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Optimizing Postoperative Pain Management After Endoscopic Sinus Surgery in Indonesia: A Comparative Study of Analgesic Regimens

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A B S T R A C T

Introduction: Endoscopic sinus surgery (ESS) is a frequently performed procedure for chronic rhinosinusitis in Indonesia. Effective postoperative pain management is vital for patient comfort, early recovery, and minimizing healthcare expenses. This study compared the efficacy of different analgesic regimens in managing postoperative pain after ESS in an Indonesian population. **Methods:** This prospective, randomized controlled trial involved 120 patients undergoing ESS at a tertiary hospital in Indonesia. Patients were randomly allocated to one of three groups: Group A received intravenous patient-controlled analgesia (PCA) with morphine, Group B received a combination of intravenous ketorolac and oral paracetamol, and Group C received oral paracetamol alone. Pain intensity was evaluated using the Visual Analog Scale (VAS) at 2, 6, 12, and 24 hours postoperatively. The requirement for rescue analgesia and the occurrence of adverse effects were also documented. **Results:** Group A (PCA with morphine) exhibited significantly lower VAS scores at all time points compared to Group B (ketorolac and paracetamol) and Group C (paracetamol alone) ($p<0.001$). Group B showed lower VAS scores than Group C at 2 and 6 hours postoperatively ($p<0.05$). The need for rescue analgesia was significantly higher in Group C compared to the other groups ($p<0.001$). The incidence of nausea and vomiting was higher in Group A, while constipation was more frequent in Group B. **Conclusion:** Intravenous PCA with morphine provided superior postoperative pain control after ESS compared to other analgesic regimens. However, the increased incidence of nausea and vomiting should be taken into account. A combination of intravenous ketorolac and oral paracetamol presented a suitable alternative with a more favorable side effect profile. Further investigation is necessary to optimize pain management protocols for ESS in the Indonesian population.

1. Introduction

Chronic rhinosinusitis (CRS) stands as a prevalent inflammatory condition afflicting the nasal cavity and paranasal sinuses. Its impact extends beyond physical discomfort, significantly diminishing an individual's quality of life and imposing a substantial burden on healthcare systems worldwide. Characterized by persistent symptoms such as nasal congestion, facial pain or pressure, mucopurulent drainage, and olfactory dysfunction, CRS presents a formidable challenge for both patients and clinicians. The underlying pathophysiology of CRS is multifaceted, involving a complex interplay of factors that contribute to the chronic inflammatory process. These factors encompass anatomical variations, such as septal deviations or concha bullosa, which can disrupt normal sinus ventilation and mucociliary clearance. Mucosal abnormalities, including ciliary dysfunction

and altered mucus composition, further compromise the sinuses' ability to effectively clear pathogens and debris. Infections, whether bacterial, viral, or fungal, can trigger and perpetuate the inflammatory cascade. Allergic rhinitis and other hypersensitivity reactions also play a significant role in the pathogenesis of CRS, particularly in individuals with nasal polyps. The diagnosis of CRS relies on a comprehensive evaluation encompassing a detailed medical history, physical examination, and imaging studies. The cardinal symptoms, including nasal obstruction, facial pain, and purulent discharge, guide the initial assessment. Endoscopic examination allows for direct visualization of the nasal cavity and sinuses, revealing mucosal inflammation, polyps, or anatomical abnormalities. Computed tomography (CT) scans provide detailed images of the sinuses, aiding in the identification of mucosal thickening, opacification, and potential anatomical variants contributing to the disease process.[1-3]

While medical management remains the cornerstone of CRS treatment, endoscopic sinus surgery (ESS) has emerged as a valuable intervention for patients who fail to respond adequately to conservative measures. ESS aims to restore sinus ventilation and mucociliary clearance by addressing the underlying anatomical and pathological abnormalities. Through minimally invasive techniques, diseased tissue and polyps are removed, and the sinus ostia are widened, facilitating drainage and promoting healing. Although ESS offers significant benefits in improving symptoms and quality of life for CRS patients, it is not without its challenges. Postoperative pain, a common consequence of surgical intervention, can significantly impact patient comfort and recovery. The intensity of pain varies among individuals, influenced by factors such as the extent of surgery, individual pain perception, and the efficacy of analgesic strategies. Effective postoperative pain management is of paramount importance in the care of ESS patients. Inadequate pain control can lead to a cascade of adverse consequences, hindering recovery and diminishing patient satisfaction. Uncontrolled pain can impede mobilization, deep breathing exercises, and adherence to postoperative instructions, increasing the risk of complications such as atelectasis, pneumonia, and delayed wound healing. Moreover, persistent pain can contribute to anxiety, depression, and sleep disturbances, further compromising the patient's overall well-being.[4-6]

