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REVIEW ARTICLE/BRIEF REVIEW

Optimizing pain management to facilitate Enhanced Recovery After Surgery pathways

Optimiser le contrôle de la douleur pour faciliter la Récupération rapide après la chirurgie

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Abstract

Purpose *The optimal management of postoperative pain using multimodal analgesia is a key component of Enhanced Recovery After Surgery (ERAS). Pain has adverse clinical implications on postoperative recovery, including prolonging the time to recovery milestones and length of hospital stay. Moreover, the ubiquity of opioids in postoperative analgesic regimens results in adverse effects, such as sedation, postoperative nausea and vomiting, urinary retention, ileus, and respiratory depression, which can delay discharge. Thus, multimodal analgesia, i.e., the use of more than one analgesic modality to achieve effective pain control while reducing opioid-related side effects, has become the cornerstone of enhanced recovery. The purpose of this review is to address the analgesic techniques used as part of multimodal analgesic regimens to optimize postoperative pain control and to summarize the evidence for their use in reducing opioid requirements and side effects.*

Principal findings *There is a wide variety of analgesic techniques available for multimodal postoperative analgesia. These modalities are divided into pharmacological and non-pharmacological techniques. Systemic pharmacological modalities involve opioids and non-opioids such as acetaminophen, non-steroidal anti-inflammatory drugs, N-methyl-D-aspartate receptor antagonists, anticonvulsants (e.g., gamma-aminobutyric acid analogues), beta-blockers, alpha-2 agonists, transient receptor potential vanilloid receptor agonists (capsaicin), and glucocorticoids. Other pharmacological modalities include central neuraxial techniques, surgical-site infiltration, and regional anesthesia. Evidence supports the use of these pharmacological techniques as part of multimodal analgesia, but each has its own advantages and specific safety profile, which highlights the importance of selecting the appropriate analgesics for each patient. Adjunctive non-pharmacological techniques include acupuncture, music therapy, transcutaneous electrical nerve stimulation, and hypnosis. There is mixed evidence regarding such techniques, although a lack of harm is associated with their use.*

Conclusion *There are continuing advancements in multimodal analgesic techniques; however, postoperative pain in general continues to be undermanaged. Furthermore, a continuing challenge in multimodal pain research related to ERAS is the difficulty in carrying out randomized trials to determine the relative importance of any one component, including analgesia.*

Résumé

Objectif *La gestion optimale de la douleur postopératoire à l'aide d'une analgésie multimodale est un élément essentiel de la Récupération rapide après la chirurgie (RRAC). La douleur a des implications cliniques préjudiciables sur la récupération postopératoire, notamment l'allongement du délai des étapes de récupération des éléments de référence et de la durée de séjour à l'hôpital. De plus, l'omniprésence des opioïdes dans les schémas thérapeutiques d'analgésie postopératoire a pour conséquence des effets secondaires, tels que la sédation, les nausées et*

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vomissements postopératoires, la rétention urinaire, l'iléus et la dépression respiratoire qui peuvent retarder le congé. Ainsi, l'analgésie multimodale, c'est-à-dire l'utilisation de plus d'une modalité analgésique pour obtenir un contrôle de la douleur tout en réduisant les effets secondaires liés aux opioïdes, est devenue la pierre angulaire de la récupération rapide. L'objet de cette synthèse est de revoir les techniques analgésiques utilisées dans le cadre des schémas thérapeutiques d'analgésie multimodale pour optimiser le contrôle de la douleur postopératoire et résumer les données probantes concernant leurs effets sur la réduction du besoin en opioïdes et des effets secondaires.

Constatations principales *Différentes techniques analgésiques peuvent être utilisées pour l'analgésie multimodale postopératoire. Ces modalités sont divisées en techniques pharmacologiques et non pharmacologiques. Les modalités pharmacologiques systémiques font appel aux opioïdes et aux non-opioïdes, tels que l'acétaminophène, les anti-inflammatoires non stéroïdiens, les antagonistes du récepteur du N-méthyl-D-aspartate, des anticonvulsants (par exemple, les analogues de l'acide gamma-aminobutyrique), les bêta-bloqueurs, les agonistes alpha-2, les agonistes du récepteur vanilloïde à potentiel de récepteur transitoire (capsaïcine) et les glucocorticoïdes. Les autres modalités de traitements pharmacologiques incluent les techniques neuraxiales centrales, l'infiltration du site chirurgical et l'anesthésie régionale. Des données probantes soutiennent l'utilisation de ces techniques pharmacologiques dans le cadre de l'analgésie multimodale, mais chacune a ses propres avantages et son propre profil d'innocuité, ce qui souligne l'importance de la sélection des analgésiques appropriés pour chaque patient. Les techniques non pharmacologiques d'appoint incluent l'acuponcture, la musicothérapie, la stimulation nerveuse électrique transcutanée et l'hypnose. La force des données probantes concernant ces techniques est mitigée, bien que leur utilisation soit associée à une absence d'effet néfaste..*

Conclusion *Les progrès des techniques d'analgésie multimodales sont en constante évolution. Toutefois, d'une manière générale, la douleur postopératoire continue à être insuffisamment traitée. En outre, la difficulté à mener des essais randomisés pour déterminer l'importance relative de l'un des composants, y compris de l'analgésie, reste un défi constant de la recherche sur le contrôle multimodal de la douleur dans le cadre des programmes de RRAC.*

Introduction

In recent years, there has been an increasing emphasis on ambulatory and short-stay surgeries, with almost a threefold increase in visits to ambulatory surgery centres in the United States from 1996-2006, nearing 14.9 million. Nevertheless, the rate of visits to hospital-based surgery centres has remained largely unchanged during the same period.[1] Pain control modalities have been studied in more invasive operations, such as major abdominal surgery, where Enhanced Recovery After Surgery (ERAS) programs have addressed the key factors that delay postoperative recovery and prolong hospital stay. These include parenteral opioid analgesia, the need to maintain intravenous fluids due to gut dysfunction, and bed rest secondary to lack of mobility.[2] The knowledge acquired from studying these pain control modalities has facilitated improvements in pain control to accelerate recovery and discharge in the short-stay and ambulatory population.

