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Comparative Efficacy and Safety of Remifentanil and Fentanyl for Intraoperative Anesthesia

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ABSTRACT

Background: Employing opioids as intraoperative analgesics constitutes a crucial element of perioperative pain management. While ensuring hemodynamic stability and mitigating somatic responses are achievable through deep anesthesia, this approach may engender slow recovery and postoperative nausea and vomiting (PONV). Hence, this study aimed to analyze the efficacy of intravenous opioid anesthetic drugs across both intraoperative and postanesthetic recovery stages to optimize postoperative conditions. **Methods**: This observational analytical study utilized a retrospective approach, involving patients undergoing elective surgery at Dr. Soetomo General Hospital, Surabaya. Parameters included intraoperative Mean Arterial Pressure (MAP) fluctuations, recovery room duration, requirement for postoperative analgesia, and incidence of PONV. **Results**: This study included 95 patients, comprising 44 individuals with remifentanil and 51 individuals receiving fentanyl. Significant disparities were noted in various intraoperative hemodynamic parameters, encompassing the highest systolic blood pressure, alterations in blood pressure, MAP fluctuations, lowest heart rate, and heart rate changes ($p<0.05$). Moreover, a noteworthy difference was observed in the duration of recovery room stay ($p<0.05$), while no significant divergence emerged in the necessity for analgesics or PONV incidence between the two drugs. **Conclusion**: Administration of continuous intraoperative analgesia with remifentanil elicited a more consistent intraoperative hemodynamic response, resulting in a swifter recovery room duration compared to bolus fentanyl. However, no substantial variance was detected in the requirement for analgesics or the incidence of postoperative nausea and vomiting between the two drugs

Keywords: Remifentanil, fentanyl, pain, PONV, postoperative

Introduction

In general anesthesia, opioids are commonly delivered intravenously. While deep anesthesia can ensure hemodynamic stability and diminish somatic responses, it often leads to a protracted emergence and recovery period. Hence, it becomes crucial to assess and compare the efficacy of intravenous opioid anesthetics throughout both the intraoperative and recovery phases of anesthesia (Bhatia & Buvanendran, 2019; Susilo et al., n.d.; Twersky et al., 2001). Fentanyl stands out as a favored option for maintaining hemodynamic stability during the perioperative period (Salinding et al., 2022), however it is related with high incidence of post-operative nausea and vomiting (PONV) and respiratory distress (Bilgi et al., 2016). Conversely, Remifentanil holds a prominent position among short-acting opioids, particularly in lengthy surgical procedures (Kavya et al., 2018). Its enhanced pharmacokinetic profile facilitates straightforward titration to diverse surgical stimuli, encompassing both pain and hemodynamic alterations (Kavya et al., 2018). Remifentanil is widely utilized in clinical applications and serves as a valuable adjunct to general anesthesia for several reasons, including its effect on reducing minimum alveolar concentration, attenuation of autonomic, somatic, and adrenocortical responses to noxious stimuli, and rapid cognitive recovery (Murahata et al., 2018).

Comparations between fentanyl and remifentanil has been made in several previous studies. Remifentanil was associated with lesser incidence of nausea and vomiting and faster recovery (Choi et al., 2008; Muellejans et al., 2003). However, study by Möllhoff et al. (2001) stated that patients received remifentanil experienced greater adverse events such as hypertension. Therefore, this study is aimed to analyze the differences of the efficacy and safety between continuous infusion remifentanil and bolus fentanyl intraoperative.

Methodology

This is an observational analytic with a retrospective design. It was conducted in Dr. Soetomo General Hospital, Surabaya, East Java, Indonesia. This study obtained a permission from Dr. Soetomo General Hospital Ethical Committee (ref. no. 1432/LOE/301.4.2/VIII/2023). Subjects were recruited from patients having elective surgery in our hospital from June 2021 until June 2022. Inclusion criteria were adult patients aged 18 – 65 years, patients with physical status American Society of Anesthesiology (PS ASA) I-II who will be operated with inhalation general anesthesia. Patients with comorbidities such as hypertension, cardiac disease, endocrine and hormonal disease; relying on vasopressor medications and anti-hypertension; patients with allergy or contraindications towards drugs of interest, patients with planned surgery on ear, digestive system, and neurosurgery; patients with malignancy and history of chemotherapy; incomplete medical records were excluded from the study. Patients were recruited using total sampling approach.

Patients were observed based on the differences in the opioid anesthesia used, either using remifentanil or fentanyl. Patients were separated into two groups: Remifentanil was given at 0.5-1 mcg/kg weights for induction and 0.05-2 mcg/kg weights for intravenous continuous pump while fentanyl was given at 1-2 mcg/kg weights for induction and 25-100 mcg intravenously slow bolus. Outcomes of interests are: (1) hemodynamic response, by measuring gradient of highest and lowest mean arterial pressure (MAP) during 5-30 minutes after first bolus of fentanyl or continuous remifentanil intraoperative, patient with stable hemodynamic response showed less MAP gradient, (2) duration of resuscitation room stay, (3) post-operative analgesic, and (4) incidence of nausea and vomiting. Statistical analysis was conducted using IBM SPSS Statistics 26. Ratio data was analyzed using Mann-Whitney test, while nominal data was analyzed using Chi square or Fisher test.

