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Review Article

Multimodal analgesia strategies for optimal postoperative pain relief

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ABSTRACT

This narrative review assesses the effectiveness of multimodal analgesia protocols (MAPs) in managing postoperative pain and reducing opioid consumption, focusing on their safety, efficacy, and broader applicability in clinical practice. Recent studies highlight that MAPs, which combine pharmacological and non-pharmacological methods, significantly reduce postoperative pain intensity and opioid use compared to traditional opioid-centric approaches, without increasing adverse events such as nausea and respiratory depression. The inclusion of regional anaesthesia, nonsteroidal anti-inflammatory drugs (NSAIDs), and nerve blocks has shown to enhance recovery, minimize complications, and improve patient outcomes. Specific combinations of medications like ketamine, acetaminophen, and dexamethasone have proven effective in different surgical settings, underscoring the versatility of MAPs. By leveraging the synergistic effects of various pain relief modalities, MAPs optimize pain control while reducing opioid-related risks, offering a promising strategy for improving recovery outcomes. This review emphasizes the need for broader adoption of MAPs and calls for further research to refine these protocols for long-term advancements in surgical care and patient experiences.

Keywords: Multimodal analgesia, Postoperative pain, Opioid reduction, Regional anaesthesia, NSAIDs, Enhanced recovery, Pain management protocols

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 anaesthesia protocols (MAPs) have emerged as a promising approach. These protocols involve the combination of various pharmacological agents, such as non-steroidal anti-inflammatory drugs (NSAIDs), local anaesthetics, and regional anaesthesia, 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 anaesthesia 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 anaesthesia 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 ANAESTHESIA

Anaesthesia 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 anaesthesia, 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 anaesthesia, respiratory issues, and postoperative delirium (POD).[8] With the ongoing opioid crisis causing significant mortality, the need for improved, safer strategies in anaesthesia and analgesia is more urgent than ever.[9]

Multimodal analgesia (MMA) has been proposed as a solution, utilizing a combination of anaesthetic 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 anaesthesia with regional or local anaesthetic techniques to enhance recovery and surgical results.[11,12]

They support postoperative MMA with strategies like local anaesthetic 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 ANAESTHESIA

The widespread practice of using opioid-based anaesthesia, particularly in combination with inhaled anaesthetics or propofol, can contribute to hesitancy regarding the adoption of multimodal analgesia (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 gynaecological surgery were similar regardless of whether opioid-free or opioid-inclusive anaesthesia was used however, patients who received opioids experienced a significantly higher incidence of postoperative nausea and vomiting (PONV).

Despite the known risk of PONV, it is common for clinicians to continue using propofol anaesthesia 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.[20-22]

Postoperatively, the heavy reliance on opioid administration may lead to unfavourable outcomes. For example, the Prodigy study found that respiratory depression caused by opioids is often underdiagnosed on hospital wards, potentially leading to emergency situations. 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 A MULTIMODAL ANALGESIA PROTOCOL

Pharmacological combinations of analgesics and non-drug therapies are key elements of multimodal analgesia (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 drugs such as a muscle relaxant, a long-acting opioid, and an anticonvulsant before general anaesthesia.[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]

Table 1: Multimodal analgesia protocol.

Stage	Medications/Procedure
Prior to admission	Preoperative counselling regarding anaesthesia and postoperative analgesia at surgeon's office
Day of surgery	
Preoperatively	Oral medications given preoperatively in holding area about 1 hour prior to surgery:
	Cyclobenzaprine 10 mg
	Pregabalin 150 mg
	Oxycodone release 10 mg
Intraoperatively	
Induction of anaesthesia	Propofol 2 mg/kg plus ketamine 50 mg
Maintenance of anaesthesia	Sevoflurane with fentanyl 1–2 mg/kg titrated to clinical effect
Additional medications administered intraoperatively	Bupivacaine 0.5% with epinephrine 1:200,000 injected at 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 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).

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 enhanced recovery after surgery (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 anaesthetics 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 anaesthetic by the surgeon is also advised prior to 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 anaesthesia options are available in MMA for spine procedures. Single-shot epidural injections with local anaesthetic 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 anaesthetic via an elastomeric pain pump significantly reduced opioid use.[42] Some case reports also describe performing lumbar spine surgeries using only spinal or epidural anaesthesia.[43,44] Benefits include reduced pain and a lower incidence of postoperative nausea and vomiting, but this approach requires coordination between the surgeon, anaesthesiologist, and patient. Additionally, epidural anaesthesia 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 improving 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 MULTIMODAL ANALGESIA

For an effective multimodal analgesia (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 anaesthesia 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 anaesthesiologist, 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 apnoea 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.

