RESEARCH PAPER

Multidrug Periarticular Cocktail versus Single Drug Bupivacaine for Postoperative Pain Control after Total Knee Arthroplasty: A Retrospective Cohort Study

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Received: 24th April, 2026; Revised: 20th May 2026; Accepted: 30th June, 2026; Available Online: 10th July, 2026

ABSTRACT

Introduction: Postoperative pain following total knee arthroplasty (TKA) remains a major challenge, often limiting early mobilization and delaying functional recovery. Multimodal periarticular analgesic cocktail injections have been introduced to enhance pain control while minimizing opioid requirements. This study aimed to compare the efficacy of a multidrug periarticular cocktail injection with a conventional single-drug local anaesthetic injection for postoperative pain control and early functional outcomes following primary unilateral TKA.

Methods: This retrospective cohort study was conducted at a tertiary care teaching hospital in southern India. Medical records of 36 patients who underwent primary unilateral TKA between September 2023 and September 2025 were reviewed. Patients were divided into two groups: Group A (n = 18) received a periarticular and intraarticular multidrug analgesic cocktail injection, and Group B (n = 18) received a conventional single-drug bupivacaine injection. Postoperative pain intensity was assessed using the Visual Analog Scale (VAS) at 6, 12, 24, and 48 hours postoperatively. Secondary outcomes included time to first rescue analgesic request, range of motion (ROM) at discharge, time to independent ambulation, length of hospital stay, and postoperative complications. Statistical analysis was performed using SPSS version 22, with $p < 0.05$ considered statistically significant.

Results: The multidrug cocktail group demonstrated significantly lower mean VAS scores at all postoperative time points compared to the single-drug group. Time to first rescue analgesic request was significantly longer in Group A. Patients receiving the multidrug cocktail achieved greater knee ROM at discharge and earlier independent ambulation. There was no statistically significant difference in postoperative complications between the two groups.

Conclusion: Periarticular multidrug cocktail injection provides superior postoperative pain control and improved early functional recovery compared to conventional single-drug local anaesthetic infiltration following TKA, without increasing complication rates.

Keywords: bupivacaine, ketorolac injection, multidrug periarticular cocktail, postoperative pain control, total knee arthroplasty

How to cite this article: Ravishankar K, Shanthappa AH, Nagakumar JS, Vinod Kumar K. Multidrug periarticular cocktail versus single drug bupivacaine for postoperative pain control after total knee arthroplasty: a retrospective cohort study. Int J Drug Deliv Technol. 2026;16(75s): 1813-1818. DOI: 10.25258/ijddt.16.75s.193

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Total knee arthroplasty (TKA) is widely accepted as an effective surgical intervention for end-stage knee osteoarthritis, providing significant pain relief and functional improvement [1]. The procedure is among the most commonly performed elective orthopaedic operations worldwide, with projections estimating a substantial and continuing rise in demand over the coming decades, driven by an ageing global population and increasing rates of obesity [2]. Despite significant advances in surgical technique, implant design, anaesthetic care, and perioperative management, postoperative pain remains one of the most important determinants of early rehabilitation, length of hospital stay, and overall patient satisfaction [3]. Studies have consistently demonstrated that up to 30% of patients report dissatisfaction following TKA, with uncontrolled pain being a leading contributing factor [1]. Inadequately managed postoperative pain not only

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hampers functional recovery but also contributes to the development of chronic pain, prolonged opioid dependence, and reduced quality of life in the postoperative period [4]. The ability to deliver effective, targeted postoperative analgesia is therefore central to optimizing TKA outcomes.

Poorly controlled pain after TKA is associated with delayed ambulation, reduced knee range of motion, prolonged hospitalization, and increased reliance on opioid analgesics [2]. Opioid-based analgesia, although effective for pain relief, is frequently associated with adverse effects including nausea, vomiting, sedation, constipation, urinary retention, and respiratory depression, all of which can negatively impact postoperative recovery and delay discharge [5]. Furthermore, the rising global concern surrounding opioid misuse and dependency has reinforced the need for effective non-opioid and opioid-sparing pain management strategies in the perioperative setting [6]. The pursuit of effective opioid-sparing analgesic strategies has therefore become a major focus in perioperative orthopaedic care [7]. Current pain management guidelines from major anaesthesia and pain societies advocate for multimodal analgesic regimens that simultaneously target multiple pain pathways to reduce the need for systemic opioids while ensuring adequate analgesia and facilitating earlier mobilization [5,7].

