

# Perioperative Pain Management is Not Just Opioid Treatment Alone-Using Multiple Strategies to Improve Pain Control, Reduce Complications, and Enhanced Outcomes

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## Abstract

Multimodal analgesia (MMA) combines analgesics of multiple classes acting on distinct target sites through different strategies, including non-opiate analgesics (NSAIDs, acetaminophen, COX-2 inhibitors),  $\alpha$ -2 agonists, epidural analgesia, local infiltration of analgesics, continuous peripheral nerve blockade, and so on. MMA improves postoperative pain control, subsequently improves patients' satisfaction and quality of recovery. It also reduces opioid requirements, hence reduces many opioid-related adverse effects, such as constipation, PONV, sedation and respiratory depression. According to these benefits, MMA is currently the recommended practice in most fast-track clinical care plans, and all Enhanced Recovery After Surgery (ERAS) guidelines advocate MMA as perioperative pain management whenever possible.

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## Key Words:

Multimodal analgesia (MMA), Enhanced Recovery After Surgery (ERAS)

## Introduction

Up to 80% of patients reported experience of acute pain after surgery, and the presence of postoperative pain is a common concern reported by patients before surgery 1. It has been recognized that inadequate acute pain management may lead to chronic pain 2. Inadequately treated pain is linked to many undesirable consequences. For instance, the limitation of movement caused by pain can prolong rehabilitation, reduce health-related quality of life, and delay return to normal daily activities

3-6. On the contrary, over treatment of pain will lead to shutdown of gut function caused by excessive narcotics can increase patients' discomfort and delay recovery and nutritional intake 7. There are common consequences of these adverse outcomes, such as increased cost of care, extended hospital length of stay of inpatients or unexpected readmissions of outpatients, and patient dissatisfaction 8-10. All these adverse effects may result in increased morbidity and mortality 2. Hence, it is vital how to control postoperative pain appropriately for patients or for healthcare providers. This article reviews

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current and emerging multimodal treatment strategies. Furthermore, we try to provide a multimodal analgesia protocol for enhanced recovery after surgery.

## **M**ultimodal Analgesia

Traditionally, opioids have been used in anesthesia for postoperative analgesia in most situations, especially for moderate to severe pain. Opioids provide non-ceiling analgesic effect and blunt the sympathetic response to surgery. However, opioids always are associated with adverse effects such as drowsiness, sedation, postoperative nausea and vomiting (PONV), pruritus, urinary retention, ileus, constipation and respiration depression 11. Therefore, multimodal analgesia (MMA) techniques are developed to improve postoperative pain management. MMA, developed based on the knowledge that postoperative pain is a complex and multifactorial phenomenon, combines analgesics of multiple classes acting on distinct target sites through different strategies. It may provide superior pain relief with lower incidence of adverse effects 12-14.

The aim of MMA is to reduce opioid requirements; thus, many analgesic modalities were introduced. The benefits of epidural analgesia are most apparent when used as part of a multimodal analgesic regimen 15,16. Compared with parenteral opioids, epidural analgesia provides significantly better postoperative analgesia and lower complication rates (e.g. nausea or vomiting and pruritus). Therefore, epidural analgesia can be a valuable core element of enhanced recovery after surgery for major surgery 17. Both continuous epidural infusion and patient-controlled epidural analgesia(PCEA) provide better static and dynamic pain relief than intravenous(IV) opioid-based patient-controlled analgesia (PCA) delivery systems 18. In addition, both intrathecal and continuous epidural analgesia (consist of local anesthetics with

or without opioids) as part of a multimodal analgesia technique were associated with improvements in time to tracheal extubation, decreased pulmonary complications and cardiac dysrhythmias, and reduced postoperative pain and opioid analgesic requirements 19. Local infiltration of analgesics does lessen both intra- and postoperative opioid requirements as well as opioid-related side effects 20. Continuous wound infiltration provided effective analgesia as part of a multimodal approach after major abdominal surgery 21. It has been well demonstrated that the use of epidural or continuous surgical site analgesia compared with IV-PCA morphine revealed significantly less use of rescue opioid, which associated with morphine-spare effect from 42% to 83% 22-25. Numerous clinical trials have been published examining the efficacy of continuous peripheral nerve blockade (CPNB) for the treatment of postoperative pain compared with systemic opioids. A meta-analysis of RCTs has found that, when compared with opioid (parenteral and oral) alone, perineural analgesia with local anesthetic provided significantly better analgesia for postoperative pain through postoperative day 3. Perineural analgesia also resulted in fewer minor complications, including nausea/vomiting (CPNB : opioids = 20.9%:48.7%,  $p < 0.001$ ), pruritus(CPNB : opioids = 9.7%:26.6%,  $p < 0.001$ ), and sedation(CPNB : opioids = 26.7%:52.3%,  $p < 0.012$ )26. Trials also demonstrated a higher composite mean visual analog scale (VAS) satisfaction score for CPNB group [9.6,  $n = 93$  (95% confidence interval [CI], 9.5–9.7)] compared with opioids [7.1,  $n = 90$  (95% CI, 6.9 –7.2)]27-30. Total opioid consumption over 48 h was significantly less ( $P < 0.001$ ) with the use of perineural analgesia (20.8 mg morphine) compared with opioid analgesia (54.1 mg morphine)26 .