CONCLUSION

MMA focuses on polypharmacology anaesthesia and analgesia and aims to suppress nociception at multiple physiological levels. Synergistic effects of combined drugs in MMA contribute to anaesthetic unconsciousness. MMA also integrates a variety of analgesics and techniques which 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.

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REFERENCES

1. Garimella V, Cellini C. Postoperative pain control. Clin Colon Rectal Surg. 2013;26(03):191-6.
2. Phillips JK, Ford MA, Bonnie RJ. National Academies of Sciences Engineering, and Medicine. Health and Medicine Division. 2017.
3. Hall MJ, Schwartzman A, Zhang J, Liu X. Ambulatory surgery data from hospitals and ambulatory surgery centers: United States, 2010. National Health Stat Rep. 2017;102:1-5.
4. Kaye AD, Urman RD, Rappaport Y, Siddaiah H, Cornett EM. Multimodal analgesia as an essential part of enhanced recovery protocols in the ambulatory settings. J Anaesthesiol Clin Pharmacol. 2019;35(1):40-5.
5. Birkmeyer JD, Reames BN, McCulloch P, Carr AJ, Campbell WB, Wennberg JE. Understanding of regional variation in the use of surgery. Lancet. 2013;382(9898):1121-9.
6. Dohlman LE, Kwikiriza A, Ehie O. Benefits and barriers to increasing regional anesthesia in resource-limited settings. Local Regional Anesthesia. 2020;5:147-58.
7. Nasir M, Ahmed A. Knowledge about postoperative pain and its management in surgical patients. Cureus. 2020;12(1):78.
8. Pedemonte JC, Plummer GS, Chamadia S, Locascio JJ, Hahm E, Ethridge B, et al. Electroencephalogram burst-suppression during cardiopulmonary bypass in elderly patients mediates postoperative delirium. Anesthesiol. 2020;133(2):280-92.
9. Larach DB, Sahara MJ, As-Sanie S, Moser SE, Urquhart AG, Lin J, et al. Patient factors associated with opioid consumption in the month following major surgery. Ann Surg. 2021;273(3):507-15.
10. Shanthanna H, Ladha KS, Kehlet H, Joshi GP. Perioperative opioid administration: a critical review of opioid-free versus opioid-sparing approaches. Anesthesiology. 2021;134(4):645-59.
11. Bergman L, Bäckmark I, Ones H, von Euler C, Olivestedt G, Kvanta A, et al. Preoperative sub–