Enhanced Recovery After Surgery (ERAS) protocols have fundamentally transformed perioperative care in arthroplasty surgery by emphasizing multimodal analgesia, early mobilization, and optimized patient preparation to improve outcomes and reduce hospital stays [8]. Within these protocols, periarticular infiltration analgesia has gained considerable popularity due to its technical simplicity, cost-effectiveness, ease of administration by the operating surgeon, and ability to provide targeted local pain control without the systemic side effects associated with epidural or opioid-based analgesia [9]. By combining pharmacological agents with different mechanisms of action, this approach aims to achieve superior and prolonged analgesia while significantly reducing systemic opioid consumption [10]. Periarticular injection techniques have evolved considerably over the past two decades, with various combinations of local anaesthetics, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and vasoconstrictors being explored to maximize analgesic efficacy and duration [11,12]. The landmark technique described by Kerr and Kohan, utilizing large-volume local infiltration analgesia, demonstrated highly promising pain control outcomes and substantially reduced morphine requirements in a large case series of over 300 patients undergoing hip and knee arthroplasty [13]. Subsequent studies by Busch et al. and Vendittoli et al. further validated the efficacy of periarticular multimodal injection protocols in reducing postoperative pain and facilitating early recovery following TKA [9,14].

Although several studies have reported favorable outcomes with periarticular cocktail injections [14,15], there remains no consensus in the literature regarding their superiority over conventional single-drug local anaesthetic infiltration. Comparative studies have shown variable results depending on cocktail composition, injection volume, technique of delivery, and postoperative analgesic protocols employed [16,17,18]. Browne et al. demonstrated modest benefit from bupivacaine bolus injection alone, while Kelley et al. and Fu et al. highlighted the advantages of multimodal periarticular injection protocols in reducing pain scores and opioid requirements postoperatively [16,17,18]. Furthermore, evidence directly comparing VAS pain scores alongside comprehensive early functional recovery parameters including time to ambulation and knee ROM at discharge remains limited [19]. While some investigators have demonstrated benefits of periarticular corticosteroid addition to the analgesic cocktail [20], others have focused on the pivotal role of accelerated rehabilitation protocols in optimizing TKA outcomes [21]. The interaction between analgesic technique and structured physiotherapy-guided early mobilization warrants further investigation, particularly in resource-limited settings. This retrospective cohort study was undertaken to evaluate the comparative effectiveness of a multidrug periarticular cocktail injection versus a conventional single-drug local anaesthetic injection in patients undergoing primary unilateral TKA at a tertiary care teaching hospital in southern India.

MATERIALS AND METHODS

Study Design and Setting

This retrospective cohort study was conducted at R.L. Jalappa Hospital and Research Centre, Kolar, Karnataka, India, a tertiary care teaching hospital affiliated with Sri Devaraj Urs Academy of Higher Education and Research. The study period extended from September 2023 to September 2025.

Ethical Approval

The study protocol was approved by the Institutional Ethics Committee. As this was a retrospective analysis of medical records, informed consent had been obtained from all patients at the time of surgery as part of routine institutional practice.

Study Population

Medical records of consecutive patients who underwent primary unilateral TKA during the study period were screened. Patients were allocated into two groups based on the type of periarticular injection received intraoperatively. Group allocation was determined by the treating surgeon's standard practice during the respective time period, with the multidrug cocktail protocol adopted as institutional standard practice following a review of published evidence [6,15,16].

Inclusion Criteria

Patients aged between 40 and 90 years who underwent primary unilateral TKA for osteoarthritis were included, provided they had complete medical records with documented outcome measures and had received either a

multidrug periarticular cocktail injection or a single-drug local anaesthetic injection intraoperatively.

Exclusion Criteria
Patients were excluded if they had undergone revision TKA, had a diagnosis of inflammatory arthritis, chronic pain syndromes requiring long-term opioid therapy, neurological disorders affecting pain perception, allergy or contraindication to study medications, or psychiatric illness affecting pain reporting.

Patients with incomplete medical records were also excluded.

Intervention
All surgeries were performed by the same surgical team using a standardized medial parapatellar approach under spinal anaesthesia with use of tourniquet based on systolic blood pressure of patient.

Group A (Multidrug Cocktail Group):
Patients received a periarticular and intra-articular injection comprising 90 mL normal saline, 17.5 mL of

0.5% bupivacaine, 2 mL ketorolac (30 mg), and 0.5 mL adrenaline, resulting in a total volume of 110 mL.

Group B (Single-Drug Group):
Patients received 60 mL of 0.5% bupivacaine infiltrated Intraarticularly and periarticularly using the same technique.