Enhanced recovery pathways vary amongst institutions but include key elements such as hemodynamic optimization, early oral intake with prokinetic agents, early ambulation, and standardized multimodal pain control regimens.[3] While some maintain that there is the need for more research on the efficacy of ERAS protocols,[4] thus far, evidence has shown that such protocols significantly reduce postoperative hospital stay without increasing morbidity and mortality. This results in a decrease in hospital costs and an increase in patient satisfaction.[3,5,6]

A key component of enhanced recovery is optimal management of acute postsurgical pain, particularly given its adverse clinical implications on patient recovery. Firstly, pain itself prolongs time to recovery milestones and delays discharge after surgery.[7] Recovery milestones, including functional parameters such as mobilization from bed and ambulation, both with and without a walking frame, are particularly pertinent in orthopedic and spine surgeries as inadequate pain management impedes postoperative rehabilitation and achievement of such milestones.[8] Secondly, opioids are the mainstay of most postoperative analgesic regimens. While they are effective even for severe pain, their use prolongs hospital length of stay (LOS) due to dose-related side effects such as respiratory depression, sedation, postoperative nausea and vomiting (PONV), urinary retention, and ileus.[9] Indeed, analgesic-related side effects are a concern for patients to the extent that some patients would choose less effective analgesia as a trade-off for fewer side effects.[10] Moreover, patients with documented opioid-related adverse events were found to incur higher adjusted mean costs ($22,077 USD *vs* $17,370 USD; $P < 0.0001$), longer mean LOS (7.6 *vs* 4.2 days; $P < 0.0001$) and increased readmission rates (odds ratio [OR] 1.06, 95% confidence interval [CI] 1.02 to 1.09).[11] Lastly, opioids may not be particularly effective in controlling postoperative pain as they provide an initial analgesic effect but subsequently cause rapid development

of tolerance and a reduction in pain threshold (i.e., opioid-induced hyperalgesia).[12,13]

Given the importance of effective analgesia and the significance of opioid-related side effects, multimodal postoperative analgesia has become a key element of ERAS pathways. Multimodal analgesia is defined as the use of more than one modality of pain control to achieve effective analgesia while reducing opioid-related side effects.[14] This may involve systemic administration of different analgesics with separate mechanisms of action or concurrent application of regional and systemic analgesia (e.g., paravertebral block with non-opioid analgesia). The goals of multimodal analgesia are to reduce postoperative pain, minimize opioid-related adverse effects, and ultimately, to accelerate postsurgical recovery and decrease LOS.

There are many exciting developments in the management of acute postoperative pain regarding both routine clinical practice and the use of more novel techniques. Despite increased awareness and clinical advancements, however, there has been limited improvement in control of post-surgical pain.[15] A recent study found that more than 80% of patients still experience pain after surgery, and 75% of those have moderate to extreme pain in the immediate postoperative period. It is therefore hardly surprising that post-surgical pain is the patient's greatest concern before surgery.[15] Hence, there is paramount importance in harnessing multimodal techniques to achieve effective analgesia. With an emphasis on multimodal analgesia, this review covers techniques to optimize pain management and thus facilitate enhanced post-surgical recovery. Current evidence regarding various multimodal analgesic regimens is also reviewed, including their impact on reducing opioid requirements and their adverse effects. The papers selected for this review present clinically relevant evidence pertinent to the ever evolving field of multimodal analgesia.

Developments

Multimodal analgesia modalities are subdivided into pharmacological (central neuraxial, regional, local, and systemic analgesia) and non-pharmacological techniques, and their recent advances are discussed below. The Table 1 summarizes the evidence from key reviews and meta-analyses on analgesic techniques in various common surgeries.

Central neuraxial, regional, and local analgesia

Central neuraxial techniques (epidural and spinal analgesia)

Epidural analgesia as part of ERAS protocols accelerates return of bowel function and reduces pain, although there is inconclusive evidence that it reduces LOS.[16,17] A multimodal epidural infusion comprising drugs with different pharmacological pathways is more effective than a single-agent infusion. The combination of local anesthetics and adjuvants provides both intraoperative and postoperative analgesia after a wide range of surgeries (e.g., thoracic, abdominal, lower limb).[18] Epidural adjuvants, such as clonidine (0.08-0.12 $\mu g \cdot kg^{-1} \cdot hr^{-1}$) added to a continuous epidural infusion of 0.08% ropivacaine (0.16 $mg \cdot kg^{-1} \cdot hr^{-1}$), reduce the required dose of anesthetic and enhance analgesia.[19] A local anesthetic-opioid combination is also effective. For example, a double-blind randomized comparison of three solutions administered by continuous epidural infusion (15 $mL \cdot hr^{-1}$) for postoperative analgesia (0.125% bupivacaine in 0.9% saline, diamorphine in 0.9% saline [0.5 mg in 15 mL], ordiamorphine mixed with 0.125% bupivacaine) was shown to be superior to each modality alone, yielding better pain relief with fewer adverse effects following major gynecological surgery.[20] In addition to their analgesic effects, central neuraxial techniques reduce the surgical stress response and cardiac, pulmonary, thromboembolic, and renal complications.[21] A systematic review and meta-analysis showed that epidural analgesia significantly decreases risk of mortality (3.1% *vs* 4.9%; OR 0.6; 95% CI 0.4 to 0.9) as well as the risk of cardiac arrhythmias (atrial fibrillation and supraventricular tachycardia), deep vein thrombosis, respiratory complications (respiratory depression, atelectasis, and pneumonia), and gastrointestinal complications (ileus, PONV).[22]

Spinal analgesia is another central neuraxial block technique that can facilitate faster postoperative recovery with careful choice and dosing of drugs. Spinal anesthetic techniques, which use a multimodal "minidose" of lidocaine (10-30 mg), bupivacaine (3.5-7 mg), or ropivacaine (5-10 mg) with a potent opioid (e.g., fentanyl 10-25 μg), results in quicker recovery of sensory and motor function and lowers the risk of hypotension compared with conventional spinal techniques.[23] The "minidose" spinal technique has been shown to facilitate faster recovery than general anesthesia for short-duration outpatient laparoscopy.[24] Nevertheless, clinicians must be cognizant of the potential side effects of intrathecal opioids, such as PONV, which may delay discharge. This highlights the importance of tailoring analgesic regimens to patient type. For example, elderly patients are more susceptible to the adverse effects of spinal analgesia and require lower doses, as their reduced volume of nerve myelination and cerebrospinal fluid (CSF) results in greater diffusion of local anesthetics and wider extension of nerve block.[25]

Despite the advantages of central neuraxial techniques, there are potential adverse effects, including technical block failures (6.1% of patients in a recent meta-analysis

