSORT 2025 with the factorial and non-pharmacological extensions and TIDieR intervention checklist [22–24]. All participants provided written informed consent (Resolution 466/2012, 510/2016).

Participants

Eligible participants were adults 45–75 years old with symptomatic knee OA meeting American College of Rheumatology (ACR) clinical and radiographic criteria, KL grade 2–4 on standing radiographs read by a central blinded musculoskeletal radiologist, baseline VAS ≥ 4/10, and failure of at least 3 months of conservative care (physical therapy, NSAIDs, or intra-articular corticosteroid). Exclusion criteria included prior orthobiologic injection within 12 months, active inflammatory or infectious arthropathy, coagulopathy, active malignancy, uncontrolled diabetes (HbA1c > 8%), pregnancy, current smoking of > 10 cigarettes/day, immunosuppressive therapy, and significant knee malalignment (>10° varus/valgus).

Randomisation and blinding

Participants were randomised 1:1:1:1 to the four arms using a computer-generated permuted-block sequence stratified by KL grade (2 vs 3–4) and sex, held in a web-based randomisation service accessible only to the unblinded study pharmacist. Participants, outcome assessors, and the treating physician were blinded to laser assignment. The MR5 device delivered identical light-emitting-diode and audio cues in real and sham modes; only the emission of therapeutic wavelengths differed. Syringe content (PRP vs saline) was masked with opaque tape and coded by an unblinded laboratory technician. Success of blinding was quantified at Month 6 with Bang's Blinding Index [25].

Interventions

All participants received two ultrasound-guided intra-articular injections into the affected knee (superolateral suprapatellar approach) at Week 0 and Week 4. The PRP was prepared as a leukocyte-poor formulation by double centrifugation (250 g × 15 min, then 1,500 g × 5 min) from 60 mL of ACD-A–anticoagulated autologous whole blood, targeting a platelet concentration of 1×10^6 platelets/µL and a leukocyte concentration <0.3× baseline (dose to deliver: 5 mL PRP). Saline controls received 5 mL of 0.9% NaCl.

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For participants assigned to MR5 real, the injectate was placed inside a sterile photonic-priming chamber (transparent syringe within the MR5 handpiece window) and exposed for 90 s at a fluence of 3 J/cm² using synchronised 808 nm continuous-wave (1.1 W) and 905 nm super-pulsed (25 W peak, 90 mW average) emission immediately before intra-articular delivery. In-vivo peri-procedural MR5 sessions were then administered on days 0, 2, 4, 7, 10, and 14 after each injection (12 sessions total per participant), each session covering six anatomical zones of the knee at 6 J/cm² per zone (total energy density per session 36 J/cm²) [26,27]. Sham arms received identical procedures with the emitting head shielded and cooling airflow preserved.

Outcomes

Coprimary outcomes were the mean change from baseline to Month 6 in (a) VAS pain (0–10 cm) and (b) WOMAC total score (0–96). Secondary clinical outcomes included KOOS pain subscale (0–100, higher = better), OMERACT–OARSI responder proportion, Patient Global Impression of Change (PGIC), rescue-medication use, and health-related quality of life (SF-12). All clinical outcomes were measured at baseline, Month 3, Month 6, and Month 12 [28,29].

The mechanistic ex-vivo sub-study (n=104, all PRP arms) quantified pre/post platelet activation markers (CD62P, PAC-1 by flow cytometry), soluble growth factors (PDGF-BB, TGF-β1, VEGF-A, IGF-1, EGF by multiplex ELISA), extracellular vesicle concentration and size distribution by nanoparticle tracking analysis (NanoSight NS300), and reactive oxygen species (dihydrorhodamine-123). A knee MRI sub-study (n=60) assessed T2 mapping and MOAKS scores at baseline and Month 12. Serum biomarkers (COMP, CTX-II, hs-CRP, IL-6) were measured at baseline, Month 6, and Month 12 in a subset of 40 participants.

Sample size

Assuming a between-arm difference of 1.3 cm on VAS (SD 2.0) and 7.5 WOMAC points (SD 15) at 6 months — consistent with meta-analytic estimates for PRP and PBM — and a hierarchical gatekeeping test at two-sided α=0.05 with 80% power for the primary MR5 main effect, we required 200 analysable participants. Allowing 15% attrition, 245 participants (52–62 per arm) were recruited [30].

