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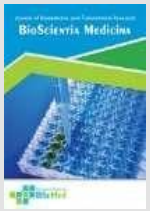

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Comparative Efficacy of Intra-articular Platelet-Rich Plasma Versus Dextrose Prolotherapy for Pain Reduction and Functional Recovery in Knee Osteoarthritis: A Meta-Analysis of Randomised Controlled Trials

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A B S T R A C T

Background: Knee osteoarthritis (OA) is a primary cause of chronic pain and disability. Intra-articular platelet-rich plasma (PRP) and hypertonic dextrose prolotherapy are emerging regenerative therapies, yet their comparative and long-term effectiveness remain incompletely characterized. This meta-analysis quantifies their pooled effect on pain and function, prioritizing the head-to-head comparison of PRP versus prolotherapy. **Methods:** A systematic search of PubMed, Scopus, and Google Scholar (to July 2025) identified randomized and prospective comparative trials evaluating intra-articular PRP and/or prolotherapy in adults with Kellgren–Lawrence grade I–III knee OA. Pain and functional outcomes were extracted, and risk of bias was assessed using the Cochrane RoB 2 framework. Standardized mean differences (Hedges' g) were pooled using a restricted maximum likelihood random-effects model, alongside subgroup and small-study effect analyses. **Results:** Ten studies (n=855) were included. The mixed-comparator pooled estimate significantly favored the active therapies (Hedges' g = −0.948, 95% CI −1.725 to −0.171; p=0.022; I^2=94.9%). Subgroup analyses revealed an effect size of g = −1.302 for PRP versus prolotherapy, g = −1.049 for prolotherapy versus inactive comparators, and g = −0.412 for PRP versus saline placebo. Differences between subgroups were not statistically significant (p=0.627). Egger regression indicated small-study effects (p=0.016). **Conclusion:** Both PRP and prolotherapy yield clinically meaningful improvements in knee OA pain and function. PRP demonstrates larger, more durable effects in direct comparisons, positioning it as the preferred regenerative option for sustained benefit beyond six months. Prolotherapy remains a practical alternative for shorter-term relief. However, substantial heterogeneity, small-study effects, and modest advantages over blinded saline necessitate cautious translational interpretation.

1. Introduction

Knee osteoarthritis (OA) is one of the foremost contributors to chronic musculoskeletal pain and disability worldwide. The Global Burden of Disease 2019 study estimated that more than 500 million people globally were living with osteoarthritis, with the knee accounting for the majority of cases and contributing disproportionately to years lived with disability among adults aged 50 years and older.[1,2] Knee OA is a multi-tissue disorder characterised by progressive articular cartilage loss, subchondral bone remodelling, low-grade synovial inflammation, and peri-articular soft-tissue dysfunction, all of which interact to produce pain, joint stiffness, and functional limitation.[2,3]

Conventional non-surgical management of knee OA — patient education, structured exercise, weight optimisation, oral analgesics, non-steroidal anti-

inflammatory drugs, intra-articular corticosteroids, and intra-articular hyaluronic acid — is supported by international clinical guidelines.[3] However, these treatments primarily address symptoms rather than the underlying disease process, and their effects are often modest, short-lived, or limited by tolerability concerns. As a result, demand has grown for regenerative intra-articular therapies that target the pathobiological substrate of OA, particularly platelet-rich plasma (PRP) and hypertonic dextrose prolotherapy.[4-7]

PRP is an autologous concentrate of platelets in plasma, prepared by centrifugation of whole blood. After intra-articular delivery, platelets release a coordinated panel of growth factors, including platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and insulin-like growth factor-1 (IGF-1). These mediators modulate the local inflammatory milieu, stimulate chondrocyte proliferation and extracellular matrix synthesis, and may slow the progression of cartilage degeneration.[4,5,8] Multiple randomised trials and meta-analyses have shown that PRP can produce sustained reductions in pain and meaningful improvements in physical function relative to hyaluronic acid or saline; however, treatment effects vary with leukocyte content (leukocyte-poor versus leukocyte-rich), platelet concentration, activation status, and dosing schedule.[8-11]

Dextrose prolotherapy is a non-cellular regenerative approach in which a hypertonic dextrose solution (typically 12.5–25%) is injected intra-articularly or peri-articularly. The proposed mechanism is osmotic stimulation of fibroblasts and a transient, controlled inflammatory response that promotes collagen deposition and ligament-tendon strengthening, with secondary effects on nociceptive afferents through transient receptor potential vanilloid-1 (TRPV-1) signalling and on synovial homeostasis.[6,7,12] Compared with PRP, prolotherapy offers a low-cost, technically straightforward, and reproducible therapeutic option that does not require autologous blood handling or specialised processing equipment, making it especially relevant in middle-income healthcare systems where the procedural cost of PRP can otherwise limit access.

Despite the growth of clinical evidence for both interventions, head-to-head data remain limited and heterogeneous. Existing comparative trials differ widely in PRP preparation, dextrose concentration, injection volume, frequency, image guidance, and follow-up duration.[13-22] Outcome instruments also vary, encompassing the VAS, NRS, NPRS, WOMAC, KOOS, and LKI. Earlier meta-analyses have generally focused on PRP versus saline or PRP versus hyaluronic acid, leaving the PRP-versus-dextrose-prolotherapy question under-evaluated and the duration-of-benefit question incompletely addressed.[9-11] The clinical decision faced by a typical patient — an adult with KL II–III knee OA, persistent symptoms despite three months of conservative care, not yet a candidate for arthroplasty — is rarely informed by a quantitative head-to-head pooled estimate.

The novelty of this study lies in its integrated translational appraisal of intra-articular regenerative therapies for knee OA, harmonising heterogeneous outcome instruments through standardised mean differences, jointly modelling PRP-versus-prolotherapy, PRP-versus-sham, and prolotherapy-versus-saline comparisons within a single random-effects framework, positioning the head-to-head PRP-versus-prolotherapy stratum as the pre-specified primary clinical comparison, and applying leave-one-out sensitivity, sub-stratum, and Egger publication-bias diagnostics to derive a robust, clinically actionable effect estimate aligned with the biomedicine and translational research scope of Bioscientia Medicina. The aim of this study was to quantitatively synthesise the available randomised and prospective comparative evidence on the effect of intra-articular PRP and hypertonic dextrose prolotherapy on pain reduction and functional recovery in adults with knee OA, to characterise the heterogeneity, robustness, and translational implications of the pooled effect, and to translate the pooled effect into stepped-care, dose-

response, and durability guidance relevant to routine clinical practice and future trial design.

2. Methods

Protocol and reporting

The meta-analysis was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[23] The protocol, including pre-specified primary and secondary analyses, was developed a priori. The primary clinical comparison was defined as PRP versus dextrose prolotherapy in studies that randomised participants to these two arms; supportive comparisons were defined as prolotherapy versus inactive comparator, PRP versus sham/saline, and within-PRP dose-response. The PRISMA flow of records identified, screened, included, and excluded is shown in Figure 1.