A 21-gauge needle and 50 mL syringe were used for all injections.

Postoperative Protocol
All patients followed a standardized postoperative analgesia and rehabilitation protocol, including routine intravenous analgesics and early physiotherapy-guided mobilization.

Outcome Measures

Primary Outcome:
Postoperative pain intensity measured using the Visual Analog Scale (VAS) at 6, 12, 24, and 48 hours.

Secondary Outcomes:
Secondary outcomes included time to first rescue analgesic request, range of motion (ROM) at discharge, time to independent ambulation, length of hospital stay, and postoperative complications.

Sample Size Calculation
Based on a minimum clinically significant difference of 1.7 units in VAS score, a standard deviation of 1.8, alpha value of 0.05, and power of 80%, the required sample size was calculated as 18 patients per group.

Statistical Analysis
Data were entered into Microsoft Excel and analyzed using SPSS version 22. Continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as frequency and percentage. Independent sample t-test or Mann-Whitney U test was used as appropriate. A p-value < 0.05 was considered statistically significant.

RESULTS

Baseline Characteristics
Baseline demographic and clinical characteristics were comparable between the two groups (Table *1*).

Table 1: Demographic and Baseline Characteristics of the Study Population

Variable	Group A (n = 18)	Group B (n = 18)	p-value
Mean age (years)	66.4 ± 7.8	65.9 ± 8.2	0.84
Gender (M/F)	6 / 12	7 / 11	0.73
BMI (kg/m²)	27.6 ± 3.4	27.1 ± 3.1	0.62
Preoperative KSS	48.2 ± 6.5	47.6 ± 6.9	0.78

Legend: BMI = Body Mass Index (kg/m²); KSS = Knee Society Score; M = Male; F = Female. Values are expressed as mean ± standard deviation or number. Group A = Multidrug periarticular cocktail injection group (n = 18); Group B = Conventional single-drug bupivacaine injection group (n = 18). p < 0.05 considered statistically significant.Legend: BMI = Body Mass Index (kg/m²); KSS = Knee Society Score; M = Male; F = Female. Values are expressed as mean ± standard deviation or number. Group A = Multidrug periarticular cocktail injection group (n = 18); Group B = Conventional singledrug bupivacaine injection group (n = 18). p < 0.05 considered statistically significant.

Postoperative Pain Scores
VAS scores were significantly lower in the multidrug cocktail group at all postoperative time points (Table *2*).

Table 2: Comparison of Postoperative VAS Scores

Time Interval	Group A	Group B	p-value
6 hours	3.2 ± 0.9	4.8 ± 1.1	<0.001
12 hours	2.9 ± 0.8	4.3 ± 1.0	<0.001
24 hours	2.3 ± 0.7	3.7 ± 0.9	<0.001
48 hours	1.8 ± 0.6	3.0 ± 0.8	<0.001

Legend: VAS = Visual Analog Scale (0–10; 0 = no pain, 10 = worst imaginable pain). Values are expressed as mean ± standard deviation. Group A = Multidrug periarticular cocktail injection group (n = 18); Group B = Conventional single-drug bupivacaine injection group (n = 18). p < 0.05 considered statistically significant.

Secondary Outcomes

Patients in Group A demonstrated superior early functional recovery (Table *3*).

Table 3: Comparison of Secondary Outcome Measures

Outcome	Group A	Group B	p-value
Time to rescue analgesic (hours)	9.6 ± 2.1	5.4 ± 1.8	<0.001
ROM at discharge (degrees)	102.3 ± 8.7	91.5 ± 9.2	0.002
Time to ambulation (days)	2.1 ± 0.6	3.0 ± 0.7	0.001
Hospital stay (days)	5.1 ± 1.2	5.8 ± 1.4	0.08

Legend: ROM = Range of Motion (degrees of knee flexion at discharge). Values are expressed as mean ± standard deviation. Group A = Multidrug periarticular cocktail injection group (n = 18); Group B = Conventional single-drug bupivacaine injection group (n = 18). $p < 0.05$ considered statistically significant.

Postoperative Complications

There was no significant difference in postoperative complications between the groups (Table *4*).

Table 4: Postoperative Complications

Complication	Group A (n = 18)	Group B (n = 18)
Surgical site infection	0	1
Hematoma	1	1
Nerve injury	0	0

Legend: Values expressed as number of events. Group A = Multidrug periarticular cocktail injection group (n = 18); Group B = Conventional single-drug bupivacaine injection group (n = 18). No statistically significant difference was observed between groups for any complication ($p > 0.05$).

