International Journal of Research in Orthopaedics
Shah DD et al. Int J Res Orthop. 2026 Jul;12(4):1067-1072
https://www.ijoro.org

DOI: https://dx.doi.org/10.18203/issn.2455-4510.IntJResOrthop20262041

Systematic Review

Periarticular injection cocktails in total knee arthroplasty: composition, dosage and technique: a systematic review of randomized controlled trials

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Received: 26 March 2026
Revised: 05 May 2026
Accepted: 06 May 2026

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ABSTRACT

Effective postoperative analgesia is essential in total knee arthroplasty (TKA) to facilitate early mobilization and reduce opioid consumption. A systematic review of 48 studies was conducted in accordance with PRISMA guidelines using PubMed, Embase and Cochrane databases from January 2000 to March 2025, of which 22 studies were included in the quantitative synthesis. Local anesthetics combined with ketorolac and epinephrine form the backbone of periarticular injection. Corticosteroids provide additional early analgesic benefit. Recent randomized controlled trials (2023-2025) support multimodal cocktails and emerging adjuvants such as magnesium sulfate and liposomal bupivacaine. Periarticular injection provides effective postoperative analgesia in total knee arthroplasty, with consistent evidence supporting multimodal regimens incorporating a long-acting local anaesthetic, ketorolac and epinephrine. Corticosteroids offer additional early benefit and structured multi-site infiltration enhances analgesic outcomes. Standardization of composition and technique remains an important area for future research.

Keywords: Total knee arthroplasty, Periarticular injection, Local infiltration analgesia, Multimodal analgesia, Ropivacaine, Ketorolac, Postoperative pain, Randomized controlled trials

INTRODUCTION

Total knee arthroplasty is associated with significant postoperative pain, which can delay rehabilitation and affect functional outcomes.[1] Multimodal analgesia has therefore become the cornerstone of perioperative pain management.[2] Periarticular injection (PAI), also known as local infiltration analgesia, is widely used due to its effectiveness, simplicity, and opioid-sparing benefits.[3,4] Various drug combinations have been described, including local anesthetics, NSAIDs, corticosteroids and vasoconstrictors.[5,6]

Despite widespread adoption, there remains no consensus on the optimal composition, dosage and technique of periarticular injection.[2-5] This systematic review aims to synthesize current evidence, including recent randomized controlled trials, to identify best practices.[11-17]

METHODS

This systematic review was conducted in accordance with PRISMA 2020 guidelines.

Search strategy

A comprehensive literature search was conducted using PubMed, Embase and Cochrane Library databases. The search included studies published between January 2000 and March 2025 using the following keywords:

“Total knee arthroplasty”,“Periarticular injection” ,“Local infiltration analgesia” ,“Cocktail” ,“Pain management”.

Inclusion criteria

The review included randomized controlled trials (RCTs) that evaluated periarticular injection in primary total knee arthroplasty (TKA). Only studies reporting relevant clinical outcomes such as pain scores, opioid consumption, or functional outcomes were considered for inclusion.

