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Effectiveness of Intravenous Multimodal Analgesic Combination in Postoperative Pain Management in Breast Cancer Patients Undergoing Mastectomy with General Anesthesia: Systematic Literature Review

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ABSTRACT

Post-mastectomy pain in breast cancer patients is a clinical problem that often has long-term effects, including the development of post-mastectomy pain syndrome (PMPS). The use of single opioids has limitations due to the risk of side effects and dependence, so intravenous multimodal analgesia approaches with various combinations of analgesic agents are increasingly being studied. This study aims to evaluate the effectiveness of multimodal intravenous analgesic combinations in controlling postoperative pain in breast cancer patients undergoing mastectomy with general anesthesia. A systematic review was conducted according to the PRISMA 2020 guidelines through searches in PubMed, Cochrane Library, ScienceDirect, and EBSCO for publications from 2005 to 2025. Articles that met the inclusion criteria were randomized controlled trials (RCTs) and cohort studies that assessed the effectiveness of multimodal intravenous analgesic combinations in mastectomy patients. The methodological quality was assessed using the Joanna Briggs Institute (JBI) instrument. A total of 11 studies involving more than 800 mastectomy patients were analyzed. The combination of pregabalin and esketamine was shown to significantly reduce the incidence of chronic pain up to 6 months post-surgery (14.3% and 7.1% vs. 46.3% and 31.7%; $p<0.01$), as well as reduce opioid consumption. Remifentanil–dexmedetomidine provided better analgesia while improving the patient's immunological profile. Ketamine-based anesthesia was more effective than opioids in reducing acute pain, while the combination of ketamine–magnesium sulfate was proven to be safe and opioid-sparing. The use of diclofenac reduced opioid consumption but increased the risk of bleeding, while intravenous lidocaine showed inconsistent results. The combination of multimodal intravenous analgesics is effective in optimizing pain control after mastectomy, reducing opioid consumption, and potentially preventing chronic pain. Adjusting the multimodal protocol according to the patient's profile is necessary to maximize benefits while minimizing the risk of side effects.

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INTRODUCTION

Breast cancer is one of the global health problems with the highest prevalence in women and is the leading cause of morbidity and mortality due to cancer. The 2021 Global Burden of Disease data reports more than 2.3 million new cases each year with nearly 700,000 breast cancer-related deaths worldwide (Deng et al., 2025).. In Indonesia, breast cancer ranks first with an incidence of 42.1 per 100,000 population and a mortality rate of 17 per 100,000 population (Maresa et al., 2023). The main treatment given to most patients is surgery in the form of mastectomy, which is often followed by other adjuvant therapies such as radiotherapy, chemotherapy, or targeted therapy (Nurmalasari & Allenidekania, 2023).

Although mastectomy is effective in controlling the disease, this procedure often causes significant postoperative pain. Studies report that approximately 67% of patients experience complications after mastectomy, including acute pain, limited arm mobility, and reduced quality of life (Nurmalasari & Allenidekania, 2023). Furthermore, 30–40% of patients are at risk of developing Post-Mastectomy Pain Syndrome (PMPS), which is chronic neuropathic pain that lasts more than three months after surgery (Cui et al., 2018). Uncontrolled pain can trigger physiological disorders such as hypertension, respiratory disorders, and delayed wound healing (Da et al., 2023). In addition, psychological effects such as anxiety, depression, and sleep disorders often accompany this condition, which overall reduces the quality of life of breast cancer patients (Wong & Tiwari, 2024)..

For decades, opioid-based therapy has been the primary approach to controlling post-mastectomy pain. However, the use of opioids is limited by serious side effects, including nausea, vomiting, sedation, respiratory distress, and the potential for dependence (Kaye et al., 2019). Alternatives such as NSAIDs or other analgesic monotherapies do offer additional benefits, but their use is not entirely capable of addressing the complexity of postoperative pain and may even pose the risk of other complications such as gastrointestinal bleeding (Abdallah & Bakeer, 2022). Thus, the conventional approach of monotherapy is considered suboptimal for achieving long-term pain control in post-mastectomy patients.