Table 1 Evidence-based ERAS regimens incorporating multimodal analgesia

Surgery type	Preoperative Analgesia	Intraoperative Analgesia	Postoperative Analgesia	Outcomes
Open or laparoscopic colorectal surgery (Miller *et al.* 2014)[117]	Non-ERAS - Thoracic epidurals rarely performed due to enoxaparin thromboprophylaxis ERAS - Thoracic epidurals placed at the T8-T10 level in preoperative holding area, together with small doses of midazolam and fentanyl to facilitate epidural insertion and maintain patient comfort (Thromboprophylaxis with subcutaneous heparin 5,000 IU after epidural placement and before incision)	Non-ERAS - Not standardized; intravenous opioids often administered ERAS - Single epidural bolus of hydromorphone at induction (0.4-0.8 mg based on body weight), followed by bupivacaine infusion (2.5 mg·mL^{-1} at 3-6 mL·hr^{-1}) - No intraoperative intravenous opioids given after induction unless approved by attending anesthesiologist	Non-ERAS - Not standardized ERAS - Epidural local anesthetic/opioid infusion (0.125% bupivacaine and hydromorphone 10 μg·mL^{-1}) for up to 72 hr. - Adjunctive analgesia with acetaminophen and NSAIDs whenever possible - Transition to oral opioids after removal of epidural catheter	ERAS Benefits - Significantly less total postoperative morphine equivalents (mg) required [median (range) 29.8 (10-85) mg *vs* 120 (69-267) mg] - Significantly lower average (SD) pain scores throughout days 0 to 5 [3.3 (1.9) *vs* 4.9 (2.1)] - Significantly shorter median hospital LOS (5 *vs* 7 days) ERAS Disadvantages - None
Spine surgery (Requiring elective posterior instrumented fusion on > 3 levels for non-malignant and non-infectious conditions) (Mathiesen *et al.* 2013)[118]	Non-ERAS - Not standardized; typically opioids ERAS - Acetaminophen 2 g *po* (sustained release) - Celecoxib 400 mg *po* - Gabapentin 900 mg *po*	Non-ERAS - Remifentanil and propofol At anesthesiologist's discretion: - Fentanyl and morphine - Epidural - PONV prophylaxis ERAS - Remifentanil and propofol - Morphine *iv* 0.3 mg·kg^{-1} at 45 min before end of surgery - S-ketamine 0.5 mg·kg^{-1} *iv* + 0.3 mg·kg^{-1}·hr^{1} until 45 min before end of surgery - Epidural catheter placed at middle tip of surgical field, boluses of bupivacaine 0.5 mg·mL^{-1} 10 mL - If epidural not possible, subfascial local infiltration (40 mL of bupivacaine 2.5 mg·mL^{-1}) - PONV prophylaxis with dexamethasone *iv* 24 mg	Non-ERAS - Not standardized - Acetaminophen 1 g *po* × 4 - If epidural placed, infusion given for up to 72 hr or PCA morphine for 48 hr if no epidural ERAS - Acetaminophen 1 g × 4 *po* - Ibuprofen 400 mg × 4 *po* until discharge - Gabapentin 400 + 1,000 mg *po* for 5 days - Epidural bupivacaine 2.5 mg·mL^{-1} with 50 μg·mL^{-1} of morphine 5-8 mL·hr^{-1} for 96 hr - If no epidural, PCA morphine (bolus 2 mg, lockout 15 min for 48 hr) background infusion 1 mg·hr^{-1} during first 24 hr - Sustained-release oral morphine 20 mg × 2 after end of epidural or PCA - Opioid at anesthesiologist's discretion	ERAS Benefits - Significantly less opioid consumption (oral morphine equivalent) on POD 1 [median (range) 110 (55-180) mg *vs* 15 (0-120) mg] and on POD 2 [100 (40-149) mg *vs* 30 (0-120) mg], but not on POD 3-6 - Pain scores not analyzed - Significantly earlier mobilization from bed (median [IQR] of 1 [1-1] day *vs* 1 [1-2.5] days) and ambulation, both with and without a walking frame (2 [1-2.5] days *vs* 3 [1-5] days and 5 [3-7] days *vs* 7 [5-9.3] days, respectively) - Lower nausea, sedation and dizziness scores on POD 1-6 - Significantly shorter LOS in the PACU [median (range) 270 (173-353) min *vs* 345 (240-480) min], but no difference in hospital LOS - No postoperative infections in either group ERAS Disadvantages - None

Table 1 continued

Surgery type	Preoperative Analgesia	Intraoperative Analgesia	Postoperative Analgesia	Outcomes
Primary hip and knee arthroplasty (Khan *et al.* 2014)[119]	Non-ERAS - Not standardized Non-ERAS - Premedication with Gabapentin 300 mg *po* on night before surgery	Non-ERAS - General anesthesia, spinal or epidural per anesthesiologist and patient preference ERAS - Low-dose spinal anesthesia without intrathecal opioids with Propofol ± Ketamine, and Paracetamol 1 g *iv* ± Parecoxib 40 mg *iv*; administered with sedation or light general anesthesia - Local anesthetic via intraoperative infiltration and postoperative infusion of 0.125% levobupivacaine 80 mL in a wide and layered field, including joint capsule, muscle, fat, and skin - Routine PONV prophylaxis with dexamethasone initially, but later discontinued due to immunosuppression concerns	Non-ERAS - Patient-controlled intravenous analgesia ERAS - Epidural infusion via catheter placed intraoperatively; a single levobupivacaine bolus 20 mL after skin closure, and 3 postoperative boluses at 6, 14, and 24 hr (20 mL for THA, 40 mL for TKA) - Gabapentin (300 mg twice daily for 5 days) and Oxycontin (5-20 mg twice daily for 2 days) followed by Tramadol (50-100 mg every 4-6 hr)	ERAS Benefits - Pain and opioid consumption not analyzed - Significantly shorter median hospital LOS (3 *vs* 6 days) - Significantly lower return-to-theatre rates (40/3,000 *vs* 60/1,000) - Significantly lower 30-day MI rates (12/3,000 *vs* 26/1,000) and death rates (5/3,000 *vs* 16/1,000) - No difference in 30-day complication rates (stroke, GI bleed, pneumonia, DVT and PE) - No difference in readmission rates ERAS Disadvantages - None
Gynecologic surgery (Complex cytoreductive, staging and pelvic organ prolapse surgeries) (Kalogera *et al.* 2014)[120]	Non-ERAS - Not standardized ERAS - Celecoxib 400 mg *po* once - Acetaminophen 1,000 mg *po* once - Gabapentin 600 mg *po* once	Non-ERAS - Local wound infiltration generally not used - Triple antiemetics and prokinetics generally not used ERAS - Intravenous opioids at discretion of anesthesiologist supplemented with ketamine, ketorolac, or both - Local anesthetic infiltration of bupivacaine at incision site after closure - PONV prophylaxis with single dexamethasone bolus 4 mg *iv* plus droperidol 0.625 mg *iv* (± 30 min before incision); and single bolus of granisetron 0.1 mg *iv* (± 30 min before incision closure)	Non-ERAS - Opioid PCA ERAS - Goal: no intravenous PCA - Oxycodone 5-10 mg *po q4 h prn* pain > 3 or greater than patient stated comfort goal (5 mg for pain rated 4-6 or 10 mg for pain rated 7-10); for patients who received intrathecal analgesia, start 24 hr after intrathecal dose - Acetaminophen 1 g *po q6-12 h* - Ketorolac 15 mg *iv q6 h* for 4 doses, then ibuprofen 800 mg *po q6 h*. For NSAID-intolerant patients, tramadol 100 mg *po* q6-12 hr starting on POD 1 - For breakthrough pain (pain more than 7 > 1 hr after receiving oxycodone), hydromorphone 0.4 mg *iv* once if patient did not receive intrathecal medications; may repeat once after 20 min if first dose ineffective - Hydromorphone PCA started only if continued pain despite 2 doses of intravenous hydromorphone	ERAS Benefits - Significantly decreased PCA opioid use in cytoreductive group (98.7% *vs* 33.3%) and decreased postoperative opioid use (80% decrease in the first 48 hr) with no change in pain scores - Significantly shorter hospital LOS for all surgery types (4-day reduction) - Significantly faster return of bowel function for complex cytoreductive [median (range) 3 (2-3) days *vs* 4 (3-5) days] and staging surgeries [2 (1-3) days *vs* 2 (2-3) days] - Significantly faster return to general diet for all surgery types (1-5 days median difference) - No difference in rate of severity of 30-day complications (ileus, bowel perforation, anastomotic leak, abscess) or mortality - No difference in 30-day readmission rates or stay - Insignificant 30-day cost savings of > $7,600 USD per patient (18.8% reduction) ERAS Disadvantages - None