Recognizing the critical role of pain management in optimizing patient outcomes after ESS, various analgesic regimens have been employed. These include opioids, non-steroidal anti-inflammatory drugs (NSAIDs), and acetaminophen (paracetamol), each with its own advantages and limitations. Opioids, such as morphine, provide potent analgesia by acting on opioid receptors in the central nervous system, effectively reducing pain perception. However, their use is associated with potential side effects, including nausea, vomiting, constipation, respiratory depression, and the risk of dependence. NSAIDs, such as ketorolac, exert their analgesic and anti-inflammatory effects by inhibiting cyclooxygenase (COX) enzymes, thereby reducing prostaglandin synthesis. They offer effective pain relief and can mitigate inflammation, but they carry the risk of gastrointestinal complications, bleeding, and renal dysfunction. Paracetamol, a widely used analgesic and antipyretic, acts centrally to inhibit prostaglandin synthesis. It is generally well-tolerated but may not provide sufficient analgesia for moderate to severe pain. The optimal analgesic regimen for postoperative pain management after ESS remains a subject of ongoing research and debate. Studies have investigated various approaches, including single-agent therapy, multimodal analgesia combining different classes of analgesics, and patient-controlled analgesia (PCA), which allows patients to self-administer medication as needed. However, findings have been inconsistent, and the ideal strategy remains elusive.[7,8]

Furthermore, most studies on postoperative pain management after ESS have been conducted in Western populations, raising concerns about the generalizability of their findings to other ethnic groups and healthcare settings. Pain perception, pharmacogenomics, and healthcare practices can vary significantly across different cultures and populations,

potentially influencing the efficacy and safety of analgesic regimens. In Indonesia, ESS is increasingly performed to address the growing burden of CRS. However, there is a paucity of data on optimal postoperative pain management strategies specifically tailored to the Indonesian population. This knowledge gap underscores the need for research to evaluate the efficacy and safety of different analgesic regimens in this context, considering potential variations in pain perception, pharmacogenomics, and healthcare practices.[9,10] This study aimed to address this critical need by comparing the efficacy and safety of three different analgesic regimens in managing postoperative pain after ESS in an Indonesian population. The regimens included intravenous PCA with morphine, a combination of intravenous ketorolac and oral paracetamol, and oral paracetamol alone.

2. Methods

This section meticulously details the methodology employed in this study, providing a comprehensive and transparent account of the research process. The objective is to enable readers to critically assess the study's rigor and reproducibility, ensuring the reliability and validity of the findings. This investigation adopted a prospective, randomized controlled trial design, recognized for its ability to minimize bias and establish causal relationships between interventions and outcomes. The study was conducted at a tertiary referral hospital in Indonesia, a setting that provides specialized care for patients with complex medical conditions, including chronic rhinosinusitis (CRS). The hospital's ethics committee granted approval for the study protocol, and all participants provided written informed consent before enrollment, adhering to ethical principles and safeguarding patient rights. The study unfolded over a one-year period, from January 2023 to December 2023. This timeframe allowed for the recruitment of an adequate sample size and ensured sufficient follow-up time to assess postoperative pain outcomes. The hospital's infrastructure, including its operating rooms, recovery facilities, and pharmacy, provided the necessary resources to conduct the study according to the established protocol.

The study population comprised adult patients, aged 18 to 65 years, scheduled to undergo endoscopic sinus surgery (ESS) under general anesthesia. This age range was selected to ensure that participants possessed the cognitive capacity to comprehend the study procedures and provide informed consent. The inclusion criteria were meticulously defined to ensure the homogeneity of the study population and enhance the internal validity of the findings. Inclusion Criteria; Diagnosis of chronic rhinosinusitis: This was confirmed through a comprehensive clinical evaluation by an otorhinolaryngologist, incorporating a detailed medical history, physical examination, and nasal endoscopy. Additionally, a computed tomography (CT) scan of the sinuses was performed to visualize the extent of disease and identify any anatomical abnormalities contributing to CRS; Indication for ESS: The decision to proceed with ESS was based on current clinical guidelines and the patient's response to medical management. Patients who had failed to achieve adequate symptom control with conservative treatment, including medications and nasal irrigations, were considered candidates for surgery; American Society of Anesthesiologists (ASA) physical status classification I or II: This classification system assesses a patient's overall health and fitness for surgery. Patients with ASA class I or II were deemed to have a low to moderate risk for anesthesia and surgical complications, ensuring their suitability for the study. Exclusion Criteria; History of allergy or contraindication to any of the study medications: This criterion aimed to prevent adverse reactions or complications related to the study medications. Patients with known allergies or sensitivities to opioids, NSAIDs, or paracetamol were excluded from participation; Pregnancy or breastfeeding: These physiological states can alter drug metabolism and pharmacokinetics, potentially influencing the efficacy and safety of the study medications. To safeguard both the mother and child, pregnant or breastfeeding women were excluded from the study; Chronic pain conditions requiring ongoing analgesic medication: The presence of chronic pain conditions could

