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Original Research Article

COMPARISON OF INTRAVENOUS ADMINISTRATION OF REMIFENTANIL WITH FENTANYL FOR INCREASED BLOOD SUGAR LEVELS IN POST-CARDIAC SURGERY PATIENTS

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ABSTRACT

Introduction: The incidence of hyperglycemia in patients with heart disease undergoing cardiac surgery reaches 50% in patients without a history of Diabetes Mellitus. This condition of hyperglycemia can increase morbidity and mortality. **Objective:** This study aims to assess the effect of using the agent remifentanil intravenously 0.5-1 µg/kgBW bolus followed by maintenance at a dose of 0.05-0.1 µg/kgBW/minute intravenously compared to the use of fentanyl 3-10 µg/kgBW followed by a maintenance dose of 0.03-0.1 µg/kgBW/minute for increased blood sugar levels in patients undergoing cardiac surgery with the Cardiopulmonary Bypass (CPB) procedure. **Methods:** This study is an experimental study with a single-blind randomized controlled design. Patients will be divided into 2 groups consisting of 12 patients each, namely group R (remifentanil) received remifentanil, and group F (fentanyl) received fentanyl. Blood sugar levels will be checked before and after surgery. **Results:** The research has been conducted at Dr. Hasan Sadikin Hospital Bandung from February 2023 to May 2023**.** The average increase in blood sugar levels in the remifentanil group was 74 mg/dl, while in the fentanyl group, it was 90 mg/dl. The p-value given is 0.214. Statistical test results showed that the value of p> 0.05. **Conclusion:** This study concludes that there is no significant difference in the increase in blood sugar levels between the two groups (remifentanil and fentanyl). This can be caused by the use of opioid doses in the lower range and more complex surgical procedures in our research.

Keywords: Blood Sugar Levels; Cardiopulmonary Bypass; Heart Disease; Remifentanil

ABSTRAK

Pendahuluan: Angka kejadian hiperglikemia pada pasien penyakit jantung yang menjalani operasi jantung mencapai 50% pada pasien tanpa riwayat diabetes melitus. Kondisi hiperglikemia ini dapat meningkatkan angka kesakitan dan kematian. **Tujuan:** Penelitian ini bertujuan untuk menilai pengaruh penggunaan agen remifentanil secara intravena bolus 0,5-1 µg/kgBB diikuti dengan dosis rumatan 0,05-0,1 µg/kgBB/menit secara intravena dibandingkan dengan penggunaan fentanil 3-10 µg/kgBB yang diikuti dengan dosis pemeliharaan 0,03-0,1 µg/kgBB/menit untuk peningkatan kadar gula darah pada pasien yang menjalani operasi jantung dengan prosedur Pintas Jantung Paru (PJP). **Metode:** Penelitian ini merupakan penelitian eksperimental dengan rancangan terkontrol acak buta tunggal. Pasien akan dibagi menjadi 2 kelompok yang masing-masing terdiri dari 12 pasien, yaitu kelompok R (remifentanil) yang mendapat remifentanil dan kelompok F (fentanil) yang mendapat fentanil. Kadar gula darah akan diperiksa sebelum dan sesudah operasi. **Hasil:** Penelitian ini dilaksanakan di RSUP Dr. Hasan Sadikin Bandung pada bulan Februari 2023 sampai dengan Mei 2023. Rata-rata kenaikan kadar gula darah pada kelompok remifentanil sebesar 74 mg/dl, sedangkan pada kelompok fentanil sebesar 90 mg/dl. Nilai p yang diberikan adalah 0,214. Hasil uji statistik menunjukkan nilai p > 0,05. **Kesimpulan:** Kesimpulan penelitian ini adalah tidak terdapat perbedaan peningkatan kadar gula darah yang signifikan antara kedua kelompok (remifentanil dan fentanil). Hal ini dapat disebabkan oleh penggunaan dosis opioid dalam rentang yang lebih rendah dan prosedur bedah yang lebih kompleks dalam penelitian kami.

