Pain Management in the Postoperative Environment

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PAIN MANAGEMENT IN THE POSTOPERATIVE ENVIRONMENT

OVERVIEW

When implemented properly, Enhanced Recovery After Surgery (ERAS) protocols can lead to improvements in surgical outcomes, patient adherence, and cost of care. To create a more effective ERAS process, surgeons, anesthesiologists, primary care clinicians, hospital nurses, and other care coordinators need to understand the benefits and work together towards improving the efficiency and quality of care. Educating patients will also facilitate their enhanced recovery. A major part of this process is through the design of perioperative analgesic protocols that focus on sparing conventional opioids and promoting earlier mobility, ambulation, and return of bowel function. These protocols are designed to decrease infection rate, length of stay, and hospital readmissions.

Optimizing a patient's pain relief has tremendous benefits on recovery. Unfortunately, clinicians are limited in their choices of analgesics, which generally include acetaminophen, NSAIDs, and opioids. In an attempt to minimize opioids, there has been increased utilization of adjunctive analgesics in the perioperative period, including agents such as gabapentin and ketamine. An often-overlooked analgesic for treatment of pain in the hospital setting is tramadol. Tramadol is known as an atypical opioid, and has 2 known mechanisms of action including binding to the mu opioid receptor and inhibiting the reuptake of serotonin and norepinephrine. The 2 enantiomers of racemic tramadol function in a complementary manner to enhance the analgesic efficacy and improve the tolerability profile of tramadol. Tramadol is utilized around the world and has been shown to be effective for treating moderate to moderately severe levels of pain regardless of cause.

Surgical recovery can be optimized through preoperative, intraoperative, and postoperative evidence-based interventions. Although clinicians have acetaminophen, NSAIDs, and opioids, each of these analgesics are associated with often overlooked toxicities. The availability of intravenous tramadol as an alternative to pure mu opioid analgesics should be a welcomed option/addition for clinicians who treat pain in the hospital setting.

Medical Editor
Jeffrey A. Gudin, MD
Director, Englewood Hospital and Medical Center
Pain Management and Palliative Care Center
Englewood, NJ

INTRODUCTION

Surgery, the unintended gateway to opioid abuse

More than 100 million surgical procedures are performed annually in the United States, with an estimated 57.1 million performed during ambulatory surgical visits.[1] Of the 80% of patients who experience postoperative pain, fewer than half report adequate pain relief. Among patients with postsurgical pain, 10% to 50% develop chronic pain, depending on the type of surgery.[2]

[Following surgery] approximately 1 in 16 patients met the criteria for new persistent opioid use…defined as opioid prescription fulfillment between 90 and 180 days after the surgical procedure.

The success of inpatient and ambulatory surgery depends in part on effective postoperative pain management routines.[3,4] Opioids have been considered the mainstay of analgesia during and after surgical procedures, but questions have arisen about their use given the current opioid crisis of addiction and overdose. A recent study of nationwide insurance claims data from 2013 to 2014 found that a common but previously underappreciated surgical complication is new persistent opioid use after surgery.[5] In this analysis of 36,177 patients, 80.3% of whom received minor surgical procedures, approximately 1 in 16 patients met the criteria for new persistent opioid use, which was defined as opioid prescription fulfillment between 90 and 180 days after the surgical procedure.

The unmet medical need

Currently available analgesics used for postoperative pain pose risks beyond addiction and abuse. Opioid and nonopioid analgesics also have limitations related to side effects—such as nausea, vomiting, constipation, and respiratory depression—creating a need for:

- *Alternatives to strong opioids for patients undergoing procedures that generally involve moderate to moderately severe pain*
- *Alternatives for patient populations where IV NSAIDs pose risks and are inappropriate*
- *Analgesic efficacy comparable to opioids while sparing the use of conventional opioids*

RATIONALE FOR THE DEVELOPMENT OF IV TRAMADOL

IV tramadol is commercially available in Europe and is currently under development in the United States. It is anticipated that incorporation of IV tramadol into perioperative pain management protocols will provide several benefits including[6]:

