Analysis of Risk Factors for Postoperative Nausea and Vomiting in the use of Intraoperative Remifentanil at Dr. Soetomo Hospital

Mahisa Pribadi Brahmana[1], Agustina Salinding[2], Pesta Parulian Maurid Edwar[2], Prananda Surya Airlangga[2], Maulydia[2], Atika[2]
[1]Universitas Airlangga, Dr. Soetomo Hospital Surabaya, Indonesia. **(Corresponding Author)**
[2]Lecturer at the Universitas Airlangga, Dr. Soetomo Hospital Surabaya, Indonesia.

Abstract

Objectives: Postoperative nausea and vomiting (PONV) are common complications that can have negative effects on patients, such as increasing hospital stay and trauma from subsequent surgeries and anesthesia. Remifentanil is a fast-acting opioid analgesic used during anesthesia and is believed to cause less PONV compared to other opioids. Therefore, study aims to analyze the incidence and risk factors of PONV with the use of intraoperative remifentanil at Dr. Soetomo Regional General Hospital, Surabaya.

Methodology: This was an observational analytical study with a cross-sectional design of patients who underwent general anesthesia and received intraoperative remifentanil during surgery at Dr. Soetomo General Hospital in Surabaya. Data from medical records were collected, including age, gender, PONV status, type of surgery, smoking status, and remifentanil dose range. The data were then analyzed using Easy R (EZR).

Results: Of the 50 patients who received intraoperative remifentanil, 5 (10.0%) patients experienced PONV. The highest incidence of PONV was in the group undergoing head and neck surgery (33.3%), non-smokers (22.7%), women (29.4%), those aged 17-25 years (37.5%), those aged 26-35 years (28.6%), and a remifentanil dose range of 0.16-0.20 μg/kg/min (66,7%). In this study, non-smoking, female gender, young age (17-25 years old), and high dosage range were significantly associated with postoperative nausea and vomiting ($p<0.05$).

Conclusion: Non-smokers, women, young age, and high dosage range were associated with PONV in the use of intraoperative remifentanil at Dr. Soetomo general hospital. However, further studies are required to confirm these findings

Keywords: Postoperative Nausea and Vomiting, Remifentanil, Risk Factors

INTRODUCTION

Post-Operative Nausea and Vomiting (PONV) refers to the occurrence of nausea and/or vomiting within 24 hours after surgery. It is the most common source of patient discomfort following postoperative anesthesia. Aside from causing complications such as wound opening, esophageal rupture, aspiration, dehydration, increased intracranial pressure, and pneumothorax, PONV can also prolong recovery time in the Recovery Room (RR) and increase the likelihood of readmission, resulting in higher medical costs (Wallden et al., 2016).

PONV affects approximately 20-40% of surgical patients, with high-risk individuals experiencing rates as high as 80% (Cao et al., 2017). Multiple factors can influence the occurrence of PONV, including patient-related factors, anesthesia-related factors, and characteristics of the surgical procedure. General anesthesia has been identified as a significant risk factor compared to local anesthesia, and the duration of general anesthesia is also linked to the development of PONV (Hamzah et al., 2020; Pierre dan Whelan, 2013). Additionally, risk factors such as age, female gender, nonsmoker status, and a history of preoperative PONV can contribute to the incidence of PONV (Černý, 2014).

The vomiting center can be activated either directly by irritants or indirectly through four key areas: the gastrointestinal tract, cerebral cortex and thalamus, vestibular region, and chemoreceptor trigger zone (CTZ). Opioids, including morphine, fentanyl, and remifentanil, are frequently administered during the intraoperative period for pain management and to achieve balanced anesthesia (Lestari et al., 2020). However, opioids are known to induce nausea and vomiting upon single administration (Teshome et al., 2020).

Nausea is an unpleasant sensation accompanied by the urge to vomit. It is typically felt in the epigastrium and stomach and is often followed by vomiting (Dorland, 2019). Nausea is commonly accompanied by increased activity of the parasympathetic nervous system, leading to symptoms such as diaphoresis, salivation, bradycardia, pallor, and decreased respiratory frequency. Vomiting, on the other hand, refers to the forceful expulsion of gastric contents through the mouth, usually triggered by a strong urge (Schwinghammer et al., 2021).

Nausea and vomiting can arise in various situations,

including after surgery or as a side effect of chemotherapy. They can also be symptoms of digestive system disorders or diseases. Sometimes, patients may experience nausea and vomiting without an identifiable cause. While acute episodes of nausea and vomiting associated with specific triggers, such as motion sickness, are relatively easier to manage, chronic episodes can significantly impact a patient's quality of life and pose management challenges. These chronic episodes may be related to conditions like gastroparesis (delayed gastric emptying) or functional disorders without a clear physical cause (Heckroth et al., 2021).

Multiple stimuli can trigger nausea and vomiting, including olfactory and visual factors, psychological factors, and disturbances in balance or the vestibular system. The medulla oblongata serves as the central regulator of the nausea and vomiting reflex and contains numerous nerve bundles. It is closely situated to other visceral centers, such as the respiratory and vasomotor centers, resulting in complex interactions and influences from various organs (Gan et al., 2016). The medulla oblongata houses an extensive network of nerve fibers, connecting the brain with peripheral regions. The brainstem, including the medulla oblongata, is covered by a diffuse network of neurons known as the reticular formation, which contains autonomic regulation centers vital for numerous bodily functions.

PONV is commonly defined as nausea, vomiting, or retching that occurs within the first 24-48 hours after surgery, affecting approximately 20-30% of patients (Pierre and Whelan, 2013). Another definition describes PONV as nausea and/or vomiting that arises within 24 hours after surgery (Rother, 2012). Despite advances in anesthesia and surgical techniques, PONV still remains a frequent occurrence. It can affect around 25% - 30% of surgical patients, and even higher rates of 70% - 80% among those at high risk (Amirshahi et al., 2020).

Risk factors for PONV can generally be categorized into three groups: non-anesthetic (individual) factors, anesthetic factors, and surgery-related factors (Wang dan Argalious, 2020).

1) Individual/Patient Factors:

Several individual factors contribute to the risk of PONV. These include gender, age, obesity, history of PONV or motion sickness, and smoking.

2) Preoperative Factors:

Preoperative factors that can influence the occurrence of PONV include the nature of the surgery and pre-medication. Surgeries involving organs such as the head (with increased intracranial pressure), digestive tract obstruction or disruption, pregnancy or gynecological obstetrics requiring laparotomy, or patients undergoing chemotherapy are associated with higher risks of PONV (Setiawan, 2014). Pre-medication can also play a role, as substances like atropine can stimulate the chemoreceptor trigger zone (CTZ) and opioids can increase gastric secretion and reduce motility (Setiawan, 2014).

3) Intraoperative Factors:

During the surgery itself, several factors can contribute to the occurrence of PONV. Anesthesia factors such as intubation, mask ventilation, and vestibular stimulation upon changes in head position can trigger vomiting. The choice of anesthetic drugs is also important, with emetogenic opioids and inhaled anesthetics like ether increasing the risk of PONV, while intravenous anesthetics such as propofol can reduce it. Additionally, the type of anesthesia technique used, with general anesthesia having a higher PONV rate compared to spinal anesthesia, and regional anesthesia being the least emetogenic, can impact the occurrence of PONV (Hasegawa *et al.*, 2021).

4) Surgical Factors:

The duration of the surgical procedure is a significant surgical factor that affects the risk of PONV. Longer procedures carry a higher risk. The anatomical area of surgery also plays a role, with certain areas like craniotomy, intra-abdominal, and gynecology surgeries being associated with a higher incidence of PONV.

5) Postoperative Factors:

After the surgery, several postoperative factors can influence the occurrence of PONV. Pain management plays a role, as relieving pain can reduce the incidence of nausea and vomiting. Other factors include the influence of pain mechanisms on gastric emptying time, the direct stimulation of the CTZ by opioids, the influence of ambulation on the vestibular component, orthostatic hypotension or dehydration, hypoglycemia resulting from extended fasting periods, hypoxemia, and early oral intake.

Opioids are derived from the plant papaver somniferum and are the basis for 20 opioid alkaloids used in anesthesia. The medicinal use of opioids dates back to 300 BC, and the isolation of morphine in 1803, codeine in 1832, and papaverine in 1848 marked significant milestones in their development. Opioids primarily affect the central nervous system (CNS) and have analgesic effects, including pain relief, euphoria, respiratory depression, cough suppression, pupil constriction, nausea, and vomiting. These effects are achieved through the inhibition of pain transmission pathways, activation of descending pain control systems, suppression of the respiratory center, inhibition of the cough reflex, activation of emetic chemoreceptors, and parasympathetic stimulation (Cruz dan Granados-Soto, 2015). While opioids have minimal impact on peripheral resistance and blood pressure, orthostatic hypotension risk is increased in patients with blood loss. Opioids are classified as opioid agonists, opioid antagonists, or opioid agonist-antagonists (Flood et al., 2015).

