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Research Article

Comparison of the Analgesic Effects of Intra-Articular Injection of Methylprednisolone versus Methylprednisolone-Ketorolac in Knee Osteoarthritis

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ABSTRACT

Background: Knee osteoarthritis (OA) is one of the most common causes of chronic pain and functional limitation, particularly among middle-aged and elderly populations. Intra-articular corticosteroid injections are widely used for short-term pain relief; however, their analgesic effect is often limited in duration. The addition of nonsteroidal anti-inflammatory drugs (NSAIDs) may enhance therapeutic efficacy. This study aimed to compare the analgesic effects of intra-articular methylprednisolone versus methylprednisolone-ketorolac in patients with knee osteoarthritis.

Methods: In this randomized clinical trial, 82 patients with knee osteoarthritis were enrolled at Sina Hospital between 2024 and 2026. Patients were randomly assigned to receive either intra-articular methylprednisolone (Group T) or Methylprednisolone-ketorolac (Group TK). Pain intensity was assessed using the Numeric Rating Scale (NRS) during walking, rising after prolonged sitting or waking up, and stair climbing at baseline and at 2 and 4 weeks post-injection. Statistical analyses were performed using appropriate tests, with a significance level set at $P<0.05$.

Results: A total of 79 patients were included in the final analysis. Both treatment groups demonstrated significant reductions in pain scores compared with baseline. However, the reduction in walking-related pain was significantly greater in the methylprednisolone-ketorolac group at both 2 and 4 weeks of follow-up ($P<0.001$). No statistically significant differences were observed between the two groups regarding pain during stair climbing or post-rest stiffness. No major adverse events were reported in either group.

Conclusion: The findings suggest that adding ketorolac to intra-articular methylprednisolone provides a clinically and statistically superior analgesic effect on walking-related pain in patients with knee osteoarthritis, likely due to synergistic inhibition of inflammatory pathways. This combination appears to be a safe and more effective short-term treatment option for pain control in knee OA. Further studies with larger sample sizes and longer follow-up periods are recommended to evaluate long-term outcomes and structural joint effects.

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Introduction

Knee osteoarthritis (KOA) is one of the most prevalent chronic and degenerative joint disorders and represents a leading cause of persistent pain, functional disability, and reduced quality of life among adult and elderly populations worldwide. The disease is characterized by progressive articular cartilage degradation, subchondral bone remodeling, synovial inflammation, and narrowing of the joint space. Owing to the global increase in life expectancy, rising prevalence of obesity, and sedentary lifestyle patterns, the incidence and burden of knee osteoarthritis have increased substantially over recent decades, posing a major challenge to healthcare systems [1-2].

The management of knee osteoarthritis primarily focuses on pain relief, inflammation control, improvement of joint function, and enhancement of patients' quality of life. Therapeutic strategies include non-pharmacological interventions such as weight reduction, physical therapy, and lifestyle modification, as well as pharmacological treatments including oral and topical medications, intra-articular injections, and ultimately, surgical procedures in advanced cases. Among these approaches, intra-articular injection therapies have gained considerable attention due to their localized effect, rapid onset of action, reduced systemic adverse effects, and relative ease of administration, particularly in patients with moderate to severe knee pain [3].

Corticosteroids have long been regarded as one of the most effective agents for intra-articular injection in the treatment of knee osteoarthritis. Methylprednisolone is among the most commonly used intra-articular corticosteroids and exerts its anti-inflammatory and analgesic effects through inhibition of phospholipase A2, suppression of prostaglandin synthesis, and down-regulation of pro-inflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α). Numerous studies have demonstrated that intra-articular methylprednisolone injection can significantly reduce pain and improve knee joint function in the short term [4-5].

Despite the well-established efficacy of corticosteroids, concerns have been raised regarding their repeated or long-term use. Emerging evidence suggests that frequent intra-articular corticosteroid injections may be associated with accelerated cartilage degeneration, reduced cartilage thickness, and potential adverse effects on joint structure. Moreover, the analgesic benefits of corticosteroids are often transient, and some patients experience suboptimal or insufficient pain relief [6-7]. These limitations have prompted researchers to explore alternative agents or combination therapies that may provide enhanced efficacy with fewer adverse effects. In recent years, intra-articular administration of nonsteroidal anti-inflammatory drugs (NSAIDs) has attracted increasing interest as a potential therapeutic option for knee osteoarthritis. Ketorolac is a potent NSAID that produces significant analgesic and anti-inflammatory effects by inhibiting cyclooxygenase enzymes (COX-1 and COX-2) and reducing prostaglandin synthesis. Compared with oral NSAIDs, intra-articular injection of ketorolac may minimize systemic complications such as gastrointestinal, renal, and cardiovascular adverse effects while delivering effective local pain control within the knee joint [8-9]. Several studies have investigated the efficacy of intra-articular ketorolac injection in patients with knee osteoarthritis, reporting pain reduction and functional improvement comparable to those achieved with corticosteroids, but without the potential cartilage-related concerns associated with steroid use [10]. Nevertheless, there remains no clear consensus regarding the precise role of ketorolac as a standalone alternative or as an adjunct to corticosteroids in the management of knee osteoarthritis.

