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Comparative Analysis of Postoperative effect between Opioid Free Anesthesia (Ketamin + Lidocaine 2%) and Opioid Anesthesia (Fentanyl) in Elective Surgery Patients at RSUD Dr. Soetomo

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ABSTRACT

Background : Opioid Free Anesthesia (OFA) is an anesthetic technique that avoids intraoperative opioids to minimize side effects of opioids, reduce the need for postoperative opioids and produce better postoperative outcomes. This study aims to analyze the comparison of the side of OFA and opioid anesthesia (OA) in elective surgery patients at Dr. Hospital Soetomo

Method : This study is an experimental study with Single Blind randomized involving adult patients undergoing elective surgery from May 2021 to August 2021 under general anesthesia for airway management intubation at RSUD DR. Soetomo. Side observed were Wong Baker Face Scale (WBFS), incidence of hypoxia, ileus, delirium and postoperative nausea and vomiting.

Results: 60 samples obtained 30 subjects in the control group and 30 people in the treatment group with 23 male and 37 female. Evaluation of postoperative pain found 5 subjects with moderate-severe WBFS scale in the control group and 3 subjects in the treatment group (0.706); and significant differences in the incidence of hypoxia (9 subjects in the control group and 2 subjects with hypoxia (p = 0.020); ileus in the form of 14 subjects in the control group and 2 subjects in the treatment group (p = 0.002); the incidence of delirium (p = 0.026) in the form of 8 subjects in the control group. and 1 subject in the treatment group, and the incidence of nausea and vomiting (p=0.012) in 14 subjects in the control group while 5 subjects in the treatment group.

Conclusion: Both groups received adequate analgesics so that they had similar WBFS, but the incidence of side was significantly different in the two groups where the incidence of hypoxia, ileus, delirium, and postoperative nausea and vomiting are lower. So that OFA could be considered as an anesthetic technique of choice.

Keywords: delirium, hypoxia, ileus, nausea and vomiting, opioid free anesthesia, WBFS

INTRODUCTION

Anesthesiologist and Surgeons encounter three challenges in the efforts to provide optimal perioperative pain management. The first challenge is giving an adequate perioperative analgesic. The second challenge is minimizing or preventing the side effects of postoperative opioids, such as nausea and vomiting (50-60%), hypoxia and respiratory depression (20-40%), ileus and constipation (10,3%), as well as delirium (25-50%). The third challenge is increasing

number of opioids use, related to increased abuse, addiction, and overdose especially in United States and extends all over the world.

In Indonesia, the use of preoperative opioids reach >90% of the total operations performed per day. In the last two decades there is a significant change in the approach of operation surgery to minimally invasive surgery (laparoscopy). Although the operating time is longer than the minimally invasive surgery, but the hospital treatment time is shorter, and the need for analgesic and antiemetics is significantly reduced compared to open surgery. However, the optimalization of anesthesia element from the patient perioperative care is still not enough.

Anesthesia Without Opioid/Opioid Free Anesthesia (OFA) is one of the anesthesia techniques which appeared in this decade that by avoiding perioperative opioid will minimize the side effects of opioid, decrease the need for postoperative opioid, and produce a better postoperative outcome. Nevertheless, postoperative multimodal analgesic has remained as the gold standard for over 25 years.

OFA adheres to the multimodal principle, namely the use of more than one type of drugs thus achieving a good quality of general anesthesia without the need for opioids. The OFA protocol combines : N-Methyl-D-Aspartate (NMDA) antagonists such as ketamine, magnesium sulfate, Sodium Channel blockers (local anesthesia), anti-inflammation (NSAID, dexamethasone) and α-2 agonists (dexmedetomidine, clonidine). Those drugs are not given at the same time to the same patient for toxicity and side effects reasons that may result from each drug.

Based on the explanations above, the opioid minimum principle provides maximum advantage with minimum side effects as well as equally good anesthesia results with opioid principle. Therefore, the modern postoperative analgesic principle is based on the opioid minimum principle. Furthermore, researcher wants to know whether there is a meaningful difference in the postoperative effects incidence between opioid free technique (Ketamine + Lidocaine 2%) and opioid anesthesia (Fentanyl) in patients undergoing elective surgery in Dr. Soetomo RPH Surabaya.

METHOD

This research is an experimental research with Single Blind Randomized. In this research there are two groups namely control and treatment groups. Before dividing into two groups, group coding and randomization will be conducted to each group. The group codes are unknown to the patients.