Remifentanil is a short-acting opioid of the

phenylpiperidine class that is more potent than alkaloid opioids, exerts an agonist effect on mu receptors, and is widely used in the field of anesthesia, both general and conscious anesthesia since its acceptance by the Food and Drug Administration (FDA) in the United States in 1996. Remifentanil can be used as an alternative to fentanyl to prevent acute hyperdynamic reactions at the time of action with a strong and short pain effect (Hughes et al., 2023).

Remifentanil has a rapid onset, is not metabolized in the body, and is quickly eliminated through plasma cholinesterase metabolism independent of renal function. These characteristics of remifentanil contribute to its lower incidence of PONV and respiratory depression during extubation (Komatsu et al., 2007). While the clinical effects of remifentanil manifest within 2-5 minutes, its side effects, such as nausea, vomiting, pruritus, muscle stiffness, and cardiopulmonary depression, are dose-dependent (Jensen, 2015).

Remifentanil will reduce cerebral blood flow dose-dependently in parts of the brain involved in pain perception. At the highest infusion rate (0.15 mcg/kg/min), regional cerebral blood flow will also be modified in areas believed to regulate consciousness. When used in conjunction with N2O, blood flow to all parts of the brain will be reduced, and ultimately, will lead to a decrease in intracranial pressure (Flood et al., 2015).

Numerous studies have investigated the efficacy and side effects of remifentanil as an opioid for anesthetic analgesia. However, there remains considerable controversy surrounding the potential of this drug to trigger PONV. Given the existing controversies, the aim of this study is to examine the relationship between risk factors and the incidence of postoperative nausea and vomiting in patients undergoing general anesthesia with remifentanil at Dr. Soetomo Regional General Hospital.

Research Hypotheses:

Based on the specific aims of the study, the following hypotheses were formulated:

1. There is a relationship between the type of surgery and the incidence of postoperative nausea and vomiting in patients undergoing general anesthesia with intraoperative remifentanil use.
2. There is a relationship between smoking history and the incidence of postoperative nausea and vomiting in patients undergoing general anesthesia with intraoperative remifentanil use.
3. There is a relationship between gender and the incidence of postoperative nausea and vomiting in patients undergoing general anesthesia with intraoperative remifentanil use.
4. There is a relationship between age and the incidence of postoperative nausea and vomiting in patients undergoing general anesthesia with intraoperative remifentanil use.
5. There is a relationship between the home dose range of remifentanil and the incidence of postoperative nausea and vomiting in patients undergoing general anesthesia with intraoperative remifentanil use.

METHODOLOGY

This study employed an observational analytic design with a cross-sectional approach to determine the incidence of postoperative nausea and vomiting at Dr. Soetomo Regional General Hospital in Surabaya. The research was conducted at Dr. Soetomo Regional General Hospital in Surabaya, starting from February 16, 2023, to March 16, 2023, after obtaining the ethical certificate on February 13, 2023, with ethical number 0588/KEPK/II/2023.

The study population consisted of patients who underwent general anesthesia and received intraoperative remifentanil during surgery at Dr. Soetomo Regional General Hospital in Surabaya, from February 16, 2023, to March 16, 2023. The sample for this study included all patients who met the inclusion and exclusion criteria of Dr. Soetomo Regional General Hospital, and the total sampling method was used.

Inclusion criteria for the study were patients aged 18 to 60 years, patients undergoing general anesthesia with a Physical Status American Society of Anesthesiology (PS ASA) score of 1-2, and patients who received intraoperative remifentanil. Exclusion criteria were patients with a history of motion sickness or previous postoperative nausea and vomiting, pregnant patients, patients with a decreased level of consciousness, patients requiring postoperative ventilator use, patients with a history of preoperative opioid use, patients undergoing planned ear, digestive, or neurosurgical surgeries, and patients with malignancy or a history of chemotherapy.

The independent variables in this study were risk factors for postoperative nausea and vomiting, including the type of surgery, smoking history, gender, and age. The dependent variable was the incidence of postoperative nausea and vomiting. Research instruments used included a questionnaire and medical record data.

To collect the research data, the researcher obtained ethical approval from the hospital's Health Research Ethics Committee. Informed consent was obtained from the patients a day before the surgery, and the researcher conducted interviews with the patients using the questionnaire sheet on the day after the surgery.

Data processing and presentation involved several steps. First, the data were edited to check for accuracy and completeness. Then, the collected data were manually coded by the researcher before being processed by a computer. The coded data were entered

into a computer program and checked for data entry errors through data cleaning. The data were saved for analysis. In the initial stage of analysis, the data were analyzed univariably to determine frequency distribution. Bivariable analysis was conducted using the Fischer exact statistical test and the Contingency Correlation Test. The Easy R (EZR) program was used for data analysis.

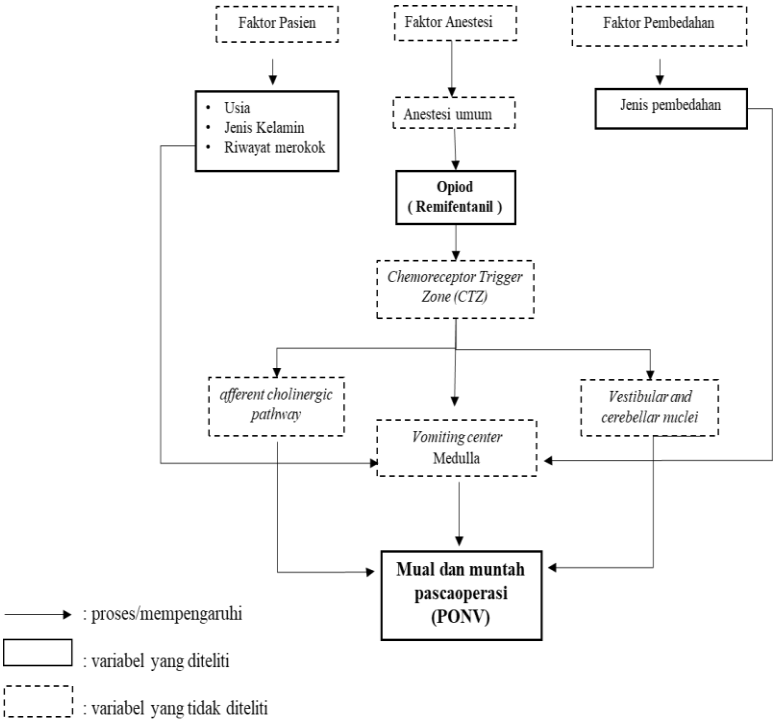

Figure (1) Conceptual Framework

Postoperative nausea and vomiting (PONV) can be caused by three main factors: anesthesia administration, the type and duration of surgery, and patient-related factors. On the patient's side, factors such as age, gender, smoking history, and history of anti-emetic prophylaxis can influence the incidence of PONV. Opioids, including remifentanil, which is an ultra-short-acting opioid, have direct effects on the chemoreceptor trigger zone (CTZ) and the vomiting center, potentially leading to postoperative nausea and vomiting. Opioids can also stimulate the vestibular apparatus, causing dizziness and subsequent nausea and vomiting. Furthermore, opioids can disrupt intestinal peristalsis, leading to constipation, which can activate the afferent cholinergic pathway and result in nausea and vomiting. Remifentanil, with its rapid onset, minimal accumulation, independent metabolism via plasma cholinesterase, and rapid elimination, is associated with a lower incidence of PONV.

RESULTS

Demographic Characteristics of Research Subjects:

This study is an observational analytic study with a cross-sectional design that analyzes the risk factors for postoperative nausea and vomiting in the use of intraoperative remifentanil at Dr. Soetomo Hospital Surabaya. Table 1 presents the demographic characteristics of the study subjects. The incidence of postoperative nausea and vomiting in this study was 10%, experienced by five patients. The first patient who experienced postoperative nausea and vomiting was a female orthopedic patient aged 17-25 years, who received a remifentanil maintenance dose ranging from 0.16 to 0.2 µg/kg/mi. The second patient who experienced postoperative nausea and vomiting was a female patient aged 17-25 years undergoing head and neck surgery, also receiving a remifentanil maintenance dose ranging from 0.16 to 0.2 µg/kg/min. The third patient who experienced postoperative nausea and vomiting was a female patient aged 17-25 years undergoing eye surgery, receiving a remifentanil maintenance dose ranging from 0.11 to 0.15 µg/kg/min. The fourth patient who experienced postoperative nausea and vomiting was a female patient aged 26-30 years undergoing head and neck surgery, receiving a remifentanil maintenance dose ranging from 0.11 to 0.15 µg/kg/min. The last patient was a female patient aged 26-30 years undergoing oral surgery, receiving a remifentanil maintenance dose ranging from 0.11 to 0.15 µg/kg/min.

