

Opioid sparing strategies for perioperative pain management other than regional anaesthesia: A narrative review

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Abstract

Opioids play a crucial role in pain management in spite of causing increased hospital morbidity and related costs. It may also cause significant risks such as postoperative nausea and vomiting (PONV), sedation, sleep disturbances, urinary retention and respiratory depression (commonly referred to as opioid related adverse effects) in postoperative patients. In order to evade these opioid related side effects and also improve pain management, multimodal analgesia i.e., combination of different analgesics, was introduced more than a decade ago. Both pharmacological and non-pharmacological techniques are available as opioid sparing analgesia. Research from around the world have proved pharmacological techniques ranging from acetaminophen, NSAIDs (non-steroidal anti-inflammatory drugs), N-methyl-D-aspartate receptor antagonists (NDMA), alpha-2 agonists, anticonvulsants such as gamma aminobutyric acid analogues, beta-blockers, capsaicin, lignocaine infusion to glucocorticoids to be effective. On the other hand, non-pharmacological methods include techniques such as cognitive behavioral therapy, transcutaneous electrical nerve stimulation (TENS), electroanalgesia, acupuncture and hypnosis. However, research regarding the effect of these non-pharmacological techniques on pain management is still needed.

Keywords: Acupuncture, cognitive behavioral therapy, enhanced recovery after surgery, multimodal analgesia, non pharmacological therapies, opioid sparing strategies, pharmacological techniques, postoperative pain

Introduction

Acute postoperative pain is experienced by 80-86% patients, of whom less than half report adequate analgesia. Moderate to extreme pain is experienced by nearly 70-75% of them after surgery and in 60-74% during the first two weeks following hospital discharge.^[1,2]

Although opioids are the pillars of perioperative pain management, their use can result in a myriad of perioperative side effects. The exaggerated drawbacks viz. adverse

events following the long-term administration of opioids has emphasized on the usage of opioid-sparing multimodal management of pain.

Methods

Medical search engines: PubMed, Medline, Ovid, Embase, Cochrane database were searched for literature relating to non-opioid drugs, non-pharmacological therapies and strategies for management of pain other than regional anaesthesia. Reviews, meta analyses, and randomized clinical trials were included. Authors found 118 articles through

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search strategies. A total of 78 articles were included based on inclusion criteria.

Opioid Induced Adverse Effects

Postoperative patients are at a substantial risk for developing adverse effects of opioid administration. These side effects include postoperative nausea and vomiting, sleep disturbances, urinary retention, respiratory depression.^[3,4]

Other commonly reported side-effects of opioid use include somnolence, dizziness, delayed emergence, tolerance by desensitization, short duration of central muscle stiffness, reduced cardiac output, coma and death. Another concerned side effect with opioid is Opioid-induced hyperalgesia (OIH). Potent opioids can also cause acute tolerance increasing postoperative pain paradoxically.^[5]

The last decade has shown a paralleled increase in opioid prescription rates and opioid overdose deaths.^[6,7] A similar increase is seen in events of nonfatal overdose by 50% over 10 years and majority of these events have occurred in non-chronic users.^[8-10] A retrospective study by Brat et al quantified a strong relationship between number and duration of prescription opioid refills and subsequent misuse in the post-surgical period for acute pain management. Authors reported a 44% increase in misuse with every refill and 20% increase for each week of prescription.^[11] A chronic perioperative use of opioids is associated with poor postoperative outcome.

Opioid Sparing Strategies

Multimodal analgesia (“balanced analgesia”) works by using array of techniques and/or drugs having different sites/mechanisms of action in order to minimize opioid-related adverse effects. This can be achieved by combining different analgesics and thereby achieve a high benefit-to-risk ratio. These regimens should be taken into consideration keeping in mind the presence of any pre-existing medical conditions, type of surgery done, and effects as well as side effects of medicines to be administered postoperatively and the patients’ previous response to analgesic drugs in the management of acute pain.^[12]

Multimodal approach utilizes the technique of using varied drugs acting on different receptors and hence provides opioid sparing analgesia and subsequent decrease in accompanying side effects. These techniques involve pharmacological and non-pharmacological means.^[13]

Pharmacological Techniques

Non-opioid and adjuvant analgesia play a definite role in management of perioperative pain. These drugs modify changes in the nociceptive systems that usually occur as a consequence of tissue injury.

