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Etoricoxib Versus Diclofenac Sodium Intramuscular Injections in Acute Orthopaedic Pain Management: A Randomized, Open-Label Pilot Trial

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Abstract

Background

Acute orthopaedic pain is a common clinical challenge in emergency and inpatient settings, with the use of injectable non-steroidal anti-inflammatory drugs (NSAIDs) as the mainstay of pharmacological treatment. Although intramuscular diclofenac sodium has long dominated this therapeutic area, its non-selective inhibition of Cyclooxygenase-1 (COX-1) and Cyclooxygenase-2 (COX-2) enzymes raises safety concerns. An intramuscular formulation of etoricoxib, a highly selective COX-2 inhibitor, has recently become accessible, providing a mechanistically distinct alternative.

Methods

A prospective, open-label randomized controlled study was conducted in the outpatient orthopaedic department of a tertiary care hospital. 70 eligible patients were randomised into Group A (n = 35) receiving Intramuscular Etoricoxib (90mg) and Group B (n = 35) receiving Intramuscular Diclofenac Sodium (75mg), presenting with acute orthopaedic pain. Pain intensity scores were recorded using VAS and VNRS at baseline and follow-up post-administration. Adverse events were systematically monitored, including injection-site pain, gastrointestinal symptoms, renal function parameters, and hypersensitivity reactions. Statistical analysis was performed using Python (version 3.12).

Results

The mean age was 41.71 ± 15.63 years in Group A and 41.49 ± 13.87 years in Group B ($p = 0.95$). Both groups had a similar gender distribution with a slight female predominance. Both intramuscular etoricoxib and diclofenac sodium significantly reduced pain intensity from baseline at all post-injection time points ($p < 0.0001$). A statistically significant difference in pain intensity emerged at 12 hours. An exploratory secondary analysis of Drug x Time interaction in a repeated-measures ANOVA ($F(4,272) = 7.795$; $p < 0.0001$). Patients receiving etoricoxib reported a higher incidence of injection-site discomfort (68.57 vs. 42.86%; $p = 0.03$). No significant systemic adverse effects were reported in either group.

Trial Registration

Registered prospectively in Clinical Trial Registry India (CTRI) as CTRI/2025/07/091721 on 25th July,2025.

INTRODUCTION

Acute orthopaedic pain is commonly encountered in emergency departments and outpatient clinics. It arises from fractures, soft-tissue tears, ligamentous injuries, and damage to periarticular structures. In

2019, bone fractures accounted for 178 million new cases and 455 million prevalent cases globally, representing a substantial burden of acute and chronic symptoms that resulted in 25.8 million years lived with disability[1]. Across all musculoskeletal disorders, more than 322 million incident cases were recorded in the same year, contributing 150 million disability-adjusted life years (DALYs) globally[2]. Rapid and effective pain control is clinically important: patients with higher pain scores mobilize later and have higher rates of postoperative complications, and undertreated acute pain is a strong predictor of persistent pain and prolonged opioid dependence. Non-steroidal anti-inflammatory drugs (NSAIDs) are the mainstay of treatment, representing approximately 84% of analgesic prescriptions in outpatient orthopaedic settings[3]. Accordingly, the Orthopaedic Trauma Association recommends the use of NSAID's as part of multimodal regimens for acute musculoskeletal trauma.

Intramuscular (IM) diclofenac sodium is widely used as the default parenteral NSAID for acute pain due to its low cost, rapid onset, and established clinical familiarity. However, its safety profile remains a concern. Diclofenac exhibits dose-dependent COX-2 selectivity similar to celecoxib, carrying risks of gastrointestinal mucosal damage, renal dysfunction, myocardial infarction, and stroke, as confirmed across large observational datasets and randomized trials[4]. The Food and Drug Administration's (FDA) boxed warning on cardiovascular risks reflects these concerns. Similarly, the 2023 American Geriatrics Society (AGS) Beers Criteria flags non-selective NSAIDs, including diclofenac, as potentially inappropriate for older adults due to their gastrointestinal and cardiovascular risks[5]. Clinical guidelines recommend using alternative analgesics that offer effective pain relief with improved safety margins, particularly for older or high-risk patients[6].

Etoricoxib is a highly selective COX-2 inhibitor with a well-characterized efficacy profile in both acute and chronic pain settings. Selective inhibition of COX-2 targets the primary source of inflammatory pain while producing significantly fewer gastroduodenal ulcers and clinically important ulcer complications compared to non-selective NSAIDs. The recently developed parenteral formulation of etoricoxib (90mg/mL) is used in the acute trauma settings where patients cannot tolerate oral medications. Currently, there is no direct randomized comparison of intramuscular etoricoxib and diclofenac for acute orthopaedic pain. A search of databases such as PubMed, EMBASE, and ClinicalTrials.gov using the terms "etoricoxib," "intramuscular," "diclofenac," and "orthopaedic pain" confirmed the absence of such trials.