Table (1) Demographic Characteristics of Study Subjects

Variable	Total
PONV	5 (10,0%)
No PONV	45 (90,0%)
Operation Type	
Eye	15 (30,0%)
Orthopedics	13 (26,0%)
Head Neck Surgery	6 (12,0%)
Oral Surgery	16 (32,0%)
Smoking History	
Smokers	28 (56,0%)
Nonsmokers	22 (44,0%)
Gender	
Man	33 (66,0%)
Woman	17 (34,0%)
Age (years)	
17-25	8 (16,0%)
26-35	7 (14,0%)
36-45	8 (16,0%)
46-55	12 (24,0%)
56-60	15 (30,0%)
Optimal Maintenance Dose Range of Remifentanil (μg/kg/min)	
0,05-0,10	38 (76,0%)
0,11-0,15	9 (18,0%)
0,16-0,20	3 (6,0%)

The Relationship between Type of Surgery and the Incidence of Postoperative Nausea and Vomiting in Patients Undergoing General Anesthesia with Intraoperative Remifentanil:

Table 2 presents the relationship between the type of surgery and the incidence of postoperative nausea and vomiting. In this study, no significant relationship was found between the type of surgery and the incidence of postoperative nausea and vomiting ($p>0.05$). The highest incidence of postoperative nausea and vomiting was observed in patients undergoing head and neck surgery, with 2 cases (33.3%). Table 3 displays the incidence of postoperative nausea and vomiting categorized by the type of surgery and the dose of remifentanil used. Postoperative nausea and vomiting were observed at remifentanil doses of 0.11-0.15 and 0.16-0.20 μg/kg/min, while no cases were reported at doses of 0.05-0.10 μg/kg/min.

Table (2) Relationship between the type of surgery and the incidence of postoperative nausea and vomiting in patients undergoing general anesthesia with intraoperative remifentanil

Operation Type	PONV	No PONV	p *value*	c
Eye	1 (6,7%)	14 (93,3%)	0,247[a]	0,277[b]
Orthopedics	1 (7,7%)	12 (92,3%)		
Head Neck Surgery	2 (33,3%)	4 (66,7%)		
Oral Surgery	1 (6,3%)	15 (93,8%)		

a. Fischer exact test
b. Contingency Coefficient

Table (3) Remifentanil use by type of surgery

Operation Type	Remifentanil Maintenance Dosage (μg/kg/min)	PONV	No PONV
Eye	0,05-0,10	0 (0,0%)	14 (100,0%)
	0,11-0,15	1 (100,0%)	0 (0,0%)
	0,16-0,20	0 (0,0%)	0 (0,0%)
Orthopedics	0,05-0,10	0 (0,0%)	7 (100,0%)
	0,11-0,15	0 (0,0%)	4 (100,0%)
	0,16-0,20	1 (50,0%)	1 (50,0%)
Head Neck Surgery	0,05-0,10	0 (0,0%)	4 (100,0%)

	0,11-0,15	1 (100,0%)	0 (0,0%)
	0,16-0,20	1 (100,0%)	0 (0,0%)
Oral Surgery	0,05-0,10	0 (0,0%)	13 (100,0%)
	0,11-0,15	1 (33,3%)	2 (66,7%)
	0,16-0,20	0 (0,0%)	0 (0,0%)

Relationship between Smoking History and the Incidence of Postoperative Nausea and Vomiting in Patients Undergoing General Anesthesia with Intraoperative Remifentanil:

Table 4 illustrates the relationship between smoking history and the incidence of postoperative nausea and vomiting. In this study, a weak but statistically significant association was observed between smoking history and the incidence of postoperative nausea and vomiting ($c = 0.352$; $p < 0.05$). The incidence of postoperative nausea and vomiting was identified in the non-smoker group, with 5 cases (22.7%) reported. Table 5 presents the use of remifentanil categorized by smoking history and the administered dose. Postoperative nausea and vomiting occurred at remifentanil doses of 0.11-0.15 and 0.16-0.20 μg/kg/min, specifically in the non-smoker group.

Table (4) Relationship between Smoking History and the Incidence of Postoperative Nausea and Vomiting in Patients Undergoing General Anesthesia with Intraoperative Remifentanil

Smoking History	**PONV**	**No PONV**	**p *value***	**c**
Smokers	0 (0,0%)	28 (100,0%)	0,012[a]	0,352[b]
Nonsmokers	5 (22,7%)	17 (77,3%)		

a. Fischer exact test
b. Contingency Coefficient

Table (5) Remifentanil use Based on Smoking History

Smoking History	**Remifentanil Maintenance Dosage (μg/kg/min)**	**PONV**	**No PONV**
Smokers	0,05-0,10	0 (0,0%)	22 (100,0%)
	0,11-0,15	0 (0,0%)	5 (100,0%)
	0,16-0,20	0 (0,0%)	1 (100,0%)
Nonsmokers	0,05-0,10	0 (0,0%)	16 (100,0%)
	0,11-0,15	3 (75,0%)	1 (25,0%)
	0,16-0,20	2 (100,0%)	0 (0,0%)

Relationship between Gender and the Incidence of Postoperative Nausea and Vomiting in Patients Undergoing General Anesthesia with Intraoperative Remifentanil

Table 6 depicts the relationship between gender and the incidence of postoperative nausea and vomiting. In this study, a moderate and significant relationship was observed between gender and the incidence of postoperative nausea and vomiting ($c = 0.421$; $p < 0.05$). The female group exhibited a higher incidence of nausea and vomiting compared to the male group (5 cases (29.4%) vs. 0 cases (0.0%)). Table 7 presents the incidence of postoperative nausea and vomiting categorized by gender and the maintenance dose of remifentanil. The occurrence of postoperative nausea and vomiting was found in females receiving doses of 0.11-0.15 and 0.16-0.20 μg/kg/min.

Table (6) Relationship between Gender and Incidence of Postoperative Nausea and Vomiting in Patients Undergoing General Anesthesia with Intraoperative Remifentanil

Gender	**PONV**	**No PONV**	**p *value***	**c**
Man	0 (0,0%)	33 (100,0%)	0,003[a]	0,421[b]
Woman	5 (29,4%)	12 (70,6%)		

a. Fischer exact test
b. Contingency Coefficient

Table (7) Use of Remifentanil Based on Gender

Gender	**Remifentanil Maintenance Dosage (μg/kg/min)**	**PONV**	**No PONV**
Man	0,05-0,10	0 (0,0%)	26 (100,0%)

	0,11-0,15	0 (0,0%)	6 (100,0%)
	0,16-0,20	0 (0,0%)	1 (100,0%)
Woman	0,05-0,10	0 (0,0%)	12 (100,0%)
	0,11-0,15	3 (100,0%)	0 (0,0%)
	0,16-0,20	2 (100,0%)	0 (0,0%)

Relationship between Age and the Incidence of Postoperative Nausea and Vomiting in Patients Undergoing General Anesthesia with Intraoperative Remifentanil:

Table 8 illustrates the relationship between age and the incidence of postoperative nausea and vomiting. In this study, a moderate and significant association was observed between age and the incidence of postoperative nausea and vomiting ($c = 458$; $p < 0.05$). The younger age group exhibited a higher incidence of nausea and vomiting, with 3 patients (37.5%) aged 17-25 years and 2 patients (28.6%) aged 26-35 years. Table 9 presents the incidence of nausea and vomiting categorized by age and the remifentanil maintenance dose (μg/kg/min). Nausea and vomiting were reported in all age groups except for the 46-55 years age group, particularly at doses of 0.11-0.15 and 0.16-0.20 μg/kg/min.

