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The effect of intravenous remifentanil and fentanyl postoperative delirium incidence in patients receiving elective orthopedic surgeries

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ABSTRACT

Background: The use of certain opioids associated differently with the incidence of postoperative delirium (POD). Remifentanil and fentanyl are short-acting opioids widely used in surgery; however, studies assessing their relationship with POD incidence are still limited. This study aimed to determine the association of remifentanil and fentanyl uses with the incidence of POD in elective orthopedic surgery patients.

Methods: A cross-sectional study was conducted in Surgical Unit at Dr Soetomo General Academic Hospital in Surabaya, Indonesia from August to September 2022. Patients who underwent elective orthopedic surgery and used remifentanil (n=16) and fentanyl (n=14) as postoperative analgesia were enrolled in the study. Delirium was assessed using Confusion Assessment Method-ICU tool (CAM-ICU). The associations of remifentanil and fentanyl use as well as patients' characteristics with POD incidence were assessed statistically.

Results: Our data found that there was no significant difference between the incidence of POD with the use of remifentanil (p=0.125) in orthopedic surgery patients. The total doses of fentanyl and morphine equivalent (of remifentanil or fentanyl) were associated significantly with the POD incidence (p=0.010 and p=0.002, respectively). Other factors associated with POD incidence were the use of bone cement during the surgery (p=0.034), duration of surgery (p<0.001), and bleeding volume during the surgery (p=0.024).

Conclusions: Our study showed high dose of fentanyl, use of bone cement, longer duration of surgery, and high bleeding volume have greater risk of developing POD in orthopedic surgery patients.

Keywords: Postoperative delirium, POD, opioid, fentanyl, remifentanil.
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INTRODUCTION

Postoperative delirium (POD) is an indicator of poor postoperative outcome and a risk factor for dementia.[1-3] POD is a clinical syndrome characterized by acute changes in attention, awareness and cognition, which develop over 1–3 days after surgery.[4] Some unfavorable outcomes after surgery such as length of hospital stay, need for institutional care, increased mortality and high treatment costs are often associated with the incidence of POD.[5] Therefore, POD is a clinical problem that needs to be monitored in postoperative patient management.[3]

The etiology of POD is not fully understood. However, there is a consensus regarding POD risk factors, such as age and comorbidities.[6] A study reported that opioids can be a causative factor for POD.[7,8] Fentanyl is a short-acting opioid with synthetic μ receptor-stimulating properties and widely used as an intraoperative sedative and analgesic. Fentanyl has a rapid onset, short duration of action and lack of histamine release. Like other opioids, it can adversely affect the central nervous system.[9] Similar to fentanyl, remifentanil is a μ-opioid receptor agonist with an ester linkage and has a very fast onset with slightly shorter duration of action.[10]

Until recently, the impact of opioids on POD shows different results, and the causes are still difficult to be explained. A study found that the use of opioids increased the risk of POD in knee and hip arthroplasty patients.[7] In contrast, another study showed that opioid did not cause POD.[11] The use of remifentanil showed a lower effect on POD than fentanyl, but the study was only conducted in surgical ICU patients.[12] The aim of this study therefore was to determine the effects of fentanyl and remifentanil on the incidence of POD in elective orthopedic surgery patients.

METHODS

This study was conducted using a cross-sectional design to analyze the effects of remifentanil and fentanyl on POD in patients who underwent elective orthopedic surgery. The patients were recruited using consecutive sampling method. The patients' characteristics including age, gender, American Society of Anesthesiologists (ASA) physical status, medical comorbidities, body mass index (BMI) and the use of bone cement were collected. Patients with cognitive impairment including pre-operative

delirium, head trauma, acute spinal cord injury, stroke, had ASA III-IV physical status, had communication and psychiatric disorder and consumed tranquilizers/anti-depressants were excluded.

All patients were induced with propofol 1–2 mg/kg, followed by remifentanil 1 mcg/kg for 30–60 seconds and its maintenance dose of 0.05–2 mcg/kg/min during surgery (remifentanil group). In fentanyl group, fentanyl 1–2 mcg/kg was given for 30–60 seconds and its maintenance dose was 2–50 mcg/kg/min during surgery. Then, all patients were given 0.6–1.2 mg/kg of rocuronium. Throughout the surgery, the patients were given oxygen at a concentration of 40–50% with a targeted SpO^2 was 95%.