This study was designed to address the gap by comparing intramuscular etoricoxib with diclofenac sodium in patients presenting with acute orthopaedic pain. We hypothesized that etoricoxib would demonstrate comparable pain relief to diclofenac with a more favorable safety and tolerability profile.

METHODS

Study Design

This prospective, open-label, randomized controlled study enrolled patients referred to the Department of Orthopaedics at the SRM Medical College Hospital & Research Centre over six months. The study protocol was approved by the Institutional Ethics Committee (IEC) under ethics clearance number SRMIEC-ST0325-2285. This study was prospectively registered with the Clinical Trials Registry – India (CTRI) under registration number CTRI/2025/07/091721 on 25th July 2025. The study adhered to the principles of the Declaration of Helsinki, and written informed consent was obtained from all participants prior to enrollment.

Study criteria

Eligible participants were adults aged 18–60 years who presented to the orthopaedic department with either acute nociceptive somatic pain or nociplastic pain of moderate-to-severe intensity (VAS > 4) warranting pharmacological intervention. Patients with any one of the factors such as fractures, ligamentous injuries, muscle and soft-tissue strains, knee arthritis, acute back pain, and acute inflammatory joint conditions were included. Patients willing to give informed consent were included.

Patients diagnosed with possible or probable neuropathic pain via a validated 3-Level Grading System were excluded[7]. Other exclusion criteria included a documented history of major comorbidities (specifically cardiovascular disease, systemic hypertension, hepatic impairment, renal impairment, cerebrovascular disorders, or gastrointestinal pathologies such as peptic ulceration, hemorrhage, and perforation). Concomitant use of interacting medications (such as diuretics, anticoagulants, rifampicin, immunosuppressants, ACE inhibitors, ARBs, lithium, oral contraceptives, and digoxin) or use of any other NSAID within 48 hours prior to enrollment; pregnancy or lactating mothers were excluded.

Randomization and Blinding

A computer-generated permuted block randomization (block size 4) was prepared by an independent biostatistician not involved in patient recruitment. Allocation was concealed using sequentially numbered, opaque, sealed envelopes. Participants were randomised in a 1:1 ratio. Group A received Intra-Muscular Etoricoxib Injection 90 mg (1 mL contains 90 mg/mL solution); Group B received Intra-Muscular Diclofenac Sodium Injection 75 mg (1 mL contains 75 mg/mL solution) as a STAT medication.

To minimize performance and detection bias, several measures were implemented. First, initial pain assessments at 30 and 60 minutes were conducted by a trained research nurse who was not involved in drug administration. Second, telephonic pain assessments at 12 and 24 hours were performed using a scripted verbal protocol by a research team member who followed a standardized question sequence without referencing prior scores. Third, all laboratory analyses were performed by the institutional central laboratory under routine clinical conditions without knowledge of study group allocation. Finally, statistical analyses were performed on a blinded dataset in which group labels were coded numerically until the primary analysis was completed.

Sample Size

Sample size estimation was performed using Python (version 3.12). The minimum sample size was calculated for a two-sided independent-samples t-test, with Cohen's d effect size of 0.7 calculated from NICE trial[8], a significance level (α) of 0.05, and a statistical power (1 − β) of 0.80. Based on these assumptions, a minimum of 32 participants per group was required. To account for potential protocol deviations and to maintain statistical power, the sample size was increased to 35 participants per group, resulting in a total target population of 70 participants.

Interventions

Participants in Group A received a single intramuscular injection of etoricoxib 90 mg (1 mL contains 90 mg/mL solution), while Group B received a single intramuscular injection of diclofenac sodium 75 mg (1 mL contains 75 mg/mL solution). All injections were administered as a deep intramuscular intragluteal injection into the upper outer quadrant of the buttock by a trained nurse using a sterile 23-gauge, 1-inch needle. Following randomization, patients underwent hypersensitivity screening using a 0.1 mL intradermal test dose of the assigned study drug. Patients were observed for 30 minutes for immediate hypersensitivity reactions; no reactions occurred in either group. The study drug was administered only if patients had a baseline Visual Analogue Scale (VAS) pain score > 4. Patients were instructed to avoid taking other analgesics or NSAIDs during the 48-hour study period. A protocol was in place to exit patients from the study and manage their pain according to standard of care if they experienced uncontrolled pain; however, no patients exited the study, and all completed the 48-hour follow-up.