Table (8) Relationship between Age and Incidence of Postoperative Nausea and Vomiting in Patients Undergoing General Anesthesia with Intraoperative Remifentanil

Age (years)	PONV	No PONV	p *value*	c
17-25	3 (37,5%)	5 (62,5%)	0,010[a]	0,458[b]
26-35	2 (28,6%)	5 (71,4%)		
36-45	0 (0,0%)	8 (100,0%)		
46-55	0 (0,0%)	12 (100,0%)		
56-60	0 (0,0%)	15 (100,0%)		

a. Fischer exact test
b. Contingency Coefficient

Table (9) Remifentanil use by Age

Age (years)	Remifentanil Maintenance Dosage (μg/kg/min)	PONV	No PONV
17-25	0,05-0,10	0 (0,0%)	3 (100,0%)
	0,11-0,15	2 (66,7%)	1 (33,3%)
	0,16-0,20	1 (50,0%)	1 (50,0%)
26-35	0,05-0,10	0 (0,0%)	3 (100,0%)
	0,11-0,15	1 (33,3%)	2 (66,7%)
	0,16-0,20	1 (100,0%)	0 (0,0%)
36-45	0,05-0,10	0 (0,0%)	6 (100,0%)
	0,11-0,15	0 (0,0%)	2 (100,0%)
	0,16-0,20	0 (0,0%)	0 (0,0%)
46-55	0,05-0,10	0 (0,0%)	12 (100,0%)
	0,11-0,15	0 (0,0%)	0 (0,0%)
	0,16-0,20	0 (0,0%)	0 (0,0%)

Relationship between the Optimal Home Dose Range of Remifentanil and the Incidence of Postoperative Nausea and Vomiting in Patients Undergoing General Anesthesia:

Table 10 illustrates the relationship between the dose range and the incidence of postoperative nausea and vomiting. In this study, a moderate and significant relationship was observed between the dose range and the incidence of postoperative nausea and vomiting ($c = 0.538$; $p < 0.05$). The incidence of postoperative nausea and vomiting was found to be 2 (66.7%) patients in the dose range of 0.16-0.20 μg/kg/min and 1 (33.3%) person in the dose range of 0.11-0.15 μg/kg/min.

Table (10) Relationship between Remifentanil Optimal Maintenance Dose Range and the Incidence of Postoperative Nausea and Vomiting in Patients Undergoing General Anesthesia

Optimal Maintenance Dose Range of Remifentanil	PONV	No PONV	Total	p *value*	c

(µg/kg/min)					
0,05-0,10	0 (0,0%)	38 (100,0%)	38 (100,0%)	0,001 [a]	0,538 [b]
0,11-0,15	3 (33,3%)	6 (66,7%)	9 (100,0%)		
0,16-0,20	2 (66,7%)	1 (33,3%)	3 (100,0%)		

a. Fischer exact test
b. Contingency coefficient

DISCUSSION

Postoperative nausea and vomiting are common complications of surgical procedures that can have various negative effects on patients, including prolonged hospital stays and potential complications for subsequent surgeries and anesthesia (Barnes, 2020). Additionally, postoperative nausea and vomiting is considered an important complication as it is comparable to postoperative pain in terms of patient discomfort. Preventing postoperative nausea and vomiting can significantly improve patient satisfaction, particularly for individuals who are prone to experiencing these symptoms (Devarakonda et al., 2022). It is known that approximately 20-30% of patients experience postoperative nausea and vomiting within the first 24-48 hours after surgery (Amirshahi et al., 2020). Early identification of high-risk patients and appropriate prophylaxis can help reduce the incidence and consequences of these complications. Despite its high prevalence, research on the incidence of postoperative nausea and vomiting in Indonesia is limited.

Remifentanil, a fast-acting opioid analgesic drug used during anesthesia, is believed to cause less postoperative nausea and vomiting compared to other opioids (Boysen et al., 2023). It acts as an agonist of µ opioid receptors, binding to esters and exhibiting a rapid onset and short duration (Aryana et al., 2022). Some studies have shown that postoperative nausea and vomiting occur less frequently with remifentanil compared to other opioids, while others have found no significant difference (Citerio et al., 2012; Constantinides dan Murphy, 2016; Sridharan dan Sivaramakrishnan, 2019; Watanabe et al., 2018). However, these studies often include patients who receive other opioids for pain management after surgery and undergo different types of procedures, such as abdominal surgery, which may increase the risk of postoperative nausea and vomiting (Constantio et al., 2021; Sridharan dan Sivaramakrishnan, 2019). Furthermore, some studies utilize anesthetics known to cause postoperative nausea and vomiting. To address these limitations, our study included only patients who received remifentanil during surgery without the use of other opioids or procedures/anesthetics known to increase the risk of postoperative nausea and vomiting. The aim of our study was to analyze the association between remifentanil and postoperative nausea and vomiting, as well as the incidence of these complications in Indonesia. In this study, patients were given a questionnaire 24 hours postoperatively to assess the occurrence of postoperative nausea and vomiting.

The incidence of postoperative nausea and vomiting in our study was found to be 10.0%. Globally, the incidence of postoperative nausea and vomiting ranges from 20-30% (Gan et al., 2014). Our lower incidence rate can be attributed to the exclusion of risk factors for postoperative nausea and vomiting, such as a history of motion sickness, previous occurrences of postoperative nausea and vomiting, pregnancy, ear surgery, digestive and neurosurgery, and a history of chemotherapy (Dwi, 2014; Setiawan, 2014; Shaikh et al., 2016). This finding is consistent with previous studies (Wu et al., 2015). Another similar study reported an incidence rate of 15.3% among postoperative patients (Matsuura et al., 2016). Similarly, this study excluded surgeries that increase the risk of postoperative nausea and vomiting, such as abdominal surgery, and did not utilize postoperative opioids.

There are five main types of neurotransmitter receptors involved in nausea and vomiting: muscarinic M1, dopamine D2, histamine H1, serotonin 5-hydroxytryptamine (HT)-3, and substance P neurokinin 1 (NK1) (Bashashati dan McCallum, 2014). On the other hand, the pathophysiology of postoperative nausea and vomiting (PONV) involves three types of mechanisms: central, peripheral, and drugs/toxins, including opioids. Opioids can induce postoperative nausea and vomiting through various mechanisms, such as directly affecting the chemoreceptor trigger zone (CTZ) in the brainstem, sensitizing the vestibular organs to motion-induced vomiting, increasing gastrointestinal secretion, causing gastric hypomotility, and delaying gastric emptying (Won et al., 2011). Another theory suggests that opioids can induce nausea and vomiting by stimulating the area postrema, located at the base of the fourth ventricle in the medulla. The area postrema communicates with the central pattern generator via

dopamine and serotonin, triggering the gag reflex (Horn et al., 2014).

Remifentanil is a short-acting opioid that does not accumulate in the body and has a half-life of 8-10 minutes (Shram et al., 2015). This characteristic may contribute to faster recovery from opioid-induced side effects, including postoperative nausea and vomiting. However, the impact of remifentanil on the incidence of postoperative nausea and vomiting is not fully understood. Previous studies have indicated that remifentanil does not cause histamine release and may block stress hormone responses that can trigger nausea and vomiting (Shram et al., 2015). In a recent study, the combination of remifentanil with sevoflurane did not increase the incidence of postoperative nausea and vomiting compared to sevoflurane alone (Lee et al., 2022). Total intravenous anesthesia (TIVA) with propofol-remifentanil has also been associated with reduced postoperative nausea and vomiting in previous studies (Chen et al., 2013; Kumar et al., 2014; Wolf et al., 2016). This study also demonstrated that patients receiving general anesthesia with intraoperative use of remifentanil had a significantly lower incidence of postoperative nausea and vomiting. However, remifentanil still exhibits typical side effects at μ opioid receptors, including nausea and vomiting, albeit with a lower incidence rate of 10% based on our study.

Research on the relationship between the type of surgery, smoking history, gender, age, and home dose range may be valuable in developing risk factors for postoperative nausea and vomiting. These risk factors can be incorporated into scoring systems to facilitate early identification of patients at high risk of postoperative nausea and vomiting. As a result, the management of these patients can be optimized, leading to improved healthcare services. A simple summation score consisting of four risk factors was utilized to identify patients at high risk of postoperative nausea and vomiting. The four risk factors are being female, having a history of postoperative nausea and vomiting, not smoking, and receiving postoperative opioids (Gunawan et al., 2020). If a patient has none or only one risk factor, the incidence of postoperative nausea and vomiting ranges from 10% to 21% (Gunawan et al., 2020). However, if a patient has at least two risk factors, the incidence of postoperative nausea and vomiting can increase to between 39% and 78% (Gunawan et al., 2020). In this study, the incidence of postoperative nausea and vomiting was 10%, which is equivalent to having one or no risk factors for postoperative nausea and vomiting.

Relationship between Type of Surgery and the Incidence of Postoperative Nausea and Vomiting in Patients Undergoing General Anesthesia with Intraoperative Remifentanil:

In this study, there was no significant association between the type of surgery and the incidence of postoperative nausea and vomiting in patients undergoing general anesthesia with intraoperative remifentanil. Some studies have also found no clear association between specific factors and postoperative nausea and vomiting. However, when surgeries are stratified by location, certain types of surgeries have been found to be associated with a higher risk of requiring anti-nausea medication in the recovery room. It is worth noting that for adults, the type of surgery is not an independent factor for predicting the risk of postoperative nausea and vomiting. However, in children, strabismus surgery has been identified as an independent risk factor for postoperative nausea and vomiting (Pierre dan Whelan, 2013).