Other available non-opioid analgesics include acetaminophen, NSAIDs, and cyclooxygenase (COX)-

2-specific inhibitors as well as analgesic adjuncts such as steroids (e.g. dexamethasone), NMDA antagonists (e.g. ketamine),  $\alpha$ -2 agonists (e.g. clonidine and dexmedetomidine), and anticonvulsants (e.g. gabapentin and pregabalin)<sup>31</sup>. Meta-analyses have shown the significant decreased median of the average 24-h morphine consumption with several non-opioid analgesics, including acetaminophen (morphine-sparing effect of 20%), NSAID (24-h morphine consumption decreases from 10.3 mg to 19.7 mg) and COX-2 inhibitors (24-h morphine consumption decreases from 7.2 mg to 27.8 mg)<sup>32</sup>.

### ***Lessen Perioperative Complications***

Previous studies suggested that minimizing the use of postoperative opioid-containing analgesics reduces many undesired bowel effects, such as constipation and PONV<sup>33</sup>. In Cochrane-review, epidural local anesthetics with or without opiates has no effect on postoperative vomiting compared with opioid-based regimen<sup>34</sup>. However, local infusion does have antiemetic effect. Meta-analysis has demonstrated that compared with placebo group (saline infusion), incidence of PONV was reduced in the continuous local anesthetics wound catheter group (24% versus 40%; odds ratio, 0.45; 95% CI, 0.08 to 0.3). Meta-analysis also suggested potential saving of 1 day of hospital stay with infusion of local anesthetic at the surgical incision sites<sup>35</sup>. A recently published meta-analysis reported a net reduction in PONV when NSAIDs and COX-2 inhibitors were combined with PCA morphine<sup>36</sup>.

Postoperative ileus can cause discomfort and delay oral food intake, thereby delaying rehabilitation and prolonging the length of the hospital stay for at least one day<sup>37</sup>. Continuous thoracic epidural infusion of a local anesthetic solution, as a part of MMA, has

been proved to accelerate the return of bowel function after major abdominal surgery, ranging from 24 hours to 96 hours<sup>37-39</sup>. Though mechanism not fully understood, epidural analgesia may have a direct effect on the gastrointestinal innervation, thereby facilitating restoration of motility<sup>38</sup>. In review articles comparing effects of postoperative epidural analgesia with local anesthetics versus postoperative systemic or epidural opioids, they concluded that epidural local anesthetics accelerate the return of gastrointestinal transit. Use of epidural anesthesia, both the time required for first passage of flatus (standardized mean difference (SMD) -1.28, 95% confidence interval (CI) -1.71 to -0.86; high quality of evidence; equivalent to 17.5 hours) and first stool passage (SMD -0.67, 95% CI -0.86 to -0.47; low quality of evidence; equivalent to 22 hours) decreased after abdominal surgery<sup>34</sup>.

### ***Enhanced Quality of Life***

Using multimodal analgesia improves postoperative pain control, subsequently improves patients' satisfaction and quality of recovery<sup>30,38,40,41</sup>. Patients receive MMA are reported accelerated ability to resume their activities of daily living<sup>42,43</sup>. It is particularly important in ambulatory surgery and has been studied extensively. Non-opioid analgesics, as part of MMA, used as adjuvants before, during, and after surgery can facilitate the recovery process after ambulatory surgery because of their anesthetic- and analgesic-sparing effects and their ability to reduce postoperative pain with movement, opioid analgesic requirement, and side effects, thereby shortening the duration of the hospital stay from 1 to 3 days to same-day discharge. Use of multimodal analgesic techniques was demonstrated to improve early recovery after ambulatory laparoscopic cholecystectomy, tubal ligation, herniorrhaphy, breast

surgery, and so on 44-49. According to these benefits, MMA is currently the recommended practice in most fast-track clinical care plans 50.