Safety Profiling

Before drug administration, a 4 mL blood sample was drawn from the antecubital vein for safety laboratory assessments. Under aseptic conditions at baseline and 48 hours following study drug administration using sterile vacutainer tubes. Hematological parameters were assessed using EDTA-anticoagulated whole blood and included hemoglobin concentration, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), packed cell volume (PCV), total red blood cell count, total white blood cell count, platelet count, and differential leukocyte counts. Hematological analyses were performed using an automated hematology analyzer (Sysmex XN-Series automated analyser with SA-10 auto sampler). For biochemical assessment, blood samples were collected in clot-activator tubes, allowed to clot at room temperature, and centrifuged at 3,500 rpm for 10 minutes to obtain serum. Renal function parameters, including serum urea, blood urea nitrogen (BUN), and serum creatinine, were measured using an automated clinical chemistry analyzer employing validated enzymatic and kinetic methodologies. Serum electrolyte concentrations, including sodium, potassium, chloride, and bicarbonate, were determined using indirect ion-selective electrode technology. All laboratory analyses were performed on the day of sample collection in the institutional central laboratory according to established quality control procedures. Adverse events were monitored

throughout the study, and injection-site pain was recorded as a binary outcome (present or absent) at the designated assessment intervals.

Outcome measures

VAS and VNRS scores were treated as equivalent and pooled for efficacy analyses [9]. The pre-specified primary efficacy endpoint was the reduction in VAS score from baseline to 60 minutes post-administration, representing the final in-clinic pain assessment conducted under direct staff assessment conducted under direct staff observation [10]. VNRS scores at 12 and 24 hours were designated as secondary and exploratory endpoints, respectively [11].

VAS

Visual Analogue Scale (VAS, 0–10 cm). 0: no pain, 1–4 cm: Mild pain, 4–6 cm: Moderate pain, 7 cm and above: Severe pain. Pain was assessed using the VAS immediately before administration and at 30 and 60 minutes post-injection. Since the study evaluated a single dose for acute relief, no repeated doses were administered. All patients were managed as outpatients and remained at the clinic for 60 minutes post-injection for pain

VNRS

Verbal Numerical Rating Scale (VNRS, 0–10). The patient was asked On a scale of 0 to 10, where 0 is no pain and 10 is the worst pain imaginable, how would you rate your pain right now?. 0: No pain, 1–3: Mild pain, 4–6: Moderate pain, 7–10: Severe pain. Pain intensity at 12 and 24 hours was evaluated via telephone follow-up.

Statistical Analysis

All statistical analyses were performed using Python 3.12 (Python Software Foundation) with the pandas, NumPy, SciPy, Pingouin, and statsmodels libraries. Continuous variables were presented as mean ± Standard Deviation, and categorical variables as percentage. Normality was assessed using the Shapiro-Wilk test and visual inspection of Q-Q plots (Supplementary Table S1 and Figure S1). While several variables violated the normality assumption to a statistically significant degree, visual inspection of Q-Q plots showed minimal deviation from linearity, with no pronounced skew or extreme outliers. Given that parametric tests are robust to moderate violations of normality in studies with adequate sample sizes (n = 35 per group), parametric analyses were performed. For pain intensity outcomes, a two-way repeated-measures ANOVA (treatment group × time) was used, with treatment group (etoricoxib vs. diclofenac sodium) as the between-subject factor and time (baseline, 30 min, 60 min, 12 h, 24 h) as the within-subject factor. Main effects of treatment and time, along with their interaction, were evaluated. Laboratory safety parameters (hematological values, renal function markers, and serum electrolytes) at baseline and 48 hours post-dose were analyzed similarly using a two-way repeated-measures ANOVA.

Significant interaction effects were followed by post-hoc between-group comparisons using independent-samples t-tests, and within-group longitudinal comparisons using paired-samples t-tests. Effect sizes are reported as partial eta squared (ηp^2). Baseline demographics and clinical characteristics were compared using independent-samples t-tests for continuous variables and chi-square tests for categorical variables. All statistical tests were two-tailed, and statistical significance was defined as $p < 0.05$. The primary between-group comparison was the mean VAS reduction from baseline to 60 minutes, analysed using an independent-sample t-test. Between-group comparisons at all other time points (30 minutes, 12 hours, 24 hours) were conducted as pre-specified secondary and exploratory analyses. As five between-group comparisons were performed across the observation period, Holm-Bonferroni correction was applied; adjusted p-values are reported alongside unadjusted values in Table 5.

RESULTS

Screening, Enrolment, and Baseline Characteristics

Among 97 patients screened, 70 met the eligibility criteria and were randomized into Group A receiving IM Etoricoxib (90mg) and Group B receiving IM Diclofenac Sodium (75mg). The primary reasons for exclusion were neuropathic pain (n = 12), active peptic ulcer disease, gastrointestinal bleeding, or renal/hepatic impairment (n = 9), and refusal to participate (n = 6). No participants were lost to follow-up during the study. The study flow chart is represented in Fig. 1.

