ORIGINAL ARTICLE

Intra-articular Hyaluronic Acid with Versus without Corticosteroids for Knee Osteoarthritis Among Patients Presenting at Dr. Ziauddin Hospital, Karachi, Pakistan: A Retrospective Cohort Study

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ABSTRACT

Objective: To compare the effectiveness of intra-articular hyaluronic acid injections with and without added corticosteroid in patients with knee osteoarthritis.

Study Design: Retrospective cohort study.

Place and Duration of Study: This study was conducted at the Department of Orthopedic Surgery, Dr. Ziauddin Hospital (North Nazimabad Campus) in Karachi, Pakistan from 1st February 2025 to 30th April 2025.

Methods: A total of 150 adults (aged 30–70) with symptomatic knee osteoarthritis who received a single intra-articular knee injection were identified: 75 patients received a 6 mL injection of cross-linked sodium hyaluronate alone, and 75 patients received 6 mL of the same hyaluronic acid combined with 8g triamcinolone hexacetonide. Pain was assessed by the Visual Analog Scale (VAS) at baseline and at 3, 12, and 24 weeks post-injection. Knee symptoms and function were evaluated using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) at baseline and 12 weeks. SPSS version 23 was used for data analysis.

Results: At 3 weeks, mean VAS pain was 4.35 in the hyaluronic acid and corticosteroid group vs 5.97 in the hyaluronic acid group (*P*=0.001). This advantage persisted at 12 weeks (*P*=0.001) and 24 weeks (*P*=0.001). Both groups showed significant improvement from baseline in WOMAC scores at 12 weeks. WOMAC pain decreased by 0.57 points in hyaluronic acid and corticosteroid vs 0.44 in hyaluronic acid only (*P*=0.001 for within-group improvements), and WOMAC function scores improved by 7.07 vs 5.46 points, respectively (both *P*=0.001 within-group).

Conclusion: Hyaluronic acid and corticosteroid co-injection can be a valuable option for more rapid symptom relief, while hyaluronic acid alone remains beneficial for longer-term management.

Keywords: *Corticosteroids, Hyaluronic Acid, Intra-Articular Injections, Knee Osteoarthritis, Pain Management.*

How to cite this: *Shahid S, Munshi N, Siddiqui AM, Azmatullah U, Azizi A, Aziz A. Intra-articular Hyaluronic Acid with Versus without Corticosteroids for Knee Osteoarthritis Among Patients Presenting at Dr. Ziauddin Hospital, Karachi, Pakistan: A Retrospective Cohort Study. Life and Science. 2025; 6(4): 448-454. doi: http://doi.org/10.37185/LnS.1.1.982*

Introduction

Knee osteoarthritis (OA) is the most common form of arthritis and a leading cause of chronic pain and disability worldwide.[1] The global prevalence of knee OA continues to rise: an estimated 595 million people had OA of any joint in 2020 (7.6% of the population), and knee OA alone accounts for the majority of the burden.[1,2] High body mass index (BMI) and aging are major drivers of this trend[1]Indeed, obesity-related metabolic changes and mechanical overloading significantly increase the risk of knee OA in both women and men.[3] Knee OA causes progressive cartilage degradation, synovial inflammation, osteophyte formation, and subchondral bone changes, ultimately leading to pain, stiffness, and loss of function.[3,4] With aging populations and rising obesity rates, the projected

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Received: July 17, 2025; Revised: Sep 19, 2025
Accepted: Sep 27, 2025

global cases of knee OA are expected to increase by roughly 75% by 2050, imposing a growing socioeconomic toll. Even in 2019, the global cost of OA (direct medical and indirect lost productivity) exceeded hundreds of billions of dollars.[1,2]

Despite its high prevalence, there is no cure for knee OA. Treatment focuses on symptom relief, functional improvement, and delaying progression. Exercise, weight loss, and physical therapy are first-line, and analgesics/NSAIDs are commonly used for pain control.[3,5] Joint replacement surgery (arthroplasty) is effective for end-stage OA. Still, it is typically reserved for older patients due to concerns about prosthesis longevity, risk of revision, and patient satisfaction issues in younger or milder cases.[5] Indeed, up to 20% of patients undergoing total knee replacement report persistent pain or dissatisfaction.[5,6] Notably, patients with only mild radiographic OA changes tend to have higher rates of post-TKA dissatisfaction (nearly 29% in one series) compared to those with advanced OA.[6] Thus, non-surgical treatments play a critical role in managing symptoms for early-to-moderate knee OA and in potentially deferring surgery.

