INTRODUCTION

Postoperative pain after surgery requires prompt and efficient treatment. Planning postoperative therapy with postoperative pain management at the forefront is becoming the norm for care after surgical operations. Doctors have traditionally prescribed opioids for postoperative pain. This thinking contributed to overprescription, worsening the US drug crisis (Deshler et al., 2023). Due to its side effects and misuse potential, low-dose or nonopioid analgesia is being considered. Improved recovery after surgery (ERAS) procedures seems promising (Bisch et al., 2021). ERAS promotes multimodal analgesia to reduce opioid consumption and side effects. Up to 9.5 million Americans aged 12 and older abused opioids in 2020, highlighting the urgent need for alternative pain management strategies.
2020. This represents 3.4% of Americans (Murphy, 2020). It included 9.3 million prescription painkiller abusers and 902,000 heroin users. At least 8.6 million people abused solely prescribed painkillers. The remaining (667,000) utilized heroin and prescription painkillers (Auty & Griffith, 2022). The opioid pandemic affects millions of Americans’ physical and mental health. It also causes national and private financial obligations. The US spent $786.8 billion in 2018. Premature death costs $603.2 billion, health care $89.1 billion, lost productivity $64.6 billion, and criminal punishment $29.9 billion. US taxpayers spent $93 billion on criminal justice and health care (Murphy, 2020).

More effective multimodal analgesia reduces opioid consumption and side effects than single modality (Martins et al., 2023). Opioids lose their analgesic efficacy, requiring greater dosages and raising the risk of addiction, overdose, and respiratory depression, which may kill (Volkow et al., 2019). Opioids have been used for years to reduce hypnotic usage and provide excellent analgesia. However, these medicines may cause nausea, vomiting, constipation, urine retention, as well as reduced pain relief if the patient is active, delayed postoperative rehabilitation, and paradoxical hyperalgesia. Opioids may also produce acute and chronic pain and immunomodulate the body, which affects infectious and malignant disorders and raises questions concerning neurotoxicity (Beloel, 2019). Many people administered opioids for acute pain, particularly postoperative discomfort, abused the medications on the black market, according to studies. Prescriptions were implicated in perioperative and chronic pain therapy. All these factors explain the decrease in opioid use postoperatively and during anesthesia.

To achieve nonopioid or low postoperative analgesia, ERAS protocols provide a viable approach. But adding ERAS to surgical procedure has other purposes as well. The ERAS Society states that these “care pathways include evidence-based items intended to alleviate perioperative stress, preserve physiological function following surgery, and expedite postoperative recovery.” (Gustafsson et al., 2019). During colorectal surgery, these procedures are most often used. Due to its success in this area, ERAS procedures have gained credibility in other surgical specialties and are becoming more widely used (Cavallaro & Bordeianou, 2019).

Concerning preoperative and postoperative treatment, it is critical to comprehend the requirements of ERAS procedures. Preanesthetic medicine including paracetamol, a nonsteroidal anti-inflammatory drug (NSAID), and gabapentinoids, with dosages tailored to age and renal function, is highly recommended by the ERAS Society for patients undergoing these procedures. Research have shown that using gabapentin or pregabalin before to surgery is linked to a reduction in postoperative pain and, as a result, use of opioids. It is critical to recognize that these medications come with a higher risk of drowsiness, vertigo, and visual impairments (J. K. Brown et al., 2018). The aim to limit opioid usage should start as soon as the patient arrives, notwithstanding the continued prescription for premedication.

The use of many analgesics with various sites of action or mechanisms of action is known as multimodal analgesia. It is a tactic that lowers the use and prescription of opioids by using non-opioid analgesics and local, regional, and/or topical analgesic procedures that have distinct modes of action and spare opioids (Martins et al., 2023). Because of the cumulative and synergistic effects of many low-dose analgesics and peripheral blocking approaches, multimodal analgesia, also known as balanced analgesia, has evolved as a means of effectively controlling postoperative pain while minimizing its side effects. The goal of the current research was to characterize the advantages of multimodal analgesia in the management of postoperative pain while also outlining the most often prescribed medications.

**METHODS**

For this literature review, a systematic search of relevant articles was conducted using electronic databases such as PubMed, Google Scholar, and Scopus. The search strategy included keywords such as “multimodal analgesia,” “postoperative pain management,” “opoid sparing,” “ERAS protocols,” “non-opioid analgesics,” “local anesthesia,” and “regional anesthesia.” The search was limited to articles published in English and within the last five years.

The initial search yielded a large number of articles, which were then screened based on their titles and abstracts to assess their relevance to the topic of multimodal analgesia and its agents. Full-text articles were retrieved for further evaluation if they were deemed potentially relevant.