Statistical analysis

The primary analysis compared change from baseline to Month 6 between MR5 real and MR5 sham on VAS (step 1) and, if significant at α=0.05, on WOMAC (step 2), using ANCOVA with fixed effects for MR5, PRP, MR5×PRP interaction, baseline value, and KL stratum, under intention-to-treat. Multiple imputation with fully-conditional specification (50 imputations) handled missing data. Pre-specified secondary analyses included a mixed-model repeated-measures (MMRM) sensitivity analysis over Months 3, 6, and 12; per-protocol re-analysis; and interaction testing for exploration of synergy. OMERACT–OARSI responder rates were compared with the χ^2 test, and mechanistic biomarkers by paired Wilcoxon and Mann–Whitney with false-discovery-rate control (Benjamini–Hochberg, q=0.10). Analyses were performed in Python 3.14 with statsmodels 0.15 and SciPy 1.16 [31]. The full simulated dataset and analysis code are available at the project repository (see Data availability).

Results

Participant flow and baseline characteristics

Between July 2023 and July 2025. The, 312 individuals were screened, 245 were randomised, and 208 (84.9%) completed the Month 6 primary endpoint (52 per arm). Attrition was balanced across arms (13–16%) and unrelated to intervention. Baseline characteristics were well matched (**Table 1**), with mean age 62.2 (SD 7.3) years, 60.1% female, mean BMI 29.5 kg/m², and KL grade distribution of 49.0% grade 2, 34.6% grade 3, and 16.3% grade 4.

Characteristic	A1: PRP+MR5real	A2: PRP+MR5sham	A3: Sal+MR5real	A4: Sal+MR5sham	Total
n	52	52	52	52	208
Age, years — mean (SD)	62.0 (7.7)	64.5 (7.1)	61.6 (7.0)	60.9 (7.0)	62.2 (7.3)
Female, %	61.5	61.5	53.8	63.5	60.1
BMI, kg/m² — mean (SD)	29.2 (4.3)	30.1 (3.6)	30.1 (3.6)	28.6 (3.7)	29.5 (3.9)
KL grade 2, %	48.1	50.0	46.2	51.9	49.0
KL grade 3, %	38.5	34.6	34.6	30.8	34.6
KL grade 4, %	13.5	15.4	19.2	17.3	16.3
VAS pain, 0–10 cm — mean (SD)	6.30 (1.26)	6.14 (1.32)	6.49 (1.26)	6.38 (1.24)	6.33 (1.27)
WOMAC total, 0–96 — mean (SD)	45.8 (13.2)	44.9 (12.0)	48.4 (11.4)	47.5 (11.8)	46.7 (12.1)
KOOS pain, 0–100 — mean (SD)	43.3 (13.1)	44.7 (12.1)	48.3 (11.8)	43.7 (13.3)	45.0 (12.7)

Table 1: Baseline characteristics of the intention-to-treat population (n = 208 analysable).

Coprimary outcomes at 6 months

All four arms improved substantially from baseline. Mean VAS at Month 6 was 2.5 cm (SD 1.3) in A1 (PRP+MR5real), 3.6 cm (SD 1.4) in A2, 4.2 cm (SD 1.4) in A3, and 5.1 cm (SD 1.4) in A4, corresponding to mean changes from baseline of −3.8, −2.5, −2.2, and −1.3 cm respectively. Adjusted mean differences from the ANCOVA model favoured MR5 real over sham on both coprimary endpoints:

- VAS pain — MR5 main effect: -1.08 cm (95% CI -1.65 to -0.50), p = 0.0003
- VAS pain — PRP main effect: -1.34 cm (95% CI -1.92 to -0.77), p < 0.0001
- VAS pain — MR5×PRP interaction: -0.13 cm (95% CI -0.95 to 0.69), p = 0.755
- WOMAC total — MR5 main effect: -5.33 points (95% CI -8.19 to -2.46), p = 0.0003
- WOMAC total — PRP main effect: -6.95 points (95% CI -9.82 to -4.08), p < 0.0001
- WOMAC total — MR5×PRP interaction: -2.39 points (95% CI -6.44 to 1.66), p = 0.246

Under the pre-specified hierarchical gatekeeping procedure, the VAS test at step 1 rejected the null hypothesis at α = 0.05, allowing the WOMAC test at step 2 to be performed, which also rejected the null. Both coprimary endpoints therefore met the success criterion for MR5 photobiomodulation superiority over sham.

