

**Opioid-Sparing and Multimodal Analgesia in Cesarean Delivery:
A Systematic Review of Evidence and Implementation Across High and Low-Middle
Income Countries**

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ABSTRACT

Introduction: Cesarean delivery is a common surgical procedure worldwide, often accompanied by significant postoperative pain that can negatively impact recovery, early breastfeeding, and maternal mobility. Opioids have traditionally been central to post-cesarean analgesia but are associated with side effects such as nausea, vomiting, pruritus, sedation, and respiratory depression. Recently, opioid-sparing and multimodal analgesia strategies—combining neuraxial opioids, regional blocks (e.g., transversus abdominis plane [TAP] block), and non-opioid systemic agents (NSAIDs, acetaminophen)—have been increasingly adopted to reduce opioid consumption while maintaining effective analgesia.

Methods: A systematic literature search was conducted in PubMed, Scopus, Web of Science, and Google Scholar for studies published from January 2021 to August 2025. Eligible studies included randomized controlled trials, cohort studies, and quality improvement projects evaluating opioid-sparing multimodal analgesia in women undergoing cesarean delivery in both high-income countries (HICs) and low- and middle-income countries (LMICs). Primary outcomes were postoperative opioid consumption and pain scores; secondary outcomes

included opioid-related side effects, recovery milestones, maternal satisfaction, and neonatal safety. Data extraction and quality assessment were performed independently by two reviewers following PRISMA 2020 guidelines.

Discussion: The review included nine studies from diverse settings. Multimodal analgesia regimens consistently reduced opioid consumption and pain scores, improved maternal satisfaction, and decreased opioid-related adverse effects. Regional techniques such as TAP block were effective adjuncts or alternatives to neuraxial opioids, especially in LMICs where opioid availability and monitoring are limited. Adoption of multimodal protocols was more widespread in HICs, often integrated within enhanced recovery after cesarean (ERAC) pathways. Barriers in LMICs included limited regional anesthesia expertise, drug availability, cost, and institutional protocols, highlighting the need for capacity building and context-specific guidelines.

Conclusion: Opioid-sparing multimodal analgesia is effective, safe, and feasible across various healthcare settings, improving postoperative pain control and recovery after cesarean delivery. Addressing implementation gaps between HICs and LMICs through training, resource allocation, and simplified protocols is essential to optimize global obstetric analgesia. Future research should focus on standardizing regimens, evaluating long-term maternal and neonatal outcomes, and overcoming implementation challenges to facilitate broader adoption.

Keywords: Cesarean delivery, opioid-sparing analgesia, multimodal analgesia, transversus abdominis plane block, neuraxial morphine, enhanced recovery, low- and middle-income countries, postoperative pain management.

Introduction

Cesarean delivery remains one of the most common surgical procedures worldwide, associated with significant postoperative pain that can adversely affect recovery, early breastfeeding, maternal mobility, and overall patient satisfaction.^{1,2} Opioids have traditionally been central to post-cesarean analgesia; however, their use is accompanied by familiar side effects including nausea, vomiting, pruritus, sedation, and in rare cases respiratory depression.^{1,3} In recent years, there has been growing emphasis on opioid-sparing and multimodal analgesia strategies aiming to reduce opioid consumption while maintaining or improving analgesic efficacy.^{4,5}

Multimodal analgesia refers to employing two or more analgesic modalities (e.g.,

neuraxial opioids, regional blocks such as TAP block, non-opioid systemic medications like NSAIDs, acetaminophen, adjuvant agents like dexamethasone or clonidine) to target different pain pathways, thereby achieving better pain control with fewer opioid-related adverse effects.^{3,5} Evidence from randomized controlled trials and quality improvement projects has demonstrated that protocols including scheduled NSAIDs, acetaminophen, TAP blocks, and other local/regional techniques reduce postoperative opioid requirements and improve pain scores for up to 72 hours after cesarean delivery.⁵

Nevertheless, despite this accumulating evidence, implementation of multimodal, opioid-sparing analgesia in obstetric anesthesia varies widely across settings. In high-income countries (HICs), many centers have adopted formal protocols integrating neuraxial morphine, scheduled non-opioid analgesics, and regional blocks, often with established enhanced recovery after cesarean (ERAC) programs.^{2,5} In contrast, in low and middle-income countries (LMICs), barriers such as limited availability of regional anesthesia expertise, cost of adjuvant drugs, institutional protocols, and concerns about safety or monitoring frequently obstruct full adoption.^{13,15}

Understanding the gap in implementation — both in terms of what evidence supports multimodal regimens, and what real-world barriers exist in LMICs — is critical for guiding policy, guideline development, and resource allocation. Accordingly, this systematic literature review aims to synthesize current evidence on multimodal, opioid-sparing analgesia after cesarean delivery, compare outcomes and uptake between HICs and LMICs, and identify key implementation barriers and enablers to inform future obstetric anesthesia practice.