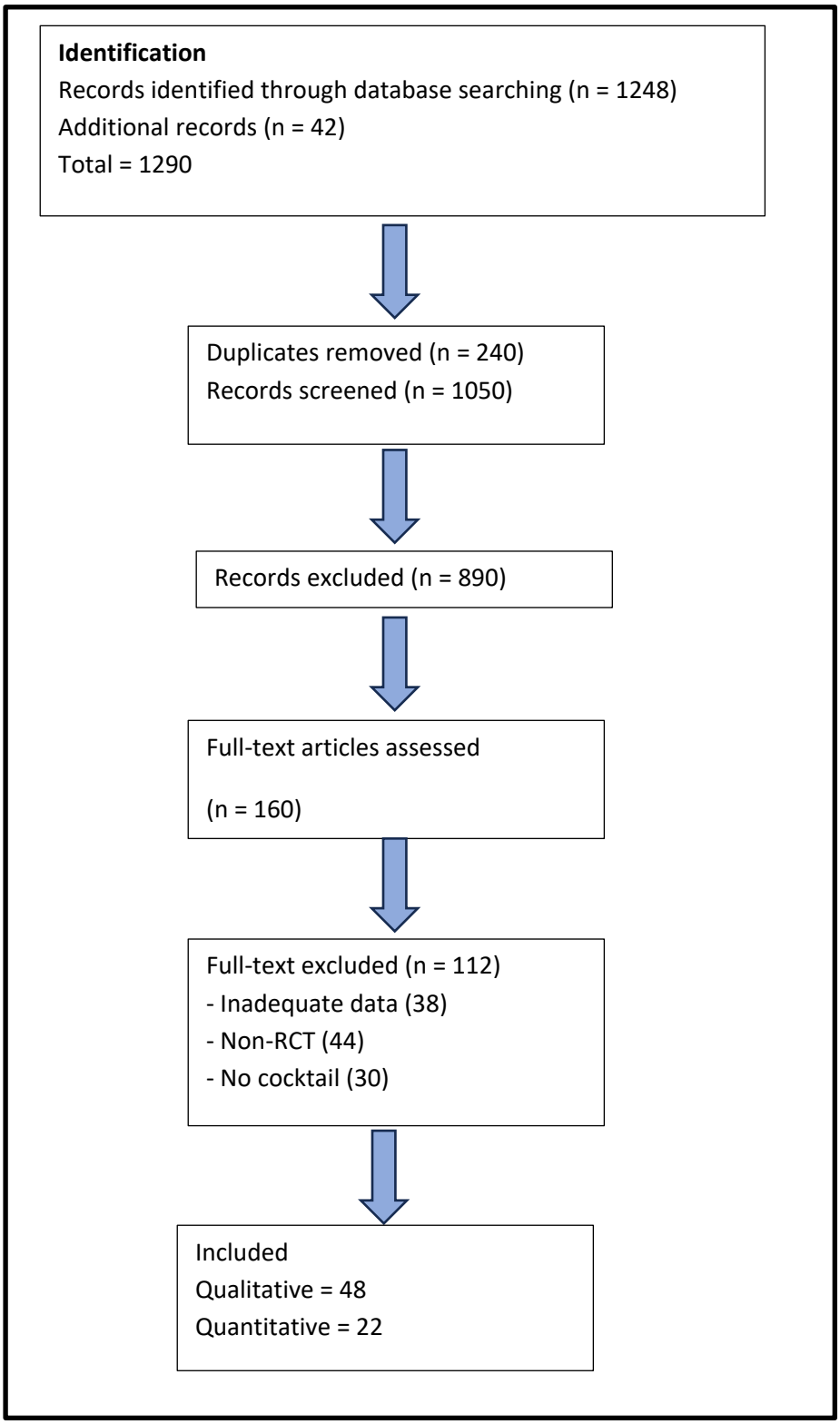

Figure 1: PRISMA diagram.

Exclusion criteria

Studies published in non-English languages were excluded, along with case reports and small case series. Studies involving revision total knee arthroplasty (TKA) were also excluded. In addition, studies that did not provide a clear description of the periarticular injection cocktail composition were not considered for inclusion.

Data extraction

Relevant data extracted from the included studies comprised the type and composition of the periarticular injection, sample size, pain scores measured using VAS or NRS, opioid consumption, functional outcomes and reported complications.

Outcome measures

The primary outcomes of interest were postoperative pain scores and opioid consumption. The secondary outcomes included range of motion, length of hospital stay and complications such as infection and wound-related issues.

Study selection (PRISMA framework)

The review was conducted in accordance with the PRISMA (Preferred reporting items for Systematic reviews and meta-analyses) guidelines.

Risk of bias assessment

The methodological quality of included randomized controlled trials was assessed using the Cochrane risk of bias 2 (RoB 2) tool. Studies were evaluated across domains including randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes and selection of reported results.

Each study was categorized as low risk, some concerns, or high risk of bias. The literature search identified 1,290 records (1,248 from databases and 42 from additional sources). After removal of 240 duplicates, 1,050 records were screened. Of these, 890 were excluded based on title and abstract screening.

A total of 160 full-text articles were assessed for eligibility, of which 112 were excluded (38 due to inadequate data, 44 non-randomized studies and 30 lacking defined cocktail composition). Finally, 48 studies were included in the qualitative synthesis, of which 22 were included in the quantitative analysis.

RESULTS

Multiple randomized controlled trials demonstrate that periarticular injection significantly improves postoperative analgesia compared to control or systemic analgesia alone.[3,4,14,20] Most included studies demonstrated low to moderate risk of bias, with common limitations including lack of blinding and variability in outcome reporting.[3,4]

Role of periarticular injection components

Local anaesthetics

Local anesthetics form the foundation of all periarticular injection (PAI) cocktails.[3,5,10] Ropivacaine is commonly preferred due to its lower cardiotoxicity and longer duration of action, whereas bupivacaine remains an effective alternative with a relatively higher toxicity profile.[10,13]

Multiple randomized controlled trials have demonstrated that these agents significantly improve postoperative pain control and reduce opioid consumption.[3,4,10,13,19]

NSAIDS (ketorolac)

Ketorolac is one of the most consistently beneficial adjuncts in PAI.[5,12,18] It reduces the inflammatory response, lowers postoperative pain scores, and decreases opioid requirements.[5] Several randomized trials have shown superior analgesic outcomes when ketorolac is combined with local anesthetics.[12-18]

Corticosteroids

Corticosteroids such as dexamethasone or methylprednisolone reduce inflammation and improve early postoperative pain relief.[6,8,13] Most studies report no significant increase in infection or wound complications, although caution is advised in high-risk patients.