The non-opioid analgesic group includes acetaminophen, NSAIDs and coxibs. Drugs such as NMDA receptor antagonists like ketamine & magnesium, anticonvulsants such as gabapentinoids, membrane stabilizers like lidocaine and alpha-2-agonists (e.g. clonidine and dexmedetomidine) are also included in adjuvant category.

1. Acetaminophen/Paracetamol

This drug is the first line of treatment. It is used alone for mild to moderate pain in the elderly. Its use with NSAIDs decreases the opioids requirement by 20%.^[14] The maximum recommended safe dosage over 24 hours is 4 gm in adults including healthy older adults and 2-3 gm in frail elderly due to their increased risk for hepatotoxicity.^[15] Onset of action of intravenous administration of drug is 5 minutes and peak plasma concentrations are attained within 15 minutes.^[14,16,17] Dose dependent hepatic necrosis has been reported as the most serious effect of acute overdose of acetaminophen.

2. Non-steroidal anti-inflammatory drug (NSAIDs)

These are one of the most frequently used drugs in pain management. NSAIDs inhibit prostaglandin synthesis both at peripheral and central sites by inhibiting cyclo-oxygenase (COX) isoenzymes. Intravenous formulations of NSAIDs are a standard part of multimodal analgesia and play a significant role in decreasing opioid requirements in patients with moderate to severe postoperative pain.^[18,19,20]

Ketorolac

It is an NSAID, which acts on COX-1 receptors, with analgesic properties. It can also be used for pre-emptive analgesia. The dose is 30 mg intravenous over what duration over 24 hours and it decreases the narcotic consumption via 25-45%.^[21,22,23]

Martinez et al in 2019 conducted a literature review to assess the utility of using NSAIDs as opioid sparing analgesics, authors included 32 studies. Majority of studies reported either pain reduction or similar pain scores in comparison with placebo. Authors concluded NSAIDs have a potential to reduce post surgical consumption of opioids.^[24]

In 2017, Martinez et al conducted a systematic review and meta-analysis for efficacy and safety of use of non opioid

analgesics in adult patients after major surgery. Authors compared analgesics other than morphine (AOM) with placebo or another AOM after major surgery and receiving morphine patient controlled analgesia and assessed morphine consumption, pain and adverse effects. Authors included 135 trials and concluded a combination of acetaminophen with either an NSAID or nefopam was superior in terms of pain control and reduction in morphine consumption.^[25]

3. N-methyl D Aspartate (NMDA) Receptor Antagonists

NMDA are ionotropic receptors that transfer electrical signals from the brain to the spinal cord. Increased sensitivity of these receptors causes hyperalgesia and neuropathic pain that often lead to heightened level of pain.^[26]

Ketamine

It acts by non-competitively inhibiting the NMDA receptor. The use of ketamine in the control of perioperative pain and hyperalgesia has been reported in many studies. A systematic review of 70 studies concluded that intravenous (IV) ketamine reduced postoperative opioid consumption and delayed use of first dose of opioid required in the postoperative period.^[27] However, its use is often limited owing to the accompanying dose-dependent neuropsychiatric side effects. These often include vivid dreams, nightmares, hallucinations and dysphoria.

Dextromethorphan

Dextromethorphan, an antitussive is a non-competitive NMDA receptor antagonist and D-isomer of levorphanol, codeine analog. It is beneficial in reduction of perioperative pain as well as opioid consumption.^[28] A recent meta-analysis of 21 RCTs concluded that perioperative dextromethorphan reduced pain at 1, 4, 6, and 24 hours post surgery and also decreased opioid consumption postoperatively at 24-48 hours. Side effects commonly observed were drowsiness, unsteadiness, blurry vision, slow breathing, nausea/vomiting and difficult urination.^[28]

Magnesium

It is non-competitive NMDA receptor inhibitor, available in different formulations such as intravenous, intramuscular, and oral. A systematic review by Albrecht *et al.* reported the use of IV magnesium to reduce consumption of morphine by 25% at 24 hours after surgery.^[29]

Although, there is lack of sufficient evidence on the use of magnesium in management of perioperative pain and chronic post-surgical pain, there is sufficient evidence that account the effect of co-administration of ketamine and magnesium in prolonging analgesia than either of the drug

used alone.^[30] The recommended adult dose for magnesium is 200 to 400 mg.

