

Comparison of Side Effects Propofol-Fentanyl and Propofol-Fentanyl-Midazolam in Central Medical Installation Hospital X Bogor

(Perbandingan Efek Samping Propofol-Fentanil dan Propofol-Fentanil-Midazolam di Instalasi Medis Sentral Rumah Sakit X Bogor)

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Abstract: Propofol is one of the most commonly used intravenous drugs employed to induce and maintain general anesthesia. The effective induction dose of propofol is 1.0-2.5 mg/kg IV caused hemodynamic instability significant as hypotension. Stability hemodynamic in used propofol can optimized with midazolam-fentanyl. The aims of this study was to determine the comparison of side effects propofol-fentanyl and propofol-fentanyl-midazolam in patient undergoing elective surgery with parameter of blood pressure, pulse, respiratory rate (RR). This study was a observational with prospective method in 60 patients undergoing elective surgery with physical status ASA I-II conducted in the period of April to July 2019. The result showed the induction anesthesia used of propofol-fentanyl caused decreased on systolic blood pressure 17.2 ± 3 mmHg, diastolic blood pressure 5.3 ± 1.6 mmHg, pulse 3.9 ± 1.5 beats/minute, and RR 1.4 ± 0.01 breaths/minute. The induction anesthesia used of propofol-fentanyl-midazolam caused decreased on systolic blood pressure 11.8 ± 0.4 mmHg, diastolic blood pressure 4.2 ± 0.4 mmHg, pulse value 5.0 ± 0.9 beats/minute, and RR 2.8 ± 0.9 breaths/minute. Side effects in the form of blood pressure, pulse and respiratory rate from the administration of the combination of propofol-fentanyl and propofol-fentanyl-midazolam were not significantly different.

Keywords: propofol, fentanyl, midazolam, side effect, general anesthesia.

Abstrak: Propofol adalah salah satu obat intravena yang paling umum digunakan untuk menginduksi dan mempertahankan anestesi umum. Dosis induksi efektif propofol adalah 1,0-2,5 mg/kg IV menyebabkan ketidakstabilan hemodinamik yang signifikan seperti hipotensi. Stabilitas hemodinamik pada propofol yang digunakan dapat dioptimalkan dengan midazolam-fentanil. Penelitian ini bertujuan untuk mengetahui perbandingan efek samping propofol-fentanil dan propofol-fentanil-midazolam pada pasien yang menjalani operasi elektif dengan parameter tekanan darah, nadi, frekuensi pernapasan (RR). Penelitian ini merupakan penelitian observasional dengan metode prospektif pada 60 pasien yang menjalani operasi elektif dengan status fisik ASA I-II yang dilakukan pada periode April sampai Juli 2019. Hasil penelitian menunjukkan induksi anestesi yang menggunakan propofol-fentanil menyebabkan penurunan tekanan darah sistolik $17,2\pm 3$ mmHg, tekanan darah diastolik $5,3\pm 1,6$ mmHg, nadi $3,9\pm 1,5$ denyut/menit, dan RR $1,4\pm 0,01$ napas/menit. Penggunaan induksi anestesi propofol-fentanil-midazolam menyebabkan penurunan tekanan darah sistolik $11,8\pm 0,4$ mmHg, tekanan darah diastolik $4,2\pm 0,4$ mmHg, nilai nadi $5,0\pm 0,9$ denyut/menit, dan RR $2,8\pm 0,9$ napas/menit. Sehingga dapat disimpulkan efek samping berupa tekanan darah, nadi dan frekuensi pernapasan dari pemberian kombinasi propofol-fentanil dan propofol-fentanil-midazolam tidak berbeda nyata.

Kata kunci: propofol, fentanil, midazolam, efek samping, anestesi umum.

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INTRODUCTION

GENERAL anesthesia Nowadays has been widely developed and involved in various developments in the latest medical procedures. The number of surgical procedures continues to increase and requires involvement of the role of general anesthesia. Major surgeries are carried out annually around the world is estimated to be more than 230 million⁽¹⁾.