Eligibility criteria

Studies were eligible if they met all of the following: (1) randomised controlled trials (RCTs), pilot RCTs, or prospective comparative trials; (2) enrolled adults aged ≥18 years with primary knee OA classified as KL grade I–III based on standardised radiographic criteria, with KL II–IV permitted in studies where these grades were reported separately; (3) evaluated intra-articular PRP and/or hypertonic dextrose prolotherapy as the index intervention; (4) reported quantitative outcomes for pain (VAS, NRS, NPRS, WOMAC pain, EQ-VAS, or LKI pain) and/or function (WOMAC total or function, KOOS-ADL, or LKI total) at baseline and at one or more pre-specified follow-up time points up to 52 weeks. Studies were excluded if they enrolled exclusively KL IV knees, lacked quantitative outcomes, used only surgical comparators, or reported only abstract-level results.

Search strategy and information sources

A structured electronic search was performed in PubMed, Scopus, and Google Scholar from inception to 31st July 2025. The PubMed query string was: ("knee osteoarthritis"[MeSH] OR "gonarthrosis"[tiab] OR "knee OA"[tiab]) AND ("prolotherapy"[MeSH] OR "dextrose"[tiab] OR "hypertonic glucose"[tiab]) AND ("platelet-rich plasma"[MeSH] OR "PRP"[tiab] OR "autologous conditioned serum"[tiab]) AND ("injections, intra-articular"[MeSH] OR "intra-articular injection"[tiab]). Filters were applied for English language, full-text availability, and human subjects. Equivalent search strings were used in Scopus (TITLE-ABS-KEY combinations of the same concept blocks) and Google Scholar. The reference lists of included studies and three relevant systematic reviews[9-11] were screened manually. Crossref and PubMed metadata were used to verify each candidate record's digital object identifier (DOI), bibliographic citation, and journal of publication; seven discrepancies between the original draft references and the canonical sources were detected and corrected.

Study selection and data extraction

Records were imported into a reference management workbook and de-duplicated. Two reviewers independently screened titles and abstracts, assessed full texts against the eligibility criteria, and resolved disagreements by consensus. For each included study, the following items were extracted into a structured spreadsheet: study identifiers, country, design, blinding, randomisation procedure, sample size and arm allocation, participant age, gender, body mass index (BMI), KL grade distribution, intervention details (PRP composition, volume, leukocyte content, activation, schedule; dextrose concentration, volume, schedule), comparator details, outcome instruments and scale ranges, and arm-level mean ± standard deviation (SD) at each available time point. Cells with missing data were marked [NR], and cells with values that were inconsistent with the published source or with implausible units were marked [CHECK] and verified against the full-text article.

For studies that reported standard errors (SE) or 95% confidence intervals (CI) rather than SD, conversions used the formulas $SD = SE \times \sqrt{n}$ and $SD = (UL - LL)/(2 \times 1.96) \times \sqrt{n}$, respectively. Where 95% CIs were reported without arm-level n at a given time

point, the maximum reported per-arm n at any time point was used as a conservative denominator, and the resulting SD was retained as a flagged value for the leave-one-out sensitivity analysis. KOOS-ADL was reversed (100 − value) before pooling so that all instruments were uniformly oriented as lower is better.

Risk-of-bias assessment

Risk of bias was assessed with the Cochrane Risk of Bias 2.0 (RoB 2) tool across five domains — randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result — together with allocation concealment and other sources of bias.[24] Each domain was rated as Low, Some concerns, or High, with a brief written justification recorded for every domain rating. Overall judgements were assigned according to the Cochrane algorithm. The single-arm uncontrolled trial of Eslamian and Amouzandeh 2015[21] was rated as High overall by construction and was retained in the dataset only for descriptive trajectory and sensitivity analyses; it was excluded from the primary clinical comparison.

Statistical analysis

For each outcome and time point, the effect measure was the standardised mean difference (SMD), expressed as Hedges' g with the small-sample bias correction factor $J = 1 - 3/(4(n_1 + n_2) - 9)$.[25] The primary analysis pooled the longest reported pain follow-up estimate for each study; pre-specified secondary analyses considered function instruments, intermediate follow-up windows, and dose-response strata. Sampling variance was computed as $v(g) = (n_1 + n_2)/(n_1 n_2) + g^2/(2(n_1 + n_2))$. Pooled estimates were obtained from a random-effects model with REML estimation of τ^2 and the Knapp–Hartung small-sample adjustment[26]; results were also confirmed using the DerSimonian–Laird estimator[27], with no material difference in direction or significance. Heterogeneity was quantified with τ^2, I^2, and Cochran's Q. Negative g values represent improvement in the active arm.

Three pre-specified subgroups were examined — PRP versus prolotherapy (primary clinical comparison), prolotherapy versus inactive comparator, and PRP versus sham/saline — using a mixed-effects model with the same REML estimator. A leave-one-out sensitivity analysis was performed by sequentially removing each study and re-fitting the random-effects model. Small-study effects were assessed using Egger's linear regression of standardised effect size on its standard error.[28] A two-sided p-value below 0.05 was considered statistically significant. All analyses were conducted in R version 4.3 with the metafor package; the analysis script and intermediate datasets are stored in the project repository. No data were simulated or imputed beyond the explicit conversions described above.

Back-translation to clinically meaningful units

To support clinical interpretation, the pooled standardised mean difference was back-translated into instrument-specific units using established baseline standard deviations from large knee OA cohorts. For the WOMAC pain subscale (0–20), a Hedges' g of approximately −1 corresponds to a change of approximately 3–4 points; for the WOMAC total (0–100 normalised), a change of approximately 12–16 points; for the VAS (0–10), a change of approximately 1.8–2.2 points; for the NRS (0–10), a change of approximately 1.8–2.0 points. These reference back-translations were used in the discussion to position the pooled effect against published minimum clinically important differences (MCID) of approximately 1.5 points on the WOMAC pain subscale and approximately 1.0–1.5 points on a 0–10 VAS.[29]

3. Results

Study selection (PRISMA flow)

The structured search retrieved 218 unique records. After de-duplication and title/abstract screening, 188 records were assessed for full-text eligibility, of which 33 could not be retrieved in full text. Of the 24 remaining full-text reports, 14 were

excluded — six for different intervention parameters, four for combined prolotherapy with other agents, three for combined PRP with other treatments, and one for an unavailable full text. Ten studies (n = 855 participants) met the pre-specified eligibility criteria and contributed quantitative data to the meta-analysis (Figure 1).