The incidence of postoperative nausea and vomiting was highest in head and neck surgery, with two patients experiencing these symptoms. This can be attributed to the strong vagal stimulation that can occur during head and neck surgery (Won et al., 2011). It is important to note that the incidence of postoperative nausea and vomiting was relatively low in this study, as it excluded surgeries known to have a high risk of these complications, such as ear surgery, digestive surgery, and neurosurgery. Previous research has demonstrated that ear, digestive, and neurosurgical procedures increase the risk of postoperative nausea and vomiting (Wallden et al., 2016).

Relationship between Smoking History and the Incidence of Postoperative Nausea and Vomiting in Patients Undergoing General Anesthesia with Intraoperative Remifentanil:

In this study, a significant association was found between smoking history and the incidence of postoperative nausea and vomiting in patients undergoing general anesthesia with intraoperative remifentanil. The non-smoker group had an incidence of postoperative nausea and vomiting, with 5 (22.7%) patients experiencing these symptoms. Previous studies have also reported a significant association between smoking and a decreased incidence of postoperative nausea and vomiting (Sinha et al., 2022; Song et al., 2023). Sinha and colleagues, as well as Song and colleagues, conducted studies using general anesthesia with a reported dose of remifentanil ranging from 0.05 to 0.20 mg/kg/min and found an association between non-smokers and the incidence of postoperative nausea and vomiting. This suggests, and is supported by the results of this study, that non-smokers can experience postoperative nausea and vomiting even when variables that may increase the risk of these complications are excluded.

Individuals who do not smoke are almost twice as likely as smokers to experience postoperative nausea and vomiting (Sinha et al., 2022; Song et al., 2023). Several other studies have supported this finding, suggesting that chronic exposure to smoke, particularly polycyclic aromatic hydrocarbons, can lead to changes in hepatic microsomal enzymes that may affect drug metabolism and the ability of drugs to cause postoperative nausea and vomiting (Wu et al.,

2015). However, it is important to note that the study conducted by Wu and colleagues was a study without the use of remifentanil. Another study also mentioned that non-smoker status is a risk factor for postoperative nausea and vomiting (Shahnazdust et al., 2015). Some studies have suggested that smokers may be more resistant to anesthetic gases and other toxins compared to non-smokers, resulting in a lower incidence of PONV. The anti-nausea effect of smoking has been confirmed by many studies (Darvall et al., 2021; Farhat et al., 2014). However, recent studies specifically related to remifentanil are limited or unavailable.

One potential explanation for the reduction in postoperative nausea and vomiting observed in smokers could be the presence of antiemetic substances in cigarette smoke. It is known that the pharmacological receptors involved in PONV are regulated by dopamine (D2), cholinergic, histamine (H1), 5-HT3, and NK1 receptors. Therefore, if antiemetic compounds are present in cigarette smoke, they most likely belong to one of these receptor-blocking drug classes (Darvall et al., 2021; Farhat et al., 2014). However, this hypothesis has not provided conclusive evidence, as other dopaminergic, cholinergic, or histaminergic effects are not always observed. Another possible explanation for the reduction of PONV in smokers is that it could be an adaptive response to repeated exposure to the emetic/vomiting stimulus. However, vomiting usually occurs only in people who do not habitually smoke or have consumed excessive amounts of tobacco (Darvall et al., 2021; Farhat et al., 2014). This suggests a role for chronic exposure to cigarettes in postoperative nausea and vomiting.

Cigarette smoke is a complex mixture of gaseous and particulate matter. The gaseous component, which accounts for 60% of tobacco smoke, includes formaldehyde, carbon monoxide, nitrogen oxides, hydrogen cyanide, and other compounds. The remaining 40% is the particulate phase, which contains about 3,500 different substances, with nicotine being the most abundant alkaloid. Other alkaloids present include nornicotine, anatabine, and anabasine. Additionally, there are acids, lactones, aldehydes, ketones, alcohols, polyphenols, nitrosamines, and polycyclic aromatic hydrocarbons. The particulate phase, excluding alkaloids and water, is commonly referred to as tar (Soleimani et al., 2022).

Most drugs are metabolized through the cytochrome P450 (CYP450) pathway. Six enzymes, namely CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4, are responsible for 90% of drug and xenobiotic compound metabolism (Farhat et al., 2014). This multi-enzyme system has evolved over thousands of years in plants and animals as an adaptive response to environmental challenges, such as exposure to toxic or harmful substances. This response leads to the expression of enzymes responsible for the metabolism of specific toxins. While this is usually beneficial, it can also result in the formation of metabolites that are pharmacologically active or even carcinogenic. Induced enzymes can also have significant effects on drug clearance and half-life (Hakkola et al., 2020).

Smoking has been shown to induce up to a threefold increase in the activity of CYP1A2 (He et al., 2015), which is the main enzyme responsible for the metabolism of several commonly used drugs by anesthesiologists. This increased enzyme activity results in a higher rate of drug metabolism, potentially requiring higher dosage requirements. For example, studies have shown that the clearance of theophylline, an asthma drug, is significantly increased in smokers, leading to a twofold reduction in its half-life (Goseva et al., 2015). Quitting smoking may result in a rapid accumulation of theophylline, necessitating dose adjustment. Smoking also affects the metabolism of various psychoactive drugs, including antidepressants, antipsychotics, and anxiolytics, which also depend on CYP1A2 (Scherf-Clavel et al., 2019). It is worth noting that smokers may require more analgesia due to increased metabolism of opioids, such as morphine and meperidine.

In contrast, CYP2E1 is responsible for the metabolism of volatile/inhaled anesthetics, which are the main cause of postoperative nausea and vomiting in the first two hours postoperatively. Cigarette smoke, through nicotine and polycyclic aromatic hydrocarbons (PAH), also triggers CYP2E1 (Maideen, 2019). Therefore, patients with smoking-induced enzyme induction have a higher rate of volatile anesthetic metabolism. Such patients may experience faster and smoother recovery from anesthesia. In this study, patients who smoked had a lower incidence of postoperative nausea and vomiting.

Relationship between Gender and the Incidence of Postoperative Nausea and Vomiting in Patients Undergoing General Anesthesia with Intraoperative Remifentanil:

In this study, there was a significant relationship between gender and the incidence of postoperative nausea and vomiting in patients undergoing general anesthesia with intraoperative remifentanil. The female group (29.4%) had a higher incidence of nausea and vomiting compared to the male group (0.0%). Previous studies using general anesthesia and intraoperative remifentanil at a dose of 0.05-0.20 mg/kg/min also found that females were associated with a higher incidence of postoperative nausea and vomiting (Sinha et al., 2022; Song et al., 2023). A multicenter study conducted on patients undergoing general anesthesia surgery identified female gender as the strongest predictor of PONV (Wallden et al., 2016). Another study by Hara et al. (2013) using remifentanil doses of 0.05-0.20 mg/kg/min and general anesthesia, found an association between female gender and the incidence of postoperative nausea and vomiting. This suggests, and is supported by the

results of this study, that female gender can contribute to postoperative nausea and vomiting, even when other variables that may increase the risk of PONV are accounted for.

The reasons why women are more prone to nausea and vomiting after surgery are still not well understood. Previous studies have indicated the influence of female hormones on the association between postoperative nausea and vomiting. This is evidenced by premenstrual women being more likely to experience nausea compared to postmenstrual women (Echeverria-Villalobos et al., 2022). The incidence of PONV is also higher during the preovulatory and menstrual phases, which may be due to the increased sensitivity of the chemoreceptor trigger zone (CTZ) and vomiting center to estrogen and Follicle-Stimulating Hormone (FSH) (Chatterjee et al., 2011). This means that the vomiting center is more sensitive due to increased estrogen and FSH levels during the preovulatory phase until menstruation. Other studies have shown that in prepubescent children, female gender does not increase the risk of PONV (Eberhart et al., 2004; Kovac, 2021; Urits et al., 2020).

Relationship between Age and the Incidence of Postoperative Nausea and Vomiting in Patients Undergoing General Anesthesia with Intraoperative Remifentanil:

In this study, there was a significant relationship between age and the incidence of postoperative nausea and vomiting in patients undergoing general anesthesia with intraoperative remifentanil. The young age group had a higher incidence of nausea and vomiting, with 3 patients (37.5%) in the 17-25 years old group and 2 patients (28.6%) in the 26-35 years old group. Previous studies have also found an association between young age and the incidence of postoperative nausea and vomiting (Sinha et al., 2022; Wallden et al., 2016). Both of these studies used general anesthesia. This suggests that the incidence of PONV tends to slightly decrease with age in adults (Sinha et al., 2022; Wallden et al., 2016). In another study using general anesthesia and remifentanil at a dose of 0.05-0.20 mg/kg/min, the incidence of postoperative nausea and vomiting was higher in younger age groups compared to nitrous oxide (Kim et al., 2016).