Baseline characteristics are summarized in Table 1. The mean age was 41.71 ± 15.63 years in Group A and 41.49 ± 13.87 years in Group B (p = 0.95). Both groups had a similar gender distribution with a slight female predominance (Group A 54.3%, Group B 51.4%; p = 0.74). Comorbidity profiles were comparable between the groups; the majority of participants had no comorbidities, and type 2 diabetes mellitus was the most common comorbidity (Group A 31.4%, Group B 22.9%; p = 0.41). Pain type distribution was balanced, with inflammatory and musculoskeletal pain similarly represented in both groups (p = 0.17). The underlying diagnoses were diverse, including fractures, ligamentous injuries, muscle strains, inflammatory arthropathies, and spinal disorders, reflecting the heterogeneity of patients presenting with acute orthopaedic pain.

Change in VAS and VNRS pain score from baseline to 24 hours post-injection

The pre-specified primary efficacy endpoint was VAS reduction from baseline to 60 minutes post-administration. Analgesic efficacy was quantified using the Visual Analogue Scale (VAS; 0–10 cm) at three serial time points (0, 30, and 60 minutes), supplemented by the Verbal Numerical Rating Scale (VNRS) at 12 and 24 hours post-administration as secondary and exploratory endpoints. Aggregate mean VAS and VNRS scores are presented alongside the two-way repeated-measures ANOVA findings.

The primary endpoints between-group VAS reduction at 60 minutes did not differ significantly (Group A: 3.23 ± 1.76 vs. Group B: 3.55 ± 2.15; mean difference − 0.32, 95% CI − 1.12 to 0.48; p = 0.598; Cohen's d =

0.17), indicating comparable early analgesic onset with both formulations. Two-way repeated-measures ANOVA showed no statistically significant main effect of drug treatment over the observation period, and the main effect of time did not reach statistical significance. However, a statistically significant drug × time interaction effect was observed with a moderate effect size (Table 3). This interaction indicates that the two drugs display distinct temporal pain-relief profiles over the 24-hour observation period, despite their overall mean pain scores being numerically similar (Table 2). After completing the 48-hour assessments, seven patients with persistent pain required subsequent management and were treated with intramuscular acetaminophen 1000 mg as ordered by the physician. Because all scheduled outcome measurements were completed before rescue medication administration, these interventions did not affect the primary analysis.

Post-Hoc analysis:

Temporal changes in VAS and VNRS scores were assessed within each treatment arm using the Paired t-test, with results presented in Table 4. Both groups achieved statistically significant pain reductions at all assessed time points ($p < 0.0001$).

Pairwise between-group comparisons at each discrete time point were conducted as pre-specified secondary and exploratory analyses using independent-samples t-tests (Table 5). As five between-group comparisons were performed, Holm-Bonferroni correction was applied; adjusted p-values are reported alongside unadjusted values. A statistically significant difference in pain intensity emerged at 12 hours (unadjusted $p = 0.019$; Holm-Bonferroni adjusted $p = 0.076$), which should be interpreted as a hypothesis-generating exploratory finding. This intermediate-phase advantage in favor of etoricoxib was the only time point at which a statistically significant between-group difference was observed, which is consistent with the drug × time interaction effect. By 24 hours, the difference between the groups had resolved, indicating convergence of pain scores at the study's terminal assessment. In summary, both drugs provided equivalent analgesia at the primary endpoint (60 minutes). The exploratory between-group comparisons suggest a time-dependent difference in intermediate-phase pain relief, with etoricoxib showing lower VNRS scores at 12 hours.

Table 1
Baseline Demographic and Clinical Characteristics of the study subjects.

Characteristic	Group A (n = 35)	Group B (n = 35)	p-value
Age (mean ± SD)	41.71 ± 15.63	41.49 ± 13.87	
Age-wise Distribution, n (%)			0.95
18–27	08(22.86)	08(22.86)	
28–37	09(25.71)	06(17.14)	
38–47	05(14.29)	08(22.86)	
48–57	10(28.57)	11(31.43)	
58–67	03(08.57)	02(05.71)	
Gender, n (%)			0.74
Male	16 (45.71)	17 (48.57)	
Female	19 (54.3%)	18 (51.4%)	
Comorbid disease, n (%)			0.41
Type 2 diabetes mellitus	11 (31.40%)	08 (22.90%)	
Hypothyroidism	01 (02.86%)	02 (05.71%)	
None	23 (65.70%)	25 (71.40%)	
Type of Pain, n (%)			0.17
Inflammatory pain	19 (54.3%)	15 (42.9%)	
Musculoskeletal pain	16 (45.71%)	20 (57.14%)	

** p < 0.05, statistically significant, analysed using Chi-Square Test, SD: standard deviation.*

Table 2
Overall Mean VAS and VNRS Score Comparison between Group A and Group B.

Parameter	Group A (N = 35)	Group B (N = 35)	95% CI	*p*- value
Overall Mean of VAS and VNRS score	4.29	4.53	−0.47 to 0.0019	0.052

*CI: Confidence Interval; * p < 0.05, statistically significant, analysed using Two-Way Repeated Measures ANOVA.*

Table 3
Two-Way Repeated-Measures ANOVA-Drug Effect, Time Effect, and Interaction.