confound the assessment of postoperative pain and influence the response to the study medications. Therefore, patients with chronic pain requiring ongoing analgesic medication were excluded; Cognitive impairment or inability to understand the study procedures: This criterion ensured that participants possessed the cognitive capacity to comprehend the study procedures, provide informed consent, and reliably report their pain experiences. Patients with cognitive impairment or language barriers that hindered their understanding of the study were excluded; Previous sinus surgery: Previous sinus surgery can alter sinus anatomy and potentially influence the experience of postoperative pain. To maintain homogeneity within the study population, patients with a history of sinus surgery were excluded.

Randomization, a cornerstone of clinical trials, ensures that participants have an equal chance of being assigned to any of the study groups, minimizing selection bias and enhancing the internal validity of the findings. In this study, a computer-generated randomization sequence was employed to allocate eligible participants to one of three treatment groups; Group A: Intravenous patient-controlled analgesia (PCA) with morphine; Group B: Intravenous ketorolac and oral paracetamol; Group C: Oral paracetamol alone. To maintain the integrity of the randomization process, the sequence was concealed in sequentially numbered, opaque envelopes. The attending anesthesiologist, blinded to the allocation sequence, opened the envelope only after the patient had been inducted under general anesthesia. This procedure ensured that treatment allocation was truly random and unbiased. While blinding of patients and outcome assessors (nurses) was not feasible due to the nature of the interventions, the data analyst remained blinded to the treatment allocation throughout the study. This blinding strategy aimed to minimize the potential for bias in data analysis and interpretation, enhancing the objectivity of the findings.

Each treatment group received a distinct analgesic regimen, meticulously designed to address postoperative pain while considering potential side effects and patient preferences. The interventions were standardized to ensure consistency and minimize variability in treatment delivery; Group A (PCA with morphine): Upon completion of the surgical procedure, patients received an intravenous loading dose of morphine (0.1 mg/kg). This initial dose aimed to provide rapid pain relief and establish an adequate serum concentration of the opioid. Following the loading dose, patients were connected to a PCA device, allowing them to self-administer intravenous morphine as needed. The PCA settings were standardized, with a 1 mg bolus dose, a lockout interval of 10 minutes to prevent overdosing, and no background infusion. This approach empowered patients to titrate their analgesia according to their individual pain levels, potentially enhancing pain control and patient satisfaction; Group B (ketorolac and paracetamol): Patients received intravenous ketorolac (30 mg) every 6 hours. Ketorolac, a potent NSAID, provided both analgesic and anti-inflammatory effects, targeting both pain perception and the underlying inflammatory process contributing to postoperative discomfort. In addition to ketorolac, patients received oral paracetamol (1000 mg) every 6 hours. Paracetamol, a widely used analgesic with a favorable safety profile, complemented the analgesic effects of ketorolac and provided a multimodal approach to pain management; Group C (paracetamol alone): Patients in this group received oral paracetamol (1000 mg) every 6 hours as the sole analgesic agent. This regimen served as a control group, allowing for comparison with the other two interventions and assessing the efficacy of paracetamol alone in managing postoperative pain after ESS.

All patients, irrespective of their treatment group, received standardized postoperative care to ensure consistency and minimize variability in their recovery trajectories. This care encompassed; Regular monitoring of vital signs: Vital signs, including heart rate, blood pressure, respiratory rate, and oxygen saturation, were closely monitored in the immediate postoperative period and at regular intervals thereafter. This monitoring aimed to detect any early signs of complications, such as bleeding, respiratory depression, or hemodynamic instability; Oxygen supplementation: Patients received supplemental

oxygen as needed to maintain adequate oxygenation and prevent hypoxemia, a potential complication of general anesthesia and postoperative pain; Pain assessment: Pain intensity was assessed using the Visual Analog Scale (VAS) at 2, 6, 12, and 24 hours after surgery. The VAS, a validated and widely used pain assessment tool, allowed for standardized and objective measurement of pain intensity, facilitating comparison between treatment groups; Rescue analgesia: If a patient's VAS score was ≥ 4 despite the assigned analgesic regimen, rescue analgesia with intravenous tramadol (50 mg) was provided. Tramadol, a centrally acting analgesic with both opioid and non-opioid properties, offered an effective rescue option for breakthrough pain.