Given the distinct mechanisms of action of methylprednisolone and ketorolac, the combined intra-articular administration of these agents may exert synergistic effects in reducing joint inflammation and pain. Such a combination may allow for improved analgesic efficacy, prolonged duration of symptom relief, and a potential reduction in the required corticosteroid dose, thereby decreasing steroid-related adverse effects. However, only a limited number of studies have directly compared intra-articular methylprednisolone alone with the combination of METHYLPREDNISOLONE and ketorolac, and the available findings remain scarce and sometimes inconsistent [11-12].

Considering the high prevalence of knee osteoarthritis, the clinical importance of effective pain control, and the limited comparative evidence regarding these two treatment strategies, the present study aimed to compare the analgesic and functional outcomes of intra-articular injection of methylprednisolone alone versus a combined injection of methylprednisolone and ketorolac in patients with knee osteoarthritis. The results of this study may provide valuable clinical evidence to support the selection of a more effective, safer, and cost-effective therapeutic approach and offer practical guidance for clinicians in the management of chronic knee pain.

Methods

Study Design and Participants

This randomized controlled clinical trial was conducted to compare the analgesic effects of intra-articular injection of methylprednisolone alone versus a combination of methylprednisolone and ketorolac in

patients with knee osteoarthritis. The study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of Tehran University of Medical Sciences; then it was officially registered in the Iranian Clinical Trials Registry (IRCT): IRCT20130304012695N20 (September 5, 2024). Written informed consent was obtained from all participants prior to enrollment. Eligible participants were adult patients diagnosed with primary knee osteoarthritis based on clinical and radiographic criteria consistent with the American College of Rheumatology (ACR) guidelines. Patients presenting with moderate to severe knee pain were recruited from the outpatient clinic during the study period.

Inclusion and Exclusion Criteria

Inclusion criteria were:

- Age ≥ 40 years
- Diagnosis of primary knee osteoarthritis
- Persistent knee pain for at least three months
- Baseline pain score ≥ 4 on the Numeric Rating Scale (NRS)

Exclusion criteria included:

- Secondary osteoarthritis (post-traumatic, inflammatory, or infectious arthritis)
- Prior intra-articular injection within the preceding three months
- History of knee surgery on the affected joint
- Known hypersensitivity to corticosteroids or NSAIDs
- Active joint infection, systemic infection, or coagulopathy
- Severe renal, hepatic, or cardiovascular disease

Randomization and Allocation

Patients were randomly assigned into two treatment groups using a computer-generated randomization sequence. Allocation concealment was ensured using sealed opaque envelopes. Participants were divided into the following:

- Group A (methylprednisolone group): received intra-articular injection of methylprednisolone.
- Group B (Ketorolac–Methylprednisolone group): received an intra-articular injection of a combination of methylprednisolone and ketorolac.

Intervention Procedure

All injections were performed under sterile conditions by an experienced clinician using a standard anterolateral approach to the knee joint. In the methylprednisolone group, patients received an intra-articular injection of methylprednisolone acetonide (40 mg/1 mL) administered separately using a 22-gauge needle. The injection was performed with the patient in the supine position and the knee in full extension, using the lateral mid-patellar approach. In the combined methylprednisolone-ketorolac group, patients received an intra-articular injection consisting of ketorolac tromethamine (30 mg/1 mL) mixed with methylprednisolone acetonide (40 mg/1 mL). The injection was administered using the same technique, needle size, and anatomical approach as in the methylprednisolone only group. No additional intra-articular medications were administered during the study period. Patients were advised to avoid strenuous physical activity for 24 h following injection and were allowed to use acetaminophen as rescue analgesia if necessary.

Outcome Measures

Patients were evaluated at three predefined time points: prior to injection (baseline) and at 2 weeks and 6 weeks after injection. At each visit, a comprehensive clinical assessment was performed and systematically recorded.

Pain intensity during various daily activities, including walking, was assessed.