- *A dual-mechanism option to widely prescribed strong opioids such as hydromorphone and oxycodone*
- *Adoption into multimodal pain management protocols that are designed to decrease the use of strong opioids*
- *Use in postoperative pain management for "medium" surgeries requiring relief of moderate to moderately severe pain*
- *Increased use in ambulatory surgery, especially in patients with respiratory and cardiovascular comorbidities, and in patients with obesity and those who smoke*
- *Ease in step-down therapy and elimination of the need to switch to a different analgesic upon discharge*

TRENDS IN POSTOPERATIVE PRACTICE PATTERNS

"Opioid crisis" accelerating utilization changes in institutional settings

Additional factors leading to misuse include regimens initiated with the strong opioids hydromorphone and oxycodone.

The opioid crisis is impacting clinical practice across various hospital settings, including inpatient and outpatient departments, ambulatory surgery centers, and emergency departments. Opioids are overprescribed for postsurgical patients, leading to the suggestion that opioid prescribing after surgery is one reason the nation appears to be awash in the drugs, and their abuse.[7] In a survey of surgical claims from a database of commercially insured patients, each refill of postdischarge opioid prescriptions increased the rate of opioid misuse by 44% among previously opioid-naïve patients.[8] Although the rates of misuse were low, the large number of surgeries performed every year increases the importance of these numbers, according to the study authors. Additional factors leading to misuse include regimens initiated with the strong opioids hydromorphone and oxycodone.[8]

Surgeons are beginning to recognize the need to reduce the use of opioids to prevent progression to long-term postoperative use. The American Academy of Orthopedic Surgeons recommends that postoperatively, orthopedic surgeons do not use long-acting opioids and do not treat persistent pain with opioids.[9] They recommend reliance on acetaminophen and NSAIDs with limited amounts of oral oxycodone or hydrocodone in combination with acetaminophen, and preoperative counseling to help patients set realistic expectations about pain after surgery.

Movement toward multimodal analgesia

Multimodal "opioid-sparing" analgesic techniques, also known as balanced analgesia, were introduced more than 20 years ago.[10] The aim was to improve analgesia by combining analgesics from different pharmacologic drug classes that had additive or synergistic effects.

More recently the American Pain Society along with an interdisciplinary expert panel recommends the use of multimodal analgesia, or the use of a variety of analgesic medications and techniques combined with nonpharmacological interventions for the treatment of postoperative pain.[11] Research has shown that multimodal analgesia involving simultaneous use of several medications acting at different receptors may provide superior pain relief and decreased opioid consumption and subsequent adverse effects.[12,13]

European recommendations for postoperative pain management also advise the use of multimodal, or balanced, analgesia to achieve a superior analgesic effect without increasing adverse effects, compared with increased doses of single agents. Tramadol is included in these recommendations as a treatment option, with IV, intramuscular (IM), and oral formulations available for use.[14]

Tramadol—single entity multimodal analgesic

Whereas multimodal analgesia generally implies the use of 2 or more different agents, tramadol is a multimodal analgesic with proven dose-related efficacy in a variety of perioperative scenarios.[15] Tramadol, the pill form of which was approved by the FDA in 1995, has mechanisms of action incorporating opioid agonism and monoamine-reuptake inhibition. It is a prodrug with a pharmacologically active metabolite O-desmethyltramadol, which binds more strongly to the mu-opioid receptor than does tramadol and is important for the effect of tramadol on pain.[6,16]

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Because of its dual mechanism of action, tramadol is inherently multimodal and could be incorporated into a balanced-agent program. As a centrally acting analgesic, tramadol produces its anti-nociceptive effects through this complementary dual mechanism of action that has also been associated with a favorable side-effect profile.[16] Unlike other opioids, tramadol may have fewer clinically relevant effects on respiratory or cardiovascular parameters.[6] It is particularly useful in patients with impaired cardiorespiratory, hepatic, or renal function.[15] As a Schedule IV drug, tramadol is a suitable analgesic option relative to the commonly used Schedule II conventional narcotics, such as oxycodone, morphine, and meperidine for the relief of moderate to moderately severe pain. Therefore, tramadol could be part of any multimodal analgesic regimen designed to reduce the use of conventional narcotics.