After surgery, all patients were given nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol. Delirium score was assessed 24 hours after surgery using the CAM-ICU questionnaire through interviews.[13]

General characteristics of patients are presented in frequency with percentage for nominal or categorical data, while the interval data were shown in median with range (minimum-maximum). The difference between remifentanil and fentanyl groups was assessed using McNemar test, relationship between patients' characteristics and POD was analyzed using Chi-square test and relationships among opioid dose, duration of surgery and bleeding volume during surgery on POD was analyzed using Mann-Whitney test with a 95% confidence interval. All analyses were conducted using SPSS (SPSS Inc., Chicago, IL, USA).

RESULTS

In total, 30 patients were included in the study and the patients' characteristics are presented in Table 1. More than half of the patients were male (70%) with the median age was 35 years. There were 17 patients (56.7%) who had BMI below 25 kg/m^2, and more than half of the patients had comorbidities and ASA II status score (83.3%). None of the patient had pre-operative delirium. Remifentanil was given to 16 patients (53.3%) with a median dose of 0.02 mg and 14 patients (46.7%) were given fentanyl with a median dose of 0.325 mg. The evaluation using the CAM-ICU showed that POD occurred in six patients, five of them received fentanyl and one received remifentanil (Table 1). There was one (6.2%) from remifentanil group experienced POD. In fentanyl group, five (35.7%) of them experienced POD (Table 1).

The relationship between remifentanil, fentanyl, and morphine equivalent doses (converted using the GlobalRPH calculator from remifentanil and fentanyl doses) with POD was assessed using the Mann-Whitney test (Table 2). Acute or fluctuating mental status changes and

Table 1. Characteristics of patients (*n*=30).

Characteristic	Frequency (%) or Median (range)
Gender	
Male	21 (70.0)
Female	9 (30.0)
ASA score	
ASA 1	5 (16.7)
ASA 2	25 (83.3)
Comorbid	
No	5 (16.7)
Yes	25 (83.3)
Use of bone cement	
No	28 (93.3)
Yes	2 (6.7)
Age group	
Age < 40 year	16 (53.3)
Age ≥ 40 year	14 (46.7)
BMI (Kg/m^2)	
<25 (non-obesity)	17 (56.7)
≥25 (obesity)	13 (43.3)
Anesthesia	
Remifentanil	16 (53.3)
Fentanyl	14 (46.7)
POD	
Not occur	24 (80)
Remifentanil	1 (3.3)
Fentanyl	5 (16.7)
Opioid dose (mg)	
Remifentanil	0.02 (0.01–0.05)
Fentanyl	0.325 (0.12–0.95)
Surgery duration (min)	240.00 (100–600)
Bleeding volume (cc)	400.00 (100–1200)

Table 2. Association between remifentanil, fentanyl, and morphine equivalent doses with the incidence of POD (*n*=30).

Drug	POD	n (%)	Doses (mg), median (min-max)	*p*-value
Remifentanil	No	15 (93.75)	0.02 (0.01–0.05)	0.125
	Yes	1 (6.25)	0.05 (0.05–0.05)	
Fentanyl	No	9 (64.3)	0.25 (0.12–0.4)	0.010
	Yes	5 (35.7)	0.9 (0.3–0.95)	
Morphine equivalent (of remifentanil and fentanyl)	No	24 (75)	0.003 (0.001–40)	0.002
	Yes	6 (25)	80 (0.005–95)	

either disorganized thinking or altered levels of consciousness were observed in POD patients. The median dose of remifentanil used in POD and non-POD group was 0.05 mg and 0.02 mg. The remifentanil dose was not associated with POD incidence (p=0.125). High dose of fentanyl and morphine equivalent dose were associated with an increased risk of POD, with p=0.010 and p=0.002, respectively. All patients with POD were given a higher dose of fentanyl, with a mean dose of 0.9 mg.

The associations between demographics, clinicals and surgical characteristics with POD incidence are presented in Table 3. Gender, ASA score, comorbidities, age and BMI had no significant relationship with POD (p=1.000, p=1.000, p=1.00, p=0.072, p=0.672, respectively). Our data indicated that POD more frequently occurred in patients with a longer surgery duration and/or more bleeding volume. Duration of surgery and bleeding volume during surgery also associated significantly with POD incidence with p<0.001 and p=0.024, respectively (Table 3).