Supported by the results of this study, young age was associated with the incidence of postoperative nausea and vomiting, even after excluding variables that may increase the risk of PONV. The incidence of postoperative nausea and vomiting appears to decrease with age based on previous studies (Darvall et al., 2021; Geralemou dan Gan, 2016; Sinha et al., 2022; Wu et al., 2015). In these studies, the incidence of postoperative nausea and vomiting in pediatric patients can be high, with the 6-10 years age group having rates of up to 34%, but tends to decrease with the onset of puberty.

One of the risk factors for PONV is age. Several studies have shown that older age is associated with a lower incidence of postoperative nausea and vomiting (Jin et al., 2020; Wang dan Argalious, 2020). The reasons for this are not entirely clear, but three explanations exist. First, older patients may have decreased sensitivity to emetogenic stimuli due to age-related changes in central and peripheral mechanisms related to nausea and vomiting. Second, older patients may receive lower doses of opioids and volatile anesthetics, which are known to increase the risk of postoperative nausea and vomiting. Third, older patients may have a higher threshold and better coping strategies. Therefore, older age may have a protective effect against postoperative nausea and vomiting, but this does not mean that older patients are immune to this complication. Older patients may also have more comorbidities and consume medications that may interact with antiemetics (Jin et al., 2020; Wang dan Argalious, 2020).

Relationship between the Optimal Home Dose Range of Remifentanil and the Incidence of Postoperative Nausea and Vomiting in Patients Undergoing General Anesthesia:

In this study, a significant relationship was found between the dose range and the incidence of postoperative nausea and vomiting in patients undergoing general anesthesia ($p<0.05$). The incidence of postoperative nausea and vomiting was observed in the dose range of 0.16-0.20 μg/kg/min, with 2 patients (66.7%), and in the dose range of 0.11-0.15 μg/kg/min, with 1 patient (33.3%). It can be concluded that higher doses are associated with a higher incidence of postoperative nausea and vomiting in patients. This dose-dependent relationship was demonstrated through statistical analysis in this study, and it is clinically known that the dose has an effect on the incidence of postoperative nausea and vomiting under general anesthesia (Choi et al., 2014). Other studies have also shown that increasing the postoperative opioid dose increases the incidence of postoperative nausea and vomiting under general anesthesia (Choi et al., 2014; Wallden et al., 2016). Research conducted in Indonesia has also demonstrated that opioids can increase the incidence of postoperative nausea and vomiting (Dwi, 2014; Setiawan, 2014). Furthermore, another study explained that a home dose of remifentanil higher than 0.2 μg/kg/min under general anesthesia can increase the incidence of PONV (Hozumi et al., 2015). It is important to note that in this study, a remifentanil dose higher than 0.2 μg/kg/min was not used.

This study has certain limitations that should be taken into account. Firstly, it was carried out exclusively in a single healthcare center, specifically a tertiary hospital. This hospital is known for providing high-complexity healthcare services and operating with a diverse range of integrated services. As a result, the findings may not accurately represent the conditions prevalent in the majority of healthcare institutions across Indonesia.

Consequently, when applying the results of this study, careful consideration is required to ensure their relevance and applicability to other healthcare settings in the country.

CONCLUSION

In conclusion, the statistical analysis and discussions on the incidence of postoperative nausea and vomiting in patients undergoing general anesthesia with intraoperative remifentanil have led to several key findings. Firstly, there is no significant relationship between the type of surgery and the occurrence of postoperative nausea and vomiting. Secondly, smoking history has been identified as a significant factor, with patients who have a smoking history being more prone to experiencing these symptoms. Additionally, gender has been found to play a role, with certain genders being more susceptible than others. Age has also been identified as a factor, with specific age groups being at a higher risk. Furthermore, the study highlights a correlation between the remifentanil home dose range and the incidence of postoperative nausea and vomiting, indicating that higher doses of remifentanil are associated with a higher likelihood of experiencing these symptoms.

Based on the results of this study, several recommendations can be made to further enhance our understanding of postoperative nausea and vomiting in patients undergoing general anesthesia with intraoperative remifentanil. Firstly, it is advisable to conduct prospective research to gather more accurate and real-time data, enabling a more comprehensive analysis of the incidence of these symptoms. Secondly, a multicenter study should be considered to validate the findings across multiple medical centers and enhance the generalizability of the results. Lastly, it is important to conduct further research focusing on identifying additional risk factors that contribute to the occurrence of postoperative nausea and vomiting. By exploring these factors, targeted interventions and preventive measures can be developed to better manage and alleviate these symptoms in at-risk patients.

By implementing these suggestions, future research endeavors can contribute to a deeper understanding of postoperative nausea and vomiting, leading to improved strategies for its prevention and management in patients undergoing general anesthesia with intraoperative remifentanil.

AUTHORS' CONTRIBUTION

MPB, AS and PPME: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to beaccountable for all aspects of the work. PSA, M and A: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all aspects of the work.

Conflict of interest: Authors declared no conflict of interest.

REFERENCES

1. Amirshahi, M., Behnamfar, N., Badakhsh, M., Rafiemanesh, H., Keikhaie, K. R., Sheyback, M., dan Sari, M. 2020. 'Prevalence of postoperative nausea and vomiting: A systematic review and meta-analysis'. *Saudi J Anaesth, 14*(1), 48-56. doi:10.4103/sja.SJA_401_19
2. Apfel, C. C., Heidrich, F. M., Jukar-Rao, S., Jalota, L., Hornuss, C., Whelan, R. P., Zhang, K., dan Cakmakkaya, O. S. 2012. 'Evidence-based analysis of risk factors for postoperative nausea and vomiting'. *British Journal of Anaesthesia, 109*(5), 742-753. doi:10.1093/bja/aes276
3. Barnes, J. 2020. 'Postoperative nausea and vomiting'. *British Journal of Hospital Medicine, 81*(6), 1-3. doi:10.12968/hmed.2019.0249
4. Bashashati, M., dan McCallum, R. W. 2014. 'Neurochemical mechanisms and pharmacologic strategies in managing nausea and vomiting related to cyclic vomiting syndrome and other gastrointestinal disorders'. *Eur J Pharmacol, 722*, 79-94. doi:10.1016/j.ejphar.2013.09.075
5. Boysen, P. G., Patel, J. H., dan King, A. N. 2023. 'Brief history of opioids in perioperative and periprocedural medicine to inform the future'. *Ochsner J, 23*(1), 43-49. doi:10.31486/toj.22.0065
6. Cao, X., White, P. F., dan Ma, H. 2017. 'An update on the management of postoperative nausea and vomiting'. *J Anesth, 31*(4), 617-626. doi:10.1007/s00540-017-2363-x
7. Černý, V. 2014. 'Consensus guidelines for the management of postoperative nausea and vomiting'. *Anesteziologie a Intenzivni Medicina, 25*(3), 244-246. doi:10.1097/01.sa.0000443065.56805.0c
8. Chatterjee, S., Rudra, A., dan Sengupta, S. 2011. 'Current concepts in the management of postoperative nausea and vomiting'. *Anesthesiology Research and Practice, 2011*(748031). doi:10.1155/2011/748031
9. Chen, L., Yu, L., Fan, Y., dan Manyande, A. 2013. 'A comparison between total intravenous anaesthesia using propofol plus remifentanil and volatile induction/ maintenance of anaesthesia using sevoflurane in children undergoing flexible fibreoptic bronchoscopy'. *Anaesth Intensive Care, 41*(6), 742-749. doi:10.1177/0310057X1304100609
10. Choi, J. B., Shim, Y. H., Lee, Y. W., Lee, J. S., Choi, J. R., dan Chang, C. H. 2014. 'Incidence and risk factors of postoperative nausea and vomiting in patients with fentanyl-based intravenous patient-controlled analgesia and single antiemetic prophylaxis'. *Yonsei Med J, 55*(5), 1430-1435. doi:10.3349/ymj.2014.55.5.1430