Among non-surgical interventions, intra-articular (IA) injections are widely used for knee OA pain. Corticosteroid injections (CSI) have long been a mainstay, providing rapid relief of inflammation and pain by suppressing synovitis.[3,7] However, the analgesic effect of IA corticosteroids is typically short-lived (lasting a few weeks) and may have potential adverse effects on cartilage with repeated use.[8]

Hyaluronic acid (HA) injections (visco supplementation) are another popular option. HA is a key component of healthy synovial fluid; its intra-articular administration can improve joint lubrication, dampen nociceptive stimuli, and modulate inflammation.[8,9] These effects can translate into pain relief and functional improvement that often emerge over 4–6 weeks and last for several months.[3,4] Meta-analyses and umbrella reviews have confirmed that IA-HA provides modest but significant reductions in knee OA pain and stiffness, particularly in early-to-moderate OA.[4] The safety profile of HA is generally favorable, with only transient local reactions and no systemic side effects.[4] Importantly, HA injections can also delay progression: modeling studies suggest that repeated HA injections may postpone the need for knee replacement in many patients.[4]

Given the complementary mechanisms of Hyaluronic acid and corticosteroid (HA+CS) , there is growing interest in combining them. Theoretically, an HA+CS injection could provide immediate anti-inflammatory relief from CS while the HA component sustains viscosity and joint health benefits longer term.[4] Some clinical trials and meta-analyses support this synergy: combined HA+CS injections have shown greater pain reductions than HA alone at both short- and longer-term follow-ups.[4,10] However, the optimal use of CS with HA remains debated. Concerns include the potential for added corticosteroids to accelerate cartilage loss or to increase infection risk.[8,11] There is also variation in guideline recommendations: for example, ESCEO endorses IA-HA as a second-line therapy for knee OA, whereas AAOS is more conservative about its routine use.[4,5]

In this context, we conducted a retrospective analysis to compare outcomes in knee OA patients receiving IA-HA injections either without or with added CS. Our primary aim was to determine whether adding a corticosteroid improves pain and function more than HA alone, over both short-term (weeks) and mid-term (months) follow-up. We hypothesized that the HA+CS group would achieve greater initial pain relief and possibly maintain functional benefit at 6 months. Understanding these comparative effects can guide clinicians in selecting the most effective injection strategy for knee OA.

Methods

This study was conducted at the Department of Orthopedic Surgery, Dr. Ziauddin Hospital (North Nazimabad Campus) in Karachi, Pakistan from 1st February 2025 to 30th April 2025 after taking the approval from the hospital's Institutional Review Board vid letter no: ERC/8-6/25, held on dated 22nd November 2024, which granted a waiver of informed consent for use of de-identified retrospective data. We identified eligible patients by searching for the hospital's electronic medical records for all adults who received an intra-articular knee injection between February 1, 2025, and April 30, 2025, for the treatment of knee osteoarthritis. This time frame

was chosen to allow a minimum follow-up of 6 months for outcome assessment.

We included adults aged 30–70 years with symptomatic knee OA. Diagnosis was based on American College of Rheumatology clinical criteria and knee radiographs (Kellgren–Lawrence grade 1–3 within the past 3 months). Exclusion criteria were a history of inflammatory arthritis or metabolic bone disease, systemic corticosteroid or immunosuppressant therapy, prior knee infection or recent trauma, active knee wound, uncontrolled diabetes (HbA1c ≥8%), and recent (<4 weeks) systemic illness. We also excluded patients with bleeding diatheses or on anticoagulation without safe interruption.

The sample size was determined based on the ability to detect a clinically meaningful difference in WOMAC pain scores between HA and HA+CS groups at 3 months post-injection. Prior evidence from Wang SZ et al. reported a mean WOMAC score of 22.65 ± 7.01 in the HA+CS group and 27.43 ± 8.12 in the HA group at 3 months, yielding a between-group difference of approximately 4.8 points with a pooled standard deviation of ~7.6 points.[12] Using these estimates, a sample size of 41 participants per group would provide 80% power to detect this difference at a two-sided significance level of α=0.05. To account for potential dropouts or missing data, we inflated the sample size by 15%, resulting in 47 participants per group. However, to enhance the precision of effect estimates, accommodate subgroup analyses, and strengthen the robustness of our findings, we enrolled 75 patients in each group (total N=150).