The inclusion criteria for articles were studies that focused on multimodal analgesia techniques and their efficacy in postoperative pain management, studies investigating the use of specific non-opioid analgesics, local anesthetics, and regional anesthesia techniques, as well as reviews and meta-analyses summarizing the current evidence on multimodal analgesia.

Studies that examined pain in non-adult patients, case studies, studies with fewer than ten patients, and studies that just focused on the use of opioids without demonstrating the value of multimodal analgesia were all removed from our...
RESULTS AND DISCUSSION

Multimodal anesthesia theory and its agents:

The nociceptive system includes nociceptors, ascending and descending routes. The spinal cord's dorsal horn cell bodies transmit one axonal process to the periphery and another to the spinal cord or brainstem. The ascending lives send peripheral sensations to the spinal cord, brainstem (medulla and midbrain), amygdala, thalamus, and main and secondary sensory cortices. The nociception pathways rise and fall (E. N. Brown et al., 2018).

Because ascending and descending routes have various neurotransmitters and mediating neuronal connections, antinociceptive drugs may target numerous targets to block nociceptive information processing. A multimodal technique for nociceptive control and multimodal general anesthetics includes addressing numerous nociceptive system targets simultaneously (Martins et al., 2023). Antinociceptive drugs reduce excitement because excitatory and nociceptive pathways are linked.

This method lists medicines that openly and implicitly sustain each of general anesthesia's primary behavioral states. Remifentanil maintains antinociception but induces unconsciousness due to its sedative properties. This strategy focuses on controlling nociception by using mechanically distinct agents in maintenance anesthetics, taking advantage of the fact that each anesthetic has an explicit and implicit effect on pharmacological combinations, especially the effect of antinociceptive agents on unconsciousness, and making multimodal pain control a fundamental goal in the postoperative period (E. N. Brown et al., 2018).

Opioids may be used with other antinociceptives during general anesthesia to maintain antinociception. Using several antinociceptives with an opioid causes the opioid-sparing effect. Each drug targets a distinct nociceptive system component to decrease transmission more effectively. Hypnotics diminish pain perception and contribute to antinociception (E. N. Brown et al., 2018). General anesthesia uses one titratable drug, such as propofol or sevoflurane, to maintain unconsciousness. Antinociceptive drugs disrupt nociceptive stimulation, causing deep unconsciousness. Since each antinociceptive diminishes alertness, its combination considerably reduces the hypnotic dosage required to sustain unconsciousness. To preserve amnesia, a patient must remain really unconscious, not only insensitive (E. N. Brown et al., 2018). Immobility may be maintained with one nicotinic anticholinergic drug. GABAergic hypnotics alleviate muscular tension by inhibiting H motor neurons in the spinal cord. As part of an antinociceptive regimen, magnesium relaxed muscles substantially. In this situation, lower muscle relaxant dose.

Non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 specific inhibitors (COX 2):

Since they prevent tissue inflammation and peripheral prostaglandin generation, NSAIDs and COX-2-specific inhibitors are helpful adjuncts to multimodal analgesia. They also considerably reduce peripheral sensitization, which is one of the main causes of postoperative pain. Celecoxib is used for all surgical operations; randomized controlled studies and their meta-analyses have shown that this lowers pain ratings and opiate use, speeds up the recovery of bowel function, allows patients to resume regular daily activities, and increases patient satisfaction. The COX-2 selective inhibitors are more effective than nonselective NSAIDs in decreasing other opioid-related adverse events, although they are equally effective in lowering postoperative nausea and vomiting owing to omission or opioid-sparing effects (Moore et al., 2015). Even with short-term usage, the incidence of stomach ulcers in high-risk individuals was much lower than that with nonselective NSAIDs and comparable to placebo. Compared to nonselective drugs, COX-2 selective inhibitors have a more favorable side effect profile. In individuals with NSAID-exacerbated respiratory illness, coifs do not induce bronchospasm. Compared to nonselective NSAID medications, COXibs do not block platelets and result in decreased bleeding after surgery (Walker et al., 2019). In a review of 10,6279 individuals having body and breast contouring surgeries, Kelley et al. found that 4,924 of them were given ketorolac. The results of multivariable regression analysis showed that ketorolac was not linked to hematoma, indicating that using NSAIDs had more advantages than disadvantages (Kelley et al., 2018). In conclusion, there is evidence to support the use of NSAIDs in individuals who are carefully chosen, despite the fact that the prevalence of hematoma development related to NSAIDs has been overestimated. Long-term use of celecoxib or short-term use of parecoxib did not correlate with cardiovascular complications of coxibs, which were detected with refecoxib (Nissen et al., 2016). Consequently, it is essential and advised to include nonselective and particularly selective COX-2 inhibitors into multimodal analgesia regimens prior to, during, and after surgery for a variety of reasons supported by data.