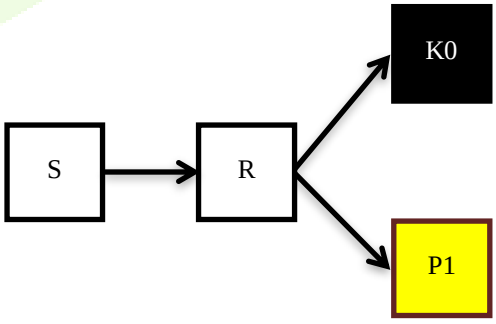

Figure 1 Research Design Scheme

The Inclusion criteria in this research are adult patients aged 18-65 years, patients with physical status condition of American Society of Anesthesiologist Physical Status (ASA 1-2), undergoing elective non-cardiac surgery and willing to participate in the research by signing an informed consent.

The research is conducted in Gedung Bedah Pusat Terpadu (GBPT) of Dr. Soetomo General Hospital Surabaya. This research received "passed the ethical review information" from the permanent committee of research ethics assessor of Faculty of Medicine Airlangga University and received written consent from each patient who has received an explanation. The populations in the research are adult patients undergoing elective surgery since May 2020 until August 2020 with general anesthesia airway management intubation in Dr. Soetomo General Hospital.

The sample collection technique with simple random sampling namely each sample is selected randomly and each individual has the same chance to be selected as research subject. The research subjects were then given the A and B labels, A label for the patients who received Ketamine + Lidocaine 2% and B label for the patients who received standard therapy. The instruments used are routine anesthesia monitoring devices namely monitor in the operating room, with syringe pump to regulate the drug infusion rate. The research samples obtained are 30 samples for each group.

The data collection is based on the observation of variable component that is examined, written, and recorded directly in the data collection sheet (Medical Record). Data will be analyzed and processed statistically with SPSS software. The research results data will be presented descriptively by presenting the data center size, data spread size as well as graphs. The research results data will also be presented analytically after the analysis is conducted by using Chi Square test. If the data do not meet the requirements of the Chi Square test, data will be analyzed by using Fisher's exact test. The difference will then be considered meaningful if the found p value < 0.05.

RESEARCH RESULTS AND ANALYSIS

The basic characteristics of research subjects are divided into demographic characteristics and clinical characteristics. The basic characteristics that constitute demographic data of control and treatment groups can be seen in **Table 1**. In this research, there is no significant difference found between groups regarding gender, age, and BMI with p value of 426; 0,129; and 0,982 respectively. Therefore, the demographic characteristics of research subjects in both groups can be said to be homogeneous.

Table 1 Demographic characteristics of the sample

Variable	Control (n=30)	Treatment (n=30)	P Score
Gender			
Male, n (%)	10 (33,3%)	13 (43,3%)	0,426*
Female, n (%)	20 (66,7%)	17 (56,7%)	
Age (Year)	39,5 (18,0-63,0)	34,5 (19,0-63,0)	0,129**
IMT (kg/m^2)	24,9 (16,4-33,3)	24,4 (17,3-35,4)	0,982**

Note : Data is expressed in median (minimum-maximum) because the data is not normally distributed, and n (%) for frequency. *Chi-square test; **Mann-Whitney test; homogeneous when p> 0.05.

The preoperative clinical characteristics are presented to compare the distribution between both groups. The preoperative clinical characteristics in the form of systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), pulse rate, respiratory rate, oxygen saturation (SpO_2), PS ASA, and WBFS from the research subjects will be presented in **Table 2**. In this research, there is no significant difference in the average of SBP, DBP, MAP in both groups (p=0,392; p=0,172; p=0,229 respectively). Moreover, in this research there is also no statistically difference found between the median of pulse rate, respiratory rate, SpO_2 in both groups (p=0,089, p=0,712, and p=0,571 respectively). There is also no significant difference found in the score of PS ASA and WBFS in both groups in this

research. Based on the analysis of demographic characteristics and clinical characteristics above, it can be said that both groups have homogeneous sample members.

