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Review Article

Enhancing Postoperative Pain Control: The Role of Multimodal Analgesia

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ABSTRACT

Purpose of review: This narrative review aims to assess the effectiveness of multimodal analgesia protocols (MAPs) in managing postoperative pain and reducing opioid consumption. The review evaluates the safety profile of MAPs, identifies the most effective components for different surgical contexts, and discusses their broader applicability in clinical practice. Given the growing concerns around opioid use, the focus is on alternative strategies that can offer comparable or superior pain relief with fewer side effects.

Recent findings: Recent studies have demonstrated that MAPs, which combine various pharmacological and non-pharmacological methods, significantly reduce postoperative pain intensity and opioid use. These protocols show superiority over traditional opioid-centric approaches without increasing adverse events like nausea and respiratory depression. Incorporating regional anesthesia, nonsteroidal anti-inflammatory drugs, and nerve blocks has enhanced recovery, minimized complications, and improved patient outcomes. Furthermore, MAPs can be tailored to specific surgical settings, with combinations of medications like ketamine, acetaminophen, and dexamethasone proving effective in different clinical scenarios.

Summary: Multimodal analgesia offers a viable approach to optimize postoperative pain management, reducing opioid-related risks and improving recovery outcomes. By utilizing the synergistic effects of different pain relief modalities, MAPs can achieve better pain control while minimizing opioid consumption. The review underscores the need for the broader adoption of MAPs and further research to refine these protocols, aiming for long-term improvements in surgical care and patient experiences.

Key words: Multimodal analgesia protocols, opioids, postoperative pain, pharmacological agents, review

INTRODUCTION

Postoperative pain management is a major component of surgical care, impacting patient recovery, satisfaction, and overall health outcomes. Traditionally, opioids have been the cornerstone of postoperative analgesia due to their potent pain-relieving properties. However, the opioid-related side effects, such as nausea, vomiting, respiratory depression, and the risk of dependency, have raised significant concerns within the medical community. [1] The opioid crisis, marked by widespread misuse and addiction, has further fueled the search for alternative pain management strategies that can provide effective pain relief with fewer risks. [2] In this context, multimodal

anesthesia protocols (MAPs) have emerged as a promising approach. These protocols involve the combination of various pharmacological agents, such as nonsteroidal anti-inflammatory drugs (NSAIDs), local anesthetics, and regional anesthesia, with non-pharmacological techniques like nerve blocks, to target different pain pathways. The rationale behind MAPs is to achieve superior pain control through synergistic effects, potentially reducing the required doses of opioids and minimizing associated side effects. [3,4]

Despite the theoretical advantages of MAPs, there is significant variability in their application across different surgical procedures and patient populations. The components of MAPs can vary widely, with some protocols emphasizing regional anesthesia while others focus on systemic analgesics or non-pharmacological interventions. [5] This variability raises questions about the generalizability and overall effectiveness of MAPs in diverse surgical settings. While several studies have explored the benefits of individual components of MAPs, such as regional anesthesia or NSAIDs, a comprehensive synthesis of the available evidence on the effectiveness of MAPs as a whole is lacking. Moreover, existing reviews have often focused on specific surgical procedures or patient populations, limiting their applicability to broader clinical practice. Therefore, a narrative review that evaluates the overall impact of MAPs on postoperative pain management across various surgical contexts is necessary to provide clear guidance for clinicians. [6,7]

The primary objective of this review is to assess the effectiveness of MAPs in reducing postoperative pain intensity and opioid consumption compared to traditional analgesic approaches. Secondary objectives include evaluating the safety profile of MAPs, particularly the incidence of adverse events such as nausea, vomiting, and respiratory depression, and identifying which components of MAPs are most effective in different surgical settings. By synthesizing the available evidence, this review aims to provide a comprehensive assessment of MAPs, offering insights into their potential benefits and limitations and guiding their implementation in clinical practice.

WHY MULTIMODAL ANESTHESIA?

Anesthesia has its roots in using substances such as ether and nitrous oxide to induce states of hypnosis, pain relief, and muscle relaxation. The development of balanced anesthesia, which incorporates hypnotics and potent pain-relieving agents, was aimed at enhancing surgical outcomes. However, standard combinations like propofol plus opioids or volatile agents with opioids may still present challenges, such as postoperative nausea and vomiting (PONV), less effective pain management, delayed emergence from anesthesia, respiratory issues, and postoperative delirium. [8] With the ongoing opioid crisis causing significant mortality, the need for improved, safer strategies in anesthesia and analgesia is more urgent than ever. [9]

Multimodal analgesia (MMA) has been proposed as a solution, utilizing a combination of anesthetic and analgesic agents with distinct mechanisms of action to achieve additive or synergistic pain relief while reducing opioid-related side effects. [10] Surgeons also play a key role in advancing MMA by combining general anesthesia with regional or local anesthetic techniques to enhance recovery and surgical results. [11,12] They support postoperative MMA with strategies like local anesthetic infiltration or the placement of surgical site catheters. [13,14] The Enhanced Recovery After Surgery (ERAS) Society advocates for "opioid stewardship," promoting a careful assessment of opioid use to ensure it is administered judiciously. [15]

ARE OPIOIDS SAFE IN EVERY ANESTHESIA?