Kata kunci: Kadar Gula Darah; Pintas Jantung Paru; Penyakit Jantung; Remifentanil

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INTRODUCTION

Cardiopulmonary bypass surgery or Heart Lung Bypass (CPB) is a procedure that is often performed in heart surgery. The act of CPB can cause an inflammatory response that increases levels of cytokines and catecholamines in plasma, resulting in hyperglycemia (1). The incidence of hyperglycemia in patients undergoing heart surgery without comorbid Diabetes mellitus reached 56.1% (2). Hyperglycemia is associated with an increase in the incidence of major side effects and mortality rate in patients undergoing heart surgery (3,4).

During the CPB procedure, the phospholipase A2 enzyme will degrade arachidonic acid which will increase inflammatory mediators such as leukotrienes, prostaglandins, and thromboxane. These mediator substances trigger activation and adhesion of neutrophils, vasoconstriction of blood vessels, platelet aggregation, and tissue damage (5). Increases in inflammatory mediators and secretion of catecholamine hormones will cause Systemic Inflammatory Response Syndrome (SIRS) which will cause insulin resistance and cause hyperglycemia which is complications that often occur after heart surgery (6,7).

Opioids are a class of drugs that are often used in surgery to control the sympathetic response during surgery and are expected to reduce surgical stress (8). One of the opioid drugs that is often used in surgery is fentanyl. Fentanyl is the most widely used opioid because it has minimal cardiovascular effects, does not cause histamine release, has a fast onset of action with a short duration of action, and is easy to use (9). Apart from fentanyl, another class of opioid drugs, remifentanil, has the same level of effectiveness as other opioids and maintains better hemodynamic stability in cardiac surgical procedures (10,11). Remifentanil is an opioid with a very short onset of action and a derivative of piperidine. Remifentanil itself has a strong analgesic effect which can reduce sympathetic stimulation and maintain pulse rate and blood pressure during surgery. Remifentanil is metabolized in plasma by nonspecific esterase with its metabolite remifentanil acid (12).

To the best knowledge of the authors, there have been no studies comparing the usefulness of fentanyl and remifentanil for cardiac surgery with CPB procedures in Indonesia. Therefore, this study aimed to compare the increased blood sugar levels in patients undergoing cardiac surgery with PJP who received fentanyl or remifentanil. We assume that the Patients who receive remifentanil therapy will experience a lower increase in blood sugar levels compared to patients who receive fentanyl therapy. To investigate this hypothesis, we compared the rate of increase in blood sugar levels in both groups of patients undergoing cardiac surgery with the CPB procedure.

MATERIAL AND METHODS

Study Design and Subjects

The design of this study was an experimental study done in a randomized crossover study, approved by the Ethics Committee of Dr. Hasan Sadikin Hospital Bandung, Indonesia on 23rd January 2023 with registered number LB.02.01/X.6.5/27/2023. Twenty-four patients who underwent cardiac surgery with the CPB procedure were subjects in this study. This research was conducted at the central surgical installation of Dr. Hasan Sadikin Hospital Bandung between February and May 2023.

Study Procedures

After obtaining approval from the Research Ethics Committee Dr. Hasan Sadikin

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Hospital Bandung, patients who meet the inclusion criteria (patients aged 18 and over undergoing elective heart surgery using a heart-lung bypass machine, patients with physical status based on the American Society of Anesthesiologists (ASA) in categories I-III) are given informed consent regarding the procedure to be carried out. Drug preparation is carried out in the cardiac surgery central operating theatre pharmacy department.

Patients were divided into 2 groups, namely group R, which received remifentanil 0.5-1 µg/kgBW/minute intravenously, and group F, which received fentanyl 3-10 µg/kgBW. Drugs are divided into two types, namely induction drugs and maintenance drugs. Remifentanil 2 mg is diluted with 0.9% NaCl 40 ml to the preparation of 50 µg/ml in a 50 ml syringe, for the induction dose using a dose range of 0.5-1 µg/kgBW/minute while the maintenance dose is given at 0.05-0.1 µg/kgBW/minute in a 50 ml syringe using a syringe pump. Fentanyl medication for induction is given bolus at a dose of 3-10 µg/kgBW. Meanwhile, for maintenance, it is given at a dose of 0.03-0.1 µg/kgBW/minute, and 400 mcg fentanyl is diluted with 40 ml of 0.9% NaCl to form a preparation of 10 mcg/ml in a 50 ml syringe.