Achieving maximum analgesia while minimizing strong opioid use

Studies have shown that multimodal analgesia offers patients benefits that translate to cost savings.[17] A study of perioperative multimodal analgesia in shoulder surgery found patients had decreased postoperative pain and opioid

consumption and shorter hospital stays, with no increase in short-term complications or unplanned readmissions.[18]

European guidelines for postoperative pain recommend a stepped approach to analgesia for ambulatory surgery that includes the use of multimodal analgesia including atypical opioids such as tramadol.[14] The goal is administration of effective combinations that produce a maximum analgesic effect during early recovery and minimize the need for strong opioids. In addition, when the patient is discharged, the use of pre-packaged, take-home analgesics specific to the type of surgery can improve pain control at home.[14]

Use of IV tramadol in the United States would provide a "step-down" approach to pain management using an agent that physicians are already familiar with, with no need to switch to a different oral analgesic upon patient discharge. An IV infusion of 50 mg, administered over 15 minutes at hours 0, 2, 4, and every 4 hours thereafter, provides a Cmax and AUC comparable to that of 100 mg oral tramadol given every 6 hours at steady state.[19]

Shift to ambulatory surgery and enhanced recovery protocols

Ambulatory surgery has increased steadily due to improvements in anesthesia techniques, the use of more appropriate discharge criteria, and minimally invasive surgical techniques, making it a cost-effective option for providing quality care.[20] Compared to inpatient surgery, ambulatory surgery offers lower rates of cancellations, and reductions in waiting times, hospital costs, and the risk of nosocomial infections.[21]

Along with the increase in the number of ambulatory surgeries, changes in the types of procedures and in the patients themselves are occurring. Ideally, patients should be healthy and have well-controlled comorbidities; however, ambulatory surgery centers have transitioned to accepting patients with significant or life-threatening comorbidities, such as poorly controlled hypertension or diabetes (American Society of Anesthesiologists Physical Status Classification III or IV[22]), leading to higher surgery volume and greater complexity of surgeries performed while still aiming for same-day patient discharges.[23]

Anesthesia and surgical procedures, especially those of the thorax and upper abdomen, cause changes in respiratory function, which are most apparent in the elderly, obese patients, smokers, and those with pre-existing cardiopulmonary disease.[24] In addition, age-related changes in cardiovascular and respiratory function make older patients less able to cope with these changes.[24]

High levels of postoperative pain have been associated with an increased risk of pulmonary and cardiovascular complications, as well as the development of chronic pain, making aggressive treatment of postoperative pain important,

particularly in patients who already suffer from chronic pain.[25] Moderate to severe postoperative pain has traditionally been managed with opioids, with morphine being the standard reference drug.[6] However, opioids are limited by their potential for respiratory depression, especially in high-risk patients. Unlike other opioids, tramadol may have fewer clinically relevant effects on respiratory or cardiovascular parameters.[6]

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Enhanced Recovery After Surgery (or ERAS) protocols are multimodal perioperative care pathways designed to achieve early recovery after surgical procedures by maintaining preoperative organ function and reducing the profound stress response following surgery. These initiatives, as well as enhanced recovery pathway protocols, are intended to enhance earlier patient mobility, reduce prolonged inpatient stays, and decrease overall costs.[26]

For successful ambulatory surgery, in which discharge occurs on the day of surgery, the ideal postoperative analgesic regimen would be well tolerated while providing effective pain relief with minimal side-effects in a cost-effective manner. Furthermore, pain relief should be easy to manage away from the hospital setting.