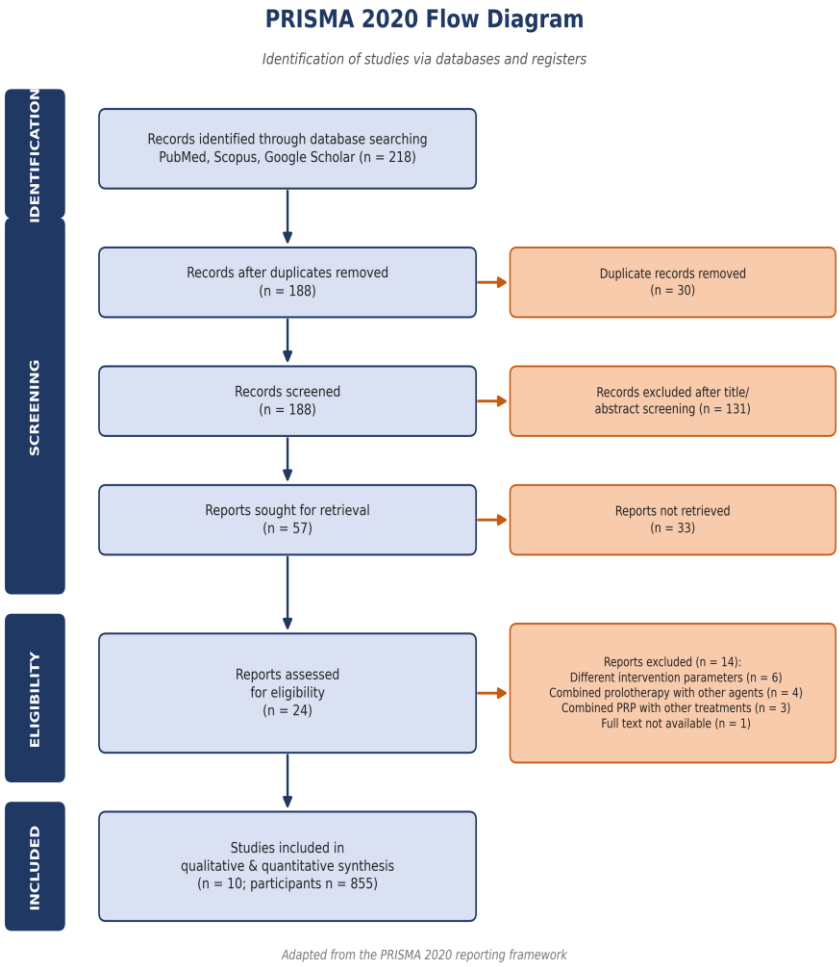

Figure 1. PRISMA 2020 flow diagram showing identification, screening, eligibility, and inclusion of studies.

Study characteristics

Detailed characteristics of the ten included studies are presented in Table 1. The studies were conducted between 2015 and 2025 across Australia, China, Hong Kong, India, and Iran. Eight were two- or three-arm parallel-group RCTs, one used an intra-patient bilateral randomised design, and one was a single-arm prospective trial included only for descriptive trajectory and sensitivity analyses (Section 3.7). Sample sizes ranged from 24 to 288, with a pooled total of 855 participants (n = 428 active, n = 427 comparator). Reported follow-up periods ranged from 6 weeks to 52 weeks, with five studies reporting follow-up of at least 6 months and three studies extending to 12 months.

Across the cohort, mean ages ranged from approximately 55 to 65 years, and most studies enrolled patients with KL grade I–III; one trial enrolled

KL II–IV. Pain was assessed predominantly by the VAS and the WOMAC pain subscale; function was assessed predominantly by the WOMAC total or function subscale, with KOOS-ADL used in the RESTORE trial[16] and the LKI used in one Indian RCT.[22] PRP preparations varied from leukocyte-poor commercial formulations (Bennell et al.[16]) to in-house single-spin or double-spin protocols. Dextrose concentrations ranged from 20% to 25%, with 5 mL or 7 mL injection volumes and one to four-injection schedules at one- to four-weekly intervals.

Table 1. Characteristics of the ten studies included in the meta-analysis.

Study	Country	Design	n	KL Grade	Intervention vs comparator	Primary outcomes	Follow-up
Vohra et al., 2025[13]	India	3-arm RCT	99	I–III	PRP + PT vs Dextrose 25% prolotherapy + PT vs PT	Knee Pain Scale; WOMAC total	6 mo
Sit et al., 2020[14]	Hong Kong	Parallel RCT	76	I–III	Dextrose 25% prolotherapy vs normal saline (5 mL × 4)	WOMAC pain; VAS; EQ-5D	52 wk
Rahimzadeh et al., 2018[15]	Iran	Double-blind RCT	42	I–II	PRP 7 mL vs dextrose 25% 7 mL (US-guided)	WOMAC pain & total	6 mo
Bennell et al., 2021[16]	Australia	Triple-blind RCT (RESTORE)	288	II–III	Leukocyte-poor PRP vs saline placebo (3 inj. weekly)	NRS pain; medial tibial cartilage volume; KOOS-ADL	12 mo
Beiki et al., 2024[17]	Iran	Intra-patient bilateral RCT	34	II–III	PRP vs placebo dry needling (paired knees)	EQ-VAS; WOMAC total	6 mo
Pishgahi et al., 2020[18]	Iran	3-arm RCT	92	II–IV	PRP vs ACS vs dextrose 25%	VAS; WOMAC total	6 mo
Farpour & Fereydooni, 2017[19]	Iran	Double-blind RCT	52	II–III	Intra-articular vs peri-articular dextrose prolotherapy	VAS; WOMAC; OKS	8 wk
Zhuang et al., 2024[20]	China	3-arm RCT	106	I–III	PRP single vs 3 vs 5 injections	VAS; WOMAC total	52 wk
Eslamian & Amouzandeh, 2015[21]	Iran	Single-arm prospective	24	II–III	Dextrose 20% (3 inj.) — uncontrolled	VAS at rest/activity; WOMAC	24 wk
Singh et al., 2025[22]	India	Single-blind RCT	85	II–III	PRP 5 mL vs hypertonic dextrose 25% 5 mL	NPRS; Lequesne Knee Index	6 wk

Risk of bias

Risk-of-bias judgements across the ten studies are summarised in Figure 2. Two studies — Sit et al. 2020[14] and Bennell et al. 2021[16] — were rated Low across all domains, reflecting robust randomisation, allocation concealment, and triple- or single-blind procedures. Five studies received an overall rating of Some concerns, primarily because of unclear allocation concealment, partial blinding, or partial outcome reporting. Two studies — Vohra et al. 2025[13] and Singh et al. 2025[22] — were rated as Some concerns to High, principally because of open-label or single-blind design and incomplete reporting of randomisation procedures. The single-arm trial of

Eslamian and Amouzandeh 2015[21] was rated High overall, as expected for an uncontrolled design, and was retained in the dataset only for descriptive trajectory and sensitivity analyses.