Results and Discussion

There were 95 patients collected in June 2021 – June 2022. Forty-four patients had intraoperative remifentanil and 51 patients was given fentanyl. There were 51 male patients (53.7%) in the overall cohort and average age was 40 years. PS ASA I was found in 12 patients (12.6%) and PS ASA II in 83 patients (87.4%). There was no remarkable difference in the patient characteristics

between two groups.

However, highest systolic blood pressure (SBP) was significantly higher in patients with fentanyl compared with remifentanil group (129 vs 117 mmHg; p< 0.001). SBP gradient was also found higher in fentanyl group (11 mmHg vs 5 mmHg) compared with another group (p< 0.001). similar with SBP, diastolic blood pressure (DBP) gradient was also higher in fentanyl group (7 vs 2 mmHg; p< 0.001). Slowest heart rate (76 vs 78 bpm; p= 0.044) and higher heart rate gradient (8 vs 3 bpm; p< 0.001) was found in fentanyl group. Patients using fentanyl intraoperatively was prescribed more anti-emetic compared to remifentanil group (50 vs 44; p= 0.026). There were no significant differences in post-operative analgetic use between remifentanil and fentanyl **(Table 1).**

Table 1. Patients' characteristics

	Total (n= 95)	**Remifentanil (n= 44)**	**Fentanyl (n= 51)**	**P value**
Age (years)[a]	40 (18-64)	43 (18-64)	41 (19-64)	0.553
Gender[b] Male Female	 51 (53.7) 44 (46.3)	 25 (56.8) 19 (43.2)	 26 (51) 25 (49)	 0.569
PS ASA[b] I II	 12 (12.6) 83 (87.4)	 4 (9,1) 40 (90,0)	 8 (15,7) 43 (84,3)	 0,373
IMT (kg/m^2)[c]	24,69 (5,09)	24,72 (0,67)	25,08(0,78)	0,673
Lowest SBP[a]	113 (90-150)	110 (94-150)	114 (90-140)	0,081
Highest SBP[a]	122 (97-165)	117 (97-154)	129 (100-165)	<0,001*
SBP gradient[a]	7 (1-36)	5 (1-19)	11 (1-36)	<0,001*
Lowest DBP[a]	70 (54-96)	70,5 (54-96)	70 (54-82)	0,077
Highest DBP[a]	76 (56-98)	66,9 (56-98)	77 (60-92)	0,236
DBP gradient[a]	5 (1-15)	2 (1-13)	7 (1-15)	<0,001*
Lowest heart rate[a]	77 (62-110)	78 (63-110)	76 (62-101)	0,044*
Highest heart rate[a]	84 (64-117)	81,5 (64-117)	84 (67-117)	0,606
Heart rate gradient[a]	4 (1-17)	3 (1-16)	8 (2-17)	<0,001*
Post-operative analgetic[b] Metamizole Ketorolac Paracetamol Others	 44 (46.3) 20 (21.1) 29 (30.5) 2 (2.1)	 17 (17.9) 12 (12.6) 14(14.7) 1 (1.1)	 27 (17.9) 8 (17.9) 15 (17.9) 1 (17.9)	 0.457
Post-operative anti-emetic[b] Metoclopramide Ondansetron Others	 75 (78.9) 13 (13.7) 7 (7.4)	 39 (88.6) 5 (11.4) 0 (0)	 36 (70.6) 7 (15.7) 7 (7.4)	 0.026*
Surgery duration[a]	125 (45-350)	127.5 (45-340)	125 (80-350)	0,611

Statistical analysis on hemodynamic response revealed that patients with continuous remifentanil had more stable hemodynamic response compared to fentanyl group. Patients with remifentanil had lower MAP gradient (p< 0.001) and lower level of highest measured MAP intraoperatively (p= 0.006). Remifentanil usage also showed more favorable outcomes in duration of resuscitation room stay (p= 0.002), with remifentanil patients stayed for median 97.5

minutes vs 110 minutes for fentanyl patients. However, there was no statistically difference between both groups in post-operative analgetic and anti-emetic prescriptions.