Effect	F (DFn, DFd)	*p*- value	Partial η^2
Drug	F (1,68) = 0.84	0.71	0.012
Time	F (4,272) = 3.85	0.05	0.054
Drug × Time	F (4,272) = 7.79	< 0.0001*	0.103

** p < 0.05, statistically significant, analysed using Two-Way Repeated Measures ANOVA. Partial η^2: effect size.*

Table 4
VAS and VNRS Score Distribution Over Time - Within-Group Comparison.

Follow Up Intervals	Group A (Mean ± SD)	*p*- value	Group B (Mean ± SD)	*p*- value
0 min	7.86 ± 1.25	< 0.0001*	7.72 ± 1.50	<0.0001*
30 min	5.75 ± 1.66		5.75 ± 1.80	
60 min	3.23 ± 1.76		3.55 ± 2.15	
12 hrs	2.52 ± 1.32		3.55 ± 1.55	
24 hrs	2.15 ± 1.38		2.12 ± 1.16	

** p < 0.05, statistically significant, analysed using Paired t-test.*

Table 5
Between-Group VAS and VNRS Score Comparison at Each Time Point.

Follow Up Intervals	Group A (Mean ± SD)	Group B (Mean ± SD)	Mean Difference (95% CI)	Unadjusted *p - value*	Holm - adjusted *p - value*
0 min	7.86 ± 1.25	7.72 ± 1.50	0.14	0.65	1.000
30 min	5.75 ± 1.66	5.75 ± 1.80	0.00	0.71	1.000
60 min	3.23 ± 1.76	3.55 ± 2.15	−0.32	0.59	1.000
12 hrs	2.52 ± 1.32	3.55 ± 1.55	−1.03	0.02*	0.076
24 hrs	2.15 ± 1.38	2.12 ± 1.16	0.03	0.24	0.723

** Primary endpoint (60 min): p = 0.598, indicating no significant between-group difference. Holm-Bonferroni correction applied across five time-point comparisons. The 12-hour finding (unadjusted p = 0.019) does not survive correction (adjusted p = 0.076) and is reported as an exploratory hypothesis-generating observation.*

Safety Measures: Local injection-site tolerability and systemic adverse event profile

The only statistically significant difference in safety outcomes was the rate of injection-site discomfort: 68.6% of patients in the etoricoxib group reported pain at the injection site compared to 42.9% of patients in the diclofenac group (p = 0.03, chi-square test). While this difference is relevant to tolerability and patient acceptability, all reported cases of injection-site discomfort were transient and resolved spontaneously.

Two-way repeated-measures ANOVA of hematological, renal, and electrolyte parameters revealed no statistically significant drug effects, time effects, or drug × time interactions for any safety variable (Tables 6, 7, 8). All laboratory parameters remained within normal reference ranges throughout the study in both groups. Although serum creatinine showed a borderline drug effect (p = 0.086), this did not reach statistical significance, and absolute creatinine values remained within normal physiological limits. No serious adverse events were reported in either treatment group.

Table 6
Laboratory Safety Assessment- Haematological Parameters. * P < 0.05, statistically significant, Analysed Using Two-Way Repeated Measures ANOVA.

Haematological Parameters (Units)	Drug Effect F (1,68)	*p*-value	Time Effect F (1,68)	*p*-value	Drug × Time F (1,68)	*p*-value
Haemoglobin (g/dL)	0.5371	0.4686	2.7278	0.1078	7.6372	0.0692
MCH (pg)	1.0852	0.3049	0.0435	0.8360	0.0205	0.8869
Lymphocytes (%)	1.0824	0.3055	0.1134	0.7383	0.0144	0.9053
Total RBC Count (×10⁶/µL)	0.0014	0.9704	0.7490	0.3929	0.0269	0.8707
MCHC (g/dL)	1.9386	0.1729	0.1114	0.7406	4.0919	0.0510
Eosinophils (%)	2.2364	0.1440	0.0705	0.7922	1.0594	0.3106
PCV (%)	0.0316	0.8600	0.1361	0.7145	4.5891	0.0594
Total WBC Count (×10³/µL)	0.7257	0.4002	0.0785	0.7810	1.6791	0.2038
Basophils (%)	0.3005	0.5872	0.0038	0.9509	0.2167	0.6445
MCV (fL)	0.0168	0.8975	0.0618	0.8052	1.0475	0.3133
Neutrophils (%)	1.8481	0.1829	0.5063	0.4816	0.4433	0.5100
Monocytes (%)	0.2991	0.5880	0.7067	0.4064	0.4744	0.4956

Table 7
Laboratory Safety Assessment- Renal Function Test.