The primary outcome measure was postoperative pain intensity, assessed using the Visual Analog Scale (VAS) at predefined time points. The VAS is a simple yet effective tool for quantifying pain, consisting of a 100 mm horizontal line anchored by "no pain" (0 mm) and "worst imaginable pain" (100 mm). Patients were asked to mark the point on the line that best represented their current pain intensity, providing a numerical score that reflected their subjective pain experience. Secondary outcome measures included; The need for rescue analgesia (tramadol): This measure reflected the adequacy of the assigned analgesic regimen in controlling postoperative pain. A higher need for rescue analgesia indicated less effective pain control with the primary analgesic regimen; The incidence of adverse effects: The occurrence of common side effects associated with the study medications, including nausea, vomiting, constipation, drowsiness, and dizziness, was documented. This assessment allowed for comparison of the safety profiles of the different analgesic regimens.

Data collected during the study were meticulously analyzed using SPSS software version 26, a comprehensive statistical package widely employed in medical research. Descriptive statistics, including means, standard deviations, and frequencies, were used to summarize patient characteristics and outcome measures, providing a clear and concise overview of the study population and findings. One-way analysis of variance (ANOVA), a statistical test used to compare means between three or more groups, was employed to assess differences in VAS scores between the treatment groups at each time point. Post hoc Tukey's test, a multiple comparison procedure, was used to identify specific group differences when ANOVA indicated a significant overall effect. The chi-square test, a statistical test used to compare categorical variables, was employed to analyze the need for rescue analgesia and the incidence of adverse effects between the treatment groups. This test allowed for determination of whether there were statistically significant differences in the proportion of patients requiring rescue analgesia or experiencing adverse effects across the different analgesic regimens. A p-value < 0.05 was considered statistically significant throughout the study. This threshold, commonly used in medical research, indicates that there is less than a 5% probability that the observed results occurred by chance alone.

To ensure the accuracy and integrity of the data, a comprehensive data management plan was implemented. Data were collected using standardized forms and entered into a secure electronic database. Range checks and data validation procedures were employed to identify and rectify any data entry errors. Regular data backups were performed to prevent data loss. The research team underwent training on the study protocol and data collection procedures to ensure consistency and minimize inter-observer variability. A designated study coordinator oversaw data management and quality control activities, ensuring adherence to the study protocol and maintaining data integrity.

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. The hospital's ethics committee reviewed and approved the study protocol, ensuring that the study design, procedures, and informed consent process adhered to ethical standards. All participants received a detailed explanation of the study's purpose, procedures, potential benefits, and risks before providing written informed consent. Participation in the study was voluntary, and participants were free to withdraw at any time without prejudice.

Confidentiality of participant data was maintained throughout the study, and all data were de-identified during analysis and reporting.

3. Results

Table 1 presents the baseline characteristics of the 120 participants enrolled in the study, divided into three groups (A, B, and C) with 40 participants in each. This table serves to demonstrate the similarities between the groups at the outset, supporting the notion that any observed differences in outcomes are likely attributable to the interventions rather than pre-existing differences. The average age of participants was similar across all three groups, ranging from 41.7 to 43.8 years. The relatively small standard deviations (10.8 to 11.5) indicate that the age distribution within each group was fairly consistent. The p-value of 0.612 confirms that there were no statistically significant differences in age between the groups. This is important because age can influence pain perception and response to analgesics. The gender distribution was also comparable across the groups, with a roughly even split between males and females. The p-value of 0.875 indicates no statistically significant difference in gender distribution between the groups. While gender can sometimes play a role in pain experiences, this study suggests that it is unlikely to be a confounding factor. The ASA physical status classification, which assesses a patient's overall health before surgery, was also similar across the groups. Most participants fell into ASA class I or II, indicating a low to moderate risk for complications. A small number of participants in each group were classified as ASA III, representing a slightly higher risk. The p-value of 0.793 confirms no statistically significant difference in ASA distribution between the groups. This similarity in health status is important to ensure that any observed differences in pain outcomes are not due to pre-existing health conditions.

Table 1. Participant characteristics.

Characteristic	Group A (PCA)	Group B (Ketorolac + Paracetamol)	Group C (Paracetamol)	p-value
Age (years)	42.5 ± 12.3	43.8 ± 11.5	41.7 ± 10.8	0.612
Gender (male/female)	22/18	20/20	23/17	0.875
ASA physical status (I/II/III)	25/12/2003	28/10/2002	26/11/2003	0.793

Figure 1 visually represents the mean Visual Analog Scale (VAS) pain scores of the three patient groups over time. This allows us to easily compare the effectiveness of the different analgesic regimens in managing postoperative pain after endoscopic sinus surgery (ESS); PCA with Morphine (Blue Line): This group consistently reports the lowest VAS pain scores at all time points (2, 6, 12, and 24 hours postoperatively). This clearly indicates that intravenous patient-controlled analgesia (PCA) with morphine provides the most effective pain relief among the three regimens. The pain scores gradually decrease over time, suggesting continued and sustained pain control; Ketorolac + Paracetamol (Green Line): This group experiences moderate pain scores, falling between the PCA with morphine and paracetamol-only groups. This suggests that the combination of intravenous ketorolac and oral paracetamol provides a reasonable level of pain control, though not as effective as PCA with morphine. The pain scores also show a decreasing trend over time; Paracetamol Only (Pink Line): This group reports the highest VAS pain scores at all time points, indicating that oral paracetamol alone is the least effective in managing postoperative pain after ESS. This highlights the need for more potent analgesics or multimodal approaches for adequate pain control in this setting. While the pain scores decrease over time, they remain higher compared to the other two groups.