In addition, joint stiffness after waking from sleep, and the patient's ability to climb stairs were evaluated at each visit. The primary outcome of the study was the reduction of knee pain and swelling, assessed using a 0–100 Numerical Rating Scale (NRS).

- The secondary outcomes included:
- Improvement in physical activity, particularly the ability to climb stairs
- Reduction in pain and joint stiffness
- Decreased consumption of systemic and analgesic medications

Statistical Analysis

Statistical analysis was performed using appropriate statistical software. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Between-group comparisons were conducted using independent-sample t-tests or Mann-Whitney U tests, as appropriate. Within-group comparisons were performed using paired t-tests or repeated-measures analysis.

A P value of less than 0.05 was considered statistically significant.

Sample Size Calculation

The minimum required sample size for this study was calculated using the formula for comparison of means between two independent groups, considering a type I error (α) of 0.05 and a statistical power of 80%. Based on the results reported by Ebru Yilmaz et al., the estimated sample size was approximately 30 participants per group.

Assuming a 10% attrition rate, the minimum required sample size was increased to 35 participants in each group, resulting in a total sample size of 70 participants for the study [13].

Results

A total of 82 patients with knee osteoarthritis, who met the predefined inclusion and exclusion criteria, were enrolled in this study. Patients were randomly assigned to two groups: the methylprednisolone group and the ketorolac-methylprednisolone group. At the end of the study, 79 patients were included in the final statistical analysis (Figure 1). The degree of knee joint involvement was comparable between the two groups, with most patients presenting with grade 2 or 3 osteoarthritis. All patients received identical care and follow-up according to the study treatment protocol.

Baseline demographic and clinical characteristics of the participants in both groups are summarized and compared in (Table 1).

Baseline Characteristics

As shown in (Table 1), patients in the Ketorolac–methylprednisolone group were slightly older than those in the methylprednisolone group ($P < 0.001$). There were no significant differences between the two groups regarding sex distribution, body weight, or body mass index (BMI).

Pain intensity during walking before injection was similar between the two groups. However, the reduction in pain intensity during walking at 2 and 6 weeks after injection was significantly greater in the Ketorolac–methylprednisolone group compared with the methylprednisolone group ($P < 0.001$).

Both groups demonstrated a similar reduction in joint stiffness after waking from sleep or following prolonged immobility after injection, with no statistically significant difference between the groups.

Regarding pain changes during stair climbing after injection, both groups showed a comparable reduction, and no significant difference was observed between them. A detailed comparison of pain score changes before and after injection, both within and between groups, is presented in (Table 2).