The widespread practice of using opioid-based anesthesia, particularly in combination with inhaled anesthetics or propofol, can contribute to hesitancy regarding the adoption of MMA, especially when patient follow-up is insufficient. Evidence suggests that administering high doses of intraoperative opioids tends to increase the need for postoperative opioids, while using lower doses has the opposite effect. [16,17]

A meta-analysis conducted in 2019 revealed that pain levels two hours after major abdominal or gynecological surgery were similar regardless of whether opioid-free or opioid-inclusive anesthesia was used; however, patients who received opioids experienced a significantly higher incidence of PONV. Despite the known risk of PONV, it is common for clinicians to continue using propofol anesthesia without restricting intraoperative opioid administration. Opioid-induced hyperalgesia remains a largely unrecognized concern, even in individuals who have not undergone surgery. [18,19]

While short-acting opioids such as remifentanil are linked to a greater risk of postoperative hyperalgesia, long-acting opioids may provide more prolonged pain relief. The involvement of *N*-methyl-D-aspartate (NMDA) receptors in controlling hyperalgesia underscores the value of including NMDA antagonists like methadone, alongside magnesium and ketamine, in contemporary pain management strategies. Recent research has uncovered neuroinflammatory mechanisms, including opioid-induced activation of mast cells and microglia-related "immunosenescence," which contribute to the development of chronic pain, particularly in the elderly. [20,21,22]

Postoperatively, the heavy reliance on opioid administration may lead to unfavorable outcomes. For example, the Prodigy study found that respiratory depression caused by opioids is often underdiagnosed on hospital wards, potentially leading to emergencies. The link between opioid use in cancer-related surgeries and poorer patient outcomes remains a contentious topic, with further research needed to clarify these associations. [23,24]

CONSTRUCTING AN MMA PROTOCOL

Pharmacological combinations of analgesics and non-drug therapies are key elements of MMA protocols. An important goal of MMA is the early introduction of antinociceptive measures, ideally before surgery, to better manage postoperative pain. The timing and dosage of these agents are crucial for optimal outcomes. The MMA protocol used at Rush University Medical Center (**Table 1**) provides an example of a comprehensive approach.

Preoperative pain management typically begins in the holding area 1 to 2 hours before surgery with various oral medications. Most MMA protocols involve a combination of

Table 1: Multimodal analgesia protocol.

Stage	Medications/procedure
Before admission	Preoperative counselling regarding anesthesia and postoperative analgesia—at the surgeon's office
Day of surgery	
Preoperatively	Oral medications given preoperatively in the holding area about 1 hour before surgery:
	- Cyclobenzaprine 10 mg
	- Pregabalin 150 mg
	- Oxycodone release 10 mg
Intraoperatively	
Induction of anesthesia	- Propofol 2 mg/kg plus ketamine 50 mg
Maintenance of anesthesia	- Sevoflurane with fentanyl 1–2 mg/kg titrated to clinical effect
Additional medications were administered intraoperatively.	
	- Bupivacaine 0.5% with epinephrine 1:200,000 injected at the incision site:
	- 20 mL per side if patient weight <70 kg
	- 30 mL per side if patient weight ≥70 kg
	- Acetaminophen 1,000 mg IV
	- Dexamethasone 10 mg IV
	- Ondansetron 4 mg IV
	- Famotidine 20 mg IV
Postoperative Day 0	
	- Cold compresses applied to the surgical area
	- Pregabalin 75 mg q12h orally
	- Cyclobenzaprine 10 mg q8h orally
	- Tramadol 50 mg q6h
	- Oxycodone immediate release:
	- 5 mg q4h as needed for pain (NRS >3), opioid naïve patients
	- 10 mg q4h as needed for pain (NRS >4), opioid tolerant patients
Postoperative Day 1	
	- Cyclobenzaprine 10 mg PO prn for spasms
	- Hydrocodone 10 mg plus acetaminophen 325 mg:
	- 1 tablet as needed for pain (NRS 1–5)
	- 2 tablets as needed for pain (NRS 6–10)