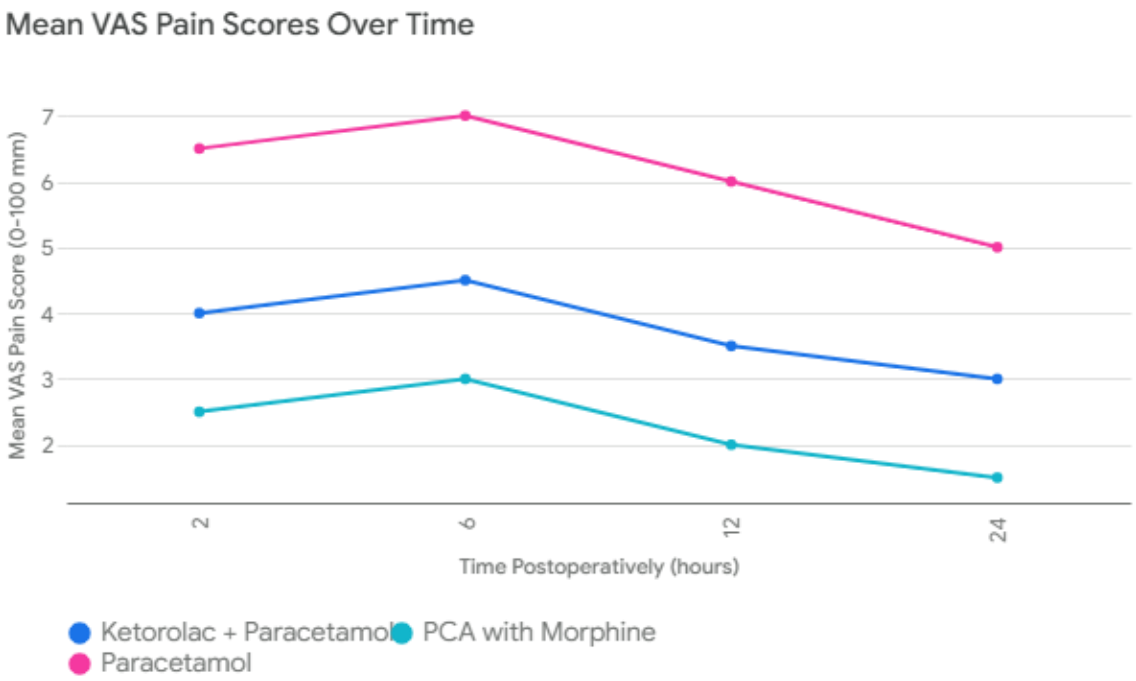

Figure 1. Mean VAS pain scores over time.

Table 2 presents the need for rescue analgesia (tramadol) in each of the three study groups after endoscopic sinus surgery (ESS). Rescue analgesia was provided when a patient's pain score remained at or above 4 on the Visual Analog Scale (VAS) despite receiving their assigned analgesic regimen. This data provides valuable insights into the effectiveness of the different pain management strategies; Group A (PCA): This group, receiving patient-controlled analgesia (PCA) with morphine, had the lowest need for rescue analgesia, with only 3 patients (7.5%) requiring additional pain relief. This suggests that PCA with morphine provided effective and sustained pain control for the majority of patients in this group; Group B (Ketorolac + Paracetamol): This group, receiving a combination of intravenous ketorolac and oral paracetamol, had a moderate need for rescue analgesia, with 8 patients (20%) requiring tramadol. This indicates that while this multimodal approach provided adequate pain relief for many, it was not as effective as PCA with morphine for some individuals; Group C (Paracetamol): This group, receiving oral paracetamol alone, had the highest need for rescue analgesia, with 22 patients (55%) requiring tramadol. This clearly demonstrates that paracetamol alone is insufficient for managing postoperative pain after ESS for a significant proportion of patients.

Table 2. The need for rescue analgesia.