Epinephrine

Epinephrine acts as a vasoconstrictor, prolonging the duration of local anesthetics and reducing systemic absorption. It may also reduce intraoperative bleeding and is widely included in multimodal PAI regimens.[3,4,10,14]

Opioids

The role of opioids in PAI remains controversial. While some studies demonstrate reduced opioid consumption, others show minimal additional benefit. Overall, current evidence does not strongly support their routine inclusion.[3,4,16]

Clonidine and other adjuvants

Adjuvants such as clonidine and magnesium sulfate have been evaluated, with some studies reporting modest improvements in analgesia. However, results are inconsistent, and these agents are not routinely recommended.[7-9]

Comparative effectiveness

Multimodal PAI cocktails consistently outperform single-agent injections. The most effective regimens typically combine a long-acting local anesthetic with ketorolac and epinephrine, with optional addition of corticosteroids for enhanced early analgesia.[3,4,15,16,21]

Recent evidence (2023-2025)

Recent randomized controlled trials have further strengthened the evidence base. The addition of magnesium sulfate and corticosteroids has shown improved early analgesia, while liposomal bupivacaine may prolong analgesic duration.[7-9]

Table 1: Common periarticular injection cocktail components and doses.

Drug class	Drug	Typical dose	Mechanism	Evidence strength
Local anesthetic	Ropivacaine	150-300 mg (0.2-0.5%)	Sodium channel blockade	Strong
Local anesthetic	Bupivacaine	75-150 mg	Long-acting analgesia	Strong
NSAID	Ketorolac	15-30 mg	Cox inhibition	Strong
Corticosteroid	Dexamethasone	4-10 mg	Anti-inflammatory	Moderate
Corticosteroid	Methylprednisolone	40-80 mg	Anti-inflammatory	Moderate
Vasoconstrictor	Epinephrine	1:200,000 (0.3-0.6 mg)	Prolongs anesthetic action	Strong
Opioid	Morphine	2-5 mg	Peripheral opioid receptor action	Weak
Alpha-2 agonist	Clonidine	50-150 mcg	Modulates nociception	Weak

Table 2: Recommended ideal periarticular injection cocktail (evidence-based).

Component	Drug	Dose	Role
Base	Ropivacaine	150-200 mg	Primary analgesia
NSAID	Ketorolac	30 mg	Anti-inflammatory, opioid-sparing
Vasoconstrictor	Epinephrine	0.3 mg	Prolong effect
Optional	Dexamethasone	8 mg	Enhances early pain relief

Table 3: Infiltration technique and anatomical distribution.

Surgical stage	Area	Volume (ml)	Notes
Before implantation	Posterior capsule	20-30	Avoid neurovascular bundle
Before implantation	Medial and lateral collateral ligaments	10-15	Deep infiltration
Before implantation	Quadriceps tendon	10	Improves early mobility
After implantation	Periarticular soft tissues	20-30	Around prosthesis
After closure	Subcutaneous tissue	10-20	Reduces superficial pain

Table 4: Representative RCT evidence summary.

Study	Year	Sample size	Cocktail	Key findings
Kim et al[5]	2020	120	Ropivacaine+ketorolac	↓ opioid use
Essving et al[4]	2010	80	Multimodal cocktail	↓ pain scores
Koh et al[6]	2014	100	+corticosteroid	Better early analgesia
Busch et al[3]	2006	64	Multimodal vs control	Superior pain relief

DISCUSSION

This review confirms that periarticular injection is an effective component of multimodal analgesia in TKA, consistent with previous systematic reviews and randomized trials.[1,2,10,11] The combination of local anesthetics with ketorolac and epinephrine demonstrates the most consistent benefit in reducing postoperative pain and opioid consumption.[3-5,10,18] Corticosteroids further enhance early analgesia without significantly increasing complication rates.[6,8,13] Several studies have reported clinically significant reductions in postoperative pain scores and opioid consumption with multimodal periarticular injection.[3,4,10,13,18] Recent randomized controlled trials (2023-2025) have expanded current understanding, demonstrating the potential role of newer adjuvants such as magnesium sulfate and liposomal bupivacaine.[7-9] These findings highlight the evolving nature of periarticular injection strategies and the need for continued refinement. Despite these advances, significant

heterogeneity remains in drug composition, dosage, and infiltration techniques across studies.[2-5] This limits the ability to establish a universally accepted protocol.[23,24]

CONCLUSION

Periarticular injection is a key component of multimodal analgesia in total knee arthroplasty. Evidence from included studies, including recent randomized controlled trials (2023-2025), demonstrates consistent use of local anesthetics combined with adjuncts such as ketorolac and epinephrine, with additional benefit observed from corticosteroids in selected patients.

A systematic, multi-site infiltration technique appears to enhance analgesic outcomes, with total volumes typically ranging from 60 to 120 ml. Despite variability in protocols, multimodal periarticular injection regimens provide reliable pain control and opioid-sparing effects. Ongoing high-quality trials are required to further define optimal drug combinations and emerging adjuvants.

ACKNOWLEDGEMENTS

The authors acknowledge the support and guidance of colleagues and faculty in the Department of Orthopaedics for their valuable input during the preparation of this manuscript. The authors also appreciate the contributions of all researchers whose work formed the basis of this review.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Shah DD, Patel CH, Deshpande SS. Periarticular injection cocktails in total knee arthroplasty: composition, dosage and technique: a systematic review of randomized controlled trials. Int J Res Orthop 2026;12:1067-72.