Acetaminophen

For a considerable amount of time, paracetamol has been a suitable option for perioperative analgesia during surgical operations. It has been shown to be effective in managing mild to moderate pain and has the potential to save
opioids. The central nervous system’s COX-mediated prostaglandin production is inhibited, and descending serotonergic pathways are activated, as the mechanism of action. Excellent safety profile applies to paracetamol. The most worrisome adverse effect is significant liver damage (above 4 grams per day). For this reason, it is advised that those with established liver illness refrain from using paracetamol. A recent meta-analysis found that for the majority of carefully chosen patients, there is no discernible benefit to parenteral vs oral dosing for postoperative pain with tramadol (Jibril et al., 2015). The 500–1000 mg oral dose regimens are often administered throughout the day. Because of the possibility of an acetaminophen overdose with such dosage schedule, it is advised against using acetaminophen-opioid combination formulations for breakthrough pain. Since NSAIDs and acetaminophen together have a greater impact than either substance alone, their combination may have an additive effect.

In order to effectively treat post-amputation pain in elderly patients with substantial comorbidities, De Jong and Shysh recommend using a multimodal analgesic approach. Their research highlights the difficulty in managing pain after lower limb amputations and the need for all-encompassing strategies that take into account various pain pathways. By addressing nociceptive and neuropathic pain processes at different levels, the protocol seeks to offer effective pain relief by the strategic administration of pharmaceutical drugs such as bupivacaine, paracetamol, gabapentin, NMDA antagonists like ketamine, and amitriptyline. Multimodal analgesia methods have the potential to benefit this vulnerable patient group by improving recovery and patient outcomes by addressing the complex nature of post-amputation pain (De Jong & Shysh, 2018).

In one research, the effects of planned caesarean sections on mother discomfort were compared. During the procedure, 12.5–15 mg of bupivacaine, along with 150–200 μg of morphine without preservative and 15–20 μg of fentanyl, were administered to each patient to induce spinal anesthesia (Forkin et al., 2022). Following surgery, the patients were sent to the mother-baby unit and subsequently the post-anesthetic recovery room (PACU). Upon arrival at the PACU, patients in the ERAC 1 (alternating administration group) were given an intravenous injection of 30 mg of ketorolac. These individuals were given 15 mg of intravenous ketorolac three hours after receiving 975 mg of oral paracetamol (with this set interval continuing for 24 hours). The patients were given paracetamol 975 mg every 8 hours and naproxen sodium 500 mg every 12 hours on the second postoperative day. Upon arrival to the PACU, patients in the ERAC 2 (combined administration group) were given 30 mg of intravenous ketorolac and 975 mg of oral acetaminophen. After six hours, the patients were given 15 mg of intravenous ketorolac and 975 mg of oral paracetamol every six hours. The patients were given 500 mg of naproxen sodium and 975 mg of mixed paracetamol orally every eight hours on the second postoperative day. Total postoperative opioid usage decreased as a consequence of the modified non-opioid analgesic regimen combining combination administration (ERAC 2) alternate administration (ERAC 1) of multimodal analgesia. When compared to the pre-ERAC group, the ERAC 2 group’s overall postoperative opioid consumption was also considerably lower (Forkin et al., 2022).

Dexamethasone

Through its anti-inflammatory properties, dexamethasone lessens surgical pain. It is also often used in anesthetic practice to minimize tiredness, enhance recovery, and avoid nausea and vomiting. Dexamethasone used as a multimodal adjunct has been shown in a 2013 meta-analysis to reduce pain ratings and opiate intake in postoperative patients. Although there may be risks associated with hyperglycemia and insulin treatment, systematic evaluations have shown that, with the exception of individuals with non-regulated diabetic mellitus, dexamethasone’s advantages exceed these risks. There is no evidence that the use of dexamethasone as one is associated with a higher risk of wound infection after surgery or wound healing issues (Polderman et al., 2019).

