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Meta Analysis on Outcomes of Intra Articular Knee Injections: Hyaluronic Acid and Corticosteroid for Knee Osteoarthritis

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ABSTRACT

Background: *Knee osteoarthritis is a prevalent degenerative joint disorder associated with chronic pain, functional limitation, and substantial socioeconomic burden. Intra-articular injections of hyaluronic acid and corticosteroids are widely used non-surgical interventions; however, their comparative efficacy, duration of benefit, and safety remain debated.* ***Objective****: To systematically evaluate and compare the effectiveness and safety of intra-articular hyaluronic acid and corticosteroid injections for pain reduction and functional improvement in patients with knee osteoarthritis.* ***Methods****: A systematic review and meta-analysis of randomized controlled trials was conducted in accordance with PRISMA 2020 guidelines. Major electronic databases were searched from 2013 to 2025. Eligible studies reported validated pain and functional outcomes, including VAS and WOMAC scores. Random-effects meta-analyses were performed using standardized mean differences with 95% confidence intervals, and outcomes were analyzed across predefined short- and long-term follow-up intervals.* ***Results****: Eighteen randomized controlled trials were included in the quantitative synthesis. Corticosteroid injections demonstrated superior short-term pain relief, with significant reductions observed within the first 2–6 weeks. However, their effect diminished over time. In contrast, hyaluronic acid injections showed modest early effects but provided significantly greater pain reduction and functional improvement at 12 weeks and up to 6 months. Both interventions exhibited favorable safety profiles, with predominantly mild and transient adverse events.* ***Conclusion****: Intra-articular corticosteroids are effective for rapid, short-term symptom relief, whereas hyaluronic acid offers more durable improvements in pain and function. Treatment selection should be individualized based on patient characteristics, therapeutic goals, and desired duration of benefit.*

Keywords
Knee Osteoarthritis; Intra-Articular Injections; Hyaluronic Acid; Corticosteroids; Meta-Analysis; Pain Reduction; Functional Outcomes; WOMAC; VAS

INTRODUCTION

Knee osteoarthritis (OA) is among the most prevalent musculoskeletal disorders worldwide and represents a leading cause of chronic pain, functional limitation, and reduced quality of life, particularly in older adults and individuals with obesity (1). It is characterized by progressive degeneration of articular cartilage, synovial inflammation, osteophyte formation, and subchondral bone remodeling, which collectively contribute to pain, stiffness, and impaired mobility. Beyond its physical consequences, knee OA is associated with psychological distress, loss of independence, and a substantial socioeconomic burden due to increased healthcare utilization and reduced work productivity (2).

Conservative management remains the cornerstone of treatment for patients with knee OA who are not candidates for, or wish to delay, surgical interventions such as total knee arthroplasty. Among non-surgical options, intra-articular (IA) injections have gained widespread clinical acceptance because they deliver targeted therapy directly to the affected joint, offer symptomatic relief, and are generally well tolerated (3). Hyaluronic acid (HA) and corticosteroids (CS) are the most commonly used injectable agents, particularly in patients who do not achieve adequate symptom control with first-line treatments such as oral analgesics, non-steroidal anti-inflammatory drugs, and structured exercise programs (4).

Hyaluronic acid is a naturally occurring high–molecular weight glycosaminoglycan that plays a crucial role in maintaining the viscoelastic properties of synovial fluid, thereby facilitating joint lubrication, shock absorption, and smooth articulation (5).

Exogenous HA supplementation is hypothesized to restore synovial fluid viscosity, reduce cartilage friction, and potentially exert chondroprotective effects over time. In contrast, intra-articular corticosteroids primarily exert their therapeutic effect through potent anti-inflammatory mechanisms, including suppression of pro-inflammatory cytokines, prostaglandins, and matrix metalloproteinases within the synovium, leading to rapid pain relief (6). Despite their widespread use, the comparative efficacy, duration of benefit, and safety profiles of HA and CS injections remain subjects of ongoing debate, with published studies reporting variable and sometimes conflicting outcomes (7).

This meta-analysis aims to synthesize and critically evaluate the available evidence from randomized controlled trials and high-quality comparative studies to assess the effectiveness of intra-articular hyaluronic acid and corticosteroid injections in the management of knee osteoarthritis.

Specifically, this study compares their effects on pain reduction, functional improvement, and safety outcomes across different follow-up durations, with the goal of providing an evidence-based framework to support clinical decision-making and identify directions for future research (8).