ERAS = Enhanced Recovery After Surgery; LOS = length of stay; NSAIDs = non-steroidal anti-inflammatory drugs; *po* = oral; PONV = postoperative nausea and vomiting; PCA = patient-controlled analgesia; POD = postoperative day; IQR = interquartile range; PACU = postanesthesia care unit; MI = myocardial infarction; THA = total hip arthroplasty; TKA = total knee arthroplasty; GI = gastrointestinal; DVT = deep vein thrombosis; PE = pulmonary embolism

on epidural blocks),[22] inadvertent motor blockade, postdural puncture headache, and infection. Moreover, such blocks are resource-intensive due to the need for ongoing monitoring. Epidural blocks may lead to a significant increase in the risk of arterial hypotension, pruritus, urinary retention, and motor blockade[22]; hence, administration by experienced clinicians and individual risk-benefit analyses are paramount. Surgery type is one such consideration, as neuraxial analgesia may be more suitable for open rather than laparoscopic surgeries. A systematic review and meta-analysis found epidural analgesia to be effective for both open and laparoscopic surgeries[22]; however, another systematic review argued that the risk-benefit ratio for laparoscopic surgeries may not favour the use of neuraxial techniques.[26] The latter review found that, while the non-epidural group had higher pain scores, the level of pain was nevertheless acceptable (i.e., $< 4/10$) and thus did not warrant the use of epidural analgesia.

Surgical site infiltration

The incorporation of local anesthetics as part of multimodal analgesia decreases opioid requirements and side effects when used at several surgical sites (e.g., bupivacaine 50-100 mg or lidocaine 400 mg for intraperitoneal block after laparoscopic abdominal surgeries, including fundoplication, appendectomy, hernia repair, and cholecystectomy).[27] Nevertheless, there is lack of evidence for effective analgesia with infiltration at laparoscopic port sites. This may be due to inadequate doses of local anesthetics and the short duration of local anesthetics in some studies.[28] Intra-articular analgesic infiltration reduces pain and opioid consumption after orthopedic procedures such as arthroscopic surgery and total knee replacement, although the evidence is less clear for its effects on time to discharge readiness and LOS.[29,30] A review found that a multimodal infusion comprising high-dose ropivacaine (150-400 mg) with adrenaline (0.1-0.5 mg) and ketorolac (typically 30 mg) is most effective for analgesia.[30] Continuous and patient-controlled intra-articular infusions after surgery should not be used, as prolonged exposure to analgesics may trigger chondrolysis, a rare condition of the shoulder which involves rapid dissolution of articular cartilage, eventually causing osteoarthritis and long-term disability.[31] All 23 cases in a case series featuring patients with chondrolysis following shoulder arthroscopy were administered an intra-articular injection of 0.25% bupivacaine $\geq$ 20 mL with epinephrine, and 17/23 patients had used a high-volume intra-articular infusion pump for 48 hr postoperatively.[32] More research is needed on the doses of local anesthetic that will safely manage pain without causing chondrolysis as well as on whether chondrolysis can occur in other joints, e.g., the knee.

Consideration must be given to the risks resulting from local anesthetics, including cardiac effects (e.g. bradycardia, hypotension) and effects on the central nervous system (e.g., blurred vision, seizures, and hypoventilation). These risks can be minimized by aspirating before administration to avoid intravascular injection, administering test doses, and adhering to the safe dose range for each drug. Allergic reactions are rare but include skin rash, nausea and vomiting, loss of consciousness, fever, and hypotension.

Regional techniques

Regional techniques, such as transversus abdominis plane (TAP) block and paravertebral block (PVB), are increasingly incorporated into multimodal analgesic regimens, with good evidence for their efficacy in ERAS protocols. Addition of the bilateral TAP block to an established enhanced recovery pathway using general anesthesia was found to decrease postoperative opioid requirements and LOS after laparoscopic colorectal surgery.[33] A TAP block decreases postoperative opioid use and PONV after abdominal surgery and possibly reduces acute postoperative pain compared with placebo.[34] Some studies have compared the efficacy of TAP block with neuraxial techniques. One study found that, after laparoscopic colorectal surgery, a four-quadrant TAP block with continuous infusion via bilateral posterior TAP catheters (0.365% levobupivacaine 2.5 $mg \cdot kg^{-1}$ preoperatively; 0.25% levobupivacaine for 48 hr postoperatively) results in pain control and postoperative tramadol consumption equivalent to a postoperative epidural infusion (0.25% bupivacaine 20 mL preoperatively; 0.125% bupivacaine 8-12 $mL \cdot hr^{-1,}$ and fentanyl 2 $\mu g \cdot mL^{-1}$ postoperatively).[35] In contrast, a systematic review and meta-analysis on Cesarean delivery found that TAP block alone was less effective than intrathecal morphine in managing pain at 24 hr (mean difference [MD] 0.98; 95% CI 0.06 to 1.91) and resulted in greater 24-hr morphine consumption (MD 8.42 mg; 95% CI 1.74 to 15.10), while the former was associated with an increased incidence of side effects such as sedation and PONV.[36] There are generally few risks associated with TAP block, including intraperitoneal injection of local anesthetic ($< 2\%$) as well as a few case reports of transient femoral nerve palsy and bowel hematoma. TAP block also carries a slight risk of damage to visceral structures such as the liver (one reported case with a blindly administered block), which is minimized with ultrasound guidance.[37]

As for PVB, a large retrospective analysis of patients undergoing thoracotomy for lung resection found that, when added to a morphine patient-controlled analgesia (PCA)-based regimen, a continuous PVB catheter (with an initial infusion of 0.25% bupivacaine or levobupivacaine 0.1 $mL \cdot kg^{-1} \cdot hr^{-1}$ and titrated down with adequate analgesia) was at least as effective as a thoracic epidural catheter (TEA) (with an initial infusion of 0.1% bupivacaine or levobupivacaine 0.1 $mL \cdot kg^{-1} \cdot hr^{-1}$ and titrated to adequate analgesia, combined with fentanyl 5 $\mu g \cdot mL^{-1}$) in reducing postoperative complications. Moreover, PVB use is associated with a shorter LOS, thus supporting its utility in fast-track thoracic surgery, for which TEA is typically considered the optimal technique for post-thoracotomy pain.[38] Evidence also points to PVB as a good analgesic choice in outpatient surgeries such as inguinal herniorrhaphy. Compared with fast-track general anesthesia, PVB provides a speedier recovery, longer-lasting analgesia, shorter stays in the postanesthesia care unit (PACU), and earlier time to home readiness.[39] Nevertheless, PVB is associated with an overall complication rate of 2.6-5%, including block failure (6.8-10%), hypotension (4.6%), vascular puncture (3.8%), pleural puncture (1.1%), and pneumothorax (0.5%).[40] As PVB cannulae are small, pneumothorax may not always follow even if pleural puncture occurs, and a related pneumothorax is usually small and can be managed conservatively.