N-Methyl D-Aspartate receptor antagonists

Magnesium sulphate, memantine, and ketamine are among them. Through non-competitive binding and allosteric inhibition of the excitatory glutamate receptor site of the NMDA channel, ketamine affects nociception (Beverly et al., 2017). Ketamine has analgesic properties, lessens surgical pain, and lessens the need for opioids at lower levels than those used in anesthetics, which may cause a dissociative condition. Its regular usage in ERAS is not advised, nevertheless; patients with cardiovascular instability are the main users of it. At dosages below the anesthetic threshold, ketamine functions as a noncompetitive antagonist of the NMDA receptor. Since ketamine acts via a specific mechanism, its advantages are often seen in patients who have had large operations and are experiencing significant neuropathic pain (VAS >7/10), particularly after thoracic, upper abdominal, and major orthopedic procedures. It is crucial to remember that NMDA receptor antagonists, like ketamine, may prevent opioid-induced hyperalgesia in clinical settings, especially when used in conjunction with remifentanil (Kogler et al., 2023).

Research involving forty patients undergoing laparoscopic bariatric surgery, adjuvants like NSAIDs and dipyrone were used along with ketamine (0.1–0.3 mg/kg/h), lidocaine (1–1.5 mg/kg/h), magnesium sulphate (30 mg/kg, after induction), and clonidine (1 mcg/kg/h, after induction). Using an inhaled anesthetic (isoflurane or sevoflurane) with one MAC in combination with remifentanil in a continuous infusion pump (8IC) 0.04–0.25 mcg/kg/min, the patients received balanced general

anesthesia. Every patient employed appropriate decurarization and neuromuscular blockers. The anesthetic techniques were effective and could save opioids (0.5–0.7 mg/kg), which would preserve excellent postoperative analgesia (Rodrigues & Palotti, 2022).

120 patients scheduled for laparoscopic cholecystectomy were split into 3 groups for randomized controlled research (Toleska et al., 2022). Three groups were given intravenous infusions: one group got 0.5 mg/kg of ketamine, another group received 1.5 g/kg of magnesium sulphate, and a third group received 1 mg/kg of lidocaine and a continuous infusion of 2 mg/kg/h of lidocaine. Postoperative pain levels were greatest for patients in the lidocaine group while they were coughing and at rest, and lowest for those in the ketamine group. The magnesium group received less rescue analgesia whereas the lidocaine group received more. Patients in the lidocaine group got the lowest amount of fentanyl during surgery, whereas those in the magnesium group received the highest dose.

Gabapentinoids

Pregabalin and gabapentin can reduce secondary hyperalgesia brought on by central sensing in post-operative neuropathic pain. Both substances are significant parts of multimodal analgesia in this situation, according to evidence-based medicine (Mishriky et al., 2015). Evidence indicates that a solitary preoperative dosage lowered pain ratings, opioid use, and side effects. These medications’ anxiolytic and anticonvulsant properties are an added bonus (Kogler et al., 2023). The usefulness of perioperative gabapentin in assisting post-operative opioid discontinuation was shown in a large randomized controlled study that included a range of surgical procedures. The regimen consisted of 1,200 mg preoperatively and 600 mg three times day postoperatively (Hah et al., 2018). Gabapentin is helpful for burn patients because it may reduce opiate usage and burn-related pruritus (Kaul et al., 2018). Dizziness, sleepiness, and respiratory depression are among the adverse symptoms linked to gabapentinoids. Gabapentinoids should only be used in individuals who have a high risk of persistent neuropathic postoperative pain when basic analgesics are contraindicated due to these adverse effects. It is recommended that aged adults with major comorbidities, poor lung function, chronic obstructive pulmonary disease, or obstructive sleep apnea avoid or take their medication in smaller doses.

Giving local or regional analgesia either preoperatively or intraoperatively at the highest dose required, utilizing paracetamol and NSAIDs intraoperatively and continuing postoperatively, together with gabapentin, is the basis for the multimodal anesthesia option in plastic surgery. For the post-operative phase, cyclobenzaprine and oxycodone are recommended. These medications have shown improved analgesia and decreased opioid use, which is supported by the evidence-based approach to multimodal pain therapy in these kinds of surgeries (Schoenbrunner et al., 2022).

In order to evaluate the effect of a multimodal analgesia strategy on opioid usage among polytrauma patients, Singer et al. carried out a retrospective analysis (Singer et al., 2021). The research examined the differences in outcomes between a pre-cohort (before to protocol implementation) and a post-cohort (after protocol implementation), with the goal of lowering opioid usage during inpatient treatment and after release. The overall inpatient MME was found to have significantly decreased from 177.5 mg to 130 mg, while the daily inpatient MME was found to have decreased from 70.8 mg to 44.7 mg. Moreover, inpatient oxycodone dropped from 45 mg to 30 mg, and intravenous hydromorphone dropped from 2 mg in the pre-cohort to 1 mg in the post-cohort. Interestingly, in the post-cohort, gabapentin use rose from 0 mg to 400 mg. At the time of discharge, the post-cohort patients received fewer MME prescriptions than the pre-cohort patients, and the percentage of patients who received a gabapentin prescription rose from 6.1% to 16%. These results highlight how well multimodal analgesia regimens work to cut down on opioid use during hospital stays and point to a change in post-discharge towards non-opioid analgesics like gabapentin that will aid in the overall goal of lowering opioid use.