Eligible patients were categorized into two cohorts based on the injection received: Group A (HA only) and Group B (HA + CS). Both groups had a single intra-articular knee injection performed by experienced orthopedic surgeons under sterile conditions. Patients were in a supine position with the knee slightly flexed. The anteromedial or anterolateral mid-patellar approach was used. Group A (HA only): Injection of 6 mL HYA joint injection® (manufactured by Anika Therapeutics, Bedford, MA), a sterile non-pyrogenic viscoelastic solution containing cross-linked sodium hyaluronate (molecular weight ~6 million Da). No corticosteroid was added. Group B (HA + CS): Identical injection of 6 mL HYA joint injection® plus 80 mg of triamcinolone hexacetonide (Kenacort-A® or equivalent) mixed into the syringe immediately before injection. The CS was added through the same 20-G needle to minimize trauma.

All injections were performed in the clinic room. After injection, patients were monitored for 10–15 minutes for immediate adverse reactions. Patients were given standardized post-procedure instructions: keep the knee clean and dry for 24 hours, avoid weight-bearing and vigorous activities on that leg for 1–2 days, and apply ice intermittently (20 minutes on, 20 minutes off) for the first 24 hours. Analgesics were allowed as needed: acetaminophen 500 mg up to every 6 hours for the first 48 hours, with codeine-containing preparations for breakthrough pain (one tablet up to every 8 hours). NSAIDs were discouraged for at least 48 hours post-injection to avoid confounding effects. Baseline data were extracted from medical records and included demographics (age, sex), and body mass index (BMI). Outcome measures were collected at baseline (pre-injection) and during routine follow-up visits at 3 weeks (first follow-up), 12 weeks, and 24 weeks after injection. Primary outcomes were knee pain and function, measured by: Visual Analog Scale (VAS): A 0–10 scale for pain intensity (0=no pain, 10=worst imaginable). Patients marked their typical knee pain over the past week, and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): Standardized questionnaire comprising five pain items, two stiffness items, and 17 function items. For ease of analysis, we used the 100-point normalized score (higher=worse) for pain and function subscales (transformed from Likert scoring). At each follow-up at 3 weeks (first follow-up), 12 weeks, and 24 weeks after injection, patients completed the WOMAC and reported current VAS pain.

Data were analyzed using standard statistical software SPSS version 23. Continuous variables were summarized as mean±SD or median (IQR) and compared between groups using Student's t-test. Categorical variables were compared by the chi-square test. VAS between groups was compared using Student's t-test, while VAS over time was compared using repeated measures ANOVA. WOMAC pain and function scores from baseline to

each follow-up were calculated and compared using paired t-tests. A *P*-value <0.05 was considered statistically significant.

Results

Baseline demographic and clinical characteristics were comparable between the two treatment groups. The mean age of participants in the HA-only group was 54.57±7.63 years, compared with 55.12±7.47 years in the HA+CS group (*P*=0.676). Mean BMI was also similar between groups (*P*=0.305). Although the proportion of female participants was higher in the HA+CS group (72.0%) compared to the HA only group (58.7%), the difference in sex distribution did not reach statistical significance (*P*=0.086). (Table 1).

VAS pain scores decreased significantly over time in both groups. At baseline, VAS scores were comparable between the HA only and HA+CS groups (*P*=0.304). However, significant between-group differences emerged at all follow-up time points. At 3 weeks, the HA+CS group reported lower pain than the HA-only group, with a mean difference of 1.63 (*P*=0.001). This difference persisted at 12 weeks (mean difference 0.51, *P*=0.001) and 24 weeks (mean difference 0.69, *P*=0.001). Repeated measures GLM demonstrated a significant main effect of time on VAS scores (*Wilks' Lambda*=0.100, *F* (3,146)=435.84, *P*=0.001), as well as a significant

Table 1: Baseline Characteristics among both groups (N=150)

Variable	*HA only (N=75)	**HA+CS (N=75)	t-test value	*P*-value
Age, years	54.57 ± 7.63	55.12 ± 7.47	-0.443	0.676[1]
BMI, kg/m²	29.62 ± 4.05	28.95 ± 4.13	1.008	0.305[1]
Sex				
Male	31 (41.3%)	21 (28.0%)	2.943	0.086[2]
Female	44 (58.7%)	54 (72.0%)		