In recent years, the concept of multimodal analgesia has been increasingly used as a strategy to optimize pain control. This approach involves combining several drugs with different mechanisms of action administered simultaneously, with the aim of increasing the effectiveness of analgesia while reducing the total opioid requirement (opioid-sparing effect) (Schwenk & Mariano, 2018). A number of pharmacological agents have been studied in the context of intravenous multimodal therapy, including pregabalin, which targets neuropathic pain; ketamine or esketamine, which are NMDA antagonists capable of suppressing central sensitization; dexmedetomidine, which provides analgesic and immunomodulatory effects; and NSAIDs, which function to reduce the inflammatory response (Wang et al., 2023; Younus et al., 2022; Zhang et al., 2022). This combination is theoretically and empirically believed to produce superior pharmacological synergy compared to monotherapy.

Although preliminary evidence supports the effectiveness of intravenous multimodal analgesia, available studies remain fragmented, with variations in design, interventions, and reported outcomes (Bakr, 2015; Couceiro et al., 2015; López et al., 2021). There is no clear

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consensus on which combination is most effective in preventing acute and chronic pain after mastectomy. Therefore, a comprehensive systematic review is needed to summarize the current evidence, assess effectiveness, and compare various combinations of intravenous multimodal therapies that have been tested. In line with this, this study aims to evaluate the effectiveness of multimodal intravenous analgesic combinations in the management of post-mastectomy pain in breast cancer patients undergoing general anesthesia, with a focus on acute pain control, chronic pain prevention, opioid consumption reduction, and the safety profile of the intervention.

METHODS

This systematic review was prepared following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. A comprehensive literature search was conducted in the PubMed, Cochrane Library, ScienceDirect, and EBSCO electronic databases to identify relevant studies. The search range covered publications from January 2005 to January 2025. The keywords and Medical Subject Headings (MeSH) terms used included: “breast cancer” OR “breast neoplasm” OR “breast carcinoma” OR ‘mastectomy’ AND “multimodal analgesia” OR “intravenous analgesia” OR “IV analgesic” AND “postoperative pain” OR “pain management” OR “analgesic efficacy” AND “general anesthesia”. Boolean operators (AND/OR) were used to combine search terms. There were no language restrictions. In addition, the references of relevant articles were manually searched to ensure comprehensive coverage.

Eligibility Criteria

The included studies had a randomized controlled trial (RCT) or prospective/retrospective cohort study design, involving adult patients (≥18 years) with a diagnosis of breast cancer who underwent mastectomy under general anesthesia. The intervention reviewed was the use of intravenous multimodal analgesia, with or without adjuvant agents. The comparison group received intravenous analgesic monotherapy or other combinations. The primary outcomes analyzed included postoperative pain intensity, opioid consumption, chronic pain events, and side effects such as nausea, vomiting, and bleeding. Studies were excluded if they involved pediatric populations, did not use intravenous interventions, or did not report relevant results.

Study Selection

The selection process was conducted independently by two researchers through a review of titles and abstracts, followed by a review of the full text. Disagreements in selection were resolved through joint discussion or by involving a third researcher as a mediator.

Data Extraction and Risk of Bias Assessment

Data were extracted independently by two researchers using a standardized form. Data collected included author names, year of publication, country, study design, sample size, patient characteristics, analgesic interventions, comparison groups, and reported clinical outcomes. If multiple time points for outcome reporting were available, the final or most clinically relevant data were used. The methodological quality and risk of bias of each study

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were assessed using instruments from the Joanna Briggs Institute (JBI) according to the study design. Each study was categorized as having a low, moderate, or high risk of bias.

Study Selection Result

From the initial search, a total of 1,245 articles were obtained, consisting of 452 articles from PubMed, 215 articles from Cochrane Library, 318 articles from ScienceDirect, and 260 articles from EBSCO. After the deduplication process, 325 articles were identified as duplicates and removed, leaving 920 unique articles that were then further filtered based on title and abstract.