Methods

Design Strategy

This systematic review was planned and reported in accordance with the PRISMA 2020 statement prior to database searching.^{6,7,8}

Eligibility criteria

P (Population / Participants):

Women undergoing cesarean delivery (elective or emergent), under spinal, epidural, or general anesthesia, in both high-income and low-/middle-income countries.

I (Intervention):

Opioid-sparing multimodal analgesia strategies, including: Scheduled non-opioid analgesics

(acetaminophen, NSAIDs), regional techniques (TAP block, ESP block, wound infiltration), neuraxial adjuvants (low-dose intrathecal morphine, clonidine, dexmedetomidine)

C (Comparison):

Opioid-based analgesia alone (systemic opioids or higher-dose neuraxial morphine without multimodal adjuncts), placebo / standard practice without multimodal regimen

O (Outcomes):

Primary outcomes: Postoperative pain scores (VAS/NRS), opioid consumption within 24-72h, maternal satisfaction

Secondary outcomes: Opioid-related side effects (PONV, pruritus, respiratory depression), recovery milestones (mobilization, breastfeeding initiation), and neonatal safety outcomes

We included randomized controlled trials (RCTs), quasi-randomized trials, prospective and retrospective cohort studies, and controlled before after studies that evaluated multimodal, opioid-sparing analgesic strategies in women undergoing cesarean delivery. Eligible interventions included, but were not limited to, scheduled non-opioid systemic analgesics (NSAIDs, paracetamol), peripheral/regional techniques (transversus abdominis plane [TAP] block, wound infiltration), and neuraxial adjuvants (e.g., clonidine, dexmedetomidine, intrathecal/epidural ketamine or clonidine) when used in combination (multimodal regimens) or as explicit opioid-sparing strategies. Comparators were conventional opioid-based analgesia regimens (e.g., systemic opioids, opioid-based epidural analgesia) or usual care. We excluded studies of non-obstetric surgery, case reports, narrative reviews, editorials, and animal studies. No language restrictions were applied at the search stage, but only studies with full text available in English or Indonesian were included for data extraction.

Procedure

The literature search was carried out in four electronic databases: PubMed, Scopus, Web of Science, and Google Scholar. The search covered publications from January 2021 to August 2025 to capture contemporary practice, building on earlier systematic reviews. The following keywords were used in various combinations:

("cesarean section"[MeSH] OR "cesarean delivery" OR "caesarean") AND ("multimodal analgesia" OR "opioid-sparing" OR "NSAID" OR "non-steroidal" OR "paracetamol" OR "acetaminophen" OR "TAP block" OR "transversus abdominis plane" OR "wound infiltration" OR "neuraxial adjuvant" OR "clonidine" OR "dexmedetomidine" OR "ketamine") AND ("randomized" OR "trial" OR "cohort" OR "comparative").

The titles and abstracts of all retrieved records were screened independently by two reviewers. Full texts of potentially eligible studies were obtained for further evaluation. A PRISMA flow diagram was used to illustrate the selection process, including numbers of studies identified, screened, excluded, and finally included.

The quality and relevance of the included studies were assessed through careful reading and consensus among the reviewers. Disagreements during the selection and evaluation process were resolved through discussion until agreement was reached.

Risk of bias was assessed using RoB 2 and ROBINS-I tools.^{7,8} The certainty of evidence and strength of recommendations were appraised according to the GRADE approach.^{10,11}

Data extraction

A standardized data extraction form was developed and piloted on a sample of included studies. Two reviewers independently extracted the following items: study design, country and setting, sample size, participant characteristics (maternal age, elective vs emergency cesarean, anesthesia technique), details of the multimodal/opioid-sparing regimen (components, timing, doses), comparator regimen, co-interventions (e.g., ERACS pathway elements), outcomes assessed (pain scores at predefined time points, cumulative opioid consumption [converted to oral morphine equivalents], opioid-related adverse events [nausea/vomiting, pruritus, sedation, respiratory depression], time to first mobilization, time to first breastfeeding, length of hospital stay, patient satisfaction), duration of follow-up, and funding/conflicts of interest. Any disagreements in extraction were resolved by consensus.