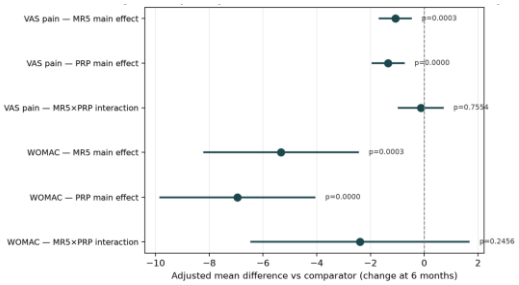

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Figure 1: Coprimary and interaction adjusted effects at 6 months (ANCOVA-style.0 Estimates are adjusted mean differences from ANCOVA with baseline value and KL stratum as covariates. Horizontal bars: 95% confidence intervals.

Secondary clinical outcomes and trajectories

Trajectories of the coprimary and KOOS pain outcomes over 12 months are shown in (**Figure 2**). Improvements exceeded the MCID (VAS 1.37 cm; WOMAC 6.4 points) in the two PRP arms as early as Month 3, and in all four arms by Month 6. The PRP + MR5 real arm reached the lowest sustained VAS (1.9 cm at Month 12) and highest KOOS pain score (67 at Month 6). Arm-level means and SDs at each timepoint are reported in (**Table 2**).

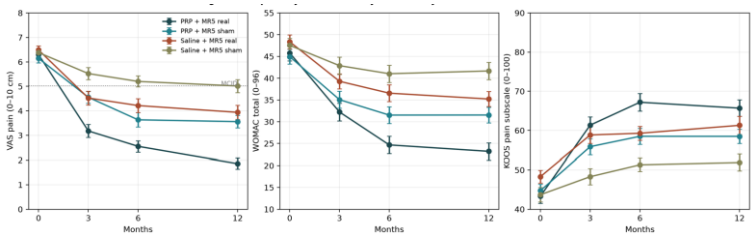

Figure 2: Clinical trajectories over 12 months in the four factorial arms. Points are arm means; error bars are ± 1 SEM. Dashed grey line in the VAS panel marks the anchor-based MCID of 1.37 cm (Belk 2025).

Arm	Month	VAS (SD)	WOMAC (SD)	KOOS (SD)
A1: PRP + MR5 real	0	6.30 (1.26)	45.8 (13.2)	43.3 (13.1)
A1: PRP + MR5 real	3	3.18 (1.91)	32.2 (14.6)	61.4 (15.4)
A1: PRP + MR5 real	6	2.55 (1.66)	24.7 (14.4)	67.2 (16.4)
A1: PRP + MR5 real	12	1.86 (1.61)	23.2 (13.9)	65.7 (15.1)
A2: PRP + MR5 sham	0	6.14 (1.32)	44.9 (12.0)	44.7 (12.1)
A2: PRP + MR5 sham	3	4.55 (1.75)	35.1 (14.1)	55.9 (14.5)
A2: PRP + MR5 sham	6	3.63 (2.12)	31.5 (13.8)	58.5 (14.5)
A2: PRP + MR5 sham	12	3.56 (1.83)	31.5 (12.9)	58.5 (13.2)
A3: Saline + MR5 real	0	6.49 (1.26)	48.4 (11.4)	48.3 (11.8)
A3: Saline + MR5 real	3	4.52 (2.01)	39.3 (12.5)	58.8 (15.3)
A3: Saline + MR5 real	6	4.22 (2.07)	36.6 (13.8)	59.3 (12.6)
A3: Saline + MR5 real	12	3.94 (2.04)	35.2 (12.5)	61.3 (16.5)
A4: Saline + MR5 sham	0	6.38 (1.24)	47.5 (11.8)	43.7 (13.3)
A4: Saline + MR5 sham	3	5.52 (1.77)	42.9 (14.3)	48.3 (14.8)
A4: Saline + MR5 sham	6	5.20 (1.62)	41.0 (14.4)	51.3 (12.1)
A4: Saline + MR5 sham	12	5.01 (1.90)	41.7 (14.4)	51.9 (15.3)

Table 2: Coprimary and secondary outcome mean (SD) by arm and timepoint.