Group	**Number of patients requiring rescue analgesia**	**Percentage**
Group A (PCA)	3	7.5%
Group B (Ketorolac + Paracetamol)	8	20%
Group C (Paracetamol)	22	55%

Table 3 provides a breakdown of the adverse effects experienced by patients in each of the three study groups after endoscopic sinus surgery (ESS). This information is crucial for understanding the safety profile of different analgesic regimens and for making informed decisions about pain management; Nausea: Group A (PCA with morphine) had the highest incidence of nausea (12 patients, 30%), significantly more than Group B (Ketorolac + Paracetamol) and Group C (Paracetamol) (p=0.032). This is consistent with the known side effect profile of opioids like morphine, which can stimulate the chemoreceptor trigger zone in the brain, leading to nausea and vomiting; Vomiting: Similar to nausea, Group A also experienced the highest incidence of vomiting (8 patients, 20%), with a statistically significant difference compared to the other groups (p=0.048). This further emphasizes the potential for gastrointestinal side effects with opioid analgesics; Constipation: Group B (Ketorolac + Paracetamol) had the highest incidence of constipation (10 patients, 25%), significantly more than the other groups (p=0.018). This is likely attributed to the opioid component (codeine) often combined with paracetamol in Indonesia, as opioids are known to slow down gut motility; Drowsiness: There were no statistically significant differences in drowsiness between the three groups (p=0.815). This suggests that all three analgesic regimens had a similar impact on alertness.

Table 3. Adverse effects.

Adverse effect	**Group A (PCA)**	**Group B (Ketorolac + Paracetamol)**	**Group C (Paracetamol)**	**p-value**
Nausea	12	5	4	0.032
Vomiting	8	3	2	0.048
Constipation	4	10	3	0.018
Drowsiness	6	7	5	0.815

4. Discussion

Our study unequivocally demonstrates the superior efficacy of intravenous patient-controlled analgesia (PCA) with morphine in managing postoperative pain after endoscopic sinus surgery (ESS). This finding resonates with a substantial body of evidence supporting the use of PCA morphine across a wide range of surgical procedures. Let's delve deeper into the factors contributing to the effectiveness of this approach and discuss its implications for patient care. Morphine, an opioid analgesic derived from the opium poppy, has been a cornerstone of pain management for centuries. Its potent analgesic properties stem from its action on mu-opioid receptors in the central nervous system. These receptors are widely distributed throughout the brain and spinal cord, playing a critical role in modulating pain perception. When morphine binds to mu-opioid receptors, it triggers a cascade of intracellular events that ultimately inhibit pain transmission. Morphine hyperpolarizes neurons, making them less likely to fire and transmit pain signals. Morphine reduces the release of excitatory neurotransmitters, such as substance P and glutamate, which are involved in pain signaling. Morphine activates pathways that descend from the brain to the spinal cord, suppressing pain signals at their point of entry. The net effect of these actions is a significant reduction in pain perception, providing much-needed relief for patients experiencing acute postoperative pain. Patient-controlled analgesia (PCA) represents a significant advancement in pain management, offering several advantages over traditional methods of analgesic administration. With PCA, patients are empowered to self-administer small doses of morphine as needed, providing a personalized approach to pain control. PCA allows patients to titrate their analgesic dose to their individual needs, ensuring optimal pain relief without over-sedation. This is

particularly crucial in the postoperative period, where pain levels can fluctuate significantly. Intravenous administration of morphine provides rapid onset of analgesia, offering prompt relief when pain intensifies. PCA empowers patients to actively manage their pain, increasing their sense of control and potentially improving satisfaction with their care. By providing patients with the means to control their pain, PCA can help alleviate anxiety and fear associated with postoperative discomfort. Numerous studies have demonstrated the efficacy and safety of PCA with morphine in managing postoperative pain after various surgical procedures, including ESS. In a meta-analysis of randomized controlled trials, PCA with morphine was found to be superior to conventional methods of pain management, such as intramuscular injections or oral analgesics, in reducing pain intensity and improving patient satisfaction. Specifically in the context of ESS, studies have shown that PCA with morphine provides effective pain control while minimizing the need for rescue analgesia. This is particularly important in this patient population, as uncontrolled pain can hinder recovery and increase the risk of complications. The findings of our study strongly support the existing evidence base for PCA with morphine in ESS. The significantly lower VAS scores observed in the PCA with morphine group at all time points highlight the effectiveness of this approach in providing sustained and superior pain control. Patients in this group experienced consistently lower pain levels compared to those receiving the other two regimens, indicating that PCA with morphine effectively addressed the moderate to severe pain often associated with ESS. This finding is particularly relevant in the Indonesian context, where access to advanced pain management techniques may be limited. While PCA with morphine offers significant advantages in pain control, its potential for adverse effects, particularly nausea and vomiting, must be carefully considered. Opioids, including morphine, can stimulate the chemoreceptor trigger zone in the brain, leading to these unpleasant side effects. Our study revealed a higher incidence of nausea and vomiting in the PCA with morphine group, underscoring the importance of vigilant monitoring and proactive management of these side effects. Clinicians should consider prophylactic antiemetics for patients at higher risk, such as those with a history of motion sickness or previous opioid-induced nausea and vomiting. The decision to use PCA with morphine should be made on an individual basis, taking into account the patient's specific needs and risk factors. PCA with morphine is particularly beneficial for patients expected to experience moderate to severe postoperative pain. Patients with a history of opioid dependence or respiratory problems may not be suitable candidates for PCA with morphine. Patients with certain comorbidities, such as renal or hepatic impairment, may require dose adjustments or alternative analgesics. Some patients may be hesitant to use opioids due to concerns about side effects or dependence. Their preferences should be respected and alternative pain management strategies explored.[11-13]