Local anesthetics:

As a standard of care in ordinary clinical practice of multimodal analgesia for a range of surgical procedures, the use of local and regional anesthesia is strongly advised (Gabriel & Ilfeld, 2018). Research indicates that the use of local anesthetics during practically all surgical operations reduces the need for opioids, lowers incidence of postoperative severe sequelae, lowers pain ratings, shortens hospital stays, and lowers healthcare costs (Rivedal et al., 2018)(Joshi et al., 2019).

The usage of anesthesiologist-only regional analgesic treatments (such as nerve blocks) has decreased recently (Soffin et al., 2019). Perineural methods are not used very often. Peripheral nerve blocks are underutilized for several causes, such as inadequate training, a lack of resources (such as ultrasound equipment), and single-injection blocks’ short duration.

Although continuous peripheral nerve blocks prolong analgesia, their use in clinical practice is restricted due to their technical difficulties and the need for specialized staff to administer them. Interfascial plane blocks, such as the transversus abdominis, serratus, quadratus lumborum, and erector spinae plane blocks, are being used more often, according to recent research (Elsharkawy et al., 2019).

These blocks are affordable, safe, effective, and simple to use technically. Furthermore, local infiltration analgesia, or
surgical site infiltration methods, are gaining popularity (Kim et al., 2018)(Pawa & El-Boghdady, 2018). The disadvantage of surgical site infiltration is that it requires a lot of local anaesthetic to be administered, while being less costly and simple to execute. Since wound catheter procedures are said to provide almost complete pain control after major thoracic and abdominal surgery, their usage is expanding quickly (Mungroo et al., 2019). The majority of local anesthetics have a short (8–12 hour) half-life that may be compensated for by using catheter infusion methods or extended-release local anaesthetic formulations such liposomal bupivacaine. In abdominal wall reconstruction, liposomal bupivacaine for transversus abdominis plane regional blockade is frequently utilized. It has been shown to reduce opioid use, shorten hospital stays, and improve pain scores compared to conventional catheter-based infusion methods without increasing the risk of wound complications (Roy et al., 2019).

To optimize the use of regional anesthesia in multimodal pain treatment methods, it is crucial for the surgeon to have a thorough understanding of anatomy and injection procedures, as well as to be part of a multidisciplinary team. Joshi et al. highlighted that surgeon expertise in intraoperative interfacial plane block administration and surgical site infiltration may address the chronic underutilization of peripheral nerve blocks (Joshi et al., 2019).

An investigation of the impact of multimodal analgesia on patients with gynecological cancer after radical resection was the aim of the research. 98 cervical cancer patients who received hospitalized laparoscopic radical resection were included in the research. Thus, multimodal analgesia was administered to 47 patients in the research group (RG) while standard postoperative analgesia was administered to 51 patients in the control group (CG). This research shown that, after laparoscopic radical excision of gynecological neoplasms, multimodal analgesia is both safe and beneficial for patients. This treatment is worthy of therapeutic use since it may enhance quality of life and hasten the healing process from the sickness. There are still several issues, nevertheless, such the short trial period, the lack of research on long-term follow-up, and the limited number of trials (Dong et al., 2021).

CONCLUSION

The literature review concludes by highlighting the vital role that multimodal anesthesia plays in improving the treatment of pain and recovery after surgery. Multimodal anesthesia provides a comprehensive approach to pain control while minimizing opioid use and its associated side effects by integrating a variety of agents and techniques, including local and regional anesthesia, adjunctive medications like dexamethasone and N-Methyl D-Aspartate receptor antagonists, and non-opioid analgesics. Research indicates that the use of multimodal anesthesia not only lowers the number of opioids used and postoperative pain, but also improves patient outcomes in a number of surgical specialties by promoting quicker healing and shorter hospital stays. Further optimizing perioperative care is the use of Enhanced Recovery After Surgery (ERAS) protocols, which emphasize the need of customized preoperative and postoperative therapies by integrating multimodal analgesia techniques. To improve surgical treatment and lessen the effects of the opioid crisis on patient health and healthcare systems, more research and practical use of multimodal anesthesia procedures are needed.

REFERENCES


Multimodal anesthesia: integrated strategies to improve pain management and recovery: a literature review