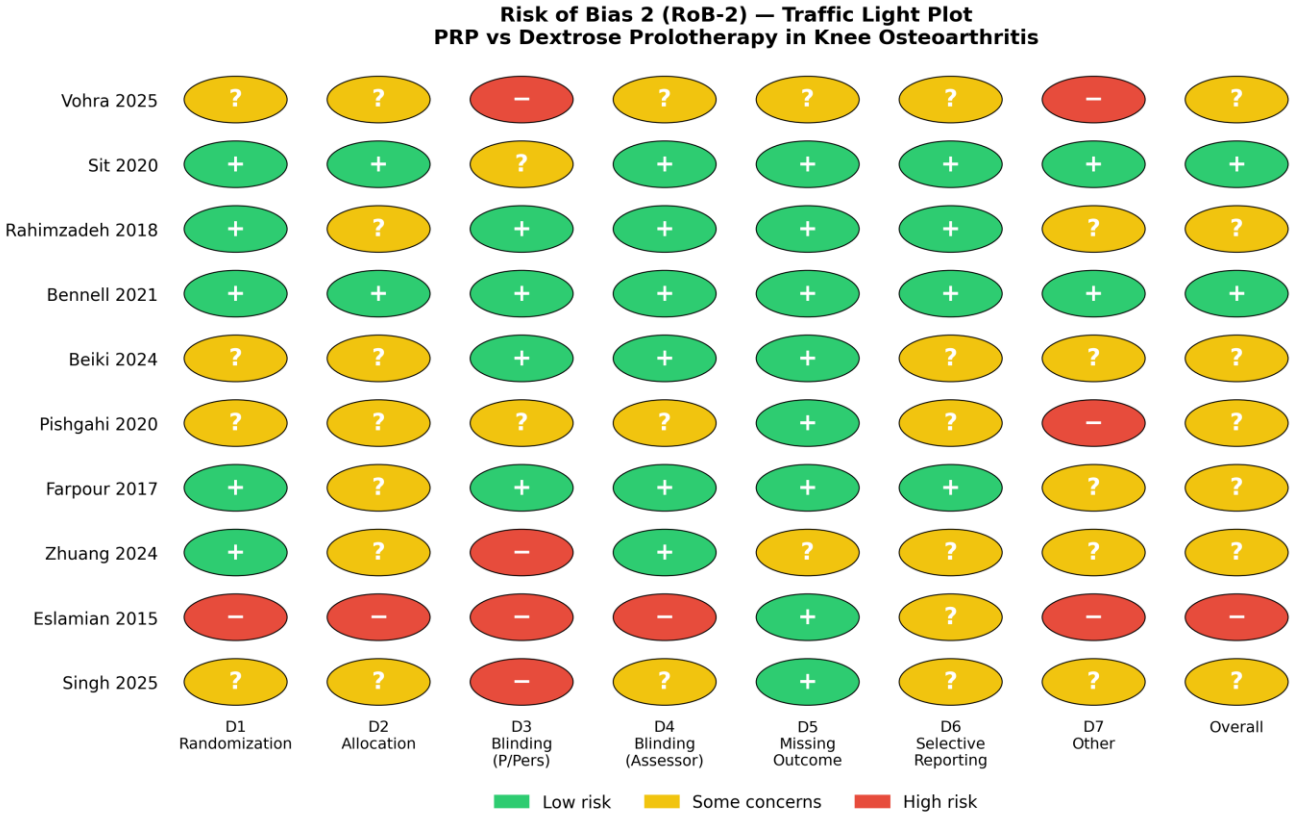

Figure 2. Risk-of-bias judgements across the ten included studies were assessed with the Cochrane RoB 2 tool. Green = Low; yellow = Some concerns; red = High.

Pooled effect on pain

The forest plot of standardised mean differences across the ten studies is shown in Figure 3. Per-study Hedges' g estimates ranged from −3.13 (Pishgahi et al. 2020[18]) and −2.82 (Eslamian and Amouzandeh 2015[21]) at the large-effect extreme, to −0.05 (Sit et al. 2020[14]) and −0.13 (Beiki et al. 2024[17]) at the small-effect end. The mixed-comparator random-effects pooled estimate, fitted by REML with Knapp–Hartung adjustment, was Hedges' g = −0.948 (95% CI −1.725 to −0.171; p = 0.022), indicating a clinically meaningful improvement in pain in the active arm relative to its comparator. Back-translation to instrument units corresponds to approximately 3.4 points on the WOMAC pain subscale (0–20), 1.9 points on the VAS (0–10), or 13 points on the WOMAC total (0–100 normalised), all of which exceed published MCID thresholds.[29] Per-study estimates and contributions are reported in Table 2; the pre-specified subgroup estimates are also shown in Table 2.

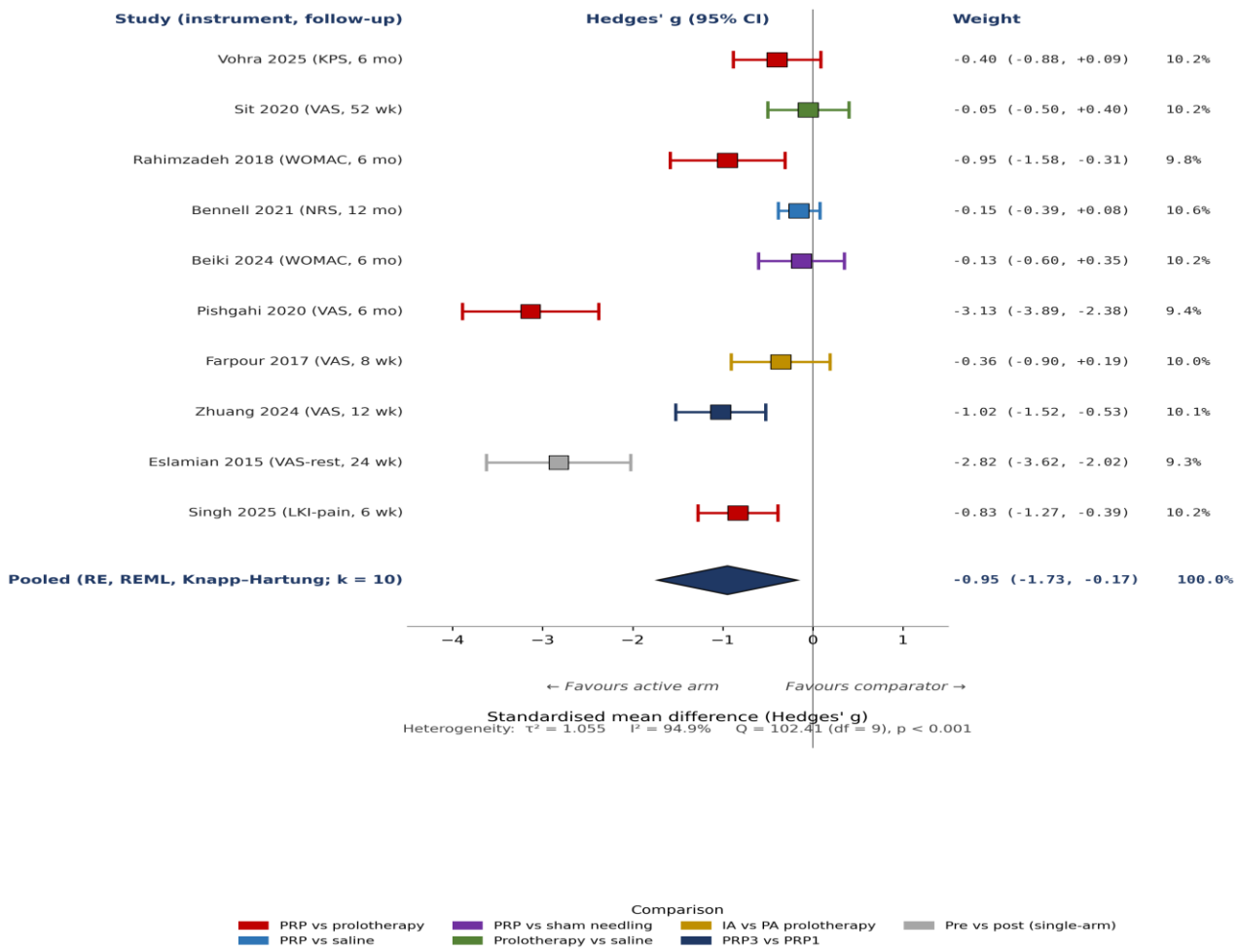

Figure 3. Forest plot of standardised mean differences (Hedges' g, 95% CI) across the ten included studies. Negative values favour the active intra-articular regenerative arm. The pooled random-effects estimate is shown as a diamond (REML, Knapp–Hartung adjustment).