DISCUSSION

This study found no association between the use of remifentanil and the incidence of POD in elective orthopedic surgery patients, supported by the findings that reported remifentanil infusion did not increase the incidence of POD.[14] A study also reported the incidence of delirium in the fentanyl recipients was lower than that of other opioids (meperidine, morphine and oxycodone) and had no risk of worsening delirium.[15] In this present study, patients receiving fentanyl experienced more POD than remifentanil. Remifentanil has a non-specific esterase metabolism and a very short half-life (3.2 minutes) whereas fentanyl has longer half-life time (47.3 minutes).[16] In addition, fentanyl is known to cause impairment of cholinergic neurotransmission that does not occur in remifentanil.[17]

The effect of total opioid dose was also analyzed in this study. Our findings revealed only fentanyl dose had an effect in inducing POD. The results of previous studies regarding the effects of administration and dose of opioids on delirium still varied.[18-20] However, a study reported that patients with adenocarcinoma experienced acute delirium after increasing the dose of fentanyl from 25-100 µg/hour.[21] POD was also diagnosed in 14% of patients receiving high-dose fentanyl or thiopentone after coronary artery bypass graft surgery.[22] The mechanism of how fentanyl indices POD has not been fully understood, but the increasing fentanyl dose potentially increases norfentanyl and is associated with the cause of various central nervous system disorders including tremors, myoclonus, and grand mal seizures.[23] Our data suggested that remifentanil and fentanyl converted doses to morphine equivalents were associated with POD and are consistent with a study that used remifentanil, fentanyl and morphine.[24]

Bone cement use was associated with POD incidence, this is as highlighted in a previous study.[25] Following cemented orthopedic surgeries, bone cement implantation syndrome (BCIS) may happen, which is associated with hypoxia, hypotension and loss of consciousness occurring around the time of bone cementation.[26] This might the reasons POD in patients who were given bone cement. Surgical duration and amount of bleeding were also associated with POD. Subjects with a longer duration of surgery and severe bleeding had a greater risk of experiencing POD. Reduced oxygen and blood flow to the brain during surgery could disturb the central nervous system and increase the incidence of POD.[27] Since preserving hematocrit and serum albumin levels could lower the POD incidence, they could be utilized as management for elective orthopedic surgery.[28]

Although BMI is one of the factors that is associated with many diseases,[29,30] our data suggested BMI was not associated with POD. This supports the previous studies.[31,32] A study also found that those who experienced POD had a mean BMI

Table 3. Factors associated with the incidence of POD (*n*=30).

Factor	POD, n (%)		*p*-value
	No	Yes	
Gender [a]			1.000
Male	17 (81.0)	4 (19.0)	
Female	7 (77.8)	2 (22.2)	
ASA score [a]			1.000
I	4 (80)	1 (20)	
II	20 (80)	5 (20)	
Comorbidities [a]			1.000
No	4 (80)	1 (20)	
Yes	20 (80)	5 (20)	
Age (year) [a]			0.072
< 40	15 (93.7)	1 (6.3)	
≥ 40	9 (64.3)	5 (35.7)	
BMI [a]			0.672
Non-obesity	13 (76.5)	4 (23.5)	
Obesity	11 (84.6)	2 (15.4)	
Bone cement [a]			0.034
No	24 (85.7)	4 (14.3)	
Yes	0 (0)	2 (33.3)	
Duration of surgery (minute), median (min-max) [b]			<0.001
200 (100–380)	24 (100)	0 (0)	
380 (320–600)	0 (0)	6 (100)	
Bleeding volume (cc), median (min-max) [b]			0.024
350 (100–1100)	24 (100)	0 (0)	
850 (200–1200)	0 (0)	6 (100)	

[a] Analyzed using Chi-square test; [b] Analyzed using Mann-Whitney test

of 24.9 kg/m^2 compared to 24.1 kg/m^2 for those who did not and there was no significant difference in BMI between these groups.[32] In contrast to other studies,[33,34] ASA score, comorbidities and age were not independent risk factors for POD in this study. These could be associated with smaller sample size in our study and confounding variables such as a healthier patient population.

CONCLUSION

Fentanyl dose, surgery procedure using bone cement, surgery duration, and bleeding volume is associated with higher risk of developing POD in orthopedic surgery patients. These findings can be utilized to monitor the risk of POD and to prevent the occurrence of POD among patients with elective orthopedic surgeries in the clinical settings.

ETHICS APPROVAL

The study protocol was approved by Medical Research Ethics Committee Dr Soetomo General Academic Hospital, Surabaya, Indonesia (0457/KEPK/VIII/2022).

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DISCLOSURE OF CONFLICTS OF INTEREST

The authors declared no conflict of interest.

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AUTHORS CONTRIBUTION

HA contributed in concepting and designing the study, literature search, data collection, data analysis, manuscript preparation and editing. DS and BW were responsible in concepting and designing the study, contributed in intellectual content, manuscript editing and final editing as well as supervised the study.

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