Renal Function Parameters (Units)	Drug Effect	*p*-value	Time Effect	*p*-value	Drug × Time	*p*-value
	F (1,68)		F (1,68)		F (1,68)	
Urea (mg/dL)	0.1695	0.6832	0.0015	0.9689	0.0108	0.9179
BUN (mg/dL)	0.0044	0.9476	0.1739	0.6793	1.8493	0.1828
Creatinine (mg/dL)	3.1330	0.0857	0.6153	0.4382	0.0756	0.7851

** P < 0.05, statistically significant, Analysed Using Two-Way Repeated Measures ANOVA.*

Table 8
Laboratory Safety Assessment- Electrolytes.

Electrolyte Parameters (Units)	Drug Effect	*p*-value	Time Effect	*p*-value	Drug × Time	*p*-value
	F (1,68)		F (1,68)		F (1,68)	
Sodium (meq/L)	0.1244	0.7265	0.7141	0.4040	0.4755	0.4951
Potassium (meq/L)	0.1058	0.7470	0.8828	0.3541	0.2991	0.5880
Chloride (meq/L)	0.0848	0.7727	0.7627	0.3886	0.3316	0.5685
Bicarbonate (meq/L)	1.0573	0.3111	0.8861	0.3532	0.3448	0.5609

** P < 0.05, statistically significant, Analysed Using Two-Way Repeated Measures ANOVA.*

DISCUSSION

This randomized controlled trial comparing a single dose of intramuscular etoricoxib 90 mg with intramuscular diclofenac sodium 75 mg for acute orthopaedic pain provides three key findings that have implications for clinical practice and the interpretation of analgesic trials. First, our findings align with real-world observational cohort studies, such as the NICE[8], [12] and NICE 2.0[12] trials, which confirmed the clinical effectiveness and safety of intramuscular etoricoxib in Indian patient populations. Second, a network meta-analysis by Pan et al. (2025)[13], pooling data from multiple randomized trials in osteoarthritis and acute musculoskeletal pain, found no significant differences in overall pain scores between selective COX-2 inhibitors and non-selective NSAIDs, which is consistent with the lack of a significant overall drug effect in the present study. However, pooled meta-analyses often cannot explore temporal interaction effects, which define the clinically relevant distinctions between these agents. Third, the higher rate of injection-site discomfort observed with etoricoxib is consistent with the known physicochemical properties of the intramuscular formulation and mirrors observations from the NICE trials[8]. While this is an important tolerability consideration, especially for patients sensitive to local

discomfort, the self-limiting and transient nature of this symptom indicates it should not contraindicate use in appropriate clinical settings.

Equivalent Means, Divergent Trajectories

The non-significant overall drug effect might be superficially interpreted as evidence that the two drugs are interchangeable. However, the statistical analysis demonstrates that the pattern of pain relief over time differs substantially between the two agents, making the comparison of pooled means pharmacologically uninformative. These temporal differences are described in detail in the context of their pharmacokinetic profiles. The present study adds an active comparator arm and, in an exploratory analysis, generates the hypothesis that etoricoxib's pharmacokinetic advantage over diclofenac may translate into measurable differences in intermediate-phase pain control, a finding that requires confirmation in a larger, pre-powered, double-blind trial. Our findings align with the systematic review by Mohammed et al., which attributed the superior pain control of etoricoxib at 12 hours to its prolonged half-life and sustained COX-2 selectivity. Specifically, diclofenac has a short elimination half-life of 1–2 hours, meaning that plasma concentrations typically fall below the therapeutic threshold within 4–6 hours of a single intramuscular dose. In contrast, etoricoxib has a half-life of approximately 22 hours, which maintains therapeutic plasma concentrations across the 12-hour window. This sustained concentration maintains COX-2 suppression and prevents the intermediate-phase pain resurgence observed in the diclofenac group[14].

Variability and Individualized Analgesic Selection

The expanding standard deviation (SD) in the diclofenac group (2.15 at 60 minutes, widening further by 12 hours) is due to clinical variation, where some patients achieved near-complete relief while others had persistent moderate pain. Genetic variations, such as CYP2C9*2/*3 polymorphisms, alter diclofenac metabolism, which can increase toxicity without improving analgesia[15]. Etoricoxib is primarily metabolized by CYP3A4, and inter-individual variability in CYP3A4 activity, driven by genetic polymorphisms, comedications, and inflammatory states may contribute to differences in drug exposure and analgesic response across patients. The 22–31% diabetic subgroup adds further complexity. Diabetes independently alters pain perception and inflammatory signalling, while also affecting how drugs are absorbed from the intramuscular injection sites.

The findings of this pilot study suggest that intramuscular etoricoxib may warrant consideration alongside diclofenac in selected clinical scenarios, particularly when sustained intermediate-phase analgesia is a priority. Intramuscular etoricoxib is not simply an equivalent alternative; it offers a distinct pharmacological profile that confers specific advantages in select clinical settings. More broadly, the inter-individual variability observed in this study highlights the limitations of a single-agent, fixed-dose analgesic model for acute orthopaedic pain.