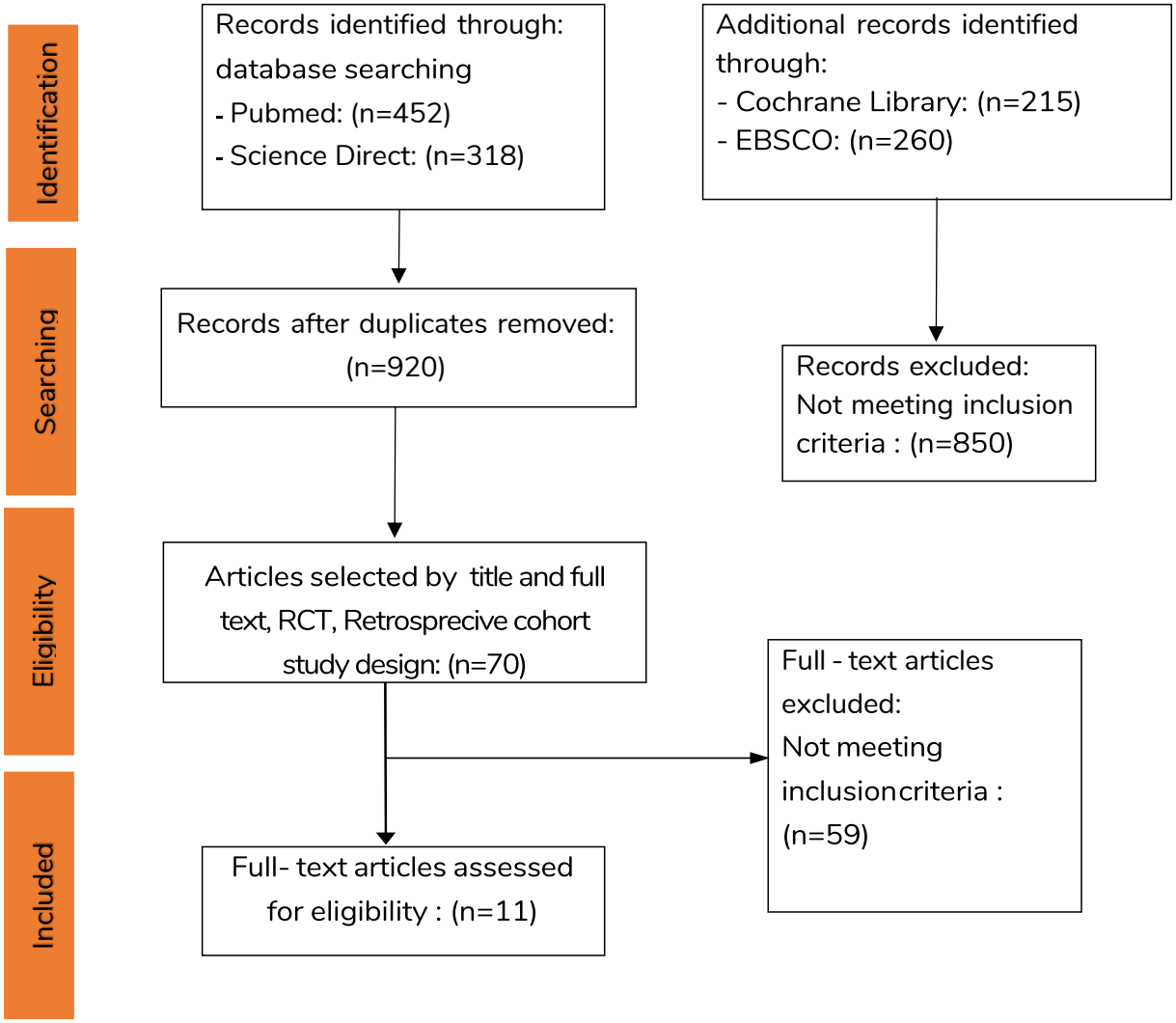

Figure 1. PRISMA Flow Diagram

During the title and abstract screening stage, 850 articles were eliminated because they were irrelevant to the research topic, for example, they did not involve breast cancer patients, did

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not use mastectomy procedures, or did not evaluate intravenous multimodal analgesia. Thus, 70 articles were selected for full text review.

From the full review, 59 articles were excluded because they did not meet the eligibility criteria, for reasons including the intervention used was not intravenous (n = 18), the study design was not an RCT or prospective cohort (n = 15), the population was not appropriate, such as pediatric or non-mastectomy studies (n = 14), and did not report outcome data relevant to this study (n = 12). After the final selection stage, a total of 11 studies that met the inclusion criteria were obtained and further analyzed in this systematic review.