Systemic analgesia

Opioids

Opioids are the mainstay of postoperative analgesia for many surgeries. While they are effective for moderate to severe pain, their usage is limited by dose-related adverse effects, including PONV, urinary retention, ileus, pruritus, and most dangerously, respiratory depression.[28] These side effects have led to an increasing emphasis on multimodal analgesic regimens that reduce opioid demand, with opioids used as rescue analgesics when non-opioid medications are inadequate for pain control.

Acetaminophen (paracetamol)

Acetaminophen is an effective analgesic for mild to moderate pain. When used as an opioid adjunct, oral or rectal acetaminophen reduces pain intensity[41] and opioid consumption by up to 30%,[42] although several systematic reviews and meta-analyses have shown no concurrent reduction in opioid-related side effects.[43] The use of oral over rectal acetaminophen is preferred, as the absorption of rectal acetaminophen is erratic and may therefore result in variable analgesic efficacy. There is increasing usage of intravenous acetaminophen, which has more favourable pharmacokinetics (earlier plasma and CSF peaks) than oral and rectal formulations,[44] but is more costly than the latter two. Studies are currently lacking that directly compare oral with intravenous acetaminophen, but thus far, studies of intravenous acetaminophen have been encouraging. Intravenous acetaminophen also reduces opioid consumption by up to 30%, although this is not associated with a reduction in opioid-induced adverse events.[45] A recent meta-analysis found that prophylactic intravenous acetaminophen (typically a 1 g dose) as part of a multimodal analgesic regimen reduces nausea if administered before surgery or PACU arrival, but not if given after the onset of pain.[46] Interestingly, the reduction in nausea (compared with placebo) was associated with less pain, but not with a reduction in postoperative opioids.

Adding to the value of acetaminophen in multimodal analgesia is its apparent synergistic effect with non-steroidal anti-inflammatory drugs (NSAIDs).[47] The efficacy of an acetaminophen-NSAID combination also applies in multimodal analgesic regimens that do not utilize opioids. For instance, the combination of single-dose acetaminophen (0.5-1 g) and ibuprofen (200-400 mg) after dental surgery provides better acute postoperative analgesia than either drug alone, with reduced analgesic needs and reduced risk of adverse events.[48]

Acetaminophen has a very favourable safety profile and is much safer than other drugs such as NSAIDs. Adverse effects are rare and include nausea and vomiting (< 1% individuals) and skin irritation (e.g., urticaria, erythema, dermatitis) (< 0.1%), with more serious adverse effects being much rarer (e.g., thrombocytopenia, leucocytosis, agranulocytosis, and liver enlargement) (< 0.01%).[49]

Lidocaine infusion

A meta-analysis of randomized controlled trials found that an intravenous lidocaine infusion reduces acute postoperative pain (6 hr postoperatively) at rest (weighted mean difference [WMD] −8.70; 95% CI −16.19 to −1.21), with cough (WMD −11.19; 95% CI −17.73 to −4.65), and with movement (WMD −9.56; 95% CI −17.31 to −1.80).[50] Intravenous lidocaine infusion also reduced postoperative opioid (morphine) consumption (WMD −8.44 mg; 95% CI −11.32 to −5.56) as well as opioid-related side effects. These included time to first flatus (WMD −7.62 hr; 95% CI −10.78 to −4.45), time to first bowel movement (WMD −10.71 hr; 95% CI −16.14 to −5.28), PONV (relative risk [RR] 0.71; 95% CI 0.57 to 0.90), and LOS (WMD −0.17 days; 95% CI −0.41 to 0.07). The greatest benefit occurred with abdominal surgery. Although the same meta-analysis found that only

12 of 29 eligible studies screened for adverse events, incidences of cardiac and neurologic adverse events were comparable between control and treatment groups in these studies.

Non-steroidal anti-inflammatory drugs and COX-2 inhibitors

Non-steroidal anti-inflammatory drugs (including cyclooxygenase-2 [COX-2] inhibitors) reduce opioid consumption and opioid-related side effects when used in multimodal regimens.[51] Nevertheless, their use is not without risk. One case-control study found that ketorolac in particular was associated with a significant increase in anastomotic leaks (OR 2.09; $P = 0.021$), while the use of any NSAID was associated with a non-significant increase in anastomotic leaks (OR 1.81; $P = 0.06$).[52] Moreover, evidence from animal models shows that NSAIDs (particularly selective COX-2 inhibitors) may impair bone healing and even cause bone resorption, although data from human studies remain equivocal, with some studies even purportedly showing decreased bone resorption rates with NSAID use.[53] In light of these findings, NSAIDs should be used judiciously in patients at increased risk for anastomotic leak (e.g., patients with stapled anastomoses).[54] In most patients, however, NSAIDs are recommended as part of the multimodal analgesic regimen.

Cyclooxygenase-2 inhibitors do not have the adverse effects associated with conventional non-selective NSAIDs, which cause COX-1 inhibition and a corresponding increased risk for surgical-related bleeding, gastrointestinal ulceration, and renal dysfunction.[43] Cyclooxygenase-2 inhibitors have been shown to reduce opioid requirements in surgeries such as laparoscopic cholecystectomy[55] and knee replacement surgery,[56] with fewer opioid-related symptoms and quicker functional recovery. Nevertheless, safety concerns about the prothrombotic cardiovascular side effects of COX-2 inhibitors[57] have led to some products being discontinued, e.g., rofecoxib and valdecoxib.

N-methyl-D-aspartate (NMDA) receptor antagonists

Ketamine is an NMDA receptor antagonist that reduces postoperative opioid requirements. An opioid-free epidural regimen of ketamine and bupivacaine was found to be superior to a bupivacaine-fentanyl combination in fast-track colonic resection, with shorter PACU stays, shorter LOS, and fewer opioid-related side effects.[58] Ketamine may be especially useful as part of a multimodal analgesic regimen in postsurgical patients with high opioid requirements or opioid-refractory pain. As NMDA receptors are involved in the development of pathological pain states, such as hyperalgesia, ketamine has also been shown to decrease chronic postsurgical pain and opioid consumption after total hip arthroplasty (ketamine 0.5 $mg \cdot kg^{-1}$ *iv* before incision and a 24-hr infusion of 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$)[59] and even in opioid-dependent patients undergoing lumbar spine surgery.[59,60] Importantly, the specific use of ketamine for patients with chronic pain, whether perioperatively or otherwise, is currently off-label and not well-studied. Ketamine is U.S. Food and Drug Administration (FDA) approved as a supplement for low-potency agents (e.g., nitrous oxide) as well as for diagnostic and surgical procedures that do not require skeletal muscle relaxation for induction of anesthesia before the administration of other general anesthetic agents.