11. Citerio, G., Pesenti, A., Latini, R., Masson, S., Barlera, S., Gaspari, F., Franzosi, M. G., dan NeuroMorfeo Study, G. 2012. 'A multicentre, randomised, open-label, controlled trial evaluating equivalence of inhalational and intravenous anaesthesia during elective craniotomy'. *Eur J Anaesthesiol, 29*(8), 371-379. doi:10.1097/EJA.0b013e32835422db
12. Constantinides, C., dan Murphy, K. 2016. 'Molecular and integrative physiological effects of isoflurane anesthesia: The paradigm of cardiovascular studies in rodents using magnetic resonance imaging'. *Front Cardiovasc Med, 3*(1), 23. doi:10.3389/fcvm.2016.00023
13. Constantio, R., Utariani, A., dan Susila, D. 2021. 'Opioid use and pain intensity as risk factors of cancer-related depression'. *International Journal of Innovative Science and Research Technology, 6*(1), 105-109.
14. Cruz, S. L., dan Granados-Soto, V. 2015. *Opioids and opiates: Pharmacology, abuse, and addiction*. New York, NY: Springer New York.
15. Darvall, J., Handscombe, M., Maat, B., So, K., Suganthirakumar, A., dan Leslie, K. 2021. 'Interpretation of the four risk factors for postoperative nausea and vomiting in the apfel simplified risk score: An analysis of published studies'. *Can J Anaesth, 68*(7), 1057-1063. doi:10.1007/s12630-021-01974-8
16. Depkes RI. 2009. *Pedoman pelaksanaan program rumah sakit sayang ibu dan bayi (rssib)*. Jakarta: Depkes RI.
17. Devarakonda, B. V., Goel, A., Singh, S., Kumar Sreevastava, D., Vadapalli, K., dan Mohan Reddy, M. 2022. 'Efficacy of evidence-based institutional protocol for prevention of postoperative nausea and vomiting: A prospective observational study'. *Med J Armed Forces India, 78*(1), 36-41. doi:10.1016/j.mjafi.2020.02.004
18. Dorland, W. A. N. 2019. *Dorland's illustrated medical dictionary 33rd edition*. Philadelphia: Saunders.
19. Dwi, S. B. 2014. 'Angka kejadian mual-muntah pada pemberian metoclopramide dibandingkan ondansetron pada pasien yang mendapat terapi tramadol pasca bedah dengan anestesi umum'. *Repository Universitas Airlangga*. doi:http://repository.unair.ac.id/id/eprint/123838
20. Eberhart, L. H. J., Geldner, G., Kranke, P., Morin, A. M., Schauffelen, A., Treiber, H., dan Wulf, H. 2004. 'The development and validation of a risk score to predict the probability of postoperative vomiting in pediatric patients'. *Anesth Analg, 99*(6), 1630-1637. doi:10.1213/01.ANE.0000135639.57715.6C
21. Echeverria-Villalobos, M., Fiorda-Diaz, J., Uribe, A., dan Bergese, S. D. 2022. 'Postoperative nausea and vomiting in female patients undergoing breast and gynecological surgery: A narrative review of risk factors and prophylaxis'. *Front Med (Lausanne), 9*, 909982. doi:10.3389/fmed.2022.909982
22. Farhat, K., Waheed, A., Pasha, A. K., Iqbal, J., dan Mansoor, Q. 2014. 'Effect of smoking on nausea, vomiting and pain in the post-operative period'. *Journal of Postgraduate Medical Institute, 28*(3), 277-281.
23. Flood, P., Rathmell, J. P., dan Shafer, S. 2015. *Stoelting's pharmacology and physiology in anesthetic practice*: Wolters Kluwer Health.
24. Gan, T. J., Diemunsch, P., Habib, A. S., Kovac, A., Kranke, P., Meyer, T. A., dan Watcha, M., et al. 2014. 'Consensus guidelines for the management of postoperative nausea and vomiting'. *Anesth Analg, 118*(1), 85-113. doi:10.1213/ANE.0000000000000002
25. Gan, T. J., Habib, A. f. S., dan Kehlet, H. 2016. *Postoperative nausea and vomiting: A practical guide*. Cambridge: Cambridge University Press.
26. Geralemou, S., dan Gan, T. J. 2016. 'Assessing the value of risk indices of postoperative nausea and vomiting in ambulatory surgical patients'. *Curr Opin Anaesthesiol, 29*(6), 668-673. doi:10.1097/ACO.0000000000000400
27. Goseva, Z., Gjorcev, A., Kaeva, B. J., Janeva, E. J., dan Angelovska, I. 2015. 'Analysis of plasma concentrations of theophylline in smoking and nonsmoking patients with asthma'. *Open Access Maced J Med Sci, 3*(4), 672-675. doi:10.3889/oamjms.2015.117
28. Gunawan, M. Y., Utariani, A., Maulydia, M., dan Surgean, A. V. 2020. 'Sensitivity and specificity comparison between apfel, koivuranta, and sinclair score ponv predictor in post general anesthesia patient'. *Qanun Medika (QM), 4*(1), 69-76. doi:DOI: http://dx.doi.org/10.30651/jqm.v4i1.2826
29. Hakkola, J., Hukkanen, J., Turpeinen, M., dan Pelkonen, O. 2020. 'Inhibition and induction of cyp enzymes in humans: An update'. *Arch Toxicol, 94*(11), 3671-3722. doi:10.1007/s00204-020-02936-7
30. Hamzah, H., Bratha, I. N. Y. D. S., Sumartono, C., Utariani, A., Semedi, B. P., dan Avidar, Y. P. 2020. 'Comparison of outcome between patients receiving general anesthesia combined with continuous epidural anesthesia and patients receiving general anesthesia combined with intermittent epidural anesthesia'. *Bali Journal of Anesthesiology (BJOA), 4*(3), 118-121. doi:https://doi.org/10.4103/BJOA.BJOA_18_20
31. Hara, R., Hirota, K., Sato, M., Tanabe, H., Yazawa, T., Habara, T., dan Fukuda, K. 2013. 'The impact of remifentanil on incidence and severity of postoperative nausea and vomiting in a university hospital-based ambulatory surgery center: A retrospective observation study'. *Korean J Anesthesiol, 65*(2), 142-146. doi:10.4097/kjae.2013.65.2.142
32. Hasegawa, H., Abe, A., Hayashi, H., Furuta, H., dan Ishihama, T. 2021. 'Risk factors for

postoperative nausea and vomiting after the removal of impacted third molars: A cross-sectional study'. *BMC Oral Health, 21*(1), 121. doi:10.1186/s12903-021-01481-8

33. He, X. M., Zhou, Y., Xu, M. Z., Li, Y., Li, H. Q., dan Li, W. Y. 2015. 'Effects of long-term smoking on the activity and mrna expression of cyp isozymes in rats'. *J Thorac Dis, 7*(10), 1725-1731. doi:10.3978/j.issn.2072-1439.2015.10.07
34. Heckroth, M., Luckett, R. T., Moser, C., Parajuli, D., dan Abell, T. L. 2021. 'Nausea and vomiting in 2021: A comprehensive update'. *J Clin Gastroenterol, 55*(4), 279-299. doi:10.1097/MCG.0000000000001485
35. Horn, C. C., Wallisch, W. J., Homanics, G. E., dan Williams, J. P. 2014. 'Pathophysiological and neurochemical mechanisms of postoperative nausea and vomiting'. *Eur J Pharmacol, 722*, 55-66. doi:10.1016/j.ejphar.2013.10.037
36. Hughes, L. M., Irwin, M. G., dan Nestor, C. C. 2023. 'Alternatives to remifentanil for the analgesic component of total intravenous anaesthesia: A narrative review'. *Anaesthesia, 78*(5), 620-625. doi:10.1111/anae.15952
37. Islam, S., dan Jain, P. 2004. 'Post-operative nausea and vomiting (ponv).: A review article'. *Indian Journal of Anaesthesia, 48*(4), 253-258.
38. Jensen, J. T. 2015. 'Safety and efficacy of remifentanil for single agent procedural sedation: A systematic review'. *International Journal of Anesthetics and Anesthesiology, 2*(3). doi:10.23937/2377-4630/2/3/1033
39. Jin, Z., Gan, T. J., dan Bergese, S. D. 2020. 'Prevention and treatment of postoperative nausea and vomiting (ponv): A review of current recommendations and emerging therapies'. *Ther Clin Risk Manag, 16*, 1305-1317. doi:10.2147/TCRM.S256234
40. Kim, M. K., Yi, M. S., Kang, H., dan Choi, G. J. 2016. 'Effects of remifentanil versus nitrous oxide on postoperative nausea, vomiting, and pain in patients receiving thyroidectomy: Propensity score matching analysis'. *Medicine (Baltimore), 95*(41), e5135. doi:10.1097/MD.0000000000005135
41. Komatsu, R., Turan, A. M., Orhan-Sungur, M., McGuire, J., Radke, O. C., dan Apfel, C. C. 2007. 'Remifentanil for general anaesthesia: A systematic review'. *Anaesthesia, 62*(12), 1266-1280. doi:10.1111/j.1365-2044.2007.05221.x
42. Kovac, A. L. 2021. 'Postoperative nausea and vomiting in pediatric patients'. *Paediatr Drugs, 23*(1), 11-37. doi:10.1007/s40272-020-00424-0
43. Kumar, G., Stendall, C., Mistry, R., Gurusamy, K., dan Walker, D. 2014. 'A comparison of total intravenous anaesthesia using propofol with sevoflurane or desflurane in ambulatory surgery: Systematic review and meta-analysis'. *Anaesthesia, 69*(10), 1138-1150. doi:10.1111/anae.12713
44. Laufenberg-Feldmann, R., Muller, M., Ferner, M., Engelhard, K., dan Kappis, B. 2019. 'Is 'anxiety sensitivity' predictive of postoperative nausea and vomiting?: A prospective observational study'. *Eur J Anaesthesiol, 36*(5), 369-374. doi:10.1097/EJA.0000000000000979
45. Lee, H. S., Lee, K. H., Lee, B., Oh, D., Shin, S. H., dan Park, Y. H. 2022. 'Effect of remifentanil on postoperative vomiting after strabismus surgery in preschool children: A prospective randomized controlled trial'. *Anesth Pain Med, 12*(1), e122160. doi:10.5812/aapm.122160
46. Lestari, L., Hanindito, E., dan Utariani, A. 2020. 'Effectiveness of ketoprofen suppositoria as preemptive analgesia for postoperative pain in patients undergoing elective surgery with general anesthesia'. *Indonesian Journal of Anesthesiology and Reanimation (IJAR), 2*(1), 20-26. doi:http://dx.doi.org/10.20473/ijar.V2I12020
47. Maideen, N. M. P. 2019. 'Tobacco smoking and its drug interactions with comedications involving cyp and ugt enzymes and nicotine'. *World Journal of Pharmacology, 8*(2), 14-25. doi:10.5497/wjp.v8.i2.14
48. Matsuura, H., Inoue, S., dan Kawaguchi, M. 2016. 'The risk of postoperative nausea and vomiting between surgical patients received propofol and sevoflurane anesthesia: A matched study'. *Acta Anaesthesiol Taiwan, 54*(4), 114-120. doi:10.1016/j.aat.2016.09.002
49. Myles, P. S., dan Wengritzky, R. 2012. 'Simplified postoperative nausea and vomiting impact scale for audit and post-discharge review'. *Br J Anaesth, 108*(3), 423-429. doi:10.1093/bja/aer505
50. Pierre, S., dan Whelan, R. P. 2013. 'Nausea and vomiting after surgery'. *Continuing Education in Anaesthesia Critical Care & Pain, 13*(1), 28-32. doi:10.1093/bjaceaccp/mks046
51. Rother, C. 2012. 'Post operative nausea & vomiting use of anti emetic agents in anaesthesia'. *Scottish Universities Medical Journal, 1*(1), page 89-97.
52. Ryan, H., Trosclair, A., dan Gfroerer, J. 2012. 'Adult current smoking: Differences in definitions and prevalence estimates--nhis and nsduh, 2008'. *J Environ Public Health, 2012*, 918368. doi:10.1155/2012/918368
53. Scherf-Clavel, M., Samanski, L., Hommers, L. G., Deckert, J., Menke, A., dan Unterecker, S. 2019. 'Analysis of smoking behavior on the pharmacokinetics of antidepressants and antipsychotics: Evidence for the role of alternative pathways apart from cyp1a2'. *Int Clin Psychopharmacol, 34*(2), 93-100. doi:10.1097/YIC.0000000000000250
54. Schwinghammer, T. L., DiPiro, J. T., Ellingrod, V. L., dan DiPiro, C. V. 2021. *Pharmacotherapy handbook* (11 ed.). New York: McGraw-Hill Medical Pub. Division.