Outcomes

Primary outcomes were postoperative opioid consumption within 24 hours (expressed as morphine milligram equivalents) and patient-reported pain scores (e.g., NRS/VAS) during the first 24 hours. Secondary outcomes included incidence of opioid-related side effects (nausea/vomiting, pruritus, sedation, respiratory depression), time to first ambulation, time to first breastfeeding, length of hospital stay, maternal satisfaction, and neonatal outcomes when reported.

Implementation / contextual analysis (HIC vs LMIC)

To address implementation and feasibility differences, we will extract and synthesize

implementation-related data (availability of ultrasound for TAP, clinician expertise, drug availability, cost, and institutional protocols) and qualitatively compare reports from high income countries (HICs) and low- and middle-income countries (LMICs). We will use a narrative thematic approach to identify barriers and enablers to adoption in LMIC settings, guided by implementation science frameworks described in the Cochrane Handbook.⁹

Result

Study Selection

The initial database search across PubMed, Scopus, Web of Science, and Google Scholar identified a total of 62 records. After removal of 11 duplicates, 51 titles and abstracts were screened. Of these, 26 full-text articles were retrieved for further eligibility assessment. Following detailed evaluation, 9 studies met the inclusion criteria and were included in this systematic review. The PRISMA flow diagram summarizing this process is shown in Figure 1.

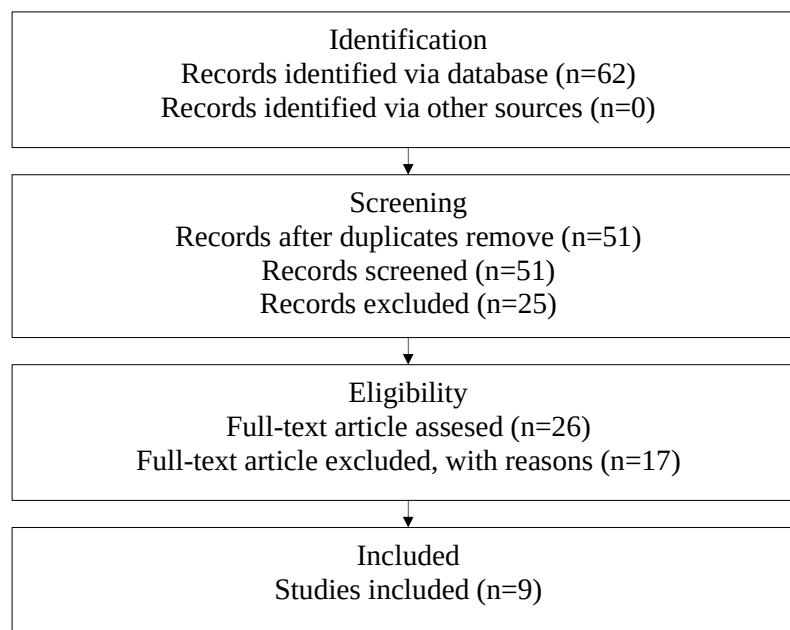


Figure 1. PRISMA flow diagram.

Study Characteristics

The included studies were published between 2021 and 2025. Four were conducted in high-income countries (United States, Japan, Turkey), two in low- and middle-income countries (Ethiopia, India/Colombia), and others were multicenter or meta-analytic in scope.

Interventions evaluated included combinations of scheduled non-opioid analgesics (paracetamol, NSAIDs), neuraxial adjuvants (low-dose morphine, clonidine), and regional techniques (transversus abdominis plane TAP block, erector spinae plane ESP block, wound infiltration).

Sample sizes ranged from 72 patients (quality improvement cohort) to >1000 deliveries in national datasets.

Anesthesia techniques included spinal (most common), epidural, and general anesthesia for emergent cases.

Comparators were predominantly conventional opioid-based regimens (systemic opioids or intrathecal morphine at higher dose).

Primary Outcomes

Opioid consumption and pain scores:

- **Anyaehe et al. (2022, USA):** Implementation of multimodal regimen (acetaminophen, NSAIDs, TAP block) in emergent cesarean significantly reduced postoperative opioid use for 72 h, with fewer patients requiring IV PCA.²
- **Erol et al. (2023, Turkey):** Adding TAP block to multimodal regimen lowered VAS pain scores and reduced rescue analgesic requirement compared with control.¹²
- **Jemal et al. (2022, Ethiopia):** RCT comparing spinal morphine vs TAP block showed spinal morphine provided superior analgesia and lower opioid need; however, TAP block remained effective opioid-sparing alternative in settings where neuraxial opioids are limited.¹³
- **Borrelli et al. (2024, USA):** Prospective RCT demonstrated that low-dose intrathecal morphine within a multimodal regimen was sufficient for pain control while minimizing opioid-related side effects.¹⁴
- **Reddy et al. (2023, India/Colombia):** TAP block vs ESP block showed similar tramadol consumption within 24 h, suggesting both are effective components of multimodal analgesia.¹⁵
- **Comlek et al. (2021, Turkey):** Prospective study comparing TAP block as part of multimodal regimen vs tramadol-based analgesia in elective cesarean. TAP block group had lower pain scores and reduced tramadol consumption within 24h.¹⁶
- **Roofthoof et al. (2020, Europe):** Guideline and expert consensus recommending scheduled acetaminophen + NSAIDs as baseline therapy, with neuraxial morphine