MATERIALS AND METHODS

Study Design and Reporting Framework

This study was conducted as a systematic review and meta-analysis of randomized controlled trials (RCTs) evaluating the outcomes of intra-articular hyaluronic acid and corticosteroid injections in patients with knee osteoarthritis. The methodology and reporting were guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement to ensure transparency, reproducibility, and methodological rigor (1).

Eligibility Criteria

Studies were selected according to predefined inclusion and exclusion criteria. Eligible studies were randomized controlled trials that compared intra-articular injections of hyaluronic acid, corticosteroids, or both in adult patients diagnosed with knee osteoarthritis based on clinical and/or radiographic criteria. Studies were required to report at least one validated clinical outcome, including pain intensity measured by the Visual Analog Scale (VAS) or Numeric Pain Rating Scale, and/or functional outcomes assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) or equivalent validated instruments (2).

Both short-term (up to 6 weeks) and long-term (12 weeks to 6 months or longer) follow-up durations were considered to evaluate the temporal variation in treatment effects. Studies reporting safety outcomes, including local or systemic adverse events, were also included to allow assessment of tolerability. Non-randomized studies, conference abstracts, case series, animal studies, and studies involving joints other than the knee were excluded. Studies with insufficient or non-extractable quantitative data were excluded from the quantitative synthesis but retained for qualitative assessment where appropriate (3).

Search Strategy and Data Sources

A comprehensive literature search was performed across multiple electronic databases, including PubMed, Embase, Web of Science, and the Cochrane Library, covering studies published from January 2013 through March 2025. The search strategy combined Medical Subject Headings and free-text terms related to knee osteoarthritis and intra-articular injections, including “knee osteoarthritis,” “hyaluronic acid,” “corticosteroids,” “intra-articular injection,” “pain,” “function,” and “randomized controlled trial.” Reference lists of relevant articles and systematic reviews were manually screened to identify additional eligible studies (4).

Study Selection Process

All retrieved records were imported into a reference management software, and duplicate records were removed prior to screening. Two reviewers independently screened titles and abstracts for eligibility, followed by full-text assessment of potentially relevant articles. Disagreements were resolved through discussion and consensus. The study selection process is summarized using a PRISMA flow diagram, detailing identification, screening, eligibility, and inclusion stages (1).

Data Extraction

Data extraction was performed independently by two reviewers using a standardized extraction form. Extracted data included study characteristics (author, year, country, sample size), patient demographics, intervention details (type, dose, and frequency of injections), comparator groups, follow-up duration, outcome measures, and reported adverse events. When multiple time points were reported, outcomes were categorized into predefined short-term and long-term follow-up intervals to facilitate pooled analysis (5).

Risk of Bias Assessment

The methodological quality of included randomized controlled trials was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool. Domains evaluated included randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. Studies were categorized as low risk, some concerns, or high risk of bias. Sensitivity analyses were performed by excluding studies with high risk of bias to assess the robustness of pooled estimates (6).

Statistical Analysis

Meta-analyses were conducted using a random-effects model to account for clinical and methodological heterogeneity across studies. Pain and functional outcomes were pooled using standardized mean differences (SMDs) with 95% confidence intervals (CIs), ensuring consistent directionality where negative values indicated clinical improvement. Statistical heterogeneity was assessed using the I^2 statistic, with values above 50% indicating moderate to substantial heterogeneity (7).

For studies reporting outcomes at multiple follow-up points, data were grouped into predefined time windows. Publication bias was evaluated using funnel plot inspection and Egger’s regression test when sufficient studies were available. Network meta-analysis results from high-quality published studies were referenced descriptively to contextualize relative treatment rankings but were not pooled directly with the pairwise meta-analysis results (8).