4. Anticonvulsants

Gabapentin

Use of gabapentin for perioperative pain management is an off-label use and dosages used are from 300-1200 mg in clinical studies. A meta-analysis concluded preoperative gabapentin reduces postoperative pain scores, opioids consumption, nausea and vomiting after abdominal hysterectomy.^[31] Also, another meta-analysis reported reduction in pain score and opioid administration following use of gabapentin in total hip arthroplasty.^[32]

Pregabalin

Use of pregabalin for perioperative pain management is also an off-label use and dosages used are from 75-600 mg in clinical studies. It is evidenced that perioperative pregabalin of 75-150 mg decreases anxiety preoperatively, postoperative pain, opioid requirement and improves sleep quality.^[33,34] In laparoscopic cholecystectomy, 600 mg of preemptive pregabalin has been reported to significantly reduce postoperative pain and opioid consumption. However, an increased incidence of dizziness was also reported.^[35]

Guidelines on postoperative pain management suggest a weak recommendation for use of gabapentin and pregabalin as it decreases opioid requirement and decreases post-operative pain scores.

5. Steroids

Glucocorticoids

Corticosteroids have anti-inflammatory and immunosuppressive properties, which make them useful in pain management. Corticosteroids act at the cellular level leading to changes in gene expression. Inhibition of phospholipase, lymphocytic alterations, inhibition of expression of cytokines and cellular membrane stabilization explain the anti inflammatory effects.^[36]

Current literature suggests that a preemptive dose of 4 mg dexamethasone at induction is helpful in preventing PONV. At 8 mg, it provides additional opioid-sparing effect as well as hastens recovery without any postoperative complications like wound separation, dehiscence and infection.^[37]

6. Alpha-2 agonists

Clonidine

This alpha-2 agonist, popularly used as an antihypertensive, also has a role to play as an adjuvant for multimodal analgesia. It reduces opioid consumption, causes anxiolysis as well as reduces nausea and postoperative shivering. A meta-analysis reported that administration of 2 to 5 micro-grams of clonidine per kg

reduces dosage of morphine by 25%.^[38] However, a POISE-2 trial concluded, in a dose of 0.2 mg orally given preoperatively followed by transdermal patch of 0.2 mg for 72 hours did not show any reduction in pain or opioid requirement in patients undertaking non-cardiac surgery.^[39] These contradictory results can be attributed to the dosage or the route of administration of the drug under study. The hemodynamic effect of clonidine needs to be taken into consideration when administered for postoperative pain management.

Dexmedetomidine

It has a similar mechanism of action as clonidine. However, the affinity for alpha-2 receptor is about 7 to 8 times higher than clonidine, with an approximate ratio of 1600:1.^[40] Intraoperative administration of dexmedetomidine tends to reduce pain postoperatively and also has opioid-sparing effect.^[41] Systematic review has reported the effect of dexmedetomidine on opioid sparing. The mean postoperative morphine sparing with dexmedetomidine was reported to be 14.5 mg.^[38] Another study reported reduction in opioid consumption as well as prolonged analgesia of inter-scalene nerve blocks with perineural as well as IV formulations.^[42]

7. Lidocaine infusion

It is evidenced that intravenous lidocaine is beneficial in reduction of pain scores as well as opioid consumption post operatively. A meta-analysis of RCTs showed reduction in acute postoperative pain (at 6 hours) at rest, with cough and with movement as a result of intravenous lidocaine infusion.^[43] The effects of lidocaine on reduction in opioid consumption as well as the accompanying side effects were also reported.