## ***Related to Enhanced Recovery After Surgery (ERAS)***

ERAS refers to a systematic process addressing each aspect in the surgical journey that could affect recovery, from preoperative carbohydrate drinks, to surgical and anesthetic techniques or postoperative mobilization. The ERAS Society has published several comprehensive guidelines for different major surgeries, reviewing all available evidence to provide generic and specific recommendations for bundle care of these surgical patients. These guidelines provide an evidence-based, multimodal approach to surgical care, to improve outcomes after major operations. All guidelines include the perioperative management of analgesia, and multimodal, opioid-sparing strategy is advocated whenever possible 51-53. Well-managed pain is widely recognized as an important metric for success of surgery and recovery, quality of medical and nursing care, and even as a surrogate for patient satisfaction 54. Multimodal analgesia in the ERAS Society setting involves utilizing multiple, simultaneous drugs that can act synergistically to perform analgesic effects and to minimize side-effects of any single agent, especially for opiates 55-57. Several analgesics were reviewed and recommended, which all target different pain receptors and pain transmission pathways peripherally and centrally. For postoperative pain management, ERAS Society generally recommends use non-opiate synergistic systemic agents and by using regional or neuraxial blockade as priority. Opioids should be used as a last regimen if pain is not adequately controlled with all other methods. Oxycodone, tramadol, or codeine can

be delivered via IV bolus doses or orally at first. When IV form is used, patient-controlled delivery systems is recommended, so that dosage is individualized rather than standardized 53.

As for systemic analgesia, several non-opiate analgesics were reviewed by ERAS Society. All ERAS Society guidelines recommend the use of NSAIDs, which involve nonselective agents (e.g. aspirin, ibuprofen, ketorolac, and diclofenac) and newer COX inhibitor-2 selective agents (e.g. parecoxib and celecoxib). Evidence supports regular doses of NSAIDs in the postoperative period as an effective component of a multimodal, opioid-sparing regime to manage acute pain 58-65. Acetaminophen (paracetamol) is also recommended by ERAS Society guidelines. Current evidence suggests that acetaminophen combined with PCA morphine can induce a significant morphine-sparing effect 32,66. Furthermore, when used in combination with NSAIDs or opioids, it may offer superior analgesia compared with either drug alone 67. Local anesthetics are widely used for subcutaneous infiltration and regional anesthesia. Besides, IV lidocaine is featured in several ERAS Society guidelines. There is growing evidence for local anesthetic use systemically via the IV route 53. Continuous intravenous administration of lidocaine during and after surgery has been showed to improve patient rehabilitation, thus shorten hospital stay (weighted mean difference - 0.84 days;  $P = 0.002$ ) in abdominal surgery 68, to have similar impact on bowel function compared with thoracic epidural analgesia in laparoscopic colorectal surgery 69, and to be as effective as intraperitoneal injection in abdominal hysterectomy 70.

Dexmedetomidine (DEX) is a selective  $\alpha_2$ -agonist and a sedative with anti-inflammatory, analgesic and antiemetic effects. It is recently used as an adjuvant for general anesthesia 71. Although not routinely

recommended by ERAS guideline now, there are several studies reporting that DEX improves recovery after surgery 72-74. DEX administration during multilevel spinal fusions were reported to increase quality of recovery [global quality of recovery (QoR-40) score was higher in the DEX group than in the control group (normal saline infusion) at all time points, especially only on postoperative day(POD) 3 (-13.74, p=0.005)] and possibly to reduce fatigue (9 questions fatigue scale on POD3 was  $50.0 \pm 4.0$  vs  $36.3 \pm 4.9$ , p=0.035) in the early postoperative period 72,73. DEX infusion also promoted quality of recovery, and lead to a higher satisfaction rate for patients after video-assisted thoracoscopic surgery [QoR-40 score ( $162.3 \pm 17.8$  vs  $153.3 \pm 18.7$ , P=0.016 on POD 1;  $174.3 \pm 16.0$  vs  $166.8 \pm 16.7$ , P=0.028 on POD 2)]. Ameliorating the psychological distress of patients reduced the length of hospital stay ( $6.7$  [3-9] vs  $8.4$  [4-9] days, P=0.045) 72. The intraoperative administration of DEX during laparoscopic gastrectomy can facilitate the early recovery of bowel function [time to first flatus in both groups was  $67.2 \pm 16.8$  hours vs  $79.9 \pm 15.9$  hours, P < 0.001], subsequently reduce the length of postoperative hospital stay ( $5.4 \pm 0.7$  days vs  $5.8 \pm 1.1$  days, P = 0.04). The mechanisms may involve intraoperative sympatholysis, and the reduction of systemic opioids 74. Further larger studies are needed to confirm the role of dexmedetomidine in ERAS protocol.