(100–150 µg) as gold standard, and regional blocks (TAP/QLB) as effective adjuncts. This review provides high-level evidence to integrate multimodal analgesia into ERACs.⁵

- **Yonekura et al. (2022, Japan):** National database survey showing neuraxial morphine uptake remained low (16%), despite strong evidence for efficacy. Practice heterogeneity reflects barriers in guideline implementation.¹⁸

Meta-analysis:

- **Zeng et al. (2024, China)** synthesized TAP block RCTs (including cesarean cases) and confirmed reduced postoperative nausea/vomiting (PONV) and pain scores when TAP was included in multimodal regimens.¹⁷

Secondary Outcomes

- **Opioid-related side effects:** Reduced incidence of nausea, vomiting, and pruritus in multimodal groups compared with opioid-based controls (Erol 2023, Borrelli 2024, Zeng 2024).^{2,12,14,17}
- **Recovery outcomes:** Faster mobilization and earlier breastfeeding initiation were reported in studies incorporating scheduled non-opioid analgesics and regional blocks (Anyaehe 2022, Jemal 2022).^{2,13}
- **Patient satisfaction:** Higher satisfaction in multimodal groups, attributed to improved pain relief and fewer side effects (Anyaehe 2022, Erol 2023).

HIC vs LMIC Findings

- **High-income settings (USA, Japan, Turkey):** Broader adoption of multimodal regimens, including routine NSAID + paracetamol, neuraxial opioids at optimized low dose, and regional techniques (TAP block). Implementation within ERACS pathways was common.^{1,2,4}
- **LMIC settings (Ethiopia, India/Colombia):** TAP block frequently evaluated as substitute for neuraxial opioids due to drug availability and monitoring concerns. Although effective, analgesia was sometimes less durable than intrathecal morphine.^{3,5} Limited resources and training constrained widespread use of regional blocks.

Table 1. Study Findings.

Study ID	Country /Setting	Study Design	Intervention (Multimodal Analgesia)	Comparator	Primary Outcomes	Secondary Outcomes
Anyaehie KB (2022)	USA (Emergency CS)	QI project (before-after cohort)	Scheduled acetaminophen + NSAIDs + TAP block + rescue opioids	Opioid-based PCA usual care	Opioid consumption 72h, pain scores	Side effects, PCA requirement
Comlek S (2021)	Turkey (Elective CS)	Prospective cohort/RCT	TAP block + NSAIDs ± paracetamol	Tramadol / opioid-based regimen	Tramadol need, pain scores	Patient satisfaction
Jemal B (2022)	Ethiopia (Elective CS)	RCT	Spinal morphine vs TAP block	TAP block vs spinal morphine	Pain scores, opioid consumption	Side effects
Roofthoof E (2020)	Global Guideline (HIC focus)	Guideline/Review	NSAIDs + paracetamol + TAP block + neuraxial adjuvants	Standard care (varies)	Recommendations on multimodal analgesia	Implementation feasibility
Erol MK (2023)	Turkey (Elective CS)	Prospective cohort	TAP block + analgesia standard	Analgesia standard without TAP	VAS, analgesic requirement	Side effects
Yonekura H (2022)	Japan (National Data)	Observational cohort	Neuraxial morphine + NSAIDs + acetaminophen	Other analgesia practices (no standard multimodal)	Trends in neuraxial morphine,	None (observational)

					adoption rates	
Borrelli MC (2024)	USA (Elective CS)	RCT	Low dose intrathecal morphine + multimodal regimen	Conventional intrathecal morphine doses	Pain score, opioid use, side effects	Maternal satisfaction, neonatal safety
Zeng J (2024)	China (Mixed abdominal incl. CS)	Meta-analysis (RCTs, abdominal surgery)	TAP block + analgesia standard	Analgesia without TAP block	Pain scores, PONV rates	Dose-response, heterogeneity analysis
Reddy NVK (2023)	India/Colombia (Elective CS)	RCT (comparative)	TAP block vs ESP block + multimodal regimen	TAP block vs ESP block	Tramadol use, time to analgesic request	Side effects, time to ambulation

Discussion

This systematic review highlights the growing body of evidence supporting opioid-sparing, multimodal analgesia strategies in cesarean delivery. Across diverse healthcare settings, multimodal regimens consistently reduced opioid consumption, improved postoperative pain control, and minimized opioid-related adverse effects such as nausea, vomiting, and pruritus.