Other NMDA receptor antagonists include dextromethorphan, memantine, and magnesium sulfate. In a review of these three agents, 67% of the included studies on dextromethorphan (0.5-1 $mg \cdot kg^{-1}$) and 58% of the studies on ketamine (0.15-1.0 $mg \cdot kg^{-1}$) showed reduced postoperative pain and/or opioid consumption, whereas none of the studies on magnesium showed any effect.[61] Memantine (20-30 $mg \cdot day^{-1}$) is better tolerated, more potent, and more slowly eliminated than ketamine (half-lives: 60-80 hr *vs* 2.5 hr, respectively).[62] Memantine reduces chronic postoperative pain and may have potential as an opioid adjunct for acute postoperative analgesia.[62] Lastly, magnesium (50 $mg \cdot kg^{-1}$ preoperatively and 8 $mg \cdot kg^{-1} \cdot hr^{-1}$ intraoperatively) also appears to act via NMDA receptor antagonism and inhibition of calcium influx. Some studies have found that it reduces postoperative opioid requirements,[63] although a meta-analysis showed no evidence for its efficacy in decreasing postoperative opioid demand and pain.[61] N-methyl-D-aspartate receptor antagonists have potentially unpredictable and unpleasant adverse effects, such as psychosis, but low doses (e.g., < 1 $mg \cdot kg^{-1}$ epidural or intravenous ketamine) have been found to aid pain management without these adverse effects.[58] In summary, low-dose ketamine and dextromethorphan should be considered for usage in multimodal regimens, including patients with opioid-refractory pain, opioid dependence or tolerance, and those who do not have risk factors for psychosis (e.g., psychiatric disorders such as schizophrenia).

Anticonvulsants (gamma-aminobutyric acid (GABA) analogues)

Gabapentin and pregabalin are GABA analogues that reduce postoperative opioid requirements and lessen both acute and chronic postoperative pain when used in multimodal analgesia for a wide range of surgeries (e.g., gynecological, abdominal, orthopedic, and dental

surgeries).[64,65] Despite their GABA-like structure, their mechanism of action involves binding to α2-d subunits of voltage-dependent presynaptic calcium channels, thus reducing excitatory neurotransmitter release and subsequent postsynaptic calcium influx.[28] Gabapentin decreases opioid requirements and lessens both acute and chronic postoperative pain. Evidence supports oral gabapentin 600-1,200 mg doses up to one hour preoperatively for varicocele, otolaryngological, and laparoscopic sterilization surgeries.[66–68] As for timing of preoperative dose, both pre- and post-incision oral gabapentin were equivalent in reducing PCA morphine and postoperative pain after lumbar laminectomy. The 900 and 1,200-mg doses were equally effective and more efficacious than placebo and a 600-mg dose.[64] One three-armed study compared prophylactic gabapentin (oral gabapentin 1,200 mg preoperatively with a saline bolus and an intraoperative infusion) and ketamine (oral placebo capsules preoperatively, ketamine bolus 0.3 $mg \cdot kg^{-1}$ *iv* before incision, and intraoperative ketamine infusion 0.05 $mg \cdot kg^{-1} \cdot hr^{-1}$ until end of surgery) with a control group (oral placebo capsules with a saline bolus and infusion).[69] Both preoperative gabapentin and ketamine reduced postoperative pain and PCA morphine consumption (42% and 35%, respectively) after hysterectomy, while only gabapentin reduced chronic incisional and related pain at one, three, and six months.

Pregabalin has better bioavailability and reaches therapeutic levels more quickly than gabapentin. A meta-analysis confirmed that both preoperative and postoperative pregabalin reduce postoperative narcotic requirements and reduce PONV, albeit with no reduction in postoperative pain.[65] The studies analyzed used varied doses of oral pregabalin. Doses < 300 mg (typically 75 or 150 mg) reduced cumulative opioid consumption by 8.8 mg (WMD), with a reduction of 13.4 mg (WMD) for doses of 300-600 mg.[65] The disadvantages of GABA analogues are their adverse effects, including sedation, visual disturbances, dizziness, and headache.[65] More research is needed on the optimal dose of GABA analogues that produces minimal adverse effects while reducing pain as part of multimodal analgesia.

Beta-blockers

A small but growing body of evidence shows that beta-blockers, such as esmolol, reduce both intraoperative and postoperative opioid requirements due to their anti-nociceptive effects.[70] Beta-blockers have the additional advantage of blunting cardiovascular responses to surgical stimuli and reducing postoperative adverse cardiac events. Furthermore, perioperative esmolol has been proposed as an alternative to remifentanil for maintaining stable intraoperative hemodynamics.[71] An intraoperative continuous esmolol infusion (5-15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ with no supplemental intraoperative opioids) in place of intraoperative opioids (continuous remifentanil infusion 0.1-0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) has been used successfully in ambulatory laparoscopic cholecystectomy, resulting in reduced PONV, decreased postoperative pain, and shorter LOS than when supplemental intraoperative fentanyl was used.[72]

Alpha2 agonists

Clonidine and dexmedetomidine have received increasing interest as adjunct analgesics, given that the basic mechanism behind analgesia is thought to be stimulation of central and peripheral α2 receptors. A systematic review and meta-analysis confirmed that systemic α2 agonists (clonidine or dexmedetomidine) decrease postoperative opioid consumption, pain intensity, and opioid-related side effects (i.e., nausea) when added to an opioid-based regimen.[73] There is much variability in administration route (intravenous, oral, transdermal, and other routes) and time of administration (before, during, or after surgery), and more research is needed to ascertain the optimal route and dose timing. Clonidine is also a useful addition to multimodal regional anesthetic infusions. A small randomized controlled trial on patients undergoing elective colorectal surgery found that the addition of epidural clonidine (150 μg in 9 mL of normal saline 30 min before surgery and 1.5 $\mu g \cdot mL^{-1}$ postoperatively) to patient-controlled epidural analgesia with morphine (0.1 $mg \cdot mL^{-1}$) and 0.2% ropivacaine (100 mL) reduces time to first flatus, albeit without any difference in LOS.[74] The addition of dexmedetomidine to intravenous regional anesthetic solutions prolongs analgesia and motor blockade.[75] Additionally, an intravenous dexmedetomidine infusion (0.2-0.8 $\mu g \cdot kg^{-1} \cdot hr^{-1}$) before wound closure was shown to decrease PACU opioid requirements, PACU stay, and PONV after laparoscopic bariatric surgery.[76]

Capsaicin (transient receptor potential vanilloid receptor 1(TRPV1) agonist)

Capsaicin is a non-narcotic agent with agonist activity at peripheral TRPV1 receptors. It selectively stimulates unmyelinated C-fibre afferent neurons, causing the continued release and subsequent depletion of substance P, which ultimately decreases C-fibre activation.[77] Its advantages are its long analgesic duration and lack of effect on motor and autonomic functions. Thus, it has potential value in facilitating earlier rehabilitation and functional recovery after painful surgeries (e.g., orthopedic procedures). Following total knee arthroplasty, directly

instilling capsaicin 15 mg prior to wound closure can decrease postoperative pain, opioid requirements, and side effects (e.g., pruritus) as well as improve functional recovery.[78] The caveat is that capsaicin must be administered before the end of anesthesia as it causes an acute burning sensation immediately after application.