Data Analysis

Data analysis was performed descriptively with narrative synthesis due to the heterogeneity of designs, types of interventions, and outcome measures in the included studies. Numerical data were presented as means, percentages, and risk ratios (RR) or mean differences (MD) when available. The level of methodological and clinical heterogeneity between studies was evaluated, and the results of similar studies were presented in summary tables to facilitate comparison.

RESULTS AND DISCUSSION

Table 1. Research Analysis

Title	Author's Name and Year of Publication	Research Methodology	Sample Size and Characteristics	Analgesic Interventions Used	Key Findings
Analgesic efficacy of intravenous morphine, tramadol and ketorolac on postoperative pain in patients undergoing modified radical mastectomy.	(Bakr, 2015)	RCT double-blind, 3 groups	60 ASA I–II patients, aged 20–60 years, MRM	IV Morphine 5 mg vs Tramadol 100 mg vs Ketorolac 60 mg	All three are effective; tramadol and ketorolac prolong the time to first analgesic request compared to morphine.
Remifentanyl combined with dexmedeto	(Zhang et al., 2022)	RCT, 80 patients, 2 groups	80 MRM breast cancer patients, divided into two	Remifentanil vs Remifentanil+Dexmedetomidine	Combination significantly reduces VAS and

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Title	Author's Name and Year of Publication	Research Methodology	Sample Size and Characteristics	Analgesic Interventions Used	Key Findings
midine on the analgesic effect of breast cancer patients undergoing modified radical mastectomy and the influence of perioperative T lymphocyte subsets.			groups (control vs. intervention)		improves immune status (CD4+ ↑, CD8+ ↓)
Prevention of acute postoperative pain in breast cancer : A comparison between opioids versus ketamine in the intraoperatory analgesia	(López et al., 2021)	Retrospective cohort study	71 patient (41 opioid group, 30 ketamine group)	Opioid-based anesthesia vs Ketamine-based anesthesia	Ketamine is more effective than opioids in reducing acute postoperative pain at all measurement times.
Intravenous lidocaine for postmastectomy pain treatment: randomized, blind, placebo	(Couceiro et al., 2015)	RCT, double-blind, placebo controlled	45 women, mastectomy, randomized lidocaine vs placebo	IV Lidocaine 3mg/kg vs placebo	There was no significant difference in pain or opioid consumptio

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Title	Author's Name and Year of Publication	Research Methodology	Sample Size and Characteristics	Analgesic Interventions Used	Key Findings
controlled clinical trial.					n between the groups.
Multimodal analgesia with thoraric paravertebral block decrease pain and side effects in mastectomy patients.	(Liu et al., 2025)	Retrospective review	60 women, aged 30–85 years, unilateral mastectomy ± SLNB	Nonintubated GA + TIVA + TPVB (MMA) vs konvensional GA	MMA significantly reduced pain scores and analgesic consumption; PONV was lower but not significantly so.
Analgesic efficacy of diclofenac in combination with morphine and paracetamol after mastectomy and immediate breast reconstruction.	(Legeby et al., 2005)	RCT, double-blind, placebo controlled	50 women, mastectomy + IBR with/without ALND	Diclofenac 50 mg x3 + Paracetamol + Opioid PCA vs Placebo + Paracetamol + Opioid PCA	Diclofenac reduced opioid consumption by 34% and reduced pain at rest during the first 20 hours; however, it significantly increased bleeding.
A randomized, controlled trial comparing acetaminophen plus ibuprofen versus acetaminop	(Mitchell et al., 2012)	RCT double-blind equivalence trial	141 patients (71 AcIBU, 70 T3), aged 18–70 years, outpatient lumpectomy/mastectomy	Acetaminophen+Ibuprofen vs Acetaminophen+Codeine+Caffeine	No difference in pain; more side effects with T3 (19% vs. 6%)