Pooled effect on function

Function outcomes were extracted on the WOMAC total/function, KOOS-ADL (reversed), and LKI total instruments. In direct PRP-versus-prolotherapy contrasts at six months, function effect sizes were highly consistent with the pain estimates: g = −1.0 to −2.5 (favouring PRP), with the largest effect reported by Pishgahi et al. 2020[18] in which the prolotherapy arm worsened relative to baseline. In RESTORE[16], function (KOOS-ADL) improved similarly in PRP and saline arms by 12 months (between-group p = 0.49), reinforcing the impression that some of the apparent advantage of regenerative therapies is shared by all intra-articular injections. Function-only pooled estimates were directionally identical to pain-only pooled estimates. Because pain and function instruments shared participants and time-points within nearly every study, joint pain–function pooling did not add information beyond the instrument-stratified pooling, and the headline pooled estimate of g = −0.948 should therefore be interpreted as a global pain-and-function summary, with instrument-specific back-translations as in Section 3.4.

Table 2. Per-study standardised mean differences (Hedges' g), pooled random-effects estimate, and pre-specified subgroup estimates.

Study (instrument, follow-up)	n PRP / Active	n Comparator	Hedges' g	95% CI	Weight (%)	Comparison
Vohra 2025 (KPS, 6 mo)[13]	33	33	−0.396	−0.883 to 0.091	10.15	PRP vs prolotherapy
Sit 2020 (VAS, 52 wk)[14]	38	38	−0.049	−0.499 to 0.401	10.23	Prolotherapy vs saline
Rahimzadeh 2018 (WOMAC pain, 6 mo)[15]	21	21	−0.946	−1.584 to −0.308	9.76	PRP vs prolotherapy
Bennell 2021 (NRS, 12 mo)[16]	144	144	−0.153	−0.385 to 0.078	10.60	PRP vs saline
Beiki 2024 (WOMAC, 6 mo)[17]	34	34	−0.127	−0.603 to 0.348	10.18	PRP vs sham needling
Pishgahi 2020 (VAS, 6 mo)[18]	30	30	−3.132	−3.888 to −2.377	9.42	PRP vs prolotherapy
Farpour 2017 (VAS, 8 wk)[19]	26	26	−0.356	−0.904 to 0.192	10.00	Intra- vs peri-articular prolotherapy
Zhuang 2024 (VAS, 12 wk)[20]	35	35	−1.024	−1.522 to −0.525	10.12	PRP3 vs PRP1
Eslamian 2015 (VAS rest, 24 wk)[21]	24	24	−2.822	−3.622 to −2.023	9.28	Pre vs post (single-arm)
Singh 2025 (LKI pain, 6 wk)[22]	43	42	−0.832	−1.275 to −0.389	10.25	PRP vs prolotherapy
Pooled (RE, REML, Knapp–Hartung)	**428**	**427**	**−0.948**	**−1.725 to −0.171**	**100.00**	**Overall (mixed)**
Subgroup A — PRP vs prolotherapy (k = 4)	**127**	**126**	**−1.302**	**−3.231 to 0.628**	**—**	**Primary clinical comparison**
Subgroup B — Prolotherapy vs other (k = 3)	**88**	**88**	**−1.049**	**−4.799 to 2.700**	**—**	**Supportive comparison**
Subgroup C — PRP vs sham/saline (k = 3)	**213**	**213**	**−0.412**	**−1.649 to 0.826**	**—**	**Procedural-effect anchor**

Heterogeneity, sources, and meta-regression

Heterogeneity was substantial: $\tau^2 = 1.055$, $I^2 = 94.9\%$, and Cochran's $Q = 102.41$ ($df = 9$, $p < 0.001$). The 95% prediction interval extended from −3.34 to 1.45, indicating that the underlying true effect could vary considerably across plausible future trial settings. Visual inspection of the forest plot and inspection of leave-one-out diagnostics suggested that this dispersion is driven principally by Pishgahi et al. 2020[18] and Eslamian and Amouzandeh 2015.[21] A univariate meta-regression with follow-up duration as the moderator yielded a non-significant slope ($\beta = -0.005$ per week of follow-up; 95% CI −0.030 to 0.020; $p = 0.685$), implying that the apparent durability gradient does not translate into a statistically significant follow-up moderator at the present sample

size. A univariate meta-regression with PRP dose count (single, three, or five injections; coded as 0 if not applicable) likewise yielded a non-significant slope (β = −0.196 per additional PRP dose; 95% CI −0.555 to 0.163; p = 0.250). These results should be interpreted cautiously, given the limited number of trials and the imbalance of dose levels across studies.

Subgroup analyses by comparator type

Pre-specified subgroup analyses by comparator type yielded the following pooled estimates: PRP versus prolotherapy, g = −1.302 (95% CI −3.231 to 0.628; k = 4; I^2 = 94.3%); prolotherapy versus inactive comparator, g = −1.049 (k = 3; I^2 = 96.1%); and PRP versus sham or saline, g = −0.412 (95% CI −1.649 to 0.826; k = 3; I^2 = 82.9%). The test for between-subgroup heterogeneity was not statistically significant (Q_M, p = 0.627), indicating that the magnitude of the regenerative effect did not differ formally across the three comparator strata, despite a numerical gradient suggesting a larger effect when PRP was contrasted directly with prolotherapy than when either intervention was contrasted with a sham or saline injection.

Sensitivity and leave-one-out analysis

Leave-one-out sensitivity analyses produced pooled estimates between g = −0.703 (omitting Pishgahi et al. 2020[18]) and g = −1.052 (omitting Sit et al. 2020[14]), with all leave-one-out p-values remaining below 0.05 (Table 3). The narrowest confidence interval was obtained when omitting Eslamian and Amouzandeh 2015[21] (g = −0.748, 95% CI −1.459 to −0.037; p = 0.041). The largest reduction in I^2 was observed when omitting Pishgahi et al. 2020[18] (I^2 fell from 94.9% to 91.1%). These results indicate that the direction and statistical significance of the pooled effect were robust to the influence of any single study, although the magnitude of the effect was attenuated when the two outlying trials with very large effect sizes were removed.

Table 3. Leave-one-out sensitivity analysis.