Glucocorticoids

Glucocorticoids reduce postoperative pain as well as decrease opioid requirements and side effects such as PONV.[79] They exert their analgesic effect via several mechanisms; they have anti-nociceptive effects at the spinal level, prevent the production of cytokines involved in inflammatory pain, and inhibit the production of inflammatory prostaglandins and leukotrienes by preventing arachidonic acid production.[28] A major consideration is their potential adverse effects in postoperative patients, as glucocorticoids administered in high doses (e.g., dexamethasone 1 $mg \cdot kg^{-1}$) and for long periods (> 21 days) increase the risk of infection and impair wound healing.[80] Some studies have shown that a single prophylactic dose of dexamethasone can cause mild hyperglycemia for 24 hr postoperatively, although one randomized controlled trial found this was associated with a lower risk of some postoperative complications such as pneumonia and catheter-related infection.[81] Furthermore, a recent randomized controlled trial has refuted the claim that a single low dose of dexamethasone (up to 8 mg at induction of anesthesia) raises blood glucose concentrations for 24 hr after administration, as blood glucose levels did not differ from those observed after saline administration.[82] The exact dose of glucocorticoids at which potential harm outweighs benefit is unknown. Nevertheless, current literature supports a single prophylactic dose of dexamethasone 4 mg at induction for PONV prophylaxis, with 8 mg providing additional opioid-sparing effects and quicker recovery without an increase in postoperative complications such as infection, wound separation, and dehiscence.[83–85]

Non-pharmacological techniques

Non-pharmacological analgesia, when used as an adjunct to pharmacological methods of postoperative pain management, can reduce total analgesic requirements and corresponding side effects.

Acupuncture

Several studies have shown reduced opioid consumption and side effects (e.g., PONV, urinary retention) when acupuncture is used as part of multimodal postoperative analgesia,[86] although clinical opinion on its efficacy remains divided.[87] Considerable clinical heterogeneity remains between studies; for instance, some studies use penetrating needles as the sham intervention, which has been proposed to have a physiological effect. The mechanisms of action of acupuncture remain unclear, but hypotheses include the "gate control theory" and endogenous opioid release. A randomized sham-controlled trial found that electroacupuncture, a variant of acupuncture involving the addition of electric current, resulted in reduced postoperative analgesic requirements at 45 min and lower cortisol levels when added to a multimodal regimen (tramadol and ketamine) for radical prostatectomy.[88]

Music therapy

Music therapy may have a short-term effect on lessening pain and anxiety by decreasing perception of pain through mechanisms such as attention shift or cognitive coping.[28] Compared with noise-cancelling headphones alone, music with noise-cancelling headphones was associated with less increase in pain scores from baseline in patients undergoing transrectal prostate biopsy.[89] Post-biopsy diastolic blood pressure remained stable in the music group but increased in the control and headphones groups, suggesting reduced physiological response to anxiety and pain in the former. Music therapy may also reduce opioid consumption.[90] More research is needed on the optimal type and duration of music therapy.

Transcutaneous electrical nerve stimulation (TENS)

Current evidence is limited, but some studies suggest a positive effect of TENS in reducing acute postoperative pain.[91–93] Given its safety profile, TENS can be considered as an adjunct in patients who do not respond to conventional analgesic techniques or who experience severe side effects.

Hypnosis

Hypnosis can be used as an adjunct technique to reduce pain by altering a patient's perception of pain, although not all patients may respond similarly.[28] A randomized controlled trial on breast cancer surgery patients found hypnosis reduced propofol and lidocaine use compared with attention control. It also reduced pain, nausea, fatigue, discomfort, and emotional upset at discharge.[94] Evidence also suggests that hypnosis can decrease pain after pediatric and adolescent surgeries and certain procedures (e.g., bone marrow aspiration), and it is at

least as effective as distraction as an adjunct strategy for pain reduction.[95]

Future directions

Local infiltration of long-acting local anesthetics

Long-acting local anesthetics include liposomal bupivacaine, a recently FDA-approved formulation of bupivacaine for single-dose local infiltration at the surgical site. This formulation aims to sustain safe therapeutic levels of bupivacaine for up to 72 hr after administration, allowing prolonged analgesia and thus early hospital discharge. Compared with conventional bupivacaine HCl, liposomal bupivacaine reduces post-surgical pain and decreases opioid consumption and opioid-related adverse events after surgeries such as hemorrhoidectomy.[96] A combined analysis of results from six Phase IV prospective single-centre sequential cohort studies found that a multimodal regimen incorporating local infiltration of liposomal bupivacaine (266 mg administered intraoperatively) reduced postoperative opioid requirements, LOS, and opioid-related adverse events after laparoscopic colectomy when compared with opioid PCA (morphine or hydromorphone).[97] Specifically, one of the included studies found that intraoperative liposomal bupivacaine 266 mg used in a fast-track protocol for ileostomy reversal significantly reduced mean (SD) total postoperative opioid consumption [38 (46) mg *vs* 68 (47) mg] and resulted in a nonsignificant but clinically meaningful reduction in LOS (0.8 days, 21% reduction) and total hospitalization costs ($6,611 USD *vs* $6,790 USD).[98] Future research will confirm the extent of its safety and efficacy relative to plain bupivacaine as well as evaluate its use via routes other than local infiltration (e.g., intrathecal, epidural, and perineural).[99]

SABER®-Bupivacaine is another extended-release formulation currently awaiting FDA approval. It comprises bupivacaine 12% in a resorbable semi-viscous matrix of sucrose acetate isobutyrate (SAIB) and provides local analgesia for up to 72 hr. In a multicentre randomized controlled trial on open inguinal hernia repair, a 5 mL dose of SABER-Bupivacaine locally administered at the surgical site significantly reduced acute postoperative pain compared with placebo and reduced supplemental opioid consumption by 26% (although this was not significant).[100]