NRS: numeric rating scale for pain (where 0 = no pain and 10 = worst possible pain).

drugs, such as a muscle relaxant, a long-acting opioid, and an anticonvulsant before general anesthesia. [25] For instance, cyclobenzaprine, a muscle relaxant, is known to alleviate symptoms of low back pain. [26] Although its combination with NSAIDs does not significantly improve pain relief for acute low back pain compared to using NSAIDs alone, it remains more effective than opioid treatment for this condition. [27]

Preoperative opioid use is based on the premise of leveraging any potential pre-emptive analgesic effects to decrease the need for intravenous opioids post-surgery, thus reducing risks like nausea, sedation, and pruritus. Anticonvulsants such as pregabalin and gabapentin work by binding to the alpha-2-delta subunit of presynaptic voltage-gated calcium channels, reducing calcium influx and decreasing neurotransmitter release. These channels are upregulated in response to surgical trauma in the spinal cord and dorsal root ganglia; thus, inhibiting them can reduce central sensitization and lower postoperative pain and analgesic needs. [28] When used in conjunction with a muscle relaxant and a long-acting opioid, these agents can offer better pain relief with fewer individual side effects. Ketorolac, when used pre- or postoperatively, can help decrease inflammation by blocking prostaglandin production, although it should be administered with caution after spinal fusion for more than two days at doses over 120 mg/day due to potential risks. Nonetheless, when safely combined with acetaminophen and pregabalin, ketorolac is associated with lower pain scores, better mobility, fewer opioid requirements, improved outcomes, and shorter hospital stays without added complications. [29]

Selective cyclooxygenase (COX-2) inhibitors like meloxicam or celecoxib can be introduced two to three days before surgery as part of some MMA protocols, based on the type of spine surgery and the surgeon's discretion. [30] In studies on colorectal surgery patients following ERAS protocols, postoperative morphine consumption was significantly lower from Days 1 to 3 in patients given COX-2 inhibitors, who also showed faster gastrointestinal recovery and shorter hospital stays. [31] These advantages may extend to other surgical procedures.

For intraoperative pain management, a standard induction typically involves the use of inhaled anesthetics and propofol, with ketamine sometimes added. Ketamine, an NMDA receptor antagonist, helps reduce postoperative opioid use by modulating opioid receptors and lowering central excitability. It can be used as a sole agent or combined with NSAIDs, acetaminophen, and opioids to achieve effective analgesia. [32] Intraoperative ketamine use has been shown to reduce postoperative opioid consumption and can alleviate pain weeks to months following surgery. [33] Liberal application of local anesthetic by the surgeon is also advised before incision, with dexamethasone and famotidine often administered to prevent nausea and vomiting pre-emptively.

Dexamethasone, used in higher doses (over 0.2 mg/kg) as part of MMA protocols, helps reduce pain scores during postoperative mobilization and shows opioid-sparing effects. [34] It can also delay the need for the first analgesic when combined with peripheral nerve blocks. [35] Throughout surgery, small fentanyl doses (1–2 mcg/kg total) may be administered. Methadone, known for its longer half-life compared to other opioids, also inhibits NMDA receptors and serotonin-norepinephrine uptake, which can help prevent opioid tolerance and improve mood. [36] Patients receiving methadone instead of intravenous hydromorphone reported lower opioid needs postoperatively and better pain scores, though optimal methadone dosing is yet to be standardized.

Intravenous lidocaine also plays a role in MMA. A study found that patients undergoing complex spine surgery who received IV lidocaine infusions (2 mg/kg/h) experienced lower pain scores and slightly fewer 30-day postoperative complications. [37] The reduction in opioid requirements was not statistically significant, possibly due to the type of pain experienced following spine surgery compared to abdominal surgery, where lidocaine has shown more pronounced effects. Most MMA protocols recommend administering intravenous acetaminophen before extubation. Acetaminophen exerts analgesic and antipyretic effects by preventing a secondary peroxidase step in prostaglandin synthesis via cyclooxygenase enzymes. When given intravenously, it provides pain relief within 25 minutes and is linked to reduced extubation time, shorter intermediate care stays, and overall shorter hospitalization. [38] Although its impact on opioid requirements varies, acetaminophen consistently improves postoperative pain scores and is being evaluated as part of ERAS protocols for spine surgeries. [39]

