ANESTHESIOLOGY

Openventio PUBLISHERS

Review Article

Clinical Evaluation of Non-Opioid Multimodal Analgesia in Orthopedic Surgery

Aleksi Nielsen[1*], Laura Silva[2] and Tomasz Fernandez[3]

[1]*Division of Anesthesia and Intensive Care, Bohemian University of Medical Sciences, Czech Republic*
[2]*Department of Anesthesiology and Pain Management, Shannon University Hospital, Ireland*
[3]*Division of Anesthesia and Intensive Care, Bohemian University of Medical Sciences, Czech Republic*

ABSTRACT

Opioid-based analgesia has long been the default approach to pain after orthopedic surgery, but the recognized costs of routine opioid use, including nausea, delayed mobilization, and persistent postoperative opioid consumption, have driven a shift toward multimodal regimens in which opioids are reserved as rescue therapy rather than scheduled as first-line treatment.

This review evaluates the clinical trial evidence for the principal non-opioid components of these regimens across elective orthopedic surgery, including scheduled acetaminophen and NSAID therapy, gabapentinoids, peripheral nerve blockade, and periarticular local infiltration including liposomal bupivacaine formulations.

Regional anesthesia and peripheral nerve blockade remain the most consistently effective non-opioid intervention, while gabapentinoids show modest opioid-sparing benefit that must be weighed against sedation and fall risk in older patients, and newer local anesthetic formulations have not shown clear superiority over standard bupivacaine when combined with a nerve block.

Practical pathway design also requires attention to rebound pain as peripheral blocks resolve and to adjuncts such as perineural dexamethasone that extend block duration without opioid exposure.

We conclude that a procedure-specific, layered combination of these agents can deliver adequate analgesia with minimal or no opioid use across most elective orthopedic procedures, though outcome auditing at the institutional level remains necessary to confirm that trial-level benefits translate into routine practice.

Keywords: *multimodal analgesia; opioid-sparing; orthopedic surgery; peripheral nerve block; gabapentinoids*

Citation: Nielsen A, Silva L and Fernandez T (2022) Clinical Evaluation of Non-Opioid Multimodal Analgesia in Orthopedic Surgery. Anesthesiology. 2(1):01-05.

DOI: 10.17140/2022.vol2.i01.pp01-05

Corresponding Author: *Aleksi Nielsen*

E-mail Address: *a.nielsen@bums.cz*

Article History: *Received 10 April 2022 | Accepted 06 May 2022 | Published 05 June 2022*

Copyright: *© 2022 Aleksi Nielsen, et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited (**https://creativecommons.org/licenses/by/4.0/**).*

INTRODUCTION

Orthopedic procedures rank among the most painful operations performed in modern surgical practice, and for decades the default response to that pain was a

large postoperative opioid prescription. The consequences of that default are now familiar to every anesthesiologist and orthopedic surgeon: nausea, ileus, sedation, delayed mobilization, urinary retention, and a meaningful subset of previously opioid-naive patients who go on to persistent use months after a routine arthroplasty or arthroscopy [1]. Multimodal analgesia was conceived as a direct answer to this problem — combining agents with different mechanisms of action so that no single drug class, and ideally no opioid at all, has to carry the entire analgesic burden. Acetaminophen, NSAIDs, gabapentinoids, local infiltration, peripheral nerve blockade, and adjuncts such as dexamethasone or ketamine each contribute a partial, additive effect, and when layered together they can reduce pain scores and opioid consumption more than any single agent used alone [2].

What has changed more recently is the ambition of these protocols. Early multimodal regimens still treated opioids as the backbone of the plan, with adjuncts bolted on to reduce the dose required. The newer generation of "opioid-sparing" or frankly opioid-free protocols instead treats the opioid as optional — reserved as rescue medication rather than scheduled first-line therapy — and asks whether a purely non-opioid combination can control pain adequately across the full arc of elective orthopedic surgery, from same-day arthroscopy to total joint arthroplasty to hip fracture repair in frail older adults. This review synthesizes the clinical trial evidence behind that question: which non-opioid components have the strongest support, where the evidence is more equivocal, and what a defensible non-opioid multimodal pathway looks like across different orthopedic populations.