Patients who will take part in the research procedure are required to fast 6 hours before surgery. The patient received fasting replacement fluid with Ringer's lactate given at 10 cc/kgBB for 30 minutes and continued with maintenance fluid at 2cc/kgBB/hour. Then the anesthesia and surgery procedures can begin and proceed according to applicable standard operational procedures.

After the patient has an arterial line installed, the patient's blood sugar level is sampled as basic data (T1). Induction is carried out with propofol 2-3 mg/kgBW intravenously, after the patient falls asleep followed by administration of rocuronium 0.8 mg/kgBW intravenously. Additional medications given by perfusion during CPB procedures such as insulin will be noted in the study. After CPB is finished, protamine is given at a dose of 1-1.3 the dose of heparin and methylprednisolone 250 mg IV bolus. After the operation is complete, the patient's blood sugar is sampled as final data (T2).

Data Collection

The first data collected was blood sugar level, which was collected just before the induction of anesthesia was performed. The second data collected was blood sugar level checked after the operation had been completed.

Statistical Analysis

This research has a crossover design. The sample size was calculated using $\alpha = 0.05$ and $\beta = 0.2$ (13). A minimum number of 12 participants was required in each random sequence. Therefore, researchers estimated that a minimum total of 24 participants are needed for this study. The data was tested statistically using Statistical Product and Service Solution (SPSS) version 26.0 for Windows. Data are presented as median (interquartile range) for numeric variables and number (percentage) for categorical variables. A value of P less than 0.05 is considered statistically significant.

RESULTS AND DISCUSSION

This research was conducted on 24 research subjects who underwent cardiac surgery with a cardiopulmonary bypass procedure at Dr. Hasan Sadikin Hospital Bandung in the period February 2023 to May 2023 which has met the inclusion criteria and is not included in the exclusion criteria. Subjects were then divided into 2 groups, namely group R which used remifentanil 0.5-1 µg/kgBW bolus followed by a maintenance dose of 0.05-

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0.1 µg/kgBW/minute intravenously, and group F which used fentanyl 3-10 µg /kgBW bolus followed by a maintenance dose of 0.03-0.1 µg/kgBW/minute, with each group consisting of 12 research subjects.

Table1. Comparison of the Characteristics of Research Subjects

Variable	Group		p-value
	Remifentanil N=12	Fentanyl N=12	
Age (year)			
Mean±SD	42 ± 12	41 ± 16	0.909[a]
Sex, n (%)			
Male	7 (58.3)	8 (66.7)	1.000[c]
Female	5 (41.7)	4 (33.3)	
BMI (kg/m^2)			
Mean±SD	21.9 ± 4.8	22.2 ± 4.7	0.854[a]
ASA, n (%)			
1	0	0	-
2	0	0	
3	12 (100)	12 (100)	
Total operation time (minute)			
Mean±SD	255 ± 58	240 ± 52	0.510[a]
Duration of operation-start of CPB (minute)			
Mean±SD	66 ± 19	68 ± 17	0.758[a]
Duration of completion of CPB - completion of surgery (minute)			
Mean±SD	97 ± 34	89 ± 25	0.522[a]
Duration of CPB			
Mean±SD	93 ± 21	83 ± 25	0.339[a]
Aortic cross-clamp duration			
Mean±SD	60 ± 20	61 ± 22	0.871[a]
Amount of bleeding			
Median	800	800	0.519[b]
Range (min-max)	500 – 3000	500 – 1600	
Operation type, n (%)			
CABG	2 (16.7)	2 (16.7)	0.430[d]
MVR	5 (41.7)	4 (33.3)	
ASD Closure	1 (8.3)	3 (25.0)	
VSD Closure	1 (8.3)	0 (0.0)	
MVR+TVr	1 (8.3)	2 (16.7)	
CABG+MVR	0 (0.0)	1 (8.3)	
MVR+ASD Closure	1 (8.3)	0 (0.0)	
MVR+TVr+ASD Closure	1 (8.3)	0 (0.0)	

Notes: Analysis uses [a]unpaired t-test, [b]Mann Whitney, [c]Fisher Exact, [d] Chi Square *meaning p<0,05

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Table 2. Comparison of Blood Sugar Levels of the Two Groups