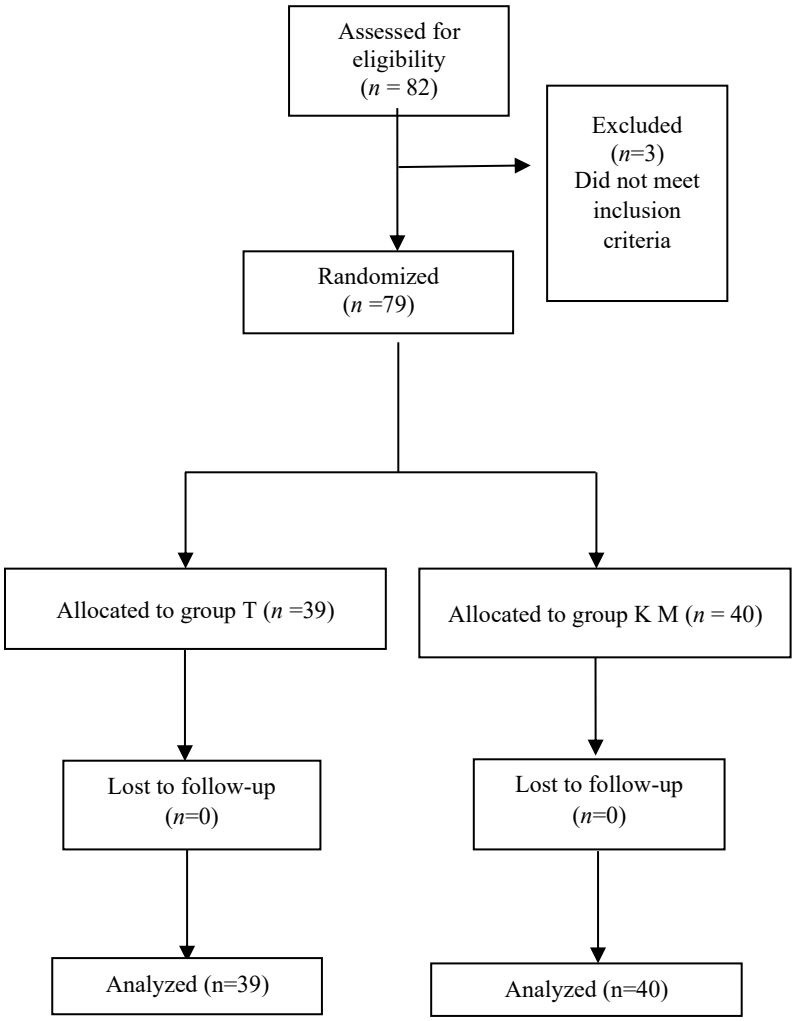

Figure 1- Study flow Diagram: T, methylprednisolone; KM, ketorolac-methylprednisolone.

Table 1- Comparison of patient's characteristics before and after intervention in two groups.

Variables		Ketorolac-Methylprednisolone (n=40)	Methylprednisolone (n=39)	P value
Age		63.55±6.92	57.58±7.21	<0.001
Sex, n(%)	Male	20 (48.8%)	21(51.2%)	0.82
	Female	20 (52.6%)	18 (47.4%)	
Weight		73.42±3.61	71.53±5.29	0.06
BMI, mean±SD		26.01±1.47	25.30±2.20	0.10
Walking 1, mean±SD		69.77±16.17	66.66±14.92	0.37
Walking 2, mean±SD		34.50±19.00	52.82±8.64	<0.001
Walking 3, mean±SD		32.50±16.94	50.25±8.65	<0.001
After walking up 1, mean±SD		62.75±12.60	58.15±9.62	0.073
After walking up 2, mean±SD		32.37±16.52	33.33±16.27	0.79
After walking up 3, mean±SD		31.75±16.54	32.43±15.08	0.84
Climbing stairs 1, mean±SD		47.50±14.36	58.97±14.74	<0.001
Climbing stairs 2, mean±SD		43.50±18.78	38.66±19.44	0.26
Climbing stairs 3, mean±SD		40.25±15.68	36.18±16.33	0.26

1=prior to injection (baseline),2= 2 weeks after injection ,3= 4 weeks after injection

Table 2- Changes in NRS in Walking, after walking up and Climbing stairs over time in two groups.

Group		After Injection			P value [a]	P value [b]	P value [c]
		Before Injection	After 2 weeks	After 4 weeks			
NRS in Walking	Ketorolac-Methylprednisolone (n=40)	69.77±2.46	34.50±2.34	32.50±2.13	<0.001	<0.001	0.046
	Methylprednisolone (n=39)	66.66±2.49	52.82±2.37	50.25±2.16	<0.001	<0.001	0.012
Between group P value		0.37	<0.001	<0.001	-	-	-
NRS in after walking up	Ketorolac-Methylprednisolone (n=40)	62.75±1.77	32.37±2.59	31.75±2.50	<0.001	<0.001	0.73
	Methylprednisolone (n=39)	58.15±1.79	33.33±2.62	32.43±2.53	<0.001	<0.001	0.62
Between group P value		0.073	0.796	0.84	-	-	-
NRS in Climbing stairs	Ketorolac-Methylprednisolone (n=40)	47.50±2.30	43.50±3.02	40.25±2.53	0.33	0.09	0.14
	Methylprednisolone (n=39)	58.97±2.33	38.66±3.06	36.18±2.59	<0.001	<0.001	0.19
Between group P value		<0.001	0.31	o.26	-	-	-

All values are expressed as mean ± SE, a There are differences between before injection and 2 weeks after injection, b There are differences between before injection and 4 weeks after injection, c There are differences between 2 weeks after injection and 4 weeks after injection.

Discussion

In this randomized clinical trial, the analgesic effects of intra articular injection of methylprednisolone alone and methylprednisolone combined with ketorolac were evaluated and compared in patients with knee osteoarthritis. The results demonstrated that both therapeutic interventions led to a significant reduction in pain intensity during the four week follow up period. However, pain reduction during walking was significantly greater and more sustained in the methylprednisolone–ketorolac group.

A noteworthy and defensible finding of the present study is that, despite the higher mean age of patients in the methylprednisolone–ketorolac group—a factor that is typically associated with a poorer response to conservative treatments—this group experienced a more pronounced reduction in pain. This observation indirectly supports the hypothesis of the superior analgesic efficacy of the ketorolac containing combination and suggests the presence of a pharmacologic synergistic effect between the corticosteroid and the NSAID [14].