Safety: The Reassurance of a Single-Dose Window

The lack of clinically significant changes in hematological, renal, and electrolyte parameters in both groups is reassuring and consistent with expectations for single-dose administration. Adverse outcomes such as nephrotoxicity, gastrointestinal mucosal injury, and platelet dysfunction are typically associated with chronic or high-dose NSAID exposure. Prostaglandin-mediated processes, such as renal vasodilation and gastric mucosal protection, require prolonged inhibition before clinical organ toxicity manifests. Consequently, a single intramuscular dose in patients with normal baseline organ function, such as those pre-screened in this study, is unlikely to produce detectable laboratory abnormalities within 48 hours.

Future Directions

To validate these findings, future research should focus on larger, multi-centre, blinded trials. These protocols should incorporate systematic screening for psychological comorbidities, pain sensitisation markers, and relevant pharmacogenomic variables to identify high-risk non-responders. Identifying these factors can guide tailored analgesic selection and proactive rescue analgesia planning. In addition, future studies should use blinded or placebo-controlled designs and mixed-effects models rather than standard repeated-measures approaches. Collecting comprehensive safety data, performing subgroup analyses, and comparing cost-effectiveness will also help translate these findings into practical clinical guidelines and policy decisions.

LIMITATIONS

This study has several limitations that should be considered. First, the open-label design was necessary because the two formulations had different physical characteristics and volumes, which could introduce performance or detection bias. Second, the sample size of 35 patients per group was chosen based on a pilot power calculation for a medium-to-large effect size, which limits our ability to detect smaller differences or perform robust subgroup analyses, such as comparing diabetic and non-diabetic cohorts. Third, pain assessment utilized different scales over time: the Visual Analogue Scale (VAS) for in-clinic measurements (0–60 minutes) and the Verbal Numerical Rating Scale (VNRS) for remote follow-up (12 and 24 hours). While both instruments are validated and correlate well, this methodological shift may introduce minor measurement variability.

Fourth, the 24-hour observation window captures the acute phase but does not assess long-term analgesic durability, rescue medication requirements, functional recovery, or delayed adverse events (such as gastrointestinal injury or nephrotoxicity). Fifth, because this was a single-center study in South India, the findings may not generalize to other patient populations with different pharmacogenomic or comorbidity profiles. Sixth, we did not collect patient-specific data on psychological pain predictors (e.g., anxiety or catastrophizing), quantitative sensory testing, or pharmacogenomics, which limits our ability to identify the precise mechanisms underlying the observed inter-individual response variability. Seventh, the doses evaluated (etoricoxib 90 mg vs. diclofenac sodium 75 mg) reflect standard clinical formulations rather than equianalgesic doses; thus, dose-related effects cannot be completely ruled out. Ninth, although VAS reduction at 60 minutes was designated as the pre-specified primary efficacy

endpoint, this designation aligns with the registered primary objective of analgesic efficacy comparison but was not specified at the individual time-point level in the CTRI registration. Readers should therefore interpret the primary endpoint finding accordingly. The 12-hour between-group difference was a pre-specified secondary exploratory comparison and does not survive Holm-Bonferroni correction for multiple comparisons; it is best interpreted as a hypothesis-generating observation.

CONCLUSION

Intramuscular etoricoxib and diclofenac sodium are both effective as safe single-dose options for acute orthopaedic pain, yielding comparable overall reductions in pain intensity over 24 hours. However, an exploratory secondary analysis identified a hypothesis-generating signal of superior pain control with etoricoxib at 12 hours post-injection, consistent with its prolonged elimination half-life, which warrants prospective evaluation in a larger blinded trial. This difference is consistent with its prolonged elimination half-life and sustained COX-2 selectivity, carrying direct clinical relevance for settings where continuous analgesic access cannot be guaranteed.

DECLARATIONS

Ethics approval and consent to participate:

The Institutional Ethics Committee of SRM Medical College Hospital & Research Centre, with reference number SRMIEC- ST0325-2285 provided approval. Informed consent was obtained from every participant in the study. After an exhaustive explanation of the purposes of the study, procedures, potential risks and benefits, and confidentiality of the data, each participant signed written informed consent. All participants were clearly informed that participation in the study was entirely at their own discretion and that they were free to withdraw at any point without adverse effects on their medical care or penalty. All the information collected was anonymized and solely for use within this research.

Consent for publication:

Not Applicable

Competing Interests:

Not Applicable

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Author Contribution

All four authors, namely Pravin Selvi Saravanan, Lokesh Ramanathan, Aishwaryaa Anand, and S. K. Lithesh, were responsible for obtaining approval from the ethics committee. A. Aishwaryaa and S. K. Lithesh carried out patient recruitment and data collection. Lokesh Ramanathan and Pravin Selvi Saravanan performed the data analysis. All four authors contributed to the preparation and writing of the manuscript. Dr. Sarumathy. S provided critical guidance during the study design and conduct, and reviewed the manuscript and Dr. Gowthaman provided clinical guidance for the conduct of the study. All authors read and approved the final manuscript.