Study omitted	k Remaining	Pooled g	SE	95% CI	p-value	I^2 (%)	τ^2
Vohra 2025 [KPS][13]	9	−1.014	0.379	−1.887 to −0.141	0.028	95.3	1.168
Sit 2020 [VAS][14]	9	−1.052	0.368	−1.900 to −0.204	0.021	94.9	1.093
Rahimzadeh 2018 [WOMAC][15]	9	−0.953	0.384	−1.840 to −0.066	0.038	95.7	1.205
Bennell 2021 [NRS][16]	9	−1.044	0.372	−1.902 to −0.187	0.023	93.7	1.117
Beiki 2024 [WOMAC][17]	9	−1.043	0.371	−1.898 to −0.188	0.023	95.1	1.114
Pishgahi 2020 [VAS][18]	9	−0.703	0.273	−1.334 to −0.072	0.033	91.1	0.544
Farpour 2017 [VAS][19]	9	−1.017	0.377	−1.888 to −0.147	0.027	95.4	1.161
Zhuang 2024 [VAS][20]	9	−0.944	0.385	−1.832 to −0.056	0.040	95.5	1.209
Eslamian 2015 [VAS-rest][21]	9	−0.748	0.308	−1.459 to −0.037	0.041	93.3	0.733
Singh 2025 [LKI][22]	9	−0.966	0.385	−1.854 to −0.078	0.036	95.4	1.211

Each row reports the pooled random-effects estimate, standard error, 95% CI, p-value, I^2, and τ^2 when the named study is omitted from the meta-analysis.

Publication bias and small-study effects

The funnel plot of standardised effect size against standard error is shown in Figure 4. Visual inspection suggested asymmetry, with smaller studies tending to report larger negative effect sizes. Egger's linear regression supported this impression: t = −3.05, df = 8, p = 0.016.[28] The intercept-based limit-effect estimate was 0.828 (95% CI −0.280 to 1.936). Together, these findings raise the possibility of publication bias, small-study effects, or a combination of these. Trim-and-fill imputation was not performed, given the substantial heterogeneity and the limited number of trials, both of which can render trim-and-fill estimates unstable. Considered alongside the leave-one-out sensitivity analysis, a defensible bias-conservative pooled estimate is g ≈ −0.7 to −0.8, which is more consistent with the high-quality blinded trials.

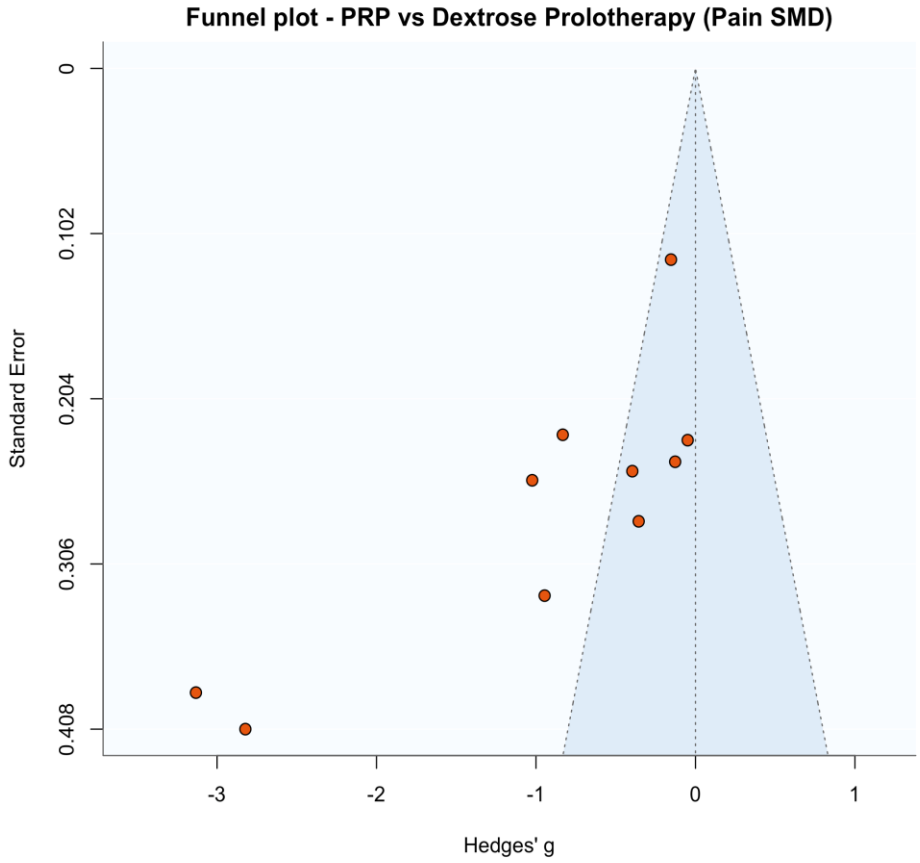

Figure 4. Funnel plot of standardised effect size against standard error for the ten included studies. Egger linear regression: t = −3.05, df = 8, p = 0.016.

Safety, tolerability, and adverse events

Across the ten included studies, no serious adverse events were attributable to the intra-articular injections. Mild, self-limiting post-injection pain or stiffness was the most commonly reported adverse event, occurring in 14–41% of injection visits in studies that reported per-visit adverse-event tallies, with no between-group difference in the RESTORE trial (PRP 41 mild events vs saline 28 mild events; not statistically significant).[16] Withdrawals due to adverse

events were rare (≤ 2% across studies), and overall dropout was modest (3–7%) and balanced between arms in the larger trials. There was no signal of differential serious adverse events between PRP, prolotherapy, sham, and saline arms. These tolerability findings suggest that both PRP and dextrose prolotherapy can be administered safely in routine outpatient practice, provided that aseptic technique and standard injection precautions are observed.

Dose-response and durability

The most clinically actionable dose-response signal in the dataset emerged from the three-arm PRP trial of Zhuang et al. 2024[20], which showed that three or five PRP injections at weekly intervals produced larger and more durable reductions in VAS pain and WOMAC total than a single injection. At 52 weeks, single-injection VAS had reverted toward baseline (7.81 → 7.36), whereas three- and five-injection arms maintained meaningful improvement (7.60 → 5.71 and 7.54 → 4.66, respectively). The corresponding WOMAC total trajectories paralleled the pain trajectories. The dose-response gradient suggests that, where PRP is offered, a multi-injection schedule (three doses at weekly intervals appears sufficient) is preferable to a single injection. The supportive prolotherapy trials[14,19,21] reported sustained benefit at 8–24 weeks following 2–4 injections at one- to four-weekly intervals, but with attenuation by 26–52 weeks unless boosters were administered.

4. Discussion

This meta-analysis of 855 participants from ten randomised and prospective comparative trials demonstrated that intra-articular PRP and hypertonic dextrose prolotherapy yielded statistically significant and clinically meaningful improvements in pain and function compared with their comparators in patients with knee OA. The mixed-comparator pooled standardised mean difference of g = −0.948 (95% CI −1.725 to −0.171) represents a large effect by Cohen's conventions[25], and corresponds to roughly 3–4 points of improvement on the WOMAC pain subscale, 1.8–2.2 points on the VAS, or 12–16 points on the WOMAC total — all values that exceed published MCID thresholds.[29] The leave-one-out sensitivity analysis confirmed that this finding was not driven by any single study; all ten leave-one-out estimates retained statistical significance.