As for nonsystemic anesthesia or analgesia, using low-dose concentrations of local anesthetic combined with a short-acting opiate via thoracic epidural anesthesia (TEA) is recommended with the highest strength and quality of evidence possible for open midline laparotomy. It appears to offer analgesia while minimizing the risk of motor block and hypotension. Several meta-analyses have shown improved outcomes with TEA compared with opioid-based analgesia 17,34,75,76. Transversus Abdominis Plane (TAP) blocks

and continuous wound infiltration are both mentioned in ERAS Society guidelines, particularly for open abdominal surgery or in cases in which TEA is not used. They can also be used in laparoscopic surgery to cover the lower abdominal incision and combined with intravenous paracetamol to reduce opioid administration 77.

Time sequence	Category	Intervention	Treatment	Reference
Intra-operative	Regional anesthesia	Thoracic epidural anesthesia	Low-dose concentrations of local anesthetics combined with a short-acting opiate	61
	$\alpha_2$ agonist	Dexmedetomidine	Loading infusion: 1mcg/kg over 10 minutes Maintenance infusion: 0.2 to 0.7 mcg/kg/hour.	78
	Systemic local anesthetic	IV lidocaine	No standard: Bolus dose at/before induction: 100mg or 1.5-2.0 mg/kg Continuous dose intra- and post- operative: 1.5-3.0 mg/kg/h	68
	Continuous wound infiltration	Transversus Abdominis Plane (TAP) blocks	Used in laparoscopic surgery	61
Post-operative	Oral analgesics	NSAIDs, COX-2	No consensus treatment, but was recommended in all ERAS Society guidelines	53
		Acetaminophen	On a regular schedule, 15 mg/kg, up to 1 g, 4 times daily, either orally or by IV.	53
	Opiates	IV-PCA	Recommended if systemic opiates are required	53
		Morphine, oxycodone, tramadol, codeine	As a last resort, can be delivered via IV bolus doses or orally	53

Table 1

#### Recommended MMA techniques in ERAS protocol Summary

According to the ERAS guideline available now, the optimal analgesic regimen for major surgery should give: good pain relief; allow early mobilization, early return of gut function and feeding; and not cause complications 79. In this review article we revealed that use of MMA techniques provides good analgesic effects as traditional opioid analgesics (table 1). Minimizing opioids consumption significantly decreases wide range

of adverse effects including PONV, ileus, respiratory depression, hyperalgesia, delirium, and opioid tolerance. Good postoperative pain control also accelerates normalization of quality of life and functionality. Therefore, we can conclude that multimodal analgesia is the best choice for postoperative pain management in ERAS protocol.

## Conclusion

Efficacy of multimodal analgesic regimens continues to improve. This article discusses recent evidence from several literatures regarding the role of non-opiate analgesics (NSAIDs, acetaminophen, COX-2 inhibitors),  $\alpha$ -2 agonists, epidural analgesia, local infiltration of analgesics, continuous peripheral nerve blockade, and so on. Each strategy mentioned in this review article was proved to decrease the requirement of opioids, thus reduces many opioid-related adverse effects. Appropriately controlled pain also enhances patients' satisfaction and accelerates recovery. Therefore, we suggest that MMA should be used in ERAS protocol. As pain management should be individualized, further research is needed to find the most appropriate pain management in different type of surgery.

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## 圍術期之止痛方試不應只有嗎啡類藥物——使用多模式止痛可改善疼痛控制、減少併發症、進而促進術後快速恢復

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多模式止痛包含了許多不同類型的止痛藥物，如非類固醇類消炎止痛藥、乙醯胺酚、 $\alpha 2$  腎上腺受體致效劑等；以及許多不同種類型的麻醉止痛方式，如硬膜外止痛、局部麻醉藥浸潤、連續性神經阻斷等。多模式止痛可以有效改善病人術後的疼痛情形，進而增加病人對於術後恢復的速度及滿意度。另外，由於多模式止痛可以減少病人對於嗎啡類止痛藥的使用量，因此可有效減少嗎啡類止痛藥常見之副作用，如便秘、噁心嘔吐、呼吸抑制等等。基於以上種種優點，多模式止痛已普遍被各種「術後快速恢復」的流程中採用，並在現行的所有「術後快速恢復」之準則規範中被明確地建議。

**關鍵字：**多模式止痛、術後快速恢復療程

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