Variable	Group		p-value (Remifentanil vs Fentanyl)
	Remifentanil N=12	Fentanyl N=12	
Preoperative blood sugar levels (mg/dl) Mean±SD	91 ± 16	95 ± 14	0.482
Postoperative blood sugar levels (mg/dl) Mean±SD	164 ± 27	185 ± 39	0.137
P value (pre vs post)	**<0,001***	**<0,001***	

Notes: Analysis uses \unpaired t-test, (pre and post) uses paired t-test*meaning p<0,05

Characteristics of research subjects include age, gender, BMI, ASA, total duration of surgery, duration of surgery until the start of PJP, duration of completion of PJP until completion of surgery, length of PJP, length of aortic cross-clamping, amount of bleeding and type of operation can be seen in Table 1 and comparison blood sugar levels for both groups can be seen in Table 2. The results of statistical tests for all the research groups above showed that the P value for all variables was greater than 0.05 (p value>0.05), which means it is not significant or not statistically significant. Thus, it can be explained that there is no statistically significant difference between all variables in patient characteristics in Group Remifentanil and Group Fentanyl. There are no differences or the same in the two research groups so it can be concluded that the two groups are homogeneous and can be compared statistically.

Table 3. Comparison of the Increase in Blood Sugar Levels of the Two Groups

Variable	Group		P-value
	Remifentanil N=12	Fentanyl N=12	
Increase in blood sugar levels Mean±SD	74 ± 24	90 ± 38	0.214

Notes: P value (Remifentanil vs Fentanyl) using unpaired t-test.*)Statistically significant (p-value < 0,05)

In the Table 3, it is found that the average increase in blood sugar levels in the remifentanil group was 74 mg/dl, and in the fentanyl group, it was 90 mg/dl. The statistical test results obtained a value of p=0.214 (p≥0.05), which means that there was no significant difference in the increase in blood sugar levels in Group Remifentanil and Group Fentanyl.

There were no significant differences in the characteristics of the research subjects between Group Remifentanil and Group Fentanyl., this shows that all samples from each group were in relatively the same range so that the two groups were homogeneous and worthy of comparison for further statistical analysis.

Based on Table 1, it is known that the average age of research subjects in group R was 42 ± 12 years, and in group F was 41 ± 16 years. The statistical test results obtained a value of p=0.909 (p≥0.05), which means that there were no significant differences in the characteristics of the research subjects based on age between group R and group F. At older ages, the ability to regulate blood sugar will decrease due to a decrease in insulin sensitivity. This is based on research by Shou which explains that the elderly population experiences a decrease in the function of the glucose transporter 4 (GLUT 4) enzyme and a decrease in insulin sensitivity. In this study, the average age of research subjects in both groups was not included in the elderly

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category so the increase in perioperative blood sugar levels can be compared (14).

The average body mass index (BMI) in group R was found to be 21.9 ± 4.8 kg/m2 and in group F the average BMI was 22.2 ± 4.7 kg/m2. The statistical test results obtained a value of p=0.854 (p≥0.05), which means that there were no significant differences in the characteristics of the research subjects based on BMI between group R and group F. Patients with a higher BMI tended to experience an increase in blood sugar levels during intraoperative. This is with research conducted by Nakadate that there is a negative correlation between BMI and insulin sensitivity (15).

In terms of total operating time, it is known that the average in group R was 255 ± 58 minutes and in group F 240 ± 52 minutes. The duration of the operation-start of CPB in group R was 66 ± 19 minutes and in group F 68 ± 17 minutes. Duration of completion of CPB - completion of surgery in group R was 97 ± 34 minutes and in group F 89 ± 25 minutes. The average CPB duration in group R was 93 ± 21 minutes and in group F 83 ± 25 minutes. The average duration of aortic cross-clamping in group R was 60 ± 20 minutes and in group F 61 ± 22 minutes. The average amount of bleeding in group R was 500 - 3000 ml and in group F 500 - 1600 ml. The CPB procedure is a procedure that is often used in cardiac surgery today. However, the CPB procedure has several disadvantages that can result in complications after surgery. This extracorporeal circulation can stimulate an inflammatory response caused by exposure of the patient's blood to the circuit of the CPB machine. Aortic cross-clamp time (ACCT) and cardiopulmonary bypass time are associated with increased morbidity and mortality after cardiac surgery, which is related to myocardial injury, ischemia, and inflammatory response. Therefore, the results of post-operative cardiac surgery can be influenced by the length of cardiac surgery and the CPB procedure. This is based on research conducted by Madhavan that a longer CPB procedure can increase the risk of postoperative complications (16).