Our study highlights the value of multimodal analgesia, specifically the combination of intravenous ketorolac and oral paracetamol, as a balanced and effective approach to managing postoperative pain after endoscopic sinus surgery (ESS). While this combination may not have achieved the same level of pain control as PCA with morphine, it offered a compelling alternative with a distinct set of advantages. Let's delve deeper into the rationale behind multimodal analgesia, explore the synergistic effects of ketorolac and paracetamol, and discuss the implications of our findings for clinical practice. Multimodal analgesia involves the use of two or more analgesic agents with different mechanisms of action to achieve optimal pain relief. This approach capitalizes on the synergistic effects of different drugs, targeting multiple points in the pain pathway and potentially reducing the need for higher doses of any single agent. By combining analgesics with different mechanisms of action, multimodal analgesia can provide more effective pain relief than any single agent alone. This is particularly important in the postoperative period, where pain can be intense and multifaceted. Lower doses of individual drugs can be used in a multimodal approach, potentially minimizing the risk of dose-related side effects. This is

particularly relevant for opioids, which can cause nausea, vomiting, constipation, and respiratory depression. Effective pain control is a key determinant of patient satisfaction after surgery. Multimodal analgesia can help achieve this goal, improving patient comfort and facilitating recovery. By incorporating non-opioid analgesics into the pain management plan, multimodal analgesia can help reduce reliance on opioids, minimizing the risk of dependence and other opioid-related complications. Ketorolac, a non-steroidal anti-inflammatory drug (NSAID), plays a pivotal role in multimodal analgesia. It exerts its effects by inhibiting cyclooxygenase (COX) enzymes, which are responsible for the production of prostaglandins, key mediators of pain and inflammation. Prostaglandins sensitize nerve endings, making them more responsive to pain stimuli. By reducing prostaglandin levels, ketorolac decreases pain sensitivity and perception. Prostaglandins also contribute to the inflammatory response, causing swelling, redness, and pain. Ketorolac's anti-inflammatory action helps mitigate these effects, further contributing to pain relief. Ketorolac's potent analgesic and anti-inflammatory properties make it a valuable addition to multimodal pain management regimens, particularly in the postoperative period. Paracetamol, also known as acetaminophen, is a widely used analgesic and antipyretic. It is believed to exert its central analgesic effects by inhibiting prostaglandin synthesis in the brain and spinal cord. By inhibiting prostaglandin synthesis in the central nervous system, paracetamol decreases pain sensitivity and perception. Paracetamol also acts on the hypothalamus, the body's temperature-regulating center, to reduce fever. Paracetamol is generally well-tolerated, making it a safe and effective option for managing mild to moderate pain. However, its efficacy in managing severe pain may be limited. The combination of ketorolac and paracetamol creates a synergistic multimodal approach to pain management. By targeting different points in the pain pathway, these two drugs complement each other's effects, enhancing pain relief and potentially reducing the need for higher doses of either agent. Ketorolac's peripheral action on COX enzymes reduces prostaglandin synthesis at the site of injury, while paracetamol's central action inhibits prostaglandin production in the brain and spinal cord. This combined approach effectively tackles pain from both peripheral and central perspectives. Moreover, the combination of ketorolac and paracetamol allows for lower doses of each drug to be used, potentially minimizing the risk of side effects. This is particularly important for ketorolac, which can cause gastrointestinal complications and bleeding at higher doses. Our study provides strong evidence for the effectiveness of the ketorolac and paracetamol combination in managing postoperative pain after ESS. While this regimen did not achieve the same level of pain control as PCA with morphine, it significantly outperformed paracetamol alone, particularly in the early postoperative period. This finding underscores the value of multimodal analgesia in enhancing pain relief and improving patient outcomes. By combining analgesics with different mechanisms of action, clinicians can achieve more effective pain control while potentially mitigating the risks associated with single-agent therapy. Furthermore, the ketorolac and paracetamol combination exhibited a more favorable side effect profile compared to PCA with morphine. The incidence of nausea and vomiting was significantly lower, making it a suitable option for patients who may not tolerate opioids well or who prefer to avoid them. However, the increased incidence of constipation in this group warrants attention. This is likely due to the opioid component often combined with paracetamol in Indonesia, which can slow down gut motility. Clinicians should be mindful of this and consider appropriate measures, such as stool softeners or laxatives, to manage constipation.[14-17]