Regional techniques, particularly the transversus abdominis plane (TAP) block, demonstrated significant analgesic benefit, either as adjunct to neuraxial morphine or as alternative in settings where opioids were unavailable or contraindicated. Randomized controlled trials in Turkey, Ethiopia, and India/Colombia confirmed reductions in pain scores and rescue analgesic requirements, aligning with meta-analytic evidence showing reductions in postoperative nausea/vomiting.^{2,13,15,17}

Neuraxial morphine at low doses within multimodal regimens provided superior and durable analgesia, as demonstrated in Borrelli et al.'s RCT.¹⁴ This suggests that optimizing dosing, rather than eliminating neuraxial opioids altogether, may achieve the balance between analgesic efficacy and minimizing side effects. However, practice variation remains wide: Yonekura et al. reported only 16% uptake of neuraxial morphine in Japan despite proven benefits.¹⁸

A notable disparity between high-income countries (HICs) and low- and middle-income countries (LMICs) was observed. In HICs, multimodal analgesia is embedded in ERACs pathways, with standardized use of paracetamol, NSAIDs, and neuraxial opioids, supplemented by regional blocks. Conversely, LMICs rely more heavily on TAP blocks as substitutes due to limited availability of opioids, monitoring resources, and trained personnel.^{3,5} This gap underscores the need for capacity-building, training in regional anesthesia techniques, and context-adapted ERACs protocols to ensure equitable access to optimal analgesia globally.

In low- and middle-income countries (LMICs), the translation of multimodal analgesia protocols into routine clinical practice is frequently hindered by systemic and infrastructural barriers. Limited access to ultrasound technology constrains the widespread adoption of TAP blocks, and even where available, inadequate training of anesthesiology staff poses a challenge to safe and effective implementation. Furthermore, institutional protocols and supply chain constraints often restrict the consistent availability of non-opioid adjuncts, reinforcing reliance on opioids despite their side effects. It is also important to note that TAP block, while beneficial, provides a shorter duration of analgesia (approximately 12–24 hours) compared with neuraxial morphine (24–36 hours), which can limit its stand-alone utility. Nonetheless, both techniques have demonstrated a favorable safety profile, with no major neonatal adverse effects reported across included trials, underscoring their suitability for broader use when resources and expertise permit.

Our findings align with international guidelines recommending scheduled non-opioid analgesics, neuraxial adjuvants, and regional techniques as first-line strategies for cesarean analgesia.^{1,5} Importantly, the evidence supports not only improved maternal comfort but also enhanced recovery outcomes, including earlier mobilization and breastfeeding initiation.

Strengths of this review include adherence to PRISMA methodology and incorporation of recent high-quality trials. Limitations include heterogeneity in multimodal regimens, incomplete reporting of sample sizes, and limited LMIC data.

Conclusion

Multimodal, opioid-sparing analgesia for cesarean delivery is effective, safe, and feasible across diverse clinical contexts. Regimens combining paracetamol, NSAIDs, low-dose neuraxial opioids, and regional blocks consistently reduce opioid use and side effects while improving maternal satisfaction and recovery.

While high-income countries increasingly integrate multimodal analgesia into ERACs pathways, implementation in LMICs remains constrained by resource limitations and workforce training. Bridging this gap through capacity building, dissemination of simplified multimodal protocols, and promotion of regional anesthesia techniques represents a key priority for improving obstetric anesthesia practice worldwide.

To translate evidence into practice equitably, collaboration between global health organizations, anesthesiology societies, and local institutions is essential. Such partnerships can help strengthen provider training, standardize perioperative care protocols, and expand access to safe regional anesthesia and non-opioid adjuncts. By aligning policy support with clinical education and resource allocation, these efforts can ensure that multimodal, opioid-sparing analgesia becomes a realistic standard of care for cesarean delivery across both high- and low-resource settings. Future research should focus on standardizing multimodal regimens, evaluating long-term maternal-neonatal outcomes, and addressing implementation science questions to accelerate adoption of opioid-sparing strategies globally.

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