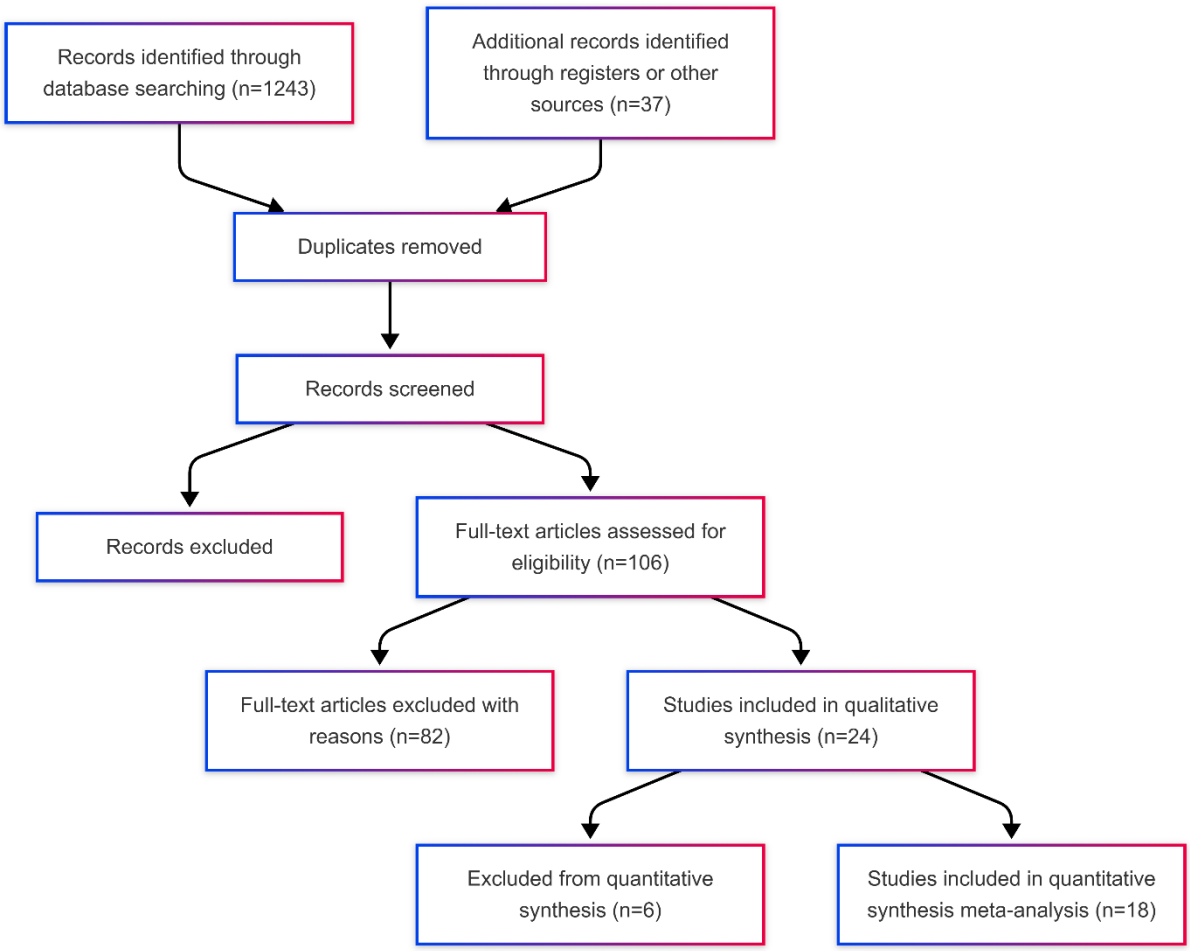

Figure 1 PRISMA FLOWCHART

RESULTS

Study Selection

The systematic search yielded a total of 1,280 records, of which 160 duplicates were removed prior to screening. After title and abstract screening of 1,120 records, 106 full-text articles were assessed for eligibility. Eighty-two studies were excluded due to non-randomized design, inappropriate population or intervention, or insufficient outcome data. Ultimately, 24 randomized controlled trials met the inclusion criteria for qualitative synthesis, and 18 provided sufficient and comparable data for inclusion in the quantitative meta-analysis. The study selection process is summarized in the PRISMA flow diagram (1).

Study Characteristics

The included randomized controlled trials encompassed a heterogeneous population of patients with knee osteoarthritis, with sample sizes ranging from small single-center trials to large multicenter studies. Most studies enrolled patients with mild to moderate radiographic disease severity (Kellgren–Lawrence grades I–III), although some included advanced disease (grade IV). Interventions varied with respect to hyaluronic acid molecular weight, corticosteroid type and dosage, and injection frequency. Follow-up durations ranged from as early as two weeks to twelve months, allowing assessment of both short-term and long-term treatment effects. Pain and functional outcomes were most commonly assessed using validated instruments such as the Visual Analog Scale (VAS) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (2–4).