Table 2 Clinical characteristics of research subjects

Characteristics Patient	Control/OA (n=30)	Treatment/OFA (n=30)	P Score
SBP, mmHg	137,0±3,1	133,4±2,8	0,392*
DBP, mmHg	78,7±2,2	74,6±1,9	0,172*
MAP, mmHg	98,1±2,4	94,3±2,1	0,229*
Heart Rate	81,0 (67,0-110,0)	86,5 (65,0-120,0)	0,089**
Respiratory Rate	20,0 (16,0-30,0)	20,0 (16,0-28,0)	0,712**
SpO2, %	97,5 (93,0-100,0)	98,0 (93,0-100,0)	0,571**
ASA Score			
1	5 (16,7%)	5 (16,7%)	1,000***
2	25 (83,3%)	25 (83,3%)	
WBFS			
Mild (0-3)	29 (96,7%)	27 (90,0%)	0,612+
Moderate to severe (>3)	1 (3,3%)	3 (10,0%)	

Note: Data is expressed in mean ±SB for normally distributed data, median (minimum-maximum) for non-normally distributed data, and n (%) for frequency. TDS = systolic blood pressure; TDD = diastolic blood pressure; SpO2= oxygen saturation; MAP= mean arterial pressure; PS-ASA= Physical Status – American Society of Anesthesiologists; WBFS= Wong-Baker Faces Pain Rating Scale. *Free sample t2 test, **Mann-Whitney test, ***Chi-square test; +Fisher's Exact Test; significant when p<0.05

The postoperative incidences which consist of WBFS score, hypoxia incidence, ileus incidence, delirium incidence, as well as nausea and vomiting incidence are the main focus of this research. The incidence of postoperative events in control/OA and treatment/OFA groups are presented in **Table 3**. In this research, there is a significant difference in the score of hypoxia incidence rate, delirium incidence rate, ileus incidence rate, and nausea and vomiting incidence rate in control group and treatment group (p=0,020; p=0,026; p=0,002; p=0,012; respectively). However, different from the postoperative incidence above, there is no significant difference found regarding postoperative pain in research subjects assessed by using WBFS with p value=0,706.

Table 3 Incidence of Postoperative Effect in Research Subjects

Variable	Control (n=30)	Treatment (n=30)	P Score
WBFS Score			
Mild (0-3), n (%)	25 (83,3%)	27 (90,0%)	0,706**
Moderate to Severe (>3), n (%)	5 (16,7%)	3 (10,0%)	
Hypoxia			
No, n (%)	21 (70,0%)	28 (93,3%)	0,020*
Yes, n (%)	9 (30,0%)	2 (6,7%)	
Ileus			
No, n (%)	16 (53,3%)	27 (90,0%)	0,002*
Yes, n (%)	14 (46,7%)	3 (10,0%)	
Delirium			
No, n (%)	22 (73,3%)	29 (96,7%)	0,026**
Yes, n (%)	8 (26,7%)	1 (3,3%)	
Nausea and Vomiting			
No, n (%)	16 (53,3%)	25 (83,3%)	0,012*
Yes, n(%)	14 (46,7%)	5 (16,7%)	

Note: Data is expressed in n (%) for frequency. *Chi-square test; **Fisher's Exact Test; significant when $p<0.05$.

DISCUSSION

The Comparison of Postoperative Pain Level

Postoperative pain is the most frequently expressed complaints by patients. Pain is one of the important vital signs to be observed while the patient is in treatment. This is because the pain felt by patient can affect the overall recovery process and length of hospitalization time (length of stay). There are many supporting tools that can be used for the pain assessment in postoperative patients, one of them is Wong Baker Face Scale (WBFS). WBFS or also often referred to as Faces Pain Scale (FPS) is one of the pain measurement tools which is quite easy to use because it consists of series of facial diagrams with increasing distress expressions. According to Walker et.al., 2019, WBFS has been studied extensively as one of the pain measurement tools and its reliability and validity has been confirmed in all age ranges.

In this research, there is no meaningful difference between postoperative pain score in the OFA group and OA group. The total of patients who felt pain with low intensity in OA group have the same number with patients who felt pain with low intensity in OFA group.

The Comparison of Hypoxia Incidence

Postoperative hypoxia is one of the most common incidences in the post anesthesia care unit (PACU). According to the study by Xue, Li, and Zhang as well as Reeder and Goldman the incidence of hypoxemia arterial postoperative after abdominal surgery ranged from 20%-40%. The residual effect from anesthesia drugs, especially opioid, are expected to play a big role in the hypoxia postoperative incidence.

This research showed that patients with OFA tend to show lower hypoxia postoperative incidence compared to patients who received OA. There is a meaningful difference statistically with p value < 0,05, precisely with p value = 0.02. This is supported by the research conducted by Mulier et.al., 2018 which shows that there is a meaningful difference in the decrease of SpO2 event incidence < 94% in postoperative patients who used oxygen mask 6 l/min, between patients with OFA and patients with OA. The logistic regression multivariate analysis results in the research

showed that there is a meaningful difference for the hypoxia incidence between patients with OFA (0,1%) and patients with OA (100%) with p value = 0,002.