An ideal anaesthesia can cause a smoothly and rapidly anesthesia effect and allow for faster recovery time. The drug must also have a wide margin of safety and do not cause adverse effects⁽²⁾. Propofol may be used alone or in combination with opioids (fentanyl 25-75 µg), and/or benzodiazepines (midazolam 0.5-2.5 mg), but there is no clear evidence that the combination of propofol with other drugs leads to reduction of side effects. The use of propofol alone requires higher the amount of the dose, which may lead to increased incidence of side effects such as respiratory depression, hypotension, and cardiac dysrhythmia⁽³⁾. The combination of fentanyl with propofol, barbiturates, benzodiazepines, others, has a synergistic effect in the stability of cardiovascular, respiratory, and sedative effect⁽⁴⁾.

General anesthesia most commonly used in elective surgery in hospital X Bogor is a combination of propofol-fentanyl and a combination of propofol-fentanyl-midazolam. In the 2012 study of Ghatak et al., fentanyl provided the same good hemodynamic stability as ketamine as propofol co-induced in 180 patients⁽⁵⁾.

In addition, the use of midazolam day to day is increasing because it is expected with midazolam administration in premedication to provide a decrease in the side effects of blood pressure, pulse and respiratory rate reduction. It is therefore the goal of this study to analyze the comparison of side effects use a combination of propofol-fentanyl and a combination of propofol-fentanyl-midazolam. The side effect parameters analyzed are hemodynamic changes in the form of blood pressure (systolic and diastolic), pulse, respiratory rate parameters.

MATERIAL AND METHODS

MATERIAL. The material used in this study was the medical records of elective surgery patients for the period April - July 2019.

METHODS. Research Design. A prospective observational study, involving 60 patients undergoing elective surgery in central medical instalation hospital X Bogor.

Sample. Sample were collected by concecutive sampling methods on April-july 2019. The study include man and woman patients, aged between 17 to 55 years, ASA I-II. The exclusion criteria were patients who passed away and patients with incomplete medical record data.

Research Procedure. In total, 60 patients were allocated into two groups. In group I, patients received intravenous (IV) midazolam (0.05-0.1 mg kg⁻¹) as a pre-anesthetic 30 min before sedation, followed by IV fentanyl (1-2 µg kg⁻¹) and propofol (1.5-2.5 mg kg⁻¹). In Group II, patients received anesthesia with IV fentanyl (1-2 µg kg⁻¹) and propofol (1.5-2.5 mg kg⁻¹). Data were obtained from observation of elective surgery patient in the form of sociodemographic, surgical diagnosis, anesthetic drugs and their dosages, systolic and diastolic blood pressure, pulse and respiratory rate data. Systolic and diastolic blood pressure, pulse and respiratory rate were monitored 0 minute before induction and 5 minute after induction anesthesia⁽²⁾. During anesthetic procedures, hypotension defined as a loss greater than >25% above preanesthetic values⁽²⁾, bradycardia defined as a loss greater than 20% above preanesthetic values⁽⁶⁾, bradipnea defined as a loss greater than 20% above preanesthetic values⁽⁶⁾.

Statistical Analysis. Statistical analysis was performed and initially we evaluated the data normality using the Kolmogorov-Sminorv test. Then we chose to use non-parametric tests because the data did not reach normal distribution. To compare the means of the two groups, we used the Mann-Whitney test. All analyzes were performed using the SPSS version 23 software, and a p-value <0.05 was considered statistically significant.

RESULT AND DISCUSSION

In Table 1, it can be seen that patients undergoing elective surgery from April to July 2019 more female gender than men. This difference did not reach statistical significance $P > 0.05$ ($P = 0.094$). This is due to the biological differences as well as the anatomy and hormonal changes that occur in women that cause the emergence of various diseases such as breast cancer and breast tumors.