55. Setiawan, A. H. 2014. 'Perbandingan efektifitas antara kombinasi ondansetron dan deksametason dengan ondansetron dalam mencegah mual dan muntah pasca operasi laparaskopi ginekologik infertilitas'. *Repository Universitas Airlangga*. doi:http://repository.unair.ac.id/id/eprint/93837
56. Shahnazdust, M., Ghanbari, A., Noori, R., dan Khalili, M. 2015. 'A comparison between postoperative nausea and vomiting in general anesthesia with isoflurane-remifentanil or isoflurane in cholecystectomy laparoscopic patients'. *J Perianesth Nurs*, *30*(5), 418-422. doi:10.1016/j.jopan.2015.03.009
57. Shaikh, S. I., Nagarekha, D., Hegade, G., dan Marutheesh, M. 2016. 'Postoperative nausea and vomiting: A simple yet complex problem'. *Anesth Essays Res*, *10*(3), 388-396. doi:10.4103/0259-1162.179310
58. Sherwood, L. 2019. *Human physiology: From cells to systems: From cells to systems* (7th ed. Vol. 9). Belmont: CA :Brooks/Cole.
59. Shram, M. J., Silverman, B., Ehrich, E., Sellers, E. M., dan Turncliff, R. 2015. 'Use of remifentanil in a novel clinical paradigm to characterize onset and duration of opioid blockade by samidorphan, a potent mu-receptor antagonist'. *J Clin Psychopharmacol*, *35*(3), 242-249. doi:10.1097/JCP.0000000000000320
60. Sinha, V., Vivekanand, D., dan Singh, S. 2022. 'Prevalence and risk factors of post-operative nausea and vomiting in a tertiary-care hospital: A cross-sectional observational study'. *Med J Armed Forces India*, *78*(Suppl 1), S158-S162. doi:10.1016/j.mjafi.2020.10.024
61. Soenarto, R. F., dan Kapuangan, C. 2012. *Buku ajar anestesiologi*. Jakarta: Departemen Anestesiologi dan Intensive Care FKUI.
62. Soleimani, F., Dobaradaran, S., De-la-Torre, G. E., Schmidt, T. C., dan Saeedi, R. 2022. 'Content of toxic components of cigarette, cigarette smoke vs cigarette butts: A comprehensive systematic review'. *Sci Total Environ*, *813*, 152667. doi:10.1016/j.scitotenv.2021.152667
63. Song, Y., Zhu, J., Dong, Z., Wang, C., Xiao, J., dan Yang, W. 2023. 'Incidence and risk factors of postoperative nausea and vomiting following laparoscopic sleeve gastrectomy and its relationship with helicobacter pylori: A propensity score matching analysis'. *Front Endocrinol (Lausanne)*, *14*, 1102017. doi:10.3389/fendo.2023.1102017
64. Sridharan, K., dan Sivaramakrishnan, G. 2019. 'Drugs for preventing post-operative nausea and vomiting in patients undergoing laparoscopic cholecystectomy: Network meta-analysis of randomized clinical trials and trial sequential analysis'. *Int J Surg*, *69*(4), 1-12. doi:10.1016/j.ijsu.2019.07.002
65. Teshome, D., Fenta, E., dan Hailu, S. (2020). Preoperative prevention and postoperative management of nausea and vomiting in resource limited setting: A systematic review and guideline. In (Vol. 27, pp. 10-17).
66. Tramer, M. R. 2003. 'Treatment of postoperative nausea and vomiting'. *BMJ*, *327*(7418), 762-763. doi:10.1136/bmj.327.7418.762
67. Urits, I., Orhurhu, V., Jones, M. R., Adamian, L., Borchart, M., Galasso, A., dan Viswanath, O. 2020. 'Postoperative nausea and vomiting in paediatric anaesthesia'. *Turk J Anaesthesiol Reanim*, *48*(2), 88-95. doi:10.5152/TJAR.2019.67503
68. Wallden, J., Flodin, J., dan Hultin, M. 2016. 'Validation of a prediction model for post-discharge nausea and vomiting after general anaesthesia in a cohort of swedish ambulatory surgery patients'. *Eur J Anaesthesiol*, *33*(10), 743-749. doi:10.1097/EJA.0000000000000473
69. Wang, M., dan Argalious, M. Y. 2020. *Smith and aitkenhead's textbook of anaesthesia, 7th ed* (Vol. 130). Edinburgh u.a: Churchill Livingstone Elsevier.
70. Watanabe, T., Moriya, K., Tsubokawa, N., dan Baba, H. 2018. 'Effect of remifentanil on postoperative nausea and vomiting: A randomized pilot study'. *J Anesth*, *32*(5), 781-785. doi:10.1007/s00540-018-2550-4
71. Wolf, R., Morinello, E., Kestler, G., Kasmann-Kellner, B., Bischoff, M., Hager, T., Schope, J., dan Eberhart, L. H. 2016. '[ponv after strabismus surgery : Risk adapted prophylaxis?]'. *Anaesthesist*, *65*(7), 507-513. doi:10.1007/s00101-016-0183-2
72. Won, Y. J., Yoo, J. Y., Chae, Y. J., Kim, D. H., Park, S. K., Cho, H. B., Kim, J. S., Lee, J. H., dan Lee, S. Y. 2011. 'The incidence of postoperative nausea and vomiting after thyroidectomy using three anaesthetic techniques'. *J Int Med Res*, *39*(5), 1834-1842. doi:10.1177/147323001103900526
73. Wu, Y. H., Sun, H. S., Wang, S. T., dan Tseng, C. C. 2015. 'Applicability of risk scores for postoperative nausea and vomiting in a taiwanese population undergoing general anaesthesia'. *Anaesth Intensive Care*, *43*(4), 473-478. doi:10.1177/0310057X1504300409