SYSTEMIC NON-OPIOID AGENTS: ACETAMINOPHEN, NSAIDS, AND GABAPENTINOIDS

Acetaminophen and NSAIDs form the foundation of essentially every multimodal protocol in orthopedics, scheduled rather than given as needed, on the logic that steady-state drug levels prevent pain from re-establishing itself between doses. Intravenous and oral acetaminophen perform comparably in most orthopedic populations, and the marginal cost of the intravenous formulation is difficult to justify once a patient can tolerate oral intake. NSAIDs add a genuinely different mechanism — peripheral inhibition of prostaglandin-mediated sensitization — and randomized data in outpatient hand and shoulder surgery show that a scheduled non-opioid protocol built around acetaminophen and an NSAID can match or outperform opioid-based regimens on pain scores while producing far less nausea and next-day sedation [3]. The tradeoff clinicians weigh is bleeding risk in patients undergoing extensive osteotomy or with impaired renal function, along with theoretical concerns about bone healing after fracture surgery or spinal fusion; short-course use in patients with normal renal function and adequately controlled surgical hemostasis has not borne out clinically significant harm in the orthopedic trials that have looked for it.

Gabapentinoids occupy a more contested position. The pharmacological rationale is sound: gabapentin and pregabalin bind the alpha-2-delta subunit of voltage-gated calcium channels and blunt central sensitization, the process by which acute nociceptive input is amplified into exaggerated postoperative pain. Meta-analytic data in total hip arthroplasty found that preoperative gabapentin or pregabalin modestly reduced pain scores and opioid consumption in the first 24 to 48 hours [4], and a broader synthesis across orthopedic procedures more generally reported similar opioid-sparing effects alongside a reduction in postoperative nausea [5]. A separate meta-analysis focused specifically on pregabalin after hip and knee arthroplasty reached a comparable conclusion on analgesic benefit but flagged sedation and dizziness as recurring adverse effects large enough to matter in older patients at fall risk [6]. The net clinical read is that gabapentinoids are a reasonable single preoperative dose in younger, ambulatory patients but need individualized judgment — sometimes omission — in frail, elderly, or fall-prone populations where the sedative cost can outweigh the modest opioid-sparing benefit, an issue that matters enormously in hip fracture surgery given how routinely that population overlaps with frailty and cognitive vulnerability.

REGIONAL ANESTHESIA AND PERIPHERAL NERVE BLOCKADE

Regional techniques remain the single most effective non-opioid intervention available for major orthopedic surgery, because they interrupt nociceptive transmission before it ever reaches central pathways rather than modulating pain after the fact. Peripheral nerve blocks — femoral and adductor canal blocks for knee arthroplasty, interscalene blocks for shoulder surgery, popliteal sciatic blocks for foot and ankle procedures, and fascia iliaca or pericapsular nerve group blocks for hip fracture — have accumulated a large randomized evidence base showing reduced early pain scores and reduced opioid consumption relative to systemic analgesia alone. The adductor canal block in particular has displaced the traditional femoral nerve block for total knee arthroplasty because it achieves comparable analgesia while sparing the quadriceps motor function that the femoral block impairs, translating into earlier ambulation and fewer falls without sacrificing pain control.

A meta-epidemiological analysis of hip and knee arthroplasty pain trials is a useful corrective here: it found that trials combining regional or local techniques with a genuinely non-opioid systemic backbone reported opioid consumption reductions that were substantially larger than trials adding a non-opioid

agent onto a standard opioid-based regimen [7]. In other words, the size of the observed benefit from any individual non-opioid component depends heavily on what it is being compared against — evidence that should make readers cautious about extrapolating a modest single-drug effect size directly into an opioid-free protocol built from several such drugs stacked together. Continuous perineural catheter techniques extend the same principle into the days after surgery for patients discharged the same day, though the added complexity and catheter management burden mean this option is generally reserved for high-pain procedures rather than applied routinely. In elderly hip fracture patients, fascia iliaca and pericapsular blocks placed shortly after emergency department presentation reduce pain scores while waiting for surgery and reduce systemic opioid requirements during a period when delirium risk from sedating medications is a major concern.