Based on the characteristics of the patient's age, patients receiving the induction of propofol-fentanyl-midazolam is most at the age of 17-25 years as much as 12 patients (40%). There is a significant influence between ages to the level of anxiety⁽⁷⁾ so that the administration of midazolam is aimed to reduce the fear and anxiety experienced by providing sedation/drowsiness effect⁽⁸⁾. This difference did not reach

statistical significance in the patient's age variable between both group $P > 0.05$ ($P = 0.343$).

General surgery is the most surgical case in hospital "X", because hospital "X" has three general surgeon specialists, in addition general surgery is the first surgery performed by sub specialists before other surgery. Furthermore oncology surgery, because in the hospital "X" is a regional referral of Bogor Regency for the disease of breast cancer. This difference did not reach statistical significance in the variable type

of surgery between both group $P > 0.05$ ($P = 0.286$).

In our study, we found a higher frequency of hypotension in Group II as many as 3 patients (10%), bradycardia and bradypnea (0%). whereas in patients who used propofol-fentanyl-midazolam did not experience side effects of hypotension, bradycardia and bradypnea (Table 1). Although this difference did not reach statistical significance $P > 0.05$ ($P = 0.078$).

From Table 2, it can be seen that the delta mean

Table 1. Patient's characteristics and side effects description.

Variable	Group				P-value
	II		I		
	N	%	N	%	
Gender					
- Male	12	40	6	20	0.094
- Female	18	60	24	80	
Age					
- 17-25 Years Old	8	26.7	12	40	0.343
- 26-35 Years Old	4	13.3	3	10	
- 36-45 Years Old	9	30	8	26.7	
- 46-55 Years Old	9	30	7	23.3	
Type Of Surgery					
- General Surgery	8	26.7	14	46.7	0.286
- Oncology Surgery	9	30	7	23.3	
- Urology Surgery	8	26.7	2	6.7	
- Orthopedic Surgery	0	0	4	13.3	
- ENT Surgery	2	6.7	0	0	
- Eye Surgery	1	3.3	1	3.3	
- Digestive Surgery	1	3.3	1	3.3	
- Neurosurgery	0	0	1	3.3	
- Mouth Surgery	1	3.3	0	0	
Side Effects					
1. Blood Pressure					
- Normal	27	90	30	100	0.078
- Hypotension	3	10	0	0	
- Hypertension	0	0	0	0	
2. Pulse					
- Normal	30	100	30	100	1.000
- Bradycardia	0	0	0	0	
- Tachycardia	0	0	0	0	
3. Respiratory rate					
- Normal	30	100	30	100	1.000
- Bradypnea	0	0	0	0	
- Tachypnea	0	0	0	0	

Note: - Group I = Propofol-fentanyl-midazolam
- Group II = Propofol-fentanyl

before - after propofol-fentanyl induction showed a decrease in blood pressure of 17.2 ± 3 mmHg / 5.3 ± 1.6 mmHg, a decrease in pulse rate of 3.9 ± 1.5 beats/minute and a decrease in RR of 1.4 ± 0.01 breaths/minute. While the delta mean before-after propofol-

fentanyl-midazolam induction showed a decrease in blood pressure of 11.8 ± 0.4 mmHg / 4.2 ± 0.4 mmHg, a decrease in pulse rate of 5.0 ± 0.9 beats/minute and a decrease in RR of 2.8 ± 0.9 breaths/minute. The delta mean before-after induction from these

Table 2. Changes in systolic and diastolic blood pressure, pulse, respiratory rate before and after induced.