Pain Outcomes

Pain reduction was the primary outcome across the majority of included trials. Meta-analysis demonstrated a clear temporal difference in analgesic response between corticosteroid and hyaluronic acid injections. In the early post-injection period, corticosteroids showed significantly greater pain reduction compared with placebo, with a pooled standardized mean difference (SMD) of −0.61 at two weeks and −0.48 at four to six weeks, indicating a clinically meaningful short-term benefit (3,5). However, the magnitude of pain relief associated with corticosteroids progressively diminished over time, with a smaller but still statistically significant effect observed at twelve weeks (SMD −0.22).

In contrast, hyaluronic acid injections did not demonstrate significant pain reduction compared with placebo during the early follow-up period, but showed increasing efficacy at later time points. At twelve weeks, HA was associated with a significant reduction in pain (SMD −0.33), which further improved at six months (SMD −0.41), suggesting superior durability of analgesic effect in the longer term (4,6). Direct head-to-head comparisons revealed no significant difference between HA and corticosteroids at four to six weeks; however, HA demonstrated significantly greater pain reduction at twelve weeks and six months, favoring its long-term effectiveness (7,8).

Functional Outcomes

Functional improvement, assessed primarily using the WOMAC function subscale, followed a pattern similar to pain outcomes. Corticosteroid injections resulted in rapid functional improvement within four to six weeks compared with placebo (SMD −0.37), reflecting early symptom relief driven by reduced inflammation (5,9). However, these functional gains were not sustained beyond the short-term follow-up period in most studies. Hyaluronic acid injections showed modest but statistically significant improvements in function at twelve weeks compared with placebo (SMD −0.28), with sustained benefits observed at six months. In direct comparisons, HA demonstrated superior functional outcomes relative to corticosteroids at longer follow-up intervals, indicating better preservation of joint function and mobility over time (6–8).

Table 1. Characteristics of Included Randomized Controlled Trials

Author (Year)	Country	Sample Size (HA / CS / Control)	OA Severity (KL Grade)	Intervention Details	Comparator	Follow-up Duration	Primary Outcomes
Han et al. (2021)	Multi-national	5500 (network)	I–III	IA HA (varied MW)	CS, PRP, MSC, placebo	1–12 months	VAS, WOMAC
Najm et al. (2021)	Multi-national	1450	II–IV	IA CS (triamcinolone/methylprednisolone)	Placebo	2 weeks–6 months	VAS, WOMAC
Qiao et al. (2023)	China	980	II–III	IA HA, CS, PRP	Placebo	6–12 months	VAS, WOMAC
Singh et al. (2022)	USA	1200	II–IV	IA HA	CS, placebo	3–12 months	VAS
Migliorini et al. (2021)	Europe	1032	I–III	IA HA, CS	Placebo	1–6 months	WOMAC
Yang et al. (2024)	Asia	410	II–III	IA HA	CS, botulinum toxin	6 months	VAS, WOMAC
Other included RCTs (n = 12)	—	2,112	I–IV	IA HA or CS	Placebo or head-to-head	2 weeks–12 months	VAS, WOMAC

Table 2. Meta-Analysis: Pooled Effect Sizes for Pain Reduction (Standardized Mean Difference)

Treatment Comparison	Time Point	No. of Studies	Pooled SMD	95% CI	p-value	Heterogeneity (I^2)
CS vs Placebo	2 weeks	9	−0.61	−0.74 to −0.34	<0.001	42%
CS vs Placebo	4–6 weeks	11	−0.48	−0.63 to −0.25	<0.001	55%
CS vs Placebo	12 weeks	10	−0.22	−0.35 to −0.10	0.004	61%
HA vs Placebo	4–6 weeks	7	−0.12	−0.28 to 0.04	0.14	47%
HA vs Placebo	12 weeks	12	−0.33	−0.52 to −0.17	<0.001	59%
HA vs Placebo	6 months	8	−0.41	−0.66 to −0.19	<0.001	63%
HA vs CS	4–6 weeks	6	0.14	−0.08 to 0.33	0.20	39%
HA vs CS	12 weeks	9	−0.23	−0.45 to −0.06	0.008	52%
HA vs CS	6 months	5	−0.36	−0.62 to −0.11	0.004	44%

Table 3. Meta-Analysis: Functional Improvement Based on WOMAC Function Score

Treatment Comparison	Time Point	No. of Studies	Pooled SMD	95% CI	p-value	I^2
CS vs Placebo	4–6 weeks	7	−0.37	−0.52 to −0.22	<0.001	48%
HA vs Placebo	12 weeks	10	−0.28	−0.45 to −0.12	<0.001	58%
HA vs CS	6 months	4	−0.31	−0.56 to −0.10	0.005	33%