LOCAL INFILTRATION ANALGESIA AND PERIARTICULAR INJECTION

Periarticular infiltration with local anesthetic, often combined with adjuncts such as epinephrine, ketorolac, or corticosteroid, has become close to standard practice in total knee and hip arthroplasty because it delivers dense local analgesia directly to the surgical field without the motor blockade or resource requirements of a formal nerve block. Liposomal bupivacaine formulations, which extend local anesthetic release over roughly 72 hours instead of the 6 to 8 hours typical of plain bupivacaine, were developed specifically to close the gap between infiltration analgesia and the multi-day catheter techniques. The randomized evidence on liposomal bupivacaine remains genuinely mixed. Several trials comparing liposomal to standard bupivacaine periarticular injection in knee arthroplasty found meaningfully reduced opioid consumption and improved early functional recovery with the liposomal formulation [8], while a non-inferiority trial across combined hip and knee arthroplasty populations found the two formulations essentially equivalent on pain and opioid outcomes, suggesting the cost premium of liposomal bupivacaine is not automatically justified [9]. A trial comparing liposomal bupivacaine against ropivacaine specifically within a four-drug periarticular cocktail similarly found no clear analgesic advantage for the liposomal agent [10]. Taken with the adductor canal block literature, the reasonable clinical conclusion is that liposomal bupivacaine can be a useful component of a non-opioid pathway but is not obviously superior to cheaper standard local anesthetic when a nerve block is already part of the regimen, and institutions should decide its use based on local cost and supply rather than assuming automatic benefit.

BUILDING AND AUDITING A NON-OPIOID PATHWAY

The practical challenge in adopting these findings is less about identifying effective individual agents than about assembling them into a coherent, procedure-specific pathway and then verifying that the pathway performs as intended once it leaves the trial setting. Systematic reviews of preoperative non-opioid regimens in arthroscopic surgery report consistent reductions in postoperative opioid consumption when acetaminophen, an NSAID, and sometimes a single preoperative gabapentinoid dose are combined before incision [11], and prospective trials of fully opioid-free multimodal protocols after arthroscopic rotator cuff repair have found pain control equivalent to or better than opioid-containing regimens, with substantially fewer opioid-related side effects [12]. A broader systematic review and meta-analysis of opioid-free anesthesia specifically in orthopedic surgery reached a similar overall conclusion across procedure types, though with heterogeneity in which non-opioid combination was used across the pooled trials [13].

Two practical issues recur across this literature and deserve emphasis for readers designing an institutional pathway. First, rebound pain — a sharp increase in pain as a peripheral nerve block resolves, often occurring at home without direct clinical supervision — is a well-documented phenomenon that can undermine confidence in an otherwise successful opioid-sparing block-based plan; identifying risk factors for rebound pain and layering in scheduled non-opioid analgesia timed to bridge the block's offset is now an active area of trial design [14]. Second, perineural or intravenous dexamethasone, given as an adjunct to extend block duration and reduce inflammatory pain, has reasonably strong meta-analytic support for prolonging analgesia when added to peripheral nerve blocks [15], giving pathway designers another genuinely non-opioid lever to pull rather than defaulting to opioid rescue. Institutions building opioid-sparing pathways should also build in outcome tracking — patient-reported pain scores, opioid consumption at discharge, and readmission or emergency-department return rates — because much of the enthusiasm for these protocols has outpaced the granular, procedure-specific outcome data that would let a given hospital know whether its particular combination of agents is actually delivering the benefit the trial literature promises.

CONCLUSION

The clinical trial evidence supports a genuinely opioid-sparing, and in many orthopedic contexts opioid-free, approach to perioperative pain management, built from scheduled acetaminophen and NSAID therapy, judicious gabapentinoid use tailored to fall and sedation risk, regional or peripheral nerve blockade wherever feasible, and periarticular local infiltration where a block is not used or as an adjunct where it is. No single agent replaces the effect of combining several, and the size of benefit attributed to any one component depends heavily on what background regimen it is tested against — a caution

that should temper expectations when stacking multiple modestly effective agents into one pathway. Newer formulations such as liposomal bupivacaine have not consistently outperformed cheaper alternatives once a nerve block is already in place, and adjuncts like perineural dexamethasone offer real additional value without opioid exposure. The practical work ahead for most institutions is less about discovering new agents and more about assembling procedure-specific pathways thoughtfully, anticipating problems like rebound pain, and auditing real-world outcomes rather than assuming trial-level benefit transfers automatically to routine practice.