Ketorolac exerts its analgesic and anti inflammatory effects primarily through inhibition of cyclooxygenase (COX) enzymes and subsequent reduction of prostaglandin synthesis, targeting an inflammatory pathway that is distinct from and complementary to that of corticosteroids [15]. In contrast, methylprednisolone suppresses inflammation by inhibiting phospholipase A2 and reducing the production of pro inflammatory

cytokines such as IL 1β and TNF α, thereby playing a key role in controlling chronic intra articular inflammation. The combination of these two agents may therefore result in the simultaneous inhibition of both acute and chronic inflammatory pathways, a mechanism that may be particularly evident during functional activities such as walking, which impose the greatest mechanical load on the knee joint and are most closely associated with patients' pain perception [16].

In the present study, pain intensity during walking at two and four weeks after injection was significantly lower in the methylprednisolone–ketorolac group compared with the methylprednisolone group ($P < 0.001$). This difference is not only statistically significant but also clinically meaningful, as pain during walking represents one of the most prominent symptoms of knee osteoarthritis and is a major determinant of patients' quality of life.

In contrast, regarding joint stiffness after waking from sleep or prolonged immobility, as well as pain during stair climbing, both groups demonstrated similar degrees of improvement, with no statistically significant differences between them. This finding may indicate that these specific dimensions of osteoarthritis symptoms are predominantly influenced by the sustained anti inflammatory effects of corticosteroids and that the addition of ketorolac does not confer a substantial incremental benefit in these domains.

From a biomechanical perspective, stair climbing is a complex functional activity that depends not only on the knee joint but also on quadriceps strength, hip function, and neuromuscular coordination. Consequently, the response of this outcome to purely intra articular interventions may be limited, which could explain the absence of significant differences between the two treatment groups.

Overall, the findings of the present study are consistent with previous research confirming the short term efficacy of intra articular corticosteroid injections in reducing pain associated with knee osteoarthritis [17–19]. However, beyond these classical observations, the current results highlight the relative advantage of adding an intra articular NSAID (ketorolac) to standard corticosteroid therapy and provide new evidence supporting the combined use of these agents.

Limitations

Despite its randomized clinical trial design and statistically significant findings, this study has several limitations that should be considered when interpreting the results.

First, the relatively small sample size and single center design may limit the generalizability of the findings to other populations and clinical settings. Although the observed statistically significant differences—particularly in pain reduction during walking—suggest a true treatment effect, larger multicenter studies are recommended to confirm these results.

Second, the short follow up period (four weeks) restricts the ability to evaluate the long term efficacy and safety of intra articular injections, particularly with respect to disease progression in knee osteoarthritis. Given the chronic and progressive nature of osteoarthritis, longer follow up durations are necessary to assess the durability of treatment effects.

Third, pain severity was assessed using the Numerical Rating Scale (NRS), which, despite its validity and widespread use, is inherently subjective and may be influenced by individual, psychological, and expectancy related factors. The concurrent use of standardized functional outcome measures, such as the WOMAC index or objective performance based tests, could have provided a more comprehensive evaluation of treatment outcomes.

Fourth, the study primarily focused on short term clinical outcomes, and structural joint changes, including cartilage status or synovial inflammation, were not assessed using imaging modalities such as MRI or ultrasonography. Therefore, no conclusions can be drawn regarding potential disease modifying effects of the drug combination.

Fifth, although no significant adverse events were reported during the study period, the sample size and follow up duration may not have been sufficient to detect rare or delayed complications, particularly those related to intra articular NSAID administration.

Finally, certain potential confounding factors—such as patients' physical activity levels, concomitant use of oral analgesics, and adherence to non pharmacological treatments (e.g., physiotherapy)—were not fully controlled and may have influenced pain outcomes.

Nevertheless, despite these limitations, the observation of statistically and clinically significant differences—even in the context of a higher mean age in the ketorolac group—supports the presence of a genuine pharmacological effect and enhances the internal validity of the study findings.

Conclusion

The results of this study indicate that both intra articular methylprednisolone–lidocaine and methylprednisolone–ketorolac–lidocaine injections are effective in reducing pain in patients with knee osteoarthritis. However, the ketorolac containing combination produced a significantly greater and clinically more meaningful reduction in pain during walking at both two and four week follow up assessments.

Given the superior efficacy of this combination—even among older patients—the use of methylprednisolone–ketorolac–lidocaine may be proposed as an effective therapeutic option for the short term management of knee

osteoarthritis pain. Future studies with larger sample sizes, longer follow up periods, and evaluation of structural joint outcomes are recommended to further assess the long term safety and effectiveness of this treatment approach.

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