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Data Availability

The anonymised dataset supporting the conclusions of this article, including individual participant pain intensity scores (VAS and VNRS), baseline demographic and clinical characteristics, and laboratory safety parameters, is openly available in the Figshare repository: Saravanan PS, Anand A, Lokesh R, Lithesh SK, Gowthaman N, Sarumathy S (2025). Dataset: Efficacy and Safety of Intramuscular Etoricoxib vs Diclofenac Sodium in Acute Orthopaedic Pain - A Randomized Open-Label Pilot Study. Figshare. 10.6084/m9.figshare.32598735.

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Figures

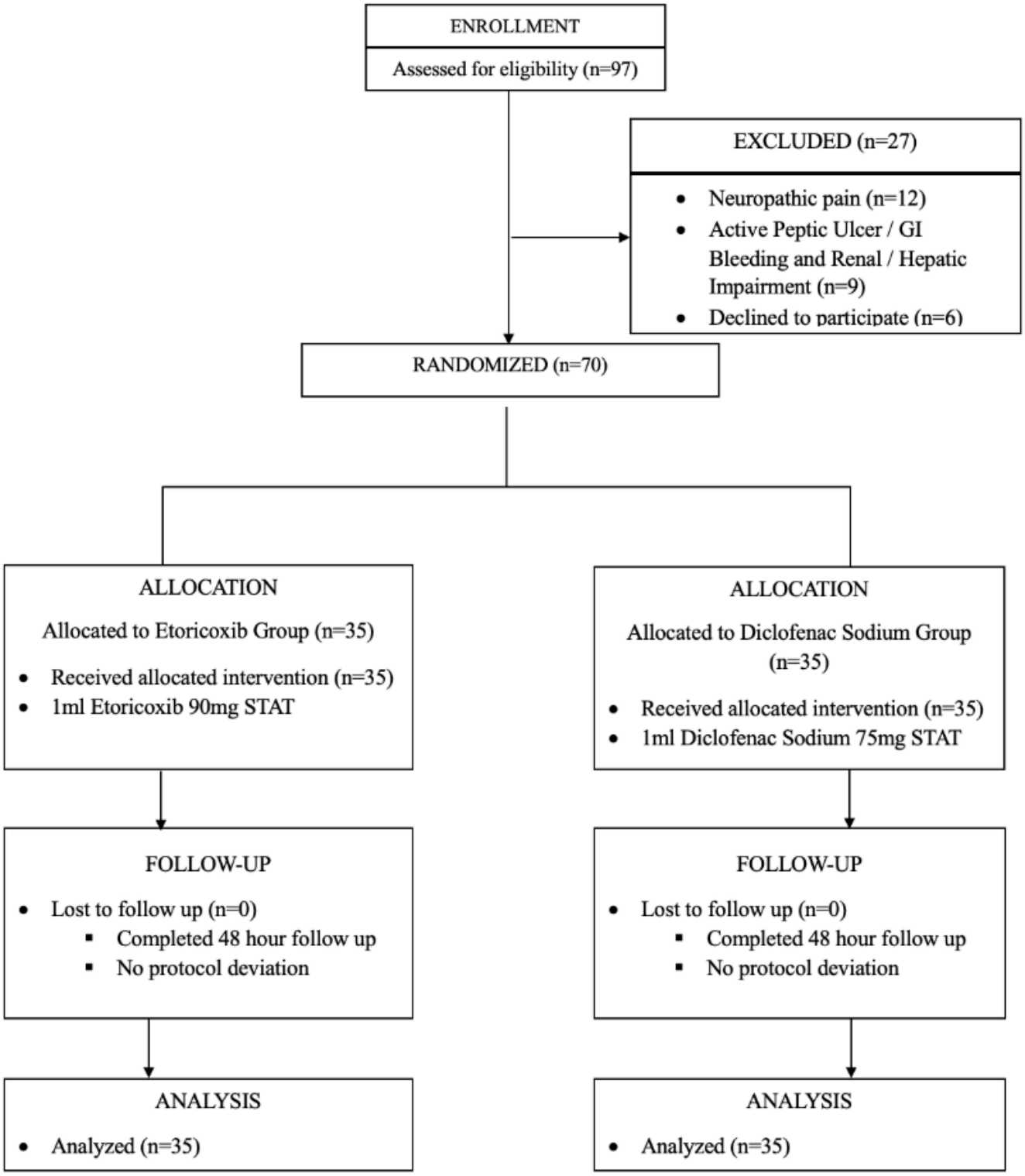


Figure 1

Study design CONSORT 2020 flow diagram

Supplementary Files

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