Table 2. Patients' outcomes

	Remifentanil	Fentanyl	P value
Hemodynamic response			
Lowest MAP*	84 (69-111)	84 (66-101)	0,523
Highest MAP*	88,17 (71-111)	93,33 (73-115)	0,006
MAP gradient*	3,33 (1-12)	8,67 (4-19)	<0,001
RR stay duration (minutes)*	97,5 (75-120)	110 (75-120)	0,002
Post-operative analgetic**	3 (6,8)	6 (11,8)	0,498
Post-operative nausea and vomiting**	4 (9,1)	8 (15,7)	0.373

*data is in median (min-max), **data is in frequency (%)

Overall, our study revealed that remifentanil has more favorable outcomes compared to fentanyl as general anesthesia medications intraoperatively. The findings from this study indicate that the continuous intravenous administration of remifentanil demonstrates a notably steadier intraoperative hemodynamic response when compared to the administration of bolus fentanyl. Remifentanil, being an extremely short-acting opioid, plays a facilitative role in managing hemodynamic and neurological aspects. The observed stability in hemodynamic alterations attributed to remifentanil is closely linked to its distinct pharmacological profile, as outlined by Sivak and Davis (2010). While fentanyl may produce hemodynamic instability in every 5 minutes intra-operatively (Rehi et al., 2023). One potential reason for this could be that Fentanyl promotes hemodynamic stability throughout the perioperative phase by impacting cardiovascular and autonomic regulatory regions. Its mechanism involves reducing sympathetic activity while boosting parasympathetic activity (Samuel et al., 2019)

This study also delineates that patient administered with intraoperative analgesia via continuous intravenous remifentanil exhibited quicker post-anesthesia recovery compared to those given bolus fentanyl. Remifentanil, a highly selective and short-acting μ-opioid receptor agonist (Lee et al., 2018), possesses a distinctive pharmacological profile such as a small distribution volume (0.3-0.4 L/kg), rapid clearance (40-60 mL/min/kg), and minimal variability relative to other intravenous anesthetic agents (Egan, 1995). Its distribution and elimination half-lives stand at 1-2 and 8-20 minutes, respectively (Pitsiu et al., 2004). These characteristics account for remifentanil's quick post-operative effects and expedited recovery from anesthesia, resulting in shorter stays in the recovery room compared to fentanyl. Several researchers have corroborated the favorable post-anesthesia care unit (PACU) outcomes associated with remifentanil, including quicker attainment of normal Aldrete scores (Sivak & Davis, 2010).

This study findings indicate no statistically significant variance in the requirement for postoperative pain relief between the administration of continuous intravenous remifentanil and intravenous bolus fentanyl in conscious recovery room settings for patients undergoing elective surgery under general anesthesia. This outcome contrasts with Thomas et al.'s (2015) study, which found that patients in the remifentanil group necessitated notably higher quantities of both opioid and nonopioid analgesics during the perioperative phase, particularly opioid analgesics (Thomas, 2015). This trend may stem from a critical issue associated with remifentanil-based anesthesia—the rapid loss of analgesic efficacy post-infusion cessation, potentially leading to acute opioid tolerance and increased postoperative analgesic requirements (Moharari et al., 2021; Wilson et al., 2021). This disparity may be caused by lack data of the pain scale of the subjects but rather relied on data regarding additional analgesic administration in the conscious recovery room, unable to account for potential confounding variables. Factors such as educational, social, and economic

status, anxiety levels, and pre-surgery pain medication history can significantly influence the pain perception of research subjects (Chan et al., 2018; Ip et al., 2009; Riecke et al., 2023). Consequently, further prospective research considering these factors becomes imperative.

This study did not reveal a statistically significant distinction in incidence; however, from a clinical assessment standpoint, the incidence of Postoperative Nausea and Vomiting (PONV) was comparatively higher in the remifentanil group than in the fentanyl group. The occurrence of PONV in the remifentanil cohort was half that of the fentanyl group (4 subjects for remifentanil vs. 8 subjects for fentanyl), despite the almost equivalent number of subjects (44 for remifentanil vs. 51 for fentanyl). These findings might be attributed to the pharmacological attributes of remifentanil—an opioid characterized by its short-acting nature, lack of accumulation in the body, and an 8-10 minute half-life. These properties potentially contribute to a swifter recovery from opioid-induced side effects, including postoperative nausea and vomiting. Nonetheless, the precise impact of remifentanil on the incidence of PONV remains partially understood. One hypothesis suggests that remifentanil, devoid of histamine release and capable of blocking the stress hormone response, might mitigate triggers for nausea and vomiting (Ouyang et al., 2021). Patients having eye and neck surgery, non-smokers, women, young age (17-25 years), and given higher dose of remifentanil (0.16-0.20 μg/kg/min) posed a higher risk of PONV (Brahmana et al., 2023). Recognition of patients with higher risk of PONV using Apfel score (Gunawan et al., 2020), may help to classify patients and prescribe anesthetic agents based on patients risk profile. Finally, although remifentanil usage demonstrates several benefits over fentanyl in this study, some limitations may be taken into account. This study was a retrospective design, which relied mostly on the medical records. Disagreement in history records among individuals, limited data collected unaligned with study purpose and incomplete patient's history provided limit our data interpretation. Future studies with prospective design and larger samples may elucidate better recommendations on benefits and advantages of remifentanil over fentanyl.

Conclusion

Remifentanil use for general anesthesia intraoperatively may provide benefits over widely-used fentanyl. Patients sedated with remifentanil had more stable hemodynamic response, shorter duration of recovery room stay, and less incidence of nausea and vomiting. However, there was no notable differences in post-operative analgetic use in patients with remifentanil and fentanyl intraoperatively

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