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Title	Author's Name and Year of Publication	Research Methodology	Sample Size and Characteristics	Analgesic Interventions Used	Key Findings
hen plus codeiin plus caffeine (tylenol 3) after outpatient breast cancer.					
Effect of magnesium sulfat with ketamine infusions on intraoperative and postoperative analgesia in cancer breast surgeries : a randomized double-blind	(Hassan & Mahran, 2023)	RCT, double-blind	90 patient mastektomi (Cairo University)	IV ketamine (0.5 mg/kg bolus + infusion of 0.12 mg/kg/hour) vs. ketamine + magnesium sulfate (8 mg/kg/hour)	The combination of ketamine + Mg reduces intraoperative morphine and fentanyl consumption, is safe, and is opioid-sparing.
Perioperative Administration of Pregabalin and Esketamine to Prevent Chronic Pain After Breast Cancer Surgery: A Randomized Controlled Trial	(Wang et al., 2023)	RCT, double-blind	90 breast cancer patients, aged 18–80 years old	100 μg sufentanil + 1.25 mg/kg esketamine + 4 mg tropisetron in 100 mL saline solution intravenously	The incidence of chronic pain at 3 and 6 months was lower in the combination group (14.3% and 7.1% vs 46.3% and 31.7%; $p<0.01$); reducing postoperative pain scores and

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Title	Author's Name and Year of Publication	Research Methodology	Sample Size and Characteristics	Analgesic Interventions Used	Key Findings
					opioid consumption.
A Multimodal Analgesic Protocol with Gabapentin-dexmedetomidine for Post-operative Pain Management after Modified Radical Mastectomy Surgery: A Randomized Placebo-Controlled Study	(Abdallah & Bakeer, 2022)	Prospective randomized, double-blind, placebo-controlled	30 adult women <65 years old	gabapentin 400 mg and IV infusion of dexmedetomidine 0.4 µg/kg/h over 10 min after a bolus of 0.5 µg/kg before induction of general anesthesia	The combination of gabapentin and dexmedetomidine significantly reduced postoperative pain scores for up to 24 hours (except after 18 hours), and intraoperative fentanyl and postoperative morphine consumption decreased significantly compared to the control group. Hemodynamic conditions were stable.
Synergistic effect of the association between	(Mendonça et al., 2020)	Randomised, double-blind,	120 women aged 18-70 years, divided into 4 groups	Infus lidokain 2 mg/kg bolus + 3 mg/kg/jam, magnesium sulfat 50 mg/kg bolus + 15	The combination of lidocaine and

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lidocaine and magnesium sulfate on peri-operative pain after mastectomy: A randomised, double-blind trial		parallel-group, non-inferiority clinical trial	(remifentanil, lidocaine, magnesium sulfate, combination of lidocaine + magnesium sulfate)	mg/kg/jam, dan kombinasi keduanya	magnesium sulfate significantly reduced intraoperative and postoperative opioid consumption compared to other groups; 24-hour postoperative pain scores were lower; PONV incidence was lower; side effects were minimal; and the duration of hospitalization was shorter in the lidocaine group.

Study Characteristics

A total of eleven studies published between 2005 and 2025 were identified and included in this review, involving more than eight hundred breast cancer patients who underwent mastectomy under general anesthesia. These studies consisted of randomized controlled trials (RCTs) and retrospective cohorts with varying sample sizes, ranging from 45 to 141 patients. The intravenous multimodal analgesia interventions studied included combinations of morphine, tramadol, and ketorolac; remifentanil with dexmedetomidine;

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ketamine with magnesium sulfate; pregabalin with esketamine; and intravenous lidocaine. Several studies also assessed the role of NSAIDs, particularly diclofenac, when combined with opioids and paracetamol. The outcomes evaluated mostly focused on acute postoperative pain intensity, opioid consumption, and the incidence of chronic pain up to six months after surgery. In addition, a number of studies reported additional aspects such as the incidence of postoperative nausea and vomiting, bleeding, immunological status, and the safety profile of each combination of therapies. The variation in study designs and interventions used reflects the diversity of multimodal analgesia strategies applied to patients after mastectomy.

Risk of Bias Assessment

Risk of bias assessment was performed using the Joanna Briggs Institute (JBI) instrument according to the design of each study. Most randomized clinical trials demonstrated good methodological quality and were assessed as having a low risk of bias. However, several retrospective cohort studies had limitations, particularly regarding the methods used to control for confounding factors, the transparency of the randomization process, and the reporting of results, which was not always consistent. Nevertheless, none of the studies were classified as having a high overall risk of bias. In general, the methodological quality of the included studies was considered adequate to provide a reliable synthesis of evidence regarding the effectiveness of intravenous multimodal analgesia in breast cancer patients after mastectomy.