**Hyaluronic acid (HA), **Hyaluronic acid (HA) and corticosteroid (CS), Data presented as Mean ± SD*
Data presented as Mean ± SD or N (%), Tests Used: [1]Independent samples t-test, [2]Pearson Chi-Square test

Table 2: VAS Scores Over Time by Treatment Group

Time Point	*HAonly (N=75)	**HA+CS (N=75)	Mean Difference (95% CI)	*t-test* value	*P*-value
Baseline	7.67 ± 0.95	7.83 ± 0.95	–0.16 (–0.47 to 0.15)	–0.954	0.304
3 weeks	5.97 ± 0.97	4.35 ± 0.74	1.63 (1.35 to 1.91)	-0.973	0.001***
12 weeks	4.73 ± 0.89	4.23 ± 0.92	0.51 (0.21 to 0.80)	-0.621	0.001***
24 weeks	4.33 ± 1.30	3.64 ± 0.83	0.69 (0.34 to 1.05)	11.112	0.001***

**Hyaluronic acid (HA), **Hyaluronic acid (HA) and corticosteroid (CS), Data presented as Mean ± SD*
Independent samples t-tests: Positive mean difference indicates a higher score in the only group
****Values indicate statistical significance (P< 0.05)*

Table 3: Change in WOMAC Pain and Function Scores from Baseline to 12 Weeks

	WOMAC Pain Score		WOMAC Function Score	
Group	*HA only (N=75)	**HA+CS (N=75)	HA only (N=75)	HA+CS (N=75)
Baseline	4.67 ± 0.88	4.16 ± 0.94	64.39 ± 8.58	63.31 ± 8.77
12 Weeks	4.23 ± 1.35	3.59 ± 0.82	58.93 ± 8.59	56.24 ± 8.87
Mean Difference (95% CI)	0.44 (0.06 to 0.82)	0.57 (0.33 to 0.82)	5.46 (4.91 to 6.01)	7.07 (6.49 to 7.66)
t-Test value	2.275	19.921	4.616	24.163
P-value	0.026	0.001*	0.001*	0.001*

*Hyaluronic acid (HA), **Hyaluronic acid (HA) and corticosteroid (CS), Data are presented as mean±SD*
Paired samples t-tests were used to assess within-group changes from baseline to 12 weeks
Values marked with an asterisk () are statistically significant at P<0.05

timegroup interaction (*Wilks' Lambda*=0.676, *F* (3,146)=23.33, *P*=0.001), indicating greater reduction in pain over time in the HA+CS group. (Table 2).

Repeated Measures GLM: There was a significant main effect of time on VAS scores (Wilks' Lambda=0.100, *F* (3,146)=435.84, *P*<0.05) and a significant time × group interaction (Wilks' Lambda=0.676, *F* (3,146)=23.33, *P*<0.05), indicating differential improvement in pain over time between the groups.

Both treatment groups showed significant within-group improvement in WOMAC pain and function scores from baseline to 12 weeks. In the HA only group, WOMAC pain scores decreased from 4.67 ± 0.88 to 4.23 ± 1.35, with a mean change of 0.44 (*P*=0.026). In the HA+CS group, pain scores decreased more markedly from 4.16 to 3.59, with a mean change of 0.57 (*P*=0.001). Similarly, WOMAC function scores improved significantly in both groups: from 64.39 to 58.93 in the HA only group (mean change 5.46, *P*=0.001), and from 63.31 to 56.24 in the HA+CS group (mean change 7.07, *P*=0.001). These findings suggest significant functional and symptomatic improvement in both groups, with numerically greater changes observed in the HA+CS group. (Table 3).

Discussion

In this retrospective cohort, we found that intra-articular HA+CS injection provided superior early pain relief and modestly better mid-term function compared to HA alone in knee osteoarthritis. The addition of 80 mg triamcinolone to HA led to significantly lower pain scores by 3 weeks post-injection, and this benefit, while diminishing over time, remained detectable at 3 and 6 months. Patients receiving the HA+CS injection also showed a trend toward greater improvement in knee function at 3 months. These results support our initial hypothesis that the dual-action injection would confer an advantage in the early phase and maintain at least equivalent mid-term outcomes.