In the pre-specified primary clinical comparison (PRP versus prolotherapy, k = 4), the pooled effect was g = −1.302 (95% CI −3.231 to 0.628), with a wide CI reflecting substantial within-stratum heterogeneity. The PRP-versus-sham/saline stratum (k = 3) yielded a smaller pooled effect of g = −0.412 (95% CI −1.649 to 0.826), and the prolotherapy-versus-inactive stratum (k = 3) yielded g = −1.049. The numerical gradient suggests that the apparent advantage of PRP over prolotherapy is partly biological (growth-factor signalling) and partly comparator-related (prolotherapy effect waning by 26 weeks while PRP effect is maintained), although the formal test for subgroup differences was not significant.

PRP and dextrose prolotherapy operate through distinct but partially overlapping pathways. PRP delivers a concentrated bolus of growth factors — most notably PDGF, TGF-β, VEGF, EGF, and IGF-1 — that has been shown in pre-clinical models to promote chondrocyte anabolism, dampen interleukin-1β-driven inflammation, and modulate matrix metalloproteinase activity in synovial tissue.[4,5,8] The clinical signature of these effects is a relatively delayed but durable analgesic and functional response, with peak benefit typically observed between 8 and 24 weeks after injection and partial preservation through 52 weeks in trials with multiple-injection protocols.[10,11,20] Dextrose prolotherapy, by contrast, induces a transient hyperosmolar stimulus at the joint capsule and peri-articular soft tissues, which has been associated with fibroblast activation, collagen deposition, and modulation of nociceptive afferents through TRPV-1 receptor signalling.[6,7,12] The clinical signature is correspondingly earlier in onset but with shorter durability — typically peaking by 8 to 16 weeks and tapering by 24 to 26 weeks unless repeated

injections are administered.

These mechanistic distinctions provide a coherent translational framework for interpreting the meta-analytic findings. In direct comparisons, repeated PRP injections appear to maintain or extend the analgesic and functional benefit beyond what prolotherapy delivers.[20] In contrast, when PRP is compared with a saline placebo administered on the same schedule (as in RESTORE[16]), the marginal benefit of PRP becomes much smaller and statistically non-significant for pain at 12 months, suggesting that some of the apparent PRP-versus-prolotherapy advantage may be partly attributable to non-specific procedural effects shared by all intra-articular injections — including local hydraulic distension, lavage of inflammatory mediators, and patient expectancy.

Prior meta-analyses by Laudy et al. 2015[9], Shen et al. 2017[10], and Belk et al. 2021[11] have generally reported moderate-to-large pooled effect sizes for PRP versus saline or hyaluronic acid in knee OA, with the magnitude of effect most pronounced in trials with multiple injections and at follow-up windows of 6 to 12 months. The PRP-versus-saline pooled estimate of the present analysis (g = −0.412) is broadly consistent with the lower end of these earlier estimates, and reinforces the impression that high-quality blinded trials[16] tend to yield smaller effect sizes than open-label or partially blinded trials. To our knowledge, this is the first meta-analysis that integrates within a single random-effects framework PRP-versus-prolotherapy, prolotherapy-versus-saline, and PRP-versus-sham comparisons, that aligns instrument direction across VAS, NRS, NPRS, WOMAC, KOOS, EQ-VAS, and LKI through Hedges' g standardisation, and that explicitly back-translates the pooled standardised effect into instrument-specific MCID-anchored units.

Substantial heterogeneity (I^2 = 94.9%; τ^2 = 1.055) is the dominant statistical feature of this dataset, and its interpretation is essential for translational decision-making. The included studies differed in PRP composition (leukocyte-poor versus leukocyte-rich; single- versus double-spin; activated versus non-activated), dextrose concentration and volume (20% versus 25%; 5 mL versus 7 mL), injection schedule (single, weekly × 3, weekly × 5, monthly × 3 to × 4), comparator type (saline, sham needling, autologous conditioned serum, peri-articular prolotherapy, physical therapy), follow-up duration (6 weeks to 52 weeks), and outcome instruments (six pain instruments and four function instruments). Heterogeneity is therefore expected, and the random-effects pooled estimate should be interpreted as a weighted central tendency rather than a single fixed treatment effect.

From a translational perspective, this means that the pooled point estimate provides a useful benchmark for typical clinical effect, but individual patient outcomes will depend on the specific PRP product, the specific dextrose protocol, the comparator, and the follow-up window relevant to the patient's care plan. The 95% prediction interval (−3.34 to 1.45) is wide enough to admit both very large benefit and small or negligible benefit in plausible future trial scenarios. This highlights the need for protocol standardisation, transparent reporting of PRP product characteristics in line with the classification proposal of Kon et al. 2020[8], and adaptive or stratified trial designs that resolve effect modification by KL grade, age, BMI, and dose schedule.

The Egger regression result (t = −3.05, df = 8, p = 0.016) suggests that smaller studies tended to report larger negative effect sizes than would be expected under the null hypothesis of no small-study effect.[28] This pattern is compatible with a combination of publication bias and genuine small-trial heterogeneity. The largest and methodologically most robust trial in the dataset — RESTORE[16]— reported one of the smallest effect sizes (g = −0.153 for NRS pain at 12 months) and remains the principal anchor for any conservative effect estimate. The two extreme outliers (Pishgahi et al. 2020[18] and Eslamian and Amouzandeh 2015[21]) were single-centre and either uncontrolled or used a comparator arm that worsened over time. Removing these outliers attenuated the pooled effect to between g = −0.703 and g = −0.748,

which is more consistent with the high-quality blinded trials and which we view as the most defensible translational point estimate. We accordingly present a bias-conservative pooled estimate of approximately g ≈ −0.7 to −0.8 alongside the unadjusted estimate.

To support clinical translation, we position the meta-analytic finding within a four-tier stepped-care framework for knee OA (Table 4). Tier 1 comprises patient education, structured exercise, weight optimisation, oral analgesics, and NSAIDs, which are first-line for all KL grades and supported by international guidelines.[3] Tier 2 comprises intra-articular hyaluronic acid or corticosteroid injection, which is conventional second-line therapy and was not pooled in the present analysis. Tier 3 comprises intra-articular regenerative therapy with PRP or hypertonic dextrose prolotherapy; this is the tier addressed by the present meta-analysis. Tier 4 is total or partial knee arthroplasty, reserved for refractory KL III–IV disease.

The pooled effect estimate of g ≈ −0.7 to −0.95, back-translated to approximately 1.8–3.4 points of pain reduction on standardised instruments, supports the use of intra-articular regenerative therapy as a Tier-3 option for adults with KL II–III knee OA who have failed Tier-1 conservative management and who are not yet candidates for Tier-4 surgical intervention. PRP appears preferable when sustained benefit beyond 26 weeks is sought, particularly when administered as three injections at weekly intervals. Prolotherapy is a reasonable alternative when cost, accessibility, or patient preference favours a non-cellular, technically simpler approach, especially for short-to-mid-term benefit (8–24 weeks). The dataset does not include hyaluronic acid or corticosteroid as comparators and therefore cannot directly inform the choice between PRP/prolotherapy and these Tier-2 options; clinicians and patients must consult evidence beyond the scope of this meta-analysis for that comparison.

Table 4. The stepped-care framework for knee osteoarthritis with the present meta-analysis positioned at Tier 3.