Several regional anesthesia options are available in MMA for spine procedures. Single-shot epidural injections with local anesthetic have demonstrated a reduction in postoperative opioid use. [40] Erector spinae plane blocks and continuous infusion catheters, which anesthetize the dorsal and ventral rami of spinal nerves, can also be used to manage pain effectively during spine surgeries without affecting neuromonitoring. [41] A study of paediatric patients undergoing spinal fusion found that continuous infusion of local anesthetic via an elastomeric pain pump significantly reduced opioid use. [42] Some case reports also describe performing lumbar spine surgeries using only spinal or epidural anesthesia. [43,44] Benefits include reduced pain and a lower incidence of PONV, but this approach requires coordination between the surgeon, anesthesiologist, and patient. Additionally, epidural anesthesia may help dampen the surgical stress response after major surgeries. [45]

Post-surgical pain management involves continuing preoperative medications, with the potential addition of scheduled acetaminophen and/or NSAIDs. Gabapentin and pregabalin have proven effective in minimizing immediate postoperative opioid use. [46] Evidence suggests that pregabalin at 150 mg is more effective than 75 mg when administered preoperatively and again 12 hours post-surgery in lowering opioid consumption. [47] Gabapentin also demonstrates a dose-dependent effect, with 600 mg being superior to 300 mg for reducing pain and fentanyl use for the first 24 hours post-surgery, although increasing the dose beyond 600 mg did not provide further benefits. [48] Gabapentin use is associated with a higher risk of sedation but lower instances of nausea, vomiting, and pruritus compared to opioids. [49] Postoperative pain management can also include tramadol, a weaker μ-opioid receptor agonist that also acts as a serotonin-norepinephrine reuptake inhibitor, potentially replacing stronger opioids such as oxycodone or hydrocodone. [50] Cold therapy, such as ice packs, can be part of postoperative MMA. While there is no specific data for spine surgery patients, a study on postpartum women with perineal pain found a significant reduction in pain for up to two hours after a 10-minute application of an ice pack. [51]

Postoperative pain can significantly contribute to stress, anxiety, depression, and the development of chronic pain. [52] MMA protocols have become widely used in spinal surgery due to their consistent benefits in reducing opioid consumption, enhancing postoperative mobility, and addressing issues like nausea, vomiting, and sedation. [53] Pain scores assessed immediately after surgery and in the days following are consistently lower in patients managed with MMA compared to those receiving opioids alone. However, further research is needed to understand the long-term impacts of these protocols. [54] The types of medications used are well-documented, but variations in dosing may significantly influence outcomes, complication rates, and readmissions within 30 to 90 days.

IMPLEMENTING A MMA

For an effective MMA approach, the cooperation of all stakeholders, including patients and caregivers, is essential. It is recommended to initiate discussions on the pain management strategy during the outpatient visit when the surgery is being scheduled and consent is obtained. [55] The surgeon's office serves as an optimal setting for these conversations, as patients tend to feel more at ease. This discussion should not only cover the intraoperative anesthesia but also address the postoperative pain management plan. The importance of each medication and the overall MMA approach should be explained, providing an opportunity for the patient to ask questions. It is crucial to discuss patient expectations, the approach to reducing opioid use after surgery, the role of non-opioid adjuvant therapies, and the patient's active involvement in the MMA strategy.

A preoperative evaluation by an anesthesiologist, ideally conducted in a preoperative clinic, is advisable for patients who might be difficult to manage with the standard MMA protocol. This is particularly significant for chronic pain patients already on high doses of opioids, as they may also have other risk factors contributing to increased postoperative pain, such as higher levels of anxiety, depression, or substance use,

including tobacco, drugs, or alcohol. [56,57] Although MMA is beneficial for all patients, it is especially advantageous for those vulnerable to opioid-related side effects, such as individuals with obstructive sleep apnea. [58] Additionally, a well-executed MMA program can offer health system benefits by decreasing opioid-related complications, which can lead to quicker recovery, earlier discharge, and better resource utilization.

CONCLUSIONS

MMA focuses on polypharmacological anesthesia and analgesia and aims to suppress nociception at multiple physiological levels. Synergistic effects of combined drugs in MMA contribute to anesthetic unconsciousness. MMA also integrates a variety of analgesics and techniques that can significantly reduce opioid consumption and improve postoperative outcomes, such as pain management, mobilization, and decreased adverse effects like nausea and sedation. It emphasizes the importance of individualized approaches based on patient needs, including preoperative planning and the use of both pharmacological and non-pharmacological methods. Surgeons should share responsibility for analgesia, and opioid stewardship is important. Postoperative analgesia should go beyond opioids; intravenous or ketamine infusion can be beneficial. Opioid analgesia poses risks, especially in certain patient populations. Further research is recommended to optimize dosing regimens and evaluate the long-term impact of MMA on recovery and complication rates.

AUTHORS' CONTRIBUTION

All authors have significantly contributed to the work, whether by conducting literature searches, drafting, revising, or critically reviewing the article. They have given their final approval of the version to be published, have agreed with the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST

None.

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