The Comparison of Ileus Incidence

Postoperative ileus (POI) is one of the gastrointestinal complications occurred in various type of operations including abdominal, pelvis, and several non-abdominal operations such as spine surgery. POI causes significant morbidity in patients and also causes discomfort in patients and decrease in the patient recovery quality as well as extension of hospitalization time. The use of opioid is considered as one of the risk factors related to postoperative bowel disfunction (POI) in non-abdominal procedure, and the extension of abdominal postoperative ileus recovery time. Gan, Robinson, and Oderda, 2015, showed that approximately 10,3% patients given opioid will show the POI incidence. Moreover, the higher the opioid dose given is also associated with higher POI incidence.

The POI incidence rate in this research is also found significantly higher in patients given OA (46,7%) if compared to the patients given OFA (10%), with p value = 0,002. This is supported by the Meta Analysis results conducted by Jorgensen et.al., 2008. The meta analysis conducted in the study with the total of 406 patients (178 patients received local anesthesia and 228 patients received OA) which showed that there is a significant reduction in time from the first time the patient passed feces in patients who received local anesthesia (-44 [-72,-17] hours) compared to patients who received OA. The same analysis is conducted in study with total patients of 265 patients (112 patients received local anesthesia and 153 patients received OA), showed that there is a significant reduction in time from the first time the patient flatus in patients who received local anesthesia (-36[-56,-17] hours) compared to patients who received OA.

The Comparison of Delirium Incidence

One of the most common complications also found in post-operative patients is delirium and postoperative cognitive dysfunction (POCD). This POCD is especially common in geriatric patients undergoing surgery. Crosby, Culley, and Dexter, 2014 as well as Card, Pandharipande, and Tomes, 2015, stated that approximately 5%-15% of geriatric patients will experience delirium after undergoing major surgery, and 12%-40% will experience POCD. The presence of this delirium and POCD will cause longer treatment and 1 year increase in mortality. Opioid is one of the risk factors of POCD, and the presence of multimodal and opioid sparing analgesia are proven to reduce the risk of delirium in geriatric patients after undergoing surgery.

Delirium incidence also obtained significantly lower in patients with OFA (3,3%) compared to patients with OA (26,7%), with p value=0,026. This is also supported by research conducted by Pandharipande et.al., 2008, where the opioid exposure such as Fentanyl is the risk factor of postoperative delirium in surgical ICU (p=0,007). In the research, the time proportion where delirium patients in surgical ICU significantly higher in patients with opioid medication compared to patients not receiving opioid medication. Moreover, other research conducted by Orena, King, and Hughes, 2016, also stated that the use of deep anesthesia and lighter sedation has the strongest evidence in reducing postoperative delirium. Perioperative dexmedetomidine, ketamine, dexamethasone, and antipsychotics also able to reduce the risk of delirium.

The Comparison of Nausea and Vomiting Incidence

Nausea and vomiting also become one of the most common side effects during the postoperative period. Approximately 80% of patients experienced nausea and vomiting after receiving the general anesthesia. This postoperative nausea and vomiting (PONV) although self-limited, but perceived by the patient as a discomfort more than postoperative pain. The use of perioperative opioid is known as one of the independent risks of PONV.

In this research, the PONV incidence is found significantly higher in patients who received OA (46,7%) compared to patients who received OFA (16,7%), with p value=0,012. Other research conducted by *Salome et.al., 2021*, in the form of Meta Analysis to compare the advantages and risks of OFA, the centralized analysis stated that there is a decrease in the nausea and vomiting incidence rate in OFA group (RR 0,46 [0,38;056]) in PACU if compared with OA group (RR 0,34 [0,21;0,56]) with relative risk reduction 54% for nausea and 66% for vomiting. Therefore it can be concluded, this PONV reduction is generally associated with no use of opioids during surgery in OFA group. The postoperative therapies such as antiemetics are still carried out according to the anesthetic procedure.

CONCLUSION AND SUGGESTION

The conclusion obtained in this research is that there is no difference from the postoperative WBFS score between opioid free technique (Ketamine + Lidocaine 2%) and opioid anesthesia (Fentanyl) in patients undergoing elective surgery. However, there is a difference from the postoperative hypoxia, ileus, delirium, as well as nausea and vomiting incidences between opioid free technique (Ketamine + Lidocaine 2%) compared to opioid anesthesia (Fentanyl). Therefore, this OFA technique can be implemented in daily clinical practice.

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