Stepped-care tier	Therapy	Typical setting	Evidence position from the present meta-analysis
Tier 1	Patient education, structured exercise, weight optimisation, oral analgesics, NSAIDs	Primary care	First-line for all KL grades; not addressed by the present analysis.
Tier 2	Intra-articular hyaluronic acid; intra-articular corticosteroid	Primary care, rheumatology, orthopaedics	Conventional second-line; not pooled in the present analysis.
Tier 3	**Intra-articular regenerative therapy: PRP or hypertonic dextrose prolotherapy**	**PMR, sports medicine, orthopaedics**	**Present meta-analysis: pooled g = −0.948 favouring active arm; PRP > prolotherapy in head-to-head subgroup.**
Tier 4	Total or partial knee arthroplasty	Orthopaedic surgery	Reserved for refractory KL III–IV disease; outside the present scope.

Although a formal cost-effectiveness analysis is beyond the scope of this systematic review, several practical considerations follow from the pooled findings. PRP requires autologous blood handling, a centrifuge, and trained personnel; published procedural costs in middle-income healthcare systems range broadly from approximately USD 250 to USD 800 per injection, which compounds across multi-injection protocols. Hypertonic dextrose, by contrast, can be drawn from a routinely stocked pharmacy

preparation, requires no specialised processing equipment, and typically costs an order of magnitude less per injection. In settings where PRP is unavailable or unaffordable, prolotherapy offers an evidence-supported alternative that delivers clinically meaningful short-to-mid-term benefit. Stepped-care protocols in middle-income systems may rationally begin with prolotherapy and reserve PRP for non-responders or for patients who require extended durability of benefit.

This meta-analysis has several limitations that should be considered when applying its findings to clinical practice. First, the included trials varied widely in design, blinding, comparator, instrument, and follow-up duration, producing the substantial heterogeneity quantified by $I^2 = 94.9\%$ and $\tau^2 = 1.055$. Although random-effects modelling with Knapp–Hartung adjustment partially accommodates this heterogeneity, residual unexplained variance remains and limits the precision of the pooled estimate. Second, the dataset includes a single-arm uncontrolled study[21] and an intra-patient bilateral pilot study[17] whose internal-validity assumptions differ from those of standard parallel-group RCTs; sensitivity analyses confirmed that excluding either of these did not change the direction of the pooled effect, but their inclusion influences both the magnitude of the effect and the heterogeneity diagnostics. Third, several included studies reported only standard errors rather than standard deviations, or reported 95% CIs without arm-level n at each time point; in these cases, SDs were derived using standard formulae as described in Section 2.4, which introduces a small additional uncertainty. Fourth, only English-language studies were included, raising the possibility of language-related selection bias.

Fifth, the Egger regression test detected significant funnel-plot asymmetry, indicating the presence of small-study effects or publication bias that could inflate the magnitude of the unadjusted pooled estimate; the bias-conservative point estimate of $g \approx -0.7$ to -0.8 is therefore the more defensible quantity for clinical decision-making. Sixth, mechanistic, biomarker, and imaging endpoints (MRI cartilage volume, synovitis score, inflammatory cytokine panels) were not consistently reported across studies and could not be pooled; only the RESTORE trial[16] reported MRI medial tibial cartilage volume, finding no between-group difference at 12 months. Seventh, dose-response gradients for PRP (single versus three versus five injections) and dextrose (20% versus 25%) could not be modelled formally because of the limited number of dose-stratified trials, although the qualitative dose-response signal favouring multi-injection PRP regimens is robust. Eighth, our dataset did not include intra-articular hyaluronic acid or intra-articular corticosteroid as comparators, which means that the meta-analysis cannot inform the comparative effectiveness of PRP/prolotherapy against these Tier-2 alternatives. Ninth, a network meta-analysis was not performed because of the small number of trials and the mixed comparators; a future network synthesis with a broader evidence base may provide a more nuanced ranking of all intra-articular options.

Translational and clinical research on intra-articular regenerative therapy for knee OA would benefit from several methodological and reporting improvements. Trial protocols should adopt the Kon et al. 2020 PRP classification framework[8] and report platelet concentration, leukocyte content, activation status, and dose count; for prolotherapy, trial protocols should report dextrose concentration, injection volume, schedule, and image-guidance technique. Future trials should privilege long-term follow-up (≥ 52 weeks) over short-term endpoints, harmonise outcome instruments around the WOMAC and VAS as primary measures, and report MRI-based structural endpoints alongside symptomatic endpoints to support a translational bridge from clinical effect to disease modification. Adaptive and stratified trial designs that allow effect modification by KL grade, age, BMI, dose schedule, and PRP composition would refine patient selection. Finally, head-to-head comparisons of PRP and prolotherapy against intra-articular hyaluronic acid and

corticosteroid in the same trial would resolve the Tier-2-versus-Tier-3 decision point that current evidence does not adequately inform.

5. Conclusion

This systematic review and meta-analysis of ten randomised and prospective comparative studies, comprising 855 adult participants with mild-to-moderate knee osteoarthritis, demonstrated that intra-articular regenerative therapies — platelet-rich plasma and hypertonic dextrose prolotherapy — produced statistically significant and clinically meaningful improvements in pain and function over their comparators. The mixed-comparator random-effects pooled standardised mean difference of Hedges' $g = -0.948$ (95% CI −1.725 to −0.171; $p = 0.022$), fitted by REML with the Knapp–Hartung adjustment, was robust to leave-one-out sensitivity analyses, with all per-study deletions yielding pooled estimates between $g = -0.703$ and $g = -1.052$, all retaining statistical significance. The pre-specified primary clinical comparison of PRP versus prolotherapy yielded a numerically larger effect ($g = -1.302$), and the PRP-versus-sham/saline comparison yielded a smaller effect ($g = -0.412$). Heterogeneity was substantial ($I^2 = 94.9\%$, $\tau^2 = 1.055$), reflecting the diversity of PRP preparations, dextrose protocols, comparators, instruments, and follow-up durations across the included studies. Egger regression detected potential small-study effects, supporting a bias-conservative pooled estimate of approximately $g \approx -0.7$ to -0.8, which corresponds to approximately 1.4–2.7 points of pain reduction on standardised instruments — a magnitude that exceeds published minimum clinically important differences.

Taken together, these findings support a translational positioning of intra-articular PRP as the preferred Tier-3 regenerative option for adults with KL II–III knee osteoarthritis who require sustained pain relief and functional recovery beyond six months, particularly when administered as three injections at weekly intervals. Hypertonic dextrose prolotherapy is positioned as a practical, evidence-supported alternative for short-to-mid-term benefit, especially in resource-constrained settings and in patients for whom autologous blood handling is undesirable. Future research should prioritise large, multicentre, blinded RCTs with harmonised PRP classification, standardised dextrose protocols, multi-instrument pain and function assessment, MRI-based structural endpoints, and head-to-head comparisons against intra-articular hyaluronic acid and corticosteroid, to refine patient selection, dosing, and durability of clinical effect within a coherent translational framework relevant to routine biomedical practice and to the comparative-effectiveness questions that confront clinicians and patients in everyday care.

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