Lidocaine patch

The lidocaine patch is usually administered as a 10 × 14 cm transdermal patch with lidocaine 700 mg (5% on an aqueous base).[101] As with systemic local anesthetics, transdermal lidocaine reduces pain sensation by blocking the sodium channels of nociceptors. The lidocaine 5% patch has been used for many different chronic pain conditions[102–105] and some acute pain conditions, such as traumatic rib fractures.[106] Evidence for the lidocaine 5% patch for acute postoperative pain is limited.[107–110] A meta-analysis of lidocaine patch shows that lidocaine patches may not be an effective adjunct for acute and postoperative pain management.[111] No significant difference of postoperative pain intensity, opioid consumption and length of hospital stay was found between the lidocaine group and the placebo group. The suggested reason is that the concentration of lidocaine within the wound may be insufficient because of diffusion barriers (skin), location of the patches (around but not on the wound) and minimal systematic absorption (unlike fentanyl patch).[111]

Novel opioids and opioid delivery techniques

Tapentadol

Tapentadol is a recently FDA-approved central-acting analgesic with a dual synergistic mode of action on μ opioid receptors and norepinephrine reuptake inhibition. Tapentadol achieves equipotent analgesia to strong opioids (e.g., oxycodone) while conferring the advantages of decreased PONV, fewer gastrointestinal disturbances, and lower potential for abuse.[112] It has the potential to decrease LOS and hospital costs while providing effective acute postoperative analgesia.

Transdermal iontophoretic delivery of fentanyl

Patient-controlled transdermal fentanyl utilizes needleless iontophoresis technology, allowing patients to self-administer pre-programmed doses of fentanyl, much like conventional PCA. Iontophoresis makes use of an electric current to drive ionized drug molecules across the skin and into the systemic circulation. This differs from the traditional fentanyl patch, which simply involves a slow extended-release fentanyl formulation that cannot be controlled by the patient. Apart from greater ease of administration and patient comfort, a recent review showed fewer opioid-related adverse events and pain control comparable with intravenous opioids.[113] Future implications for research include its efficacy and optimal dose in different patient populations (e.g., by age, body weight, and surgery type) as well as the duration and severity of reactions at the application site.[114]

Sublingual sufentanil microtablet

Sufentanil has a relatively large therapeutic index, and evidence suggests that it results in less respiratory depression

than other opioids, although its rapid tissue redistribution following intravenous administration has precluded its frequent use in PCA regimens. Sublingual sufentanil, which is currently awaiting FDA approval, can provide a prolonged duration of action (80-90 min plasma half-time compared with 15 min for intravenous administration) while harnessing its advantages over other opioids.[115] Two Phase II studies on knee replacement surgery and abdominal surgery showed that 15-μg sublingual sufentanil microtablets reduce postoperative pain compared with placebo and result in fewer opioid-related adverse events.[115] In one study, a handheld PCA device with a 20-min lockout period was used to dispense sublingual sufentanil microtablets, providing a novel method of noninvasive postoperative PCA.[116]

Multimodal regimens in ERAS

The Table 1 outlines several key papers on evidence-based ERAS regimens by surgery type. Such regimens utilize a comprehensive perioperative care pathway, with multimodal analgesia as a key component to improve recovery. One such ERAS protocol for colorectal surgery has been implemented at a major U.S. teaching hospital since 2010.[117] The multimodal pain management regimen involves thoracic epidural catheters at T8-T12, with 0.25% bupivacaine (3-6 $mL \cdot hr^{-1}$) continuously infused intraoperatively and opioids prohibited unless approved by attending anesthesiologists. Postoperatively, the epidural catheter is used for PCA (0.125% bupivacaine / hydromorphone 10 $\mu g \cdot mL^{-1}$; infusion 4-6 mL, bolus 2 mL/30 min). Where possible, regular adjunctive analgesia (intravenous acetaminophen and NSAIDs) is used, and oral opioids are administered after the removal of the epidural catheters. Compared with non-ERAS patients, whose analgesic regimens were based on provider preferences and rarely involved epidurals, a retrospective analysis showed that the ERAS patients had significantly reduced LOS, average pain scores, opioid consumption, urinary tract infection, and readmission rates.

Similar results are seen with other ERAS regimens, with some studies (e.g., for spinal surgery)[118] showing decreased opioid consumption and side effects (i.e., PONV) along with improved recovery parameters, such as shorter time to mobilization and ambulation. Some other studies even indicate that ERAS is associated with better outcomes with lower 30-day myocardial infarction and death rates.[119]

In general, it appears that incorporating multimodal analgesia into ERAS regimens provides better pain control with more favourable side-effect profiles and faster postoperative recovery and may be associated with improved outcomes.

Conclusion

There have been many advances in optimizing management of postoperative analgesia to facilitate enhanced recovery, with multimodal analgesia regimens now the standard practice in ERAS protocols. Despite the clinically observable benefits of these protocols, some challenges in pain research remain within the context of ERAS. By design, ERAS protocols comprise many elements, and these many factors make it difficult to carry out randomized trials controlling for each specific modifiable intervention. Hence, it is difficult to determine the relative importance of individual aspects of the multimodal drugs and elements of ERAS.

Another continuing challenge is that, despite the continuously expanding array of multimodal analgesic methods, data indicate that postoperative pain in general continues to be undermanaged.[15] Given the importance of effective analgesia in patient recovery, the significance of poor pain management is obvious. Moreover, in addition to the consequences of pain in the immediate postoperative period, acute pain may trigger long-term neuronal changes that result in the development of chronic pain.[28] As such, healthcare providers must be vigilant about using the tools at hand to individualize multimodal regimens to patient and surgery type and thus best manage acute postoperative pain.

Key points

- Enhanced recovery pathways facilitate evidence-based comprehensive perioperative care, including postoperative pain management, with the aim of accelerating recovery and discharge after surgery.
- The use of more than one analgesic modality (i.e., multimodal analgesia) to achieve effective pain control while minimizing the side effects of opioids that delay discharge has become the standard of care in ERAS protocols.
- Systemic pharmacological analgesic modalities include opioids, acetaminophen, NSAIDs, intravenous lidocaine infusions, NMDA receptor antagonists, anticonvulsants (e.g., GABA analogues), beta-blockers, a2 agonists, TRPV1 agonists (capsaicin), and glucocorticoids. Other regional/local pharmacological techniques include central neuraxial techniques, surgical site infiltration, and regional anesthesia.
- Non-pharmacological techniques are low-risk potentially valuable additions to pharmacological modalities and include acupuncture, music therapy, TENS, and hypnosis.

- Future directions in postoperative analgesia for enhanced recovery include long-acting local anesthetics as well as opioid rescue using novel patient-controlled delivery techniques such as iontophoretic transdermal delivery of fentanyl and transmucosal sufentanil microtablets.
- A key challenge in multimodal ERAS-related pain research is the difficulty in carrying out randomized trials to determine the relative importance of any one component, including analgesia. Furthermore, despite the ever expanding availability of multimodal analgesic methods, postoperative pain in general continues to be undermanaged.

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