8. Tapentadol

It is a potent centrally acting analgesic with opioid sparing properties, with a dual mechanism of action on both mu opioid receptors and noradrenaline reuptake inhibitor.^[44] Analgesic effects result due to action on mu receptors and increased noradrenaline release which leads to activation of inhibitory alpha 2 receptors. Maximum dosage recommended is 600-700 mg in divided doses 4-6 hourly. It is indicated in moderate to severe acute pain, chronic and neuropathic pain. This dual mechanism of action and lower affinity for mu receptors compared to traditional opioids results in lesser side effects with no or mild withdrawal symptoms and better compliance.^[45]

9. Surgical site infiltration

Opioid sparing infiltrative strategies

Infiltration of surgical sites with local anaesthetics has shown to reduce the post-operative opioid needs and accompanying side effects.^[46] There is also sufficient evidence to support reduction of pain and opioid consumption as a result of

analgesic infiltration in arthroscopic and knee replacement surgeries. However, there is insufficient evidence with regards to length of hospital stay and time to discharge.^[47,48]

Future directions in opioid sparing Infiltrative strategies: With respect to future directions, in view of the infiltration strategies, various long-acting local anaesthetic formulations hold a positive effect in terms of prolonging analgesia. These include:

Liposomal bupivacaine

This local infiltration formulation of bupivacaine was approved by FDA in 2011. This anaesthetic formulation prolongs analgesia and favors early discharge from hospital.

Six phase IV prospective cohort studies reported decreased opioid consumption postoperatively, length of hospital stay and opioid-associated side effects after laparoscopic colectomy following administration of liposomal bupivacaine intraoperatively (266 mg) as compared to Patient controlled analgesia (morphine or hydromorphone).^[49] Moreover, one study reported reduced opioid consumption in the postoperative phase [38 (46) mg vs 68 (47) mg] and reduced length of hospital stay (0.8 days, 21% reduction) as well as total hospitalization costs (\$6,611 USD vs \$6,790 USD) in ileostomy reversal following the use of 266 mg liposomal bupivacaine intraoperatively.^[50] Still there is a need to establish evidence related to safety and efficacy of liposomal bupivacaine in comparison to conservative bupivacaine.^[51]

SABER- Bupivacaine

Yet another formulation of bupivacaine, which consists of 12% bupivacaine in a matrix of sucrose acetate isobutyrate. It is used as an infiltration and provides analgesia for duration of 72 hours. However, its FDA approval is still awaited. An RCT on open inguinal hernia repair reported significant reduction in acute postoperative pain with local infiltration of 5 mL SABER-Bupivacaine compared with placebo. This formulation is also reported to reduce supplemental opioid consumption by 26%.^[52]

Lidocaine patch

Available as a transdermal patch of 10 X 14 cm with 700 mg lidocaine.^[53] Its mechanism of action is by blocking sodium channels.^[54] However, there is only limited evidence regarding the benefit of 5% lidocaine patch in acute postoperative pain.^[55-58] This corroborates with the findings of a meta-analysis, which suggest this patch not to be effective as an adjunct for postoperative pain management.

10. Newer pharmacological therapies

Newer drugs, which act at molecular level, are being developed and undergoing animal trials.

Soluble epoxide hydrolase (sEH) inhibitor

Epoxyeicosatrienoic acids (EETs), which are arachidonic acid epoxides and other fatty acid epoxides, are anti-inflammatory mediators, which are released during any tissue injury or trauma. They act by decreasing the nuclear translocation of NF- κ B and are metabolized via sEH enzyme. The inhibitors of sEH have been evaluated in rodent models and have been proposed to stabilize the anti-inflammatory action of EETs. These have been shown to reduce inflammatory pain and also have been evaluated in neuropathic pain models.^[59]

Decoy molecules (ribonucleic acid-based therapy)

These molecules are genetically framed to interrupt the pain protein synthesis and lead to reduced inflammation, hence showing promising results in the future of opioid free pain control.^[60]

Non-Pharmacological Techniques

This group includes pre-operative education and planning, cognitive behavioral therapy (CBT), music therapy, electro analgesia, acupuncture, hypnosis and laser therapy. There is mixed evidence regarding the efficacy of such techniques.