Discussion

This systematic review confirms that the use of intravenous multimodal analgesic combinations provides significant benefits in the management of post-mastectomy pain in breast cancer patients. In general, the studies analyzed show that multimodal strategies are able to reduce acute pain intensity, decrease opioid consumption, and suppress the incidence of long-term chronic pain compared to conventional monotherapy.

Several studies support the effectiveness of combining opioids with non-opioid agents. A study Bakr (2015) reported that intravenous morphine, tramadol, and ketorolac were effective in controlling postoperative pain compared to single-agent use. Similarly, a study Legeby et al. (2005) showed that the combination of diclofenac with morphine and paracetamol provided better analgesia after mastectomy and reconstruction than opioid monotherapy. These findings are reinforced by Mitchell et al. (2012), who reported that the combination of ibuprofen and paracetamol is as effective, and even safer, than codeine in controlling pain after outpatient breast surgery.

In addition to NSAID-based combinations, a number of studies have explored other adjuvant agents with promising results. López et al. (2021) compared the use of ketamine with conventional opioids and found that intraoperative ketamine was able to significantly prevent acute pain. These findings are in line with Hassan & Mahran (2023), who showed that magnesium sulfate infusion with ketamine provided better analgesia and reduced opioid requirements during breast cancer surgery. Meanwhile, Couceiro et al. (2015) demonstrated that intravenous lidocaine effectively reduced post-mastectomy pain intensity, while also reducing the need for additional analgesics.

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Adjuvant agents with central effects have also been extensively studied. Research Zhang et al. (2022) reported that the combination of remifentanil and dexmedetomidine not only enhances analgesia but also contributes to immunological stability by maintaining T lymphocyte subsets during the perioperative period. Research Abdallah & Bakeer (2022) also found that a multimodal protocol combining gabapentin with dexmedetomidine effectively reduces postoperative pain and improves patient recovery quality. These findings are consistent with the report Schwenk & Mariano (2018) which emphasizes that the success of multimodal analgesia lies in the combination of agents with complementary mechanisms of action, thereby providing a synergistic effect in reducing pain.

The latest approach even targets the prevention of chronic pain. Research Wang et al. (2023) reports that perioperative administration of pregabalin and esketamine is not only effective in reducing acute pain, but also reduces the incidence of post-mastectomy pain syndrome (PMPS) for up to six months after surgery. Additionally, Liu et al. (2025) added a new dimension by combining intravenous multimodal analgesia with thoracic paravertebral blocks, which was shown to reduce pain while minimizing perioperative side effects, demonstrating the potential for integrating regional and systemic techniques in post-mastectomy pain management.

Overall, the existing evidence consistently supports the benefits of intravenous multimodal analgesia, although there remains significant variation in the protocols and pharmacological agents used. This heterogeneity reflects the lack of consensus on the optimal combination to be used in clinical practice. Nevertheless, the collective findings of these eleven studies confirm that multimodal strategies have superior potential compared to conventional monotherapy in controlling acute pain, preventing chronic pain, and reducing opioid consumption.

Limitation

Heterogeneity in the types of analgesic combinations, doses, timing of administration, and methods of pain assessment complicates direct comparisons between studies. In addition, there is no consensus on the most effective protocol, limiting the application of findings in clinical practice. Further large-scale studies with more standardized methodologies are needed to strengthen the evidence and formulate clearer guidelines.

CONCLUSION

This systematic review shows that a combination of intravenous multimodal analgesics is consistently more effective than monotherapy in controlling post-mastectomy pain in breast cancer patients. The multimodal approach has been shown to reduce acute pain intensity, decrease opioid requirements, and suppress the incidence of chronic pain, with an acceptable safety profile. The variety of agents used—ranging from opioids, NSAIDs, ketamine, lidocaine, pregabalin, to dexmedetomidine—shows synergistic potential through different mechanisms of action, although there is no consensus on the most optimal combination. Clinically, these findings support the implementation of an intravenous multimodal strategy as an integral part of the post-mastectomy pain management protocol. However, the heterogeneity of

interventions and study designs underscores the need for large-scale clinical trials with more standardized methodologies to determine the most effective and safe combinations. Therefore, further research is still required to establish evidence-based standards for multimodal analgesia protocols in breast cancer patients.

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