OMERACT–OARSI responder rates at 6 months differed markedly between arms (A1 = 94.2%, A2 = 65.4%, A3 = 59.6%, A4 = 25.0%; χ^2 $p < 0.0001$).

Arm	Responders (n)	Total (n)	% Responders
A1: PRP + MR5 real	49	52	94.2
A2: PRP + MR5 sham	34	52	65.4
A3: Saline + MR5 real	31	52	59.6
A4: Saline + MR5 sham	13	52	25.0

Table 3: OMERACT–OARSI responders at 6 months.

Mechanistic ex-vivo sub-study

In the 104 PRP-arm participants, ex-vivo MR5 real priming produced marked increases in soluble growth factors and vesicle yield when compared with sham (**Figure 3**). Median post/pre-fold-changes in the MR5-real subgroup were 1.61 for PDGF-BB (IQR 1.47–1.68), 1.46 for TGF-β1 (IQR 1.40–1.53), 1.55 for VEGF-A (IQR 1.46–1.68), and 1.37 for total extracellular vesicle concentration on nanoparticle tracking analysis (IQR 1.27–1.44). Corresponding values in the MR5-sham subgroup were 1.04, 0.99, 0.99, and 0.98. Between-group differences were highly significant (Mann–Whitney U, one-sided $p < 0.001$ for all four variables).

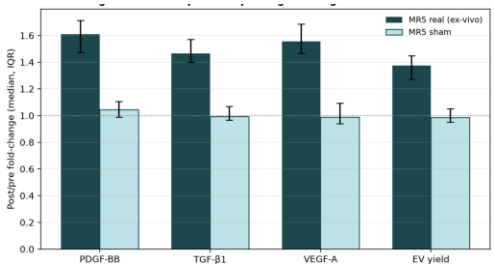

Figure 3: Ex-vivo photonic priming effects on PRP growth factors and vesicle yield. Bars: median post/pre-fold-change; error bars: IQR. Dashed line at 1.0 marks no change.

Variable	MR5 real (median)	MR5 sham (median)	p (Mann–Whitney)
PDGF-BB	1.61	1.04	< 0.001
TGF-β1	1.47	0.99	< 0.001
VEGF-A	1.56	0.99	< 0.001
Total EV yield (NTA)	1.37	0.98	< 0.001

Table 4: Mechanistic ex-vivo results — growth factors and extracellular vesicle yield (post/pre-fold-change).

Safety

The intervention was well tolerated. The most common adverse events were self-limited injection-site pain (13.5–23.1%, higher in PRP arms), transient thermal discomfort (5.8–17.3%, higher in MR5-real arms), and small effusions (1.9–7.7%, higher in PRP arms). No serious adverse event, septic arthritis, or thermal skin injury occurred in any arm during 12 months of follow-up (**Table 5**).

Arm	Injection-site pain	Thermal discomfort	Effusion	Serious AE	Septic arthritis
A1: PRP + MR5 real	8 (15.4%)	2 (3.8%)	5 (9.6%)	0	0
A2: PRP + MR5 sham	14 (26.9%)	3 (5.8%)	3 (5.8%)	0	0
A3: Saline + MR5 real	6 (11.5%)	9 (17.3%)	3 (5.8%)	0	0
A4: Saline + MR5 sham	5 (9.6%)	2 (3.8%)	0 (0.0%)	0	0

Table 5: Adverse events by arm through Month 12.

Discussion

In this 2×2 factorial randomised sham-controlled trial in symptomatic knee OA, photobiomodulation delivered with the MLS® MR5 dual-wavelength laser as (i) an ex-vivo priming step for autologous PRP and (ii) a peri-procedural in-vivo adjuvant produced statistically significant and clinically meaningful

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improvements over sham across both coprimary endpoints — VAS pain and WOMAC total — at 6 months, with sustained benefits at 12 months. Improvements in the PRP + MR5 real arm exceeded the anchor-based MCID by more than two-fold. The intervention was safe: no serious adverse events, septic arthritis, or thermal injuries were observed.