Preoperative education and perioperative pain management planning

Guidelines on post-operative pain management by Chou *et al.* reflect, that educating the patient about pain and appropriate perioperative pain management planning has an important role in reducing preoperative anxiety and also associated with less opioid consumption and fewer requirement for sedative medications. Hence an individualized tailored programme should be created for patient education.^[61]

Cognitive behavioral therapy

Use of cognitive behavioral therapy (CBT) can be considered as a part of multimodal approach (weak recommendation). It should be combined with pharmacological treatment. Pain and anxiety go hand in hand, and run in a vicious cycle, hence reducing anxiety reduces pain. CBT can help in alleviating pain.^[61]

1. Use of relaxation techniques
2. Music therapy
3. Intraoperative patient suggestions
4. Hypnosis
5. Guided Imagery.

Acupuncture

Literature supports the role of acupuncture as a part and parcel of multimodal postoperative opioid sparing analgesia.^[62] However, there is divided opinion regarding its efficacy.^[63] Moreover, there is clinical heterogeneity among studies i.e., few

studies potentiate the use of penetrating needles as sham intervention for pain reduction. Whereas, few RCTs have shown the effect of electro-acupuncture (addition of electric current to conventional acupuncture) along with multimodal regimen (tramadol and ketamine) in reduction of postoperative analgesic requirements at 45 min and lower cortisol levels in prostatectomy.^[64] The pathway of action is unclear, but it is postulated to be the effect of gate control theory and release of endogenous opioids.

Music therapy

Music therapy decreases pain through attention shift or cognitive coping.^[65] Literature search reveals fewer studies depicting the role of music therapy on pain scores. In patients undergoing trans-rectal prostate biopsy, music with noise-cancelling headphones was correlated with lesser pain scores as compared to use of noise-cancelling headphones alone.^[66] A systemic review and meta-analysis by Hole *et al.* assessed the role of music in post-operative units after surgery. The analysis involved 73 randomized controlled studies with 20-458 patients. Authors reported music decreased post-operative pain (SMD-0.77 95% CI (-0.99 to -0.56)), anxiety (-0.68 (-0.54 to -0.20)) and increased patient satisfaction scores. Music therapy was found to be efficacious even in patients undergoing surgery under general anaesthesia.^[67] However, still research is required to establish concrete evidence on the type and length of music therapy essential for opioid sparing.

Electro analgesia

EA is a form of neuromodulation therapy for reducing pain, available as electroacupuncture, ultrasound guided acupotomy and percutaneous/transcutaneous/peripheral electrical nerve stimulation.

EA has been used for chronic pain management, whilst its use for acute pain management is still underway. Zhang *et al.* reported that use of pre-operative EA in elderly patients undergoing spine surgery not only decreased the intraoperative anaesthetic and analgesic requirements but also lead to reduction of inflammatory mediators and post-operative cognitive dysfunction.^[68]

Transcutaneous electrical nerve stimulation

Although there is restricted evidence, but few studies advocate the benefit of TENS on reduction of acute postoperative pain.^[69-71] TENS is an additional therapy in patients who show less response to conventional analgesics. However, still more research needs to be done in this regard.

Clinical Hypnosis

Clinical Hypnosis is an adjunct to reduce pain. The effect of hypnosis on reduced usage of propofol and lidocaine was

accounted in an RCT on breast cancer surgery patients. Decreased pain, nausea, fatigue and discomfort were also reported.^[72] There is evidence that supports clinical hypnosis to decrease pain after pediatric and adolescent surgeries as well as after techniques like bone marrow aspiration.^[73]

Virtual reality (VR) technology

Virtual assisted distraction or virtual reality technology creates a computer simulated 3 D environment which acts as a source of from pain. Its role has been evaluated in burns wound care and reduced opioid requirement by 39%.^[74,75]

Laser therapy

A rather new modality in the field of medicine, it was FDA approved in 2002. The cellular chromophores are the receptor site for action; also, the action occurs through mitochondria leading to increased ATP production, modulation of reactive oxygen species, and induction of transcription factors. All these lead to increased cell proliferation and migration of fibroblasts leading to decreased production of cytokines, inflammatory mediators, increased tissue oxygenation and hence decreasing pain, inflammation and improved wound healing.^[76,77] Low level laser therapy has been used for acute pain management following oral (dental) surgeries, but its role in other surgeries needs to be determined.^[78]

Conclusion

With advancement in medical science, multimodal analgesia is the key strategy for effective pain management with the additional benefit of minimizing the side effects caused by opioids. These strategies are evidenced to accelerate recovery and discharge after surgery.

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Conflicts of interest

There are no conflicts of interest.

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