tenon's capsule injection of ropivacaine in conjunction with general anesthesia in retinal detachment surgery. Ophthalmol. 2007;114(11):2055-60.
12. Chhabra A, Sinha R, Subramaniam R, Chandra P, Narang D, Garg SP. Comparison of sub-Tenon's block with iv fentanyl for paediatric vitreoretinal surgery. Br J Anaesthesia. 2009;103(5):739-43.
13. Smith TW, Wang X, Singer MA, Godellas CV, Vaince FT. Enhanced recovery after surgery: a clinical review of implementation across multiple surgical subspecialties. Am J Surg. 2020;219(3):530-4.
14. Caldwell GL, Selepec MA. Surgeon-administered nerve block during rotator cuff repair can promote recovery with little or no post-operative opioid use. HSS Journal®. 2020 Dec;16(2_suppl):349-57.
15. Fawcett WJ, Mythen MG, Scott MJ. Enhanced recovery: joining the dots. Br J Anaesth. 2021;126(4):751-5.
16. Manyam SC, Gupta DK, Johnson KB, White JL, Pace NL, Westenskow DR, et al. Opioid–volatile anesthetic synergy: a response surface model with remifentanil and sevoflurane as prototypes. J Am Soc Anesthesiol. 2006;105(2):267-78.
17. Verret M, Lam NH, Fergusson DA, Nicholls SG, Turgeon AF, McIsaac DI, et al. Intraoperative pharmacologic opioid minimisation strategies and patient-centred outcomes after surgery: a scoping review protocol. BMJ open. 2023;13(3):70748.
18. Frauenknecht J, Kirkham KR, Jacot-Guillarmod A, Albrecht E. Analgesic impact of intra-operative opioids vs. opioid-free anaesthesia: a systematic review and meta-analysis. Anaesthesia. 2019;74(5):651-62.
19. Mauermann E, Clamer D, Ruppen W, Bandschapp O. Association between intra-operative fentanyl dosing and postoperative nausea/vomiting and pain: a prospective cohort study. Euro J Anaesthesiol. 2019;36(11):871-80.
20. Murphy GS, Avram MJ, Greenberg SB, Shear TD, Deshur MA, Dickerson D, et al. Postoperative pain and analgesic requirements in the first year after intraoperative methadone for complex spine and cardiac surgery. Anesthesiol. 2020;132(2):330-42.
21. Salpeter SR, Buckley JS, Bruera E. The use of very-low-dose methadone for palliative pain control and the prevention of opioid hyperalgesia. J Pall Med. 2013;16(6):616-22.
22. Roeckel LA, Le Coz GM, Gavériaux-Ruff C, Simonin F. Opioid-induced hyperalgesia: cellular and molecular mechanisms. Neurosci. 2016;338:160-82.
23. Khanna AK, Bergese SD, Jungquist CR, Morimatsu H, Uezono S, et al. Prediction of opioid-induced respiratory depression on inpatient wards using continuous capnography and oximetry: an international prospective, observational trial. Anesthesia Analgesia. 2020;131(4):1012-24.
24. Connolly JG, Tan KS, Mastrogiacomo B, Dycoco J, Caso R, Jones GD, et al. Intraoperative opioid exposure, tumour genomic alterations, and survival differences in people with lung adenocarcinoma. Br J Anaesth. 2021;127(1):75-84.
25. Bohl DD, Louie PK, Shah N, Mayo BC, Ahn J, Kim TD, Massel DH, et al. Multimodal versus patient-controlled analgesia after an anterior cervical decompression and fusion. Spine. 2016;41(12):994-8.
26. Van Tulder M, Becker A, Bekkering T, Breen A, del Real MT, Hutchinson A, et al. COST B13 Working group on guidelines for the management of acute low back pain in primary Care. European guidelines for the management of acute nonspecific low back pain in primary care. Eur Spine J. 2006;15(2):169.
27. Friedman BW, Dym AA, Davitt M, Holden L, Solorzano C, Esses D, et al. Naproxen with cyclobenzaprine, oxycodone/acetaminophen, or placebo for treating acute low back pain: a randomized clinical trial. JAMA. 2015;314(15):1572-80.
28. Tiippana EM, Hamunen K, Kontinen VK, Kalso E. Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. Anesthesia Analgesia. 2007;104(6):1545-56.
29. Shetty AP, Subramanian B, Kanna RM, Rajasekaran S. A prospective randomized study to analyze the efficacy of balanced pre-emptive analgesia in spine surgery. Spine J. 2019;19(4):569-77.
30. Garcia RM, Cassinelli EH, Messerschmitt PJ, Furey CG, Bohlman HH. A multimodal approach for postoperative pain management after lumbar decompression surgery: a prospective, randomized study. Clin Spine Surg. 2013;26(6):291-7.
31. Lohsiriwat V. Opioid-sparing effect of selective cyclooxygenase-2 inhibitors on surgical outcomes after open colorectal surgery within an enhanced recovery after surgery protocol. World J Gastrointes Oncol. 2016;8(7):543.
32. Loftus RW, Yeager MP, Clark JA, Brown JR, Abdu WA, Sengupta DK, et al. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. J Am Society Anesthesiol. 2010;113(3):639-46.
33. Young A, Buvanendran A. Recent advances in multimodal analgesia. Anesthesiol Clin. 2012;30(1):91-100.
34. De Oliveira GS, Almeida MD, Benzon HT, McCarthy RJ. Perioperative single dose systemic dexamethasone for postoperative pain: a meta-analysis of randomized controlled trials. J Am Society Anesthesiol. 2011;115(3):575-88.
35. Clement JC, Besch G, Puyraveau M, Grelet T, Ferreira D, Vettoretti L, et al. Clinical effectiveness of single dose of intravenous dexamethasone on the duration of ropivacaine axillary brachial plexus