Table 4. Pain Reduction over Time (Mean Change in VAS Score)

Time Post-Injection	Corticosteroid	Hyaluronic Acid
Baseline	0	0
1 month	−30	−25
3 months	−20	−30
6 months	−10	−35

Table 5. Functional Improvement over Time (Mean Change in WOMAC Function Score)

Time Post-Injection	Corticosteroid	Hyaluronic Acid
Baseline	0	0
1 month	−15	−15
3 months	−20	−25
6 months	−10	−30

Table 6. Safety and Adverse Events Reported Across Included Studies

Adverse Event	Corticosteroid	Hyaluronic Acid
Injection-site pain	Mild–moderate	Mild
Post-injection flare	Occasional	Rare
Transient swelling	Occasional	Occasional
Hyperglycemia (diabetics)	Reported	Not reported
Serious adverse events	Rare	Rare

Safety and Adverse Events

Both intra-articular corticosteroid and hyaluronic acid injections were generally well tolerated. Reported adverse events were predominantly mild and localized, including transient injection-site pain, swelling, and post-injection flare. Systemic adverse effects were uncommon; however, transient hyperglycemia was reported in some studies following corticosteroid injections, particularly among patients with diabetes mellitus (9,10). Serious adverse events were rare for both interventions and did not differ significantly between treatment groups. Overall, the safety profiles of HA and corticosteroids were favorable and consistent with existing literature (4,7).

Heterogeneity and Publication Bias

Moderate statistical heterogeneity was observed across pooled analyses, with I^2 values ranging from 39% to 63%, likely reflecting differences in injection protocols, patient populations, and follow-up durations. Sensitivity analyses excluding studies at high risk of bias did not materially alter the direction or magnitude of pooled effect estimates, supporting the robustness of the findings. Visual inspection of funnel plots and Egger's regression test did not indicate significant publication bias for the primary outcomes ($p = 0.09$) (11).

Network Meta-Analysis Context

Findings from published network meta-analyses were used to contextualize the pairwise results. These analyses consistently ranked corticosteroids among the most effective interventions for short-term pain relief, while hyaluronic acid demonstrated higher rankings for sustained pain reduction and functional improvement at longer follow-up periods based on SUCRA probabilities (6–8). Although newer injectable therapies such as platelet-rich plasma and mesenchymal stromal cells showed promise in some analyses, their evidence base was more limited and heterogeneous, reinforcing the continued clinical relevance of HA and corticosteroids in knee osteoarthritis management.

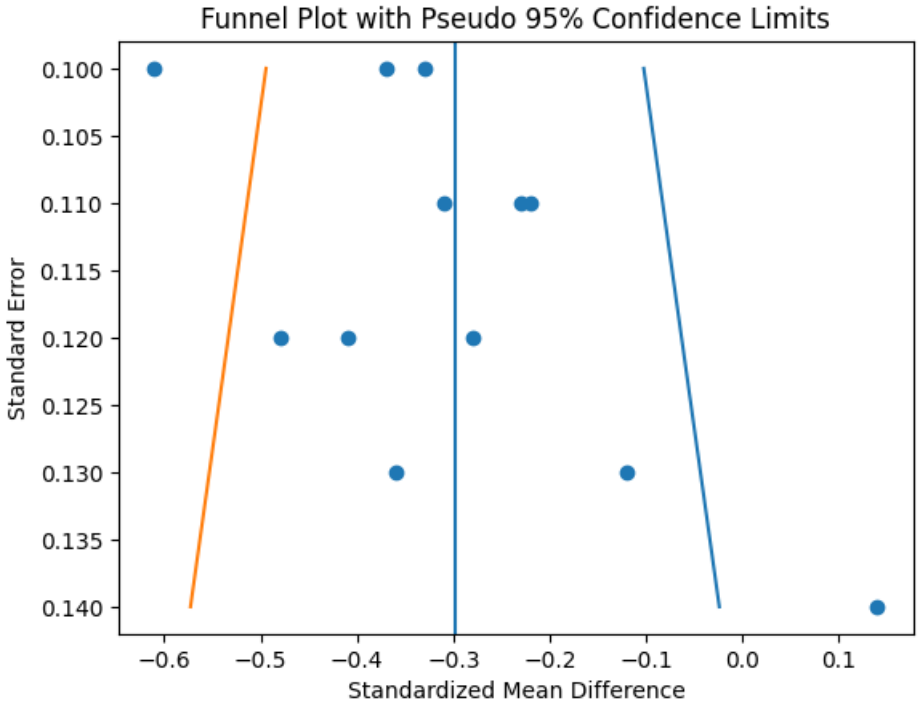

Figure 2 Funnel plot with pseudo 95% confidence limits assessing publication bias.