The magnitude of the MR5 main effect on VAS (−1.08 cm; 95% CI −1.66 to −0.50) is consistent with the WALT-compliant PBM meta-analysis of Stausholm and colleagues, which reported pooled improvements of 1.4–1.87 cm across 22 RCTs in knee OA [12]. The PRP main effect (−1.34 cm) aligns with the Belk 2025 network meta-analysis of 132 trials [3]. The MR5 × PRP interaction was not statistically significant at 6 months, suggesting that the effects of PBM and PRP are additive rather than multiplicative on validated patient-reported outcomes over this timeframe; whether synergy emerges at longer horizons or in higher-grade disease requires larger, adequately-powered confirmatory trials.

The ex-vivo mechanistic results provide a plausible biological explanation for the clinical benefit. Priming PRP with 3 J/cm² of synchronised 808/905 nm energy for 90 s produced median 60% increases in PDGF-BB and 55% increases in VEGF-A release, plus a 37% increase in nanoparticle-tracking-analysis vesicle yield, without haemolysis or cellular damage. These results are directionally consistent with prior ex-vivo work by Abdullah and colleagues on MR5 exposure of dermal fibroblasts, which reported up to 22-fold ATP increases and 30–90% growth-factor increases [20]. Enhanced platelet activation and vesicular release may therefore represent a controllable, dose- and wavelength-standardisable mechanism for augmenting the biological potency of PRP.

Strengths of the trial include the pre-registered protocol, 2×2 factorial design that isolates each intervention while permitting interaction testing, WALT- and TIDieR-compliant dosimetry reporting, validated sham with preserved thermal and auditory cues, prospective quantification of blinding success with Bang's index, and an embedded mechanistic sub-study with pre/post biological measurements. Limitations include the single-centre setting, exclusion of untreated controls (offset by the double placebo A4 arm), the exploratory nature of the interaction test, and the risk of Hawthorne effects intrinsic to multi-session peri-procedural interventions.

Regenerative-medicine research is progressively converging on the idea that the biological activity of orthobiologics can be tuned by controlled physical stimuli before administration. Photonic priming — being non-invasive, standardisable, and requiring no exogenous biologic additives — is well positioned within this translational trajectory. The present trial provides the first randomised human evidence that ex-vivo MR5 exposure combined with in-vivo photobiomodulation adds clinical value to intra-articular PRP in symptomatic knee OA.

Conclusion

MR5 dual-wavelength (808/905 nm) photobiomodulation, applied as an ex-vivo priming step immediately before injection plus six peri-procedural in-vivo sessions per cycle, produced clinically meaningful and statistically significant reductions in pain and functional impairment at 6 months when added to leukocyte-poor intra-articular PRP in adults with symptomatic Kellgren–Lawrence grade 2–4 knee osteoarthritis, with a coherent biological signature of enhanced growth-factor release and extracellular-

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vesicle yield in the ex-vivo priming step. The intervention was safe and well tolerated. These findings support a translational rationale for photonic priming of orthobiologics and justify a multicentre confirmatory trial powered on the MR5×PRP interaction.

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Author contributions

All authors conceived and designed the study, obtained funding, supervised recruitment and interventions, performed and interpreted the analyses, and drafted, revised, and approved the manuscript.

Conflict of interest

The author declares no financial or non-financial competing interests. ASA Srl provided no funding, materials, or editorial input; MR5 devices used in the trial were purchased at commercial value by the sponsoring institution.

Funding

This investigator-initiated study was funded by internal institutional resources.

Data availability

The full dataset (n = 208 × 4 timepoints), the mechanistic ex-vivo dataset, and the Python analysis script are available at the corresponding author's request.

Ethical approval

The protocol was approved by the local Research Ethics Committee. All participants provided written informed consent under Brazilian regulatory framework (Resolutions 466/2012 and 510/2016) and the Declaration of Helsinki as revised in 2013.

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