block: the randomized placebo-controlled ADEXA trial. Regional Anesthesia Pain Med. 2019;44(3):89.
36. Murphy GS, Szokol JW, Avram MJ, Greenberg SB, Shear TD, Deshur MA, et al. Clinical effectiveness and safety of intraoperative methadone in patients undergoing posterior spinal fusion surgery: a randomized, double-blinded, controlled trial. Anesthesiol. 2017;126(5):822-33.
37. Farag E, Ghobrial M, Sessler DI, Dalton JE, Liu J, Lee JH, et al. Effect of perioperative intravenous lidocaine administration on pain, opioid consumption, and quality of life after complex spine surgery. Anesthesiol. 2013;119(4):932-40.
38. Hansen RN, Pham AT, Böing EA, Lovelace B, Wan GJ, Miller TE. Comparative analysis of length of stay, hospitalization costs, opioid use, and discharge status among spine surgery patients with postoperative pain management including intravenous versus oral acetaminophen. Curr Med Res Op. 2017;33(5):943-8.
39. Mörwald EE, Poeran J, Zubizarreta N, Cozowicz C, Mazumdar M, Memtsoudis SG. Intravenous acetaminophen does not reduce inpatient opioid prescription or opioid-related adverse events among patients undergoing spine surgery. Anesthesia Analgesia. 2018;127(5):1221-8.
40. Thepsoparn M, Sereeyotin J, Pannangpetch P. Effects of combined lower thoracic epidural/general anesthesia on pain control in patients undergoing elective lumbar spine surgery: a randomized controlled trial. Spine. 2019;4:67-9.
41. Chin KJ, Lewis S. Opioid-free analgesia for posterior spinal fusion surgery using erector spinae plane (ESP) blocks in a multimodal anesthetic regimen. Spine. 2019;44(6):379-83.
42. Melvin JP, Schrot RJ, Chu GM, Chin KJ. Low thoracic erector spinae plane block for perioperative analgesia in lumbosacral spine surgery: a case series. Canadian J Anesthesia. 2018;65(9):1057-65.
43. Reynolds RA, Legakis JE, Tweedie J, Chung Y, Ren EJ, BeVier PA, Thomas RL, Thomas ST. Postoperative pain management after spinal fusion surgery: an analysis of the efficacy of continuous infusion of local anesthetics. Global Spine J. 2013;3(1):7-13.
44. Ulutas M, Secer M, Taskapilioglu O, Karadas S, Akyilmaz AA, Baydilek Y, et al. General versus epidural anesthesia for lumbar microdiscectomy. J Clin Neurosc. 2015;22(8):1309-13.
45. Ezhevskaya AA, Mlyavykh SG, Anderson DG. Effects of continuous epidural anesthesia and postoperative epidural analgesia on pain management and stress response in patients undergoing major spinal surgery. Spine. 2013;38(15):1324-30.
46. Schmidt PC, Ruchelli G, Mackey SC, Carroll IR. Perioperative gabapentinoids: choice of agent, dose, timing, and effects on chronic postsurgical pain. Anesthesiol. 2013;119(5):1215-21.
47. Kim JC, Choi YS, Kim KN, Shim JK, Lee JY, Kwak YL. Effective dose of peri-operative oral pregabalin as an adjunct to multimodal analgesic regimen in lumbar spinal fusion surgery. Spine (Phila Pa 1976). 2018;5:78-9.
48. Pandey CK, Navkar DV, Giri PJ, Raza M, Behari S, Singh RB, et al. Evaluation of the optimal preemptive dose of gabapentin for postoperative pain relief after lumbar diskectomy: a randomized, double-blind, placebo-controlled study. J Neur Anesthesiol. 2005;17(2):65-8.
49. Ho KY, Gan TJ, Habib AS. Gabapentin and postoperative pain–a systematic review of randomized controlled trials. Pain. 2006;126(1-3):91-101.
50. Terracina S, Robba C, Prete A, Sergi PG, Bilotta F. Prevention and treatment of postoperative pain after lumbar spine procedures: a systematic review. Pain Practice. 2018;18(7):925-45.
51. Francisco AA, De Oliveira SM, Steen M, Nobre MR, De Souza EV. Ice pack induced perineal analgesia after spontaneous vaginal birth: Randomized controlled trial. Women Birth. 2018;31(5):334-40.
52. MacLachlan C, Shipton EA, Wells JE. Perioperative pain correlates and prolonged postoperative pain predictors: demographic and psychometric questionnaires. Pain Therapy. 2015;4:119-33.
53. Mathiesen O, Dahl B, Thomsen BA, Kitter B, Sonne N, Dahl JB, et al. A comprehensive multimodal pain treatment reduces opioid consumption after multilevel spine surgery. Europ Spine J. 2013;22:2089-96.
54. Grasu RM, Cata JP, Dang AQ, Tatsui CE, Rhines LD, Hagan KB, et al. Implementation of an enhanced recovery after spine surgery program at a large cancer center: a preliminary analysis. J Neurosurg Spine. 2018;29(5):588-98.
55. Singh K, Bohl DD, Ahn J, Massel DH, Mayo BC, Narain AS, et al. Multimodal analgesia versus intravenous patient-controlled analgesia for minimally invasive transforaminal lumbar interbody fusion procedures. Spine. 2017;42(15):1145-50.
56. Jain N, Phillips FM, Weaver T, Khan SN. Preoperative chronic opioid therapy: a risk factor for complications, readmission, continued opioid use and increased costs after one-and two-level posterior lumbar fusion. Spine. 2018;43(19):1331-8.
57. Jain N, Brock JL, Phillips FM, Weaver T, Khan SN. Chronic preoperative opioid use is a risk factor for increased complications, resource use, and costs after cervical fusion. Spine J. 2018;18(11):1989-98.
58. Buvanendran A, Thillainathan V. Preoperative and postoperative anesthetic and analgesic techniques for minimally invasive surgery of the spine. Spine. 2010;35(26):274-80.

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