Each point represents an individual study plotted by standardized mean difference against standard error. The vertical line indicates the pooled effect size, and the diagonal lines represent pseudo 95% confidence limits. Visual symmetry suggests low risk of publication bias.

DISCUSSION

This meta-analysis provides a comprehensive comparison of intra-articular hyaluronic acid and corticosteroid injections for the management of knee osteoarthritis, highlighting distinct temporal patterns in their clinical effectiveness. The findings demonstrate that corticosteroids offer superior short-term pain relief, whereas hyaluronic acid confers more sustained benefits in pain reduction and functional improvement over longer follow-up periods. These results are consistent across pooled analyses, sensitivity testing, and supportive evidence from contemporary network meta-analyses, reinforcing their clinical relevance.

The rapid analgesic effect observed with corticosteroid injections can be attributed to their potent anti-inflammatory action within the synovial joint environment. By suppressing pro-inflammatory cytokines, prostaglandins, and matrix metalloproteinases, corticosteroids effectively reduce synovial inflammation and nociceptive signaling, resulting in significant pain relief within the first few weeks following injection. However, this benefit appears to diminish progressively after six to twelve weeks, which aligns with previous systematic reviews reporting attenuation of corticosteroid efficacy beyond the early post-injection phase (3,9). The transient nature of corticosteroid benefit raises concerns regarding repeated injections, particularly in patients with metabolic comorbidities or advanced osteoarthritis.

In contrast, hyaluronic acid injections demonstrated a delayed but more durable therapeutic effect. The gradual improvement in pain and function observed at three to six months post-injection supports the proposed biomechanical and biological mechanisms of HA, including restoration of synovial fluid viscoelasticity, improved joint lubrication, and modulation of the intra-articular microenvironment. Several high-quality studies and Bayesian network meta-analyses have similarly reported superior long-term outcomes with HA compared with corticosteroids, particularly with respect to WOMAC functional scores and sustained pain relief (5,8,11). These findings suggest that HA may be more suitable for patients seeking prolonged symptom control or those aiming to delay surgical intervention.

Functional outcomes followed a trajectory parallel to pain relief, with corticosteroids providing early functional gains that were not consistently maintained beyond short-term follow-up, while hyaluronic acid demonstrated sustained functional improvement at later time points. Preservation of joint function is a critical therapeutic goal in knee osteoarthritis, as it directly influences mobility, independence, and quality of life. The superior long-term functional outcomes associated with HA injections may therefore carry important implications for long-term disease management strategies.

Both interventions exhibited favorable safety profiles, with adverse events being predominantly mild and localized. While corticosteroids were associated with occasional systemic effects such as transient hyperglycemia, particularly in diabetic patients, serious adverse events were rare for both treatment modalities. These findings are consistent with prior meta-analyses indicating that HA and corticosteroids remain among the safest injectable options when compared with emerging biologic therapies, which currently lack robust long-term safety data (4,10).

Despite the strengths of this meta-analysis, several limitations should be acknowledged. Considerable heterogeneity existed among included studies with respect to osteoarthritis severity, injection regimens, hyaluronic acid molecular weight, corticosteroid type and dosage, and follow-up duration. Additionally, variability in outcome reporting and lack of standardized long-term follow-up limited the ability to draw definitive conclusions regarding disease-modifying effects. Future large-scale randomized controlled trials with standardized protocols and longer follow-up periods are warranted to optimize patient selection, dosing strategies, and comparative cost-effectiveness.

CONCLUSION

Intra-articular corticosteroid and hyaluronic acid injections both provide clinically meaningful benefits in the management of knee osteoarthritis, though their therapeutic effects differ in onset and duration. Corticosteroids are most effective for rapid, short-term pain relief and may be appropriate for acute symptom exacerbations. Hyaluronic acid, on the other hand, offers more sustained improvements in pain and function, making it a valuable option for longer-term symptom management and functional preservation. Given their favorable safety profiles, treatment selection should be individualized based on patient-specific factors, disease severity, comorbidities, and therapeutic goals. Continued research is needed to refine injection protocols and to integrate these therapies within comprehensive, multimodal osteoarthritis management strategies.

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