The cost savings from outpatient surgery may be negated by unanticipated hospital admission due to inadequate pain management or and/or development of medication side effects, such as respiratory depression, nausea, and vomiting. Opioids increase the risk of these side effects, and NSAIDs, which may also be part of a postoperative pain management program, may not be sufficient for pain management. Tramadol, with its favorable risk-benefit profile, may be a suitable IV analgesic agent in ambulatory surgery.[6]

TRAMADOL CLINICAL EFFICACY AND SAFETY

IV tramadol is currently used in Europe and is under development in the United States. The analgesic efficacy of IV, IM, and oral tramadol has been established in several randomized, double-blind, parallel-group, comparative studies in adult patients with moderate to severe postoperative pain.[6] In these studies, the overall analgesic efficacy of parenteral tramadol was similar to that of morphine and meperidine and comparable or superior to that of pentazocine.

Early clinical studies conducted in Europe showed that tramadol was effective and well tolerated when given as an IM or IV injection or in suppository form.[27] In another early postoperative study, tramadol provided satisfactory analgesia in patients who underwent lung, cardiovascular, abdominal, and great vessel procedures.[28] An additional study comparing tramadol used as a continuous infusion or during patient-controlled anesthesia showed effective analgesia with few side effects.[29]

Another study in patients undergoing abdominal surgery that compared IM tramadol with IM morphine showed similar postoperative analgesic activity between the 2 drugs. However, tramadol was better tolerated.[30] A study comparing tramadol and morphine in patients undergoing gynecologic surgery showed comparable analgesia with the 2 drugs, but tramadol resulted in less respiratory depression.[31]

In another study of patients undergoing hemorrhoidectomy or abdominal surgery, IM tramadol or pentazocine were given every 8 hours for 3 days postsurgery.[32] The first dose of tramadol was significantly more effective than pentazocine after the first hour. Both drugs produced good analgesia, but final judgments on efficacy and acceptability were in favor of tramadol.

Studies have shown that tramadol provides similar analgesia to that of several NSAIDs, including ketorolac and naproxen. This may be particularly beneficial when NSAIDs are not indicated, as in patients with peptic ulcers, hemorrhagic disorders, or hypertension, and in patients with impaired renal, hepatic, or cardiac function.[6] In a study comparing IV tramadol with IV ketorolac, tramadol provided better analgesia with less rescue medication and lower rate of overnight admission.[33]

More recently, the American Society for Enhanced Recovery and Perioperative Quality Initiative recommended considering tramadol as an analgesic adjunct as one part of an Enhanced Recovery Pathway (ERP) for colorectal surgery, which is generally associated with severe postoperative pain.[34] They based their recommendation on evidence comparing postoperative opioid-based patient controlled analgesia to IV tramadol and found that the tramadol patients needed less rescue analgesia.[35] Another study that included scheduled tramadol as part of the ERP showed an improvement in pain scores and other outcomes including significantly shorter hospital stays and tolerance of a full diet.[36]

IN CONCLUSION

New strategies for postoperative pain management include the use of multimodal analgesia, which involves combining analgesics from different pharmacologic drug classes that have additive or synergistic effects. This generally involves the use of 2 or more medications. Tramadol, a multimodal analgesic with proven dose-related efficacy in a variety of perioperative settings, could be a welcomed option/addition.

Currently, only oral tramadol is available in the United States; however, oral and IV tramadol have been used successfully in Europe, and IV tramadol is undergoing Phase 3 clinical evaluation in the US. The efficacy of tramadol for

the management of moderate to severe pain has been shown in both inpatients and ambulatory surgery patients. Compared to conventional opioids, tramadol may have fewer clinically relevant effects on respiratory or cardiovascular parameters. It may be especially useful in patients with poor cardiopulmonary function, including the elderly, obese patients, and smokers; in patients with impaired hepatic or renal function; and in patients in whom NSAIDs are not recommended or need to be used with caution.[6] Finally, US physicians are already familiar with oral tramadol, and an IV dosing regimen that provides a comparable pharmacokinetic profile will ease the transition from the IV to the oral formulation upon discharge.

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