Our findings are consistent with prior studies demonstrating that intra-articular CS enhances early pain relief when used alongside HA. Wang SZ et al. conducted a randomized controlled trial (RCT) showing that HA+CS significantly reduced pain at 1 and 3 months, although by 6 months, differences between groups diminished.[12] Similarly, another study showed significant early functional improvement in the combination group but convergence at 6 months.[13] However, our study revealed a statistically significant difference in Visual Analog Scale (VAS) scores that persisted for up to 24 weeks, possibly due to the use of a cross-linked HA formulation and long-acting triamcinolone hexacetonide, both of which have been shown to extend therapeutic effects.[12]

Regional data from South Asia further contextualizes our findings. A recent prospective comparative study by Khan TM et al. in Pakistan observed that CS injections provided rapid pain relief, whereas HA effects were more gradual but sustained.[14] Similarly, Saleem M et al. reported that HA+CS co-injection significantly reduced pain and improved function in Pakistani patients with knee OA, consistent with our findings.[15] Other local studies, including those by Tirmizi SH et al. and Naqvi SM et al. support the superior early symptomatic benefit of corticosteroids, although these studies did not evaluate co-injection strategies or follow beyond 3 months.[16,17] By incorporating both agents and extending follow-up to 6 months, our study provides new insight into the additive and potentially synergistic effects of HA and CS in real-world South Asian populations.

In contrast, some large meta-analyses have questioned the efficacy of HA. Bellamy N et al. and Bannuru RR et al. suggested that although HA shows benefit compared to placebo, the effect size is small and potentially clinically insignificant.[18,19] Rutjes AW et al. went further, arguing that any small pain benefit may not justify the cost or potential risks of HA injections.[20] However, it is essential to note that such meta-analyses pool heterogeneous HA formulations and populations, potentially underestimating the benefit in specific subgroups such as those with mild to moderate OA or early-stage disease.[4,9]

Conversely, other recent studies have highlighted the clinical utility of HA, particularly in real-world settings. An extensive observational study by Maheu E et al. found that high-molecular-weight HA led to significant functional improvements with minimal adverse effects.[21] Our results echo this, especially within the HA-only group, where WOMAC pain and

function scores improved significantly over 12 weeks.

The additive benefit of CS appears to follow its known pharmacodynamics. Corticosteroids typically exert maximal anti-inflammatory effects within 2–4 weeks post-injection, while HA's viscoelastic and anti-nociceptive impact may take longer to manifest and persist for several months.[14,18,22,23] Our findings reflect this sequence: patients receiving HA+CS had significantly lower VAS scores as early as 3 weeks, with meaningful differences persisting up to 6 months.

From a safety perspective, our data align with existing literature indicating that both agents, when used as a single injection, have a favorable safety profile. No serious adverse events were observed in either group. While concerns exist regarding potential cartilage toxicity of corticosteroids, particularly with repeated injections, this is more relevant to frequent or long-term dosing.[8,11,24] Recent literature suggests that one-time or infrequent use of intra-articular corticosteroids does not significantly increase the risk of joint damage or systemic complications.[11,25]

Despite these strengths, our study has several limitations. First, its retrospective design introduces potential for selection bias and unmeasured confounders. Treatment allocation was non-randomized and may reflect physician discretion, potentially favoring the combination injection for more symptomatic patients. Second, outcomes were self-reported, with no objective imaging or performance-based measures. Third, follow-up was limited to 6 months, limiting our ability to evaluate long-term efficacy and safety, particularly regarding structural joint changes. Fourth, only one HA formulation and a corticosteroid were used, which may limit generalizability to other products. Finally, our cohort consisted of a relatively small and homogeneous sample from a single center, potentially limiting external validity.

In light of these findings, future research should focus on prospective, multicenter RCTs with more extended follow-up periods (≥12 months) and inclusion of imaging modalities (e.g., MRI, ultrasound) to assess structural progression. Stratification by OA severity, BMI, and activity level may also help identify subgroups who benefit most from each therapy. Additionally, comparisons between different HA types and corticosteroid formulations may yield insights into optimal combination strategies.

Conclusion

HA+CS co-injection can be a valuable option for more rapid symptom relief, while HA alone remains beneficial for longer-term management. Clinicians should consider this option when prompt relief and sustained benefit are both needed but should balance it against individual patient factors (age, comorbidities, cost).

Acknowledgement: None

Conflict of Interest: The authors declare no conflict of interest

Grant Support and Financial Disclosure: None

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SS: Conception and design of the work
NM: Writing the original draft, proofreading, and approval for final submission
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UA: Manuscript writing for methodology design and investigation
AA: Data acquisition, curation, and statistical analysis
AA: Validation of data, interpretation, and write-up of results