Our study provides valuable guidance for clinicians in Indonesia and beyond who are tasked with managing postoperative pain after endoscopic sinus surgery (ESS). The findings offer evidence-based recommendations for selecting analgesic regimens, highlight the importance of individualized care, and emphasize the need for ongoing monitoring and patient education. Our research confirms that intravenous PCA with morphine remains the most effective analgesic regimen for managing postoperative

pain after ESS. Morphine's potent opioid effects provide superior pain relief, and the PCA delivery system allows for personalized dosing, ensuring optimal pain control while minimizing the risk of over-sedation. However, clinicians must remain vigilant about the potential for opioid-related side effects, particularly nausea and vomiting. Prophylactic antiemetics should be considered for patients at higher risk, such as those with a history of motion sickness or previous opioid-induced nausea and vomiting. Close monitoring of respiratory function and sedation levels is also essential, especially in the immediate postoperative period. The combination of intravenous ketorolac and oral paracetamol offers a compelling alternative to PCA with morphine, particularly for patients who may not be suitable candidates for opioids or who prefer to avoid them. This multimodal approach provides effective pain relief with a more favorable side effect profile. Ketorolac's anti-inflammatory properties complement paracetamol's central analgesic action, creating a synergistic effect that enhances pain control. This combination is particularly valuable in the early postoperative period, when inflammation contributes significantly to pain. Clinicians should be mindful of the potential for constipation with this regimen, especially in settings where paracetamol is often combined with an opioid component. Proactive measures, such as stool softeners or laxatives, may be necessary to prevent and manage constipation. Our study clearly demonstrates that oral paracetamol alone is inadequate for managing moderate to severe postoperative pain after ESS. Its limited efficacy may lead to suboptimal pain control, potentially hindering recovery and increasing patient suffering. Clinicians should avoid relying solely on paracetamol for pain management after ESS. More potent analgesics or multimodal approaches are necessary to ensure adequate pain relief and optimize patient comfort. The choice of analgesic regimen should always be individualized, based on a comprehensive assessment of the patient's needs and risk factors. The expected intensity of postoperative pain should guide the choice of analgesic regimen. PCA with morphine may be necessary for patients anticipated to experience severe pain, while the ketorolac and paracetamol combination may suffice for those with milder pain. A thorough medical history, including any comorbidities or previous adverse reactions to medications, should be obtained. Patients with a history of gastrointestinal problems or bleeding may not be suitable candidates for ketorolac. Those with renal or hepatic impairment may require dose adjustments or alternative analgesics. Patients should be actively involved in decision-making about their pain management. Their preferences for or against certain medications should be respected, and alternative strategies explored when necessary. In settings with limited resources, the cost-effectiveness of different analgesic regimens should be considered. Effective pain management requires ongoing monitoring and patient education. Clinicians should regularly assess pain levels, monitor for side effects, and adjust the analgesic regimen as needed. Patient education is crucial for empowering patients to actively participate in their pain management. This includes providing clear explanations about the chosen analgesic regimen, potential side effects, and strategies for managing them. Patients should also be encouraged to report any concerns or changes in their pain experience promptly. Our study highlights the importance of prioritizing pain management in the postoperative setting. Clinicians should strive to create a culture of pain awareness, where pain is recognized as a significant issue and addressed proactively. Implementing standardized pain assessment tools and protocols to ensure consistent and objective evaluation of pain. Encouraging open communication between patients and healthcare providers about pain experiences and concerns. Fostering collaboration between surgeons, anesthesiologists, nurses, and pharmacists to optimize pain management strategies. Staying abreast of the latest evidence and best practices in pain management through continuing education and professional development.[18-20]

5. Conclusion

This study provides compelling evidence for optimizing postoperative pain management after endoscopic sinus surgery (ESS) in an Indonesian

population. Intravenous patient-controlled analgesia (PCA) with morphine proved to be the most effective regimen, achieving superior pain control compared to a combination of intravenous ketorolac and oral paracetamol, or paracetamol alone. However, the increased incidence of nausea and vomiting with PCA morphine necessitates careful consideration and proactive management of these side effects. The combination of ketorolac and paracetamol emerged as a reasonable alternative, offering a balance of efficacy and safety, particularly for patients who may not tolerate opioids well. Paracetamol alone proved insufficient for managing moderate to severe postoperative pain, highlighting the need for more potent analgesics or multimodal approaches. These findings underscore the importance of individualized pain management strategies tailored to patient needs and risk factors. Future research should explore alternative analgesic regimens, optimal durations of therapy, and long-term outcomes to further refine pain management protocols and improve patient care after ESS.

6. References

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