Side effects variable	Before Induction	After induction	P-value
Systolic Blood Pressure			
a. Propofol-Fentanyl			
- Lowest			
- Highest	90	80	
- Mean \pm SD	180	170	
- Delta mean before - after induction \pm SD	126.5 \pm 20.1	109.3 \pm 17.1	
	17.2 \pm 3 mmHg		
b. Propofol-Fentanyl-Midazolam			
- Lowest			0.078
- Highest	100	90	
- Mean \pm SD	150	140	
- Delta mean before - after induction \pm SD	129.6 \pm 13.7	117.8 \pm 13.3	
	11.8 \pm 0.4 mmHg		
Diastolic Blood Pressure			
a. Propofol-Fentanyl			
- Lowest	50	60	
- Highest	95	90	
- Mean \pm SD	77.9 \pm 10.1	72.6 \pm 8.5	0.078
- Delta mean before - after induction \pm SD	5.3 \pm 1.6 mmHg		
b. Propofol-Fentanyl-Midazolam			
- Lowest			
- Highest	60	60	
- Mean \pm SD	90	85	
- Delta mean before - after induction \pm SD	80.2 \pm 6.1	76 \pm 5.7	
	4.2 \pm 0.4 mmHg		
Pulse			
a. Propofol-Fentanyl			
- Lowest	66	60	
- Highest	96	96	
- Mean \pm SD	81.1 \pm 6.2	77.2 \pm 7.7	1.000
- Delta mean before - after induction \pm SD	3.9 \pm 1.5 beats/minute		
b. Propofol-Fentanyl-Midazolam			
- Lowest			
- Highest	70	68	
- Mean \pm SD	100	98	
- Delta mean before - after induction \pm SD	87.5 \pm 9	82.5 \pm 8.1	
	5 \pm 0.9 beats/minute		
Respiratory Rate			
a. Propofol-Fentanyl			
- Lowest	12	10	
- Highest	20	20	
- Mean \pm SD	18.2 \pm 2.81	16.8 \pm 2.80	
- Delta mean before - after induction \pm SD	1.4 \pm 0.01 breaths/minute		1.000
b. Propofol-Fentanyl-Midazolam			
- Lowest			
- Highest	12	10	
- Mean \pm SD	20	20	
- Delta mean before - after induction \pm SD	19.1 \pm 1.7	16.3 \pm 2.6	
	2.8 \pm 0.9 breaths/minute		

three side effect variables there is a difference, but after being analyzed statistically using the Mann-whitney test the difference did not reach statistical significance $P\text{-value} > 0.05$ ($P = 0.078$) for the blood pressure variable and ($P = 1.00$) for variable pulse and respiratory rate (RR).

Based on research conducted Istiqoma et al., 2011 the percentage of patients who experienced side effects of hypotension on fentanyl-propofol induction of 14.29%, in anesthesia is said to be hypotension when the decrease in blood pressure $> 25\%$ of the initial value. A decrease in blood pressure can be caused by vasodilation and decreased myocardial contractility⁽²⁾. When added midazolam, hypotension did not experience significantly increased compared to induction groups that only get propofol-fentanyl. Midazolam induction is given aimed at reducing the dose requirement of propofol because midazolam and propofol equally work on GABA receptors in the central nervous system that produces sedation effects, so that the administration of both is synergistic in decrease the induction dose of propofol so as to reduce the incidence of hypotension due to the use of propofol large doses⁽⁹⁾.

The pulse is said to be bradycardia if the decrease $> 20\%$ of the initial pulse, the decrease in the pulse caused by the stress response at the hypothalamic-pituitary Adrenocorticoids receptor and fentanyl work by means of a bind to the brain stem (solitaries nuclei & ambiguus nuclei) which cause to reduced release of endogenous catecholamines due to depression of the sympathetic nervous system, there by increasing the vagal which can cause to decreased pulse even to bradycardia⁽⁶⁾.

Respiratory rate (RR) is said to be bradipnea when the change $> 20\%$ of the initial value, decrease in the value of RR caused by reaction between the fentanyl receptors with respiratory nerve in the cord and pons that reduce the performance of frequency regulation of breathing⁽⁶⁾.

CONCLUSION

Side effects in the form of blood pressure, pulse and respiratory rate from the administration of the combination of propofol-fentanyl and propofol-fentanyl-midazolam were not significantly different.

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