The surgical procedures carried out in this study were divided into three large groups, namely valve replacement surgery, Coronary Artery Bypass Graft, and septal closure. Valve replacement surgery was the most common surgical procedure performed in both groups, namely 5 cases (41.7%) in group R and 4 cases (33.3%) in group F, CABG surgery in both groups amounted to 2 cases (16.7%), surgery closure of the septum hole in group R amounted to 2 cases (16.7%) and in group F there were 3 cases (25%), the remaining cases studied included two valve replacement operations, CABG with valve replacement, closure of the septum hole and valve replacement. This is different from the surgical procedures carried out by Lee where the type of surgery in all research samples was valve replacement surgery (17). Meanwhile, in this study the surgical procedures carried out were more diverse with several surgical procedures covering two groups of surgical procedures.

The results of this study also showed that after surgery, the average increase in blood sugar levels in group R was 164 mg/dl, and in group F was 185 mg/dl. The statistical test results obtained a value of p=0.137 (p≥0.05) indicating that there was no significant difference in blood sugar levels after surgery between group R and group F.

Blood sugar levels in group R and group F seen from each group before surgery and after surgery showed a significant difference (p<0.001), this shows that there was a significant influence on the treatment given to group R and group F. Previous research conducted by Umpierrez in the GLUCO-CABG study also explained that the incidence

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of hyperglycemia is something that often occurs in patients undergoing cardiac surgery with an incidence of more than 50% in patients without a history of diabetes mellitus (18). This can be caused by tissue damage that occurs during cardiac surgery using the CPB procedure.

Research conducted by Lee shows that remifentanil is more effective in reducing cytokines in cardiac surgery accompanied by PJP procedures. This is indicated by an increase in IL-6 and IL-8 levels which is lower than in the group of patients who used the drug fentanyl. Lee divided 2 groups of patients who received the opioid remifentanil with an induction dose of 0.5-1.0 µg/kg and a maintenance dose of 0.05-0.1 µg/kg/min with a group of patients who received the opioid fentanyl with an induction dose of 3-10 µg/kg and a maintenance dose 0.03-0.1 µg/kg/min (17). In research conducted at Dr. Hasan Sadikin General Hospital, the induction dose in group R was 1.0 µg/kg and the maintenance dose was in the lower range, namely 0.05 µg/kg/min and the induction dose was in the lower range, namely 3 µg/kg and the average maintenance dose is 0.05 µg/kg/min where the use of this dose takes into account the patient's hemodynamic condition. Apart from that, the depth of anesthesia in this study was also not assessed, which allowed inadequate sedation and opioid medication to be given so that the stress response due to surgical trauma continued and there was an increase in postoperative blood sugar levels.

Another difference in patient characteristics is the type of surgical procedure performed, where this study involved valve replacement surgery, CABG, septal closure, and a combination of surgical procedures. Meanwhile, in Lee's research, the surgical procedure involved only valve replacement. This also influences research outcomes where various surgical procedures will trigger wider tissue damage and cause a higher sympathetic response.

Some limitations of this research are that the study did not look at postoperative outcomes such as length of treatment in the intensive care room, complications after surgery, mortality rate, and the number of samples in this study was 24 with each group of 12 patients, so this will affect the statistical calculations on this research.

CONCLUSION

There was no significant difference in the increase in blood sugar levels after surgery in the group receiving the opioid remifentanil and the opioid fentanyl. This could be because the number of samples in this study was 12 patients in each group. It is hoped that future research can involve a larger sample size so that it can represent the population. Apart from that, the use of doses with different ranges will certainly affect different research outcomes in each group. Various types of surgery also influence the outcome of the operation where this study involved valve replacement surgery, CABG, septal closure, and a combination of surgical procedures.

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Conflict of Interest

The authors declare that they have no conflict of interest regarding the publication of this article.

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Authors' Contributions

IT, DT, RW planned the study and contributed to data collection and analysis. All authors have reviewed and approved the final manuscript.

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