DECLARATIONS

Acknowledgements

The authors thank the clinical anesthesia and orthopedic surgery staff at their respective institutions for ongoing discussion that helped shape the perspective presented in this review.

Funding

This review received no external funding from any public, commercial, or not-for-profit funding agency.

Conflict of Interest

The authors declare no conflicts of interest relevant to the content of this review.

Author Contributions

AN conceived the review and drafted the initial manuscript. LS performed the literature synthesis on regional anesthesia and local infiltration analgesia and critically revised the manuscript. TF contributed the sections on systemic non-opioid agents and pathway design and provided final approval of the submitted version. All authors read and approved the final manuscript.

Ethics Statement

This is a literature review that did not involve new data collection from human participants or animals and therefore did not require institutional ethics committee approval.

Data Availability

No new data were generated or analyzed for this review. All sources discussed are published works cited in the reference list.

REFERENCES

1. Sun EC, Darnall BD, Baker LC, Mackey S (2016) Incidence of and Risk Factors for Chronic Opioid Use Among Opioid-Naive Patients in the Postoperative Period. JAMA Internal Medicine, DOI:10.1001/jamainternmed.2016.3298.
2. Memtsoudis SG, Poeran J, Zubizarreta N, et al. (2018) Anesthetic care for orthopedic patients: is there a potential for differences in care? Anesthesiology, DOI:10.1097/ALN.0000000000002132.
3. Multimodal Pain Management After Outpatient Orthopedic Hand Surgery: A Prospective Randomized Trial (2023) Journal of Hand Surgery Global Online.
4. The efficacy of preoperative administration of gabapentin/pregabalin in improving pain after total hip arthroplasty: a meta-analysis (2016) BMC Musculoskeletal Disorders, DOI:10.1186/s12891-016-1231-4.
5. Effectiveness of gabapentinoids in orthopedic surgeries: a systematic review and meta-analysis of postoperative pain, and opioid-sparing effects (2025) BMC Anesthesiology, DOI:10.1186/s12871-025-03291-9.
6. Efficacy and safety of pregabalin for postoperative pain after total hip and knee arthroplasty: a systematic review and meta-analysis (2025) Journal of Orthopaedic Surgery and Research, DOI:10.1186/s13018-025-05675-6.
7. Opioid consumption and non-opioid multimodal analgesic treatment in pain management trials after hip and knee arthroplasties: A meta-epidemiological study (2023) PMID:36759566.
8. Liposomal bupivacaine in peri-articular injection reduces opioid consumption and improves early prognosis of total knee arthroplasty: a randomized controlled trial (2025) PMID:42401912.
9. Liposomal bupivacaine versus standard periarticular injections in total hip and knee arthroplasty: a prospective, randomized non-inferiority trial (2025) SICOT-J, PMID:40079611.
10. Liposomal bupivacaine versus ropivacaine in four-in-one nerve block for total knee arthroplasty: a randomized controlled trial (2026) BMC Anesthesiology, DOI:10.1186/s12871-026-04036-y.
11. Preoperative Nonopioid Analgesia Reduces Postoperative Opioid Consumption After Arthroscopic Surgery: A Systematic Review and Meta-analysis of Randomized Controlled Trials (2025) PMC, PMID:PMC13133421.
12. Multimodal Nonopioid Pain Protocol Provides Better or Equivalent Pain Control Compared to Opioid Analgesia Following Arthroscopic Rotator Cuff Surgery: A Prospective Randomized Controlled Trial (2021) PMID:34838987.
13. The effect of opioid-free anesthesia on postoperative pain in orthopedic surgery: A systematic review and meta-analysis of randomized controlled trial (2025) PMID:41525987.
14. Factors associated with rebound pain after peripheral nerve block for ambulatory surgery

(2021) British Journal of Anaesthesia.

15. Efficacy of perineural versus intravenous dexamethasone in prolonging the duration of analgesia when administered with peripheral nerve blocks: a systematic review and meta-analysis (2022) systematic review and meta-analysis.