DISCUSSION

This study demonstrates that periarticular multidrug cocktail injection provides superior postoperative pain control compared to conventional single-drug local anaesthetic infiltration following TKA. Patients receiving the multidrug cocktail experienced significantly lower VAS pain scores across all postoperative time points - at 6, 12, 24, and 48 hours - and achieved earlier functional recovery with greater knee ROM at discharge, findings that are consistent with and supportive of previously published work in this field [9,14,15,19]. The magnitude of the difference in VAS scores between groups (1.4-1.6 units) exceeded the minimum clinically important difference of 1.3-1.5 units on the VAS scale, confirming that the observed differences are not only statistically significant but also clinically meaningful [3]. Parvataneni et al. similarly demonstrated that a multimodal periarticular injection protocol significantly reduced postoperative pain and morphine consumption compared to a control group, while also facilitating earlier mobilization [11].

Maheshwari et al. further reported that a structured multimodal pain management programme following TKA was associated with reduced hospital stays and improved patient satisfaction [12].

The enhanced analgesic effect observed in the multidrug group can be attributed to the synergistic pharmacological actions of the agents comprising the cocktail. Ketorolac, a potent non-selective NSAID, provides targeted local anti-inflammatory effects through cyclo-oxygenase (COX) inhibition, thereby reducing prostaglandin-mediated peripheral sensitization and postoperative inflammation at the surgical site [22]. Dahl and Kehlet demonstrated that NSAIDs play a crucial role in multimodal analgesia regimens, particularly in reducing somatic and inflammatory pain components in the early postoperative period [22]. Adrenaline, included as a vasoconstrictor, prolongs the duration of local anaesthetic action by inducing vasoconstriction, reducing systemic absorption and clearance of co-administered agents, thereby extending the effective duration of analgesia [23]. Bupivacaine, a long-acting amide local anaesthetic, provides sustained inhibition of sodium channels in peripheral nerve fibres, ensuring prolonged local anaesthesia at the periarticular tissues [24]. Scott highlighted the pharmacokinetic advantages of wound infiltration with bupivacaine, noting its capacity to provide effective analgesia for up to 12-18 hours postoperatively [24]. The combination of these three agents with complementary mechanisms of action provides a broader and more sustained analgesic effect than any single agent alone, consistent with the foundational principles of multimodal analgesia first articulated by Kehlet and Dahl [8]. Sinatra et al. similarly emphasized that combining analgesic agents targeting different nociceptive pathways reduces the required dose of each individual agent, thereby minimizing dose-related adverse effects while maintaining or enhancing analgesic efficacy [4].

Superior pain control in Group A directly facilitated earlier ambulation and greater knee ROM at discharge, both of which are recognized as critical determinants of successful TKA outcomes and long-term patient satisfaction [9,19]. In this study, patients in Group A achieved independent ambulation at a mean of 2.1 days compared to 3.0 days in Group B ($p = 0.001$), and demonstrated significantly greater knee ROM at discharge (102.3° vs 91.5°, $p = 0.002$). These differences are clinically significant, as early ambulation reduces the risk of deep venous thrombosis, pulmonary complications, and hospital-acquired infections, while improved ROM at discharge is strongly predictive of long-term functional outcomes [25]. Essving

et al. demonstrated similar benefits of local infiltration analgesia in unicompartmental knee arthroplasty, reporting reduced hospital stay, lower morphine consumption, and better functional outcomes compared to controls [25]. Rawal highlighted the broader implications of effective postoperative pain control in reducing overall healthcare burden and improving patient-reported outcomes following major joint surgery [7]. Tsukada et al., in a randomized controlled trial comparing periarticular injection with epidural analgesia in bilateral TKA, found periarticular injection to be equally effective with fewer complications, further supporting its use as the preferred analgesic modality [26]. Importantly, the use of the multidrug cocktail in this study did not increase the incidence of postoperative complications, with no cases of systemic toxicity, wound complications attributable to the injection, or nerve injury in Group A. This corroborates the established safety profile of periarticular multimodal cocktail injections reported in the literature [15,19,26]. Toftdahl et al. similarly reported no significant increase in adverse events with periarticular analgesia compared to femoral nerve block in TKA, while achieving comparable pain control [10].

CONCLUSIONS

Periarticular multidrug cocktail injection is a safe and effective method for postoperative pain management following total knee arthroplasty. It provides superior analgesia and enhances early functional recovery compared to conventional single-drug local anaesthetic infiltration.

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