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Comparison of the VAS Values for the Administration of Preemptive Analgesia with Intravenous Ibuprofen 800 Mg and Intravenous Ketorolac 30 Mg for Postoperative Patients after Gynecological Abdominal Surgery under General Anesthesia

Muhammad Izhar Yafizham
Department of Anesthesiology and Intensive Care, Medical Faculty, North Sumatera University, Haji Adam Malik General Central Hospital, Medan, Indonesia

Abstract:-

- ***Background*** :

Pain is still becoming post-operative problem. The untreated pain will cause chronic pain which is difficult to heal. Ibuprofen and ketorolac are non-steroid anti-inflammatory agent (NSAID) which are usually used for mild to moderate pain management.

- ***Objective :***

To obtain the comparison of visual analogue scale on the administration of preemptive intravenous ibuprofen 800 mg and ketorolac 30 mg on post-operative abdominal gynecology patients with general anesthesia.

- ***Methods :***

This study is a double blind based study. After obtaining the inform consent from University of North Sumatera Ethics Committee, 50 subjects were collected, with the range of 18-60 years old, PS ASA I-II who will undergo abdominal gynecology elective operation by general anesthesia. The statistics result shows that all samples are divided equally into 2 groups. Group A is given intravenous ibuprofen 800 mg, while group B is given intravenous ketorolac 30 mg. Ibuprofen and ketorolac are given 30 minutes before anesthesia induction. This study's result was analyzed using Mann-Whitney test, Chi-square test with 95% confidence interval ($p < 0,05$).

- ***Result*** **:**

The result shows that the significant difference between mean VAS score of group A and B since the 4 hour observation until 24 hour observation ($p < 0,001$) and additional analgesia administration for both groups (0% vs 24%).

- ***Conclusion :***

The administration of intravenous ibuprofen 800 mg shows lower VAS compared to intravenous ketorolac 30 mg as preemptive analgesia for abdominal gynecology post operative patients.

Keywords:- *Ibuprofen, Ketorolac, NSAID, VAS, Preemptive Analgesia.*

I. INTRODUCTION

The preemptive and preventive analgesia combination results in better pain management in opioid needs. Some authors stated that preemptive analgesia is given in the preoperative stage and preventive analgesia is given in the intraoperative stage (Gottschalk & Smith, 2001). The preventive analgesia is administered to prevent postoperative pain, in fact, chronic pain can occur in 10-50% of cases of patients who do not get good analgesic after surgery. The concept of preemptive analgesia is the administration of the analgesia before the onset of a pain stimulus to prevent central sensitization and reduce the occurrence of subsequent pain. Preemptive analgesia has a 'protective' effect on the nociceptors that is potential to be more effective than similar analgesics in administration after surgery. So that postoperative pain can be reduced and not become chronic pain (Gottschalk & Smith, 2001) (Onk, 2005).

Singla, in 2010, studied the benefits of preemptive analgesia in reducing pain scores in postoperative recovery rooms. From the study, it was found that preemptive analgesia reduced pain scores, reduced the opioid analgesic needs, and extended the time for first demand for postoperative analgesia or postoperative rescue analgesia. (Singla, 2010).

Although there are many types of analgesia and protocols in dealing with postoperative pain, there is still a lack of effective pain management found for the patients. Opioids are the main choice for pain therapy in patients who experience postoperative pain with moderate and severe pain. However, administration of opioids is limited because of its side effects such as respiratory depression, sedation, nausea and vomiting, and, pruritus (Kurihara, 2008) (Fabregat-Cid, 2011).

The Agency for Health Care Policy and Research from the Department of Health and Human Services of United States published practical guidelines for the

management of acute pain, where if there is no contraindication, pharmacological therapy for mild to moderate postoperative pain should begin with nonsteroidal anti-inflammatory drugs (Bookstaver, 2010).

NSAIDs reduce the level of inflammatory mediators in the area of trauma, they also do not cause sedation or respiratory depression. In this study, the researcher used intravenous ibuprofen as one of the inhibitors of Cyclooxygenase-1 (COX-1) and Cyclooxygenase-2 (COX-2) activity. Ibuprofen inhibits the activity of COX-1 and COX-2 with a ratio of 2.5:1 which implies a low risk for bleeding or gastrointestinal and kidney disorders. While the ketorolac has a higher COX-1 and COX-2 ratio of 330: 1 so that it has a higher risk for bleeding and gastrointestinal disorders (Kroll, 2012).

In 2016 Andrea Gago studied 206 patients who underwent abdominal or orthopedic surgery using general anesthesia. All samples were randomly divided into 2 groups. Group A received intravenous ibuprofen 800 mg and group B received placebo. The results of the study found a decrease in the value of group A's VAS when the patient mobilized with a value of p=0.002, while the assessment when the patient stayed still, it was found that the VAS score decreased with a value of p=0.002. The use of morphine was reduced in group A compared to group B with a value of p = 0.015 (Gago, 2016).

Rajesh Gutta in 2013 studied 85 patients who underwent molar tooth extraction surgery under general anesthesia. The patients were randomly divided into 2 groups, the intravenous ketorolac 30 mg group (38 patients) and the placebo group (27 patients) which were administered 5 minutes before the induction of anesthesia. The results showed that the intravenous ketorolac 30 mg group had a lower VAS value than placebo ($p<0.01$), whereas, there was no significant difference for the rescue analgesia use between the two groups (p=0.39) (Gutta, 2013)

From the background above, the researcher wanted to analyze whether the administration of intravenous ibuprofen 800 mg as preemptive analgesia could further reduce postoperative VAS values compared with intravenous ketorolac 30 mg.

II. RESEARCH METHODS

A. Design

This study used a double-controlled and randomized clinical trial method to compare the value of Visual Analogue Scale (VAS) for the administration of preemptive analgesia with intravenous ibuprofen 800 mg and intravenous ketorolac 30 mg for postoperative patients after gynecological abdominal surgery under general anesthesia.

B. Place and time

The study was conducted at H. Adam Malik Central General Hospital and Dr. Pirngadi Hospital in Medan. The time of the study was in November 2016 or after passing ethical clearance from the Health Research Ethics Committee of the Medical Faculty, University of North Sumatra and also the Health Research Ethics Committee at the H. Adam Malik Central General Hospital and dr. Pirngadi Hospital Medan until the number of samples fulfilled.

C. Population and Samples

The population was all patients who underwent elective surgery for gynecological abdominal surgery under general anesthesia at Haji Adam Malik Central General Hospital and Dr. Pirngadi Hospital in Medan. The population who would undergo elective abdominal gynecological surgery under general anesthesia had to meet the inclusion and exclusion criteria. After being statistically calculated, all samples randomized by block were divided into 2 groups. Group A received intravenous ibuprofen 800 mg and group B received intravenous ketorolac 30 mg.

D. Inclusion and Exclusion Criteria

The inclusion criteria in this study were the patients who were willing to take part in the study, aged 18-60 years, ASA PS 1-2, preoperative VAS 0-1. The exclusion criteria in this study were the patients who had a history of contraindications to the drugs used in this study and a history of taking the Non-Steroid Anti-Inflammatory drug (NSAID) 12 hours earlier**. The dropout criteria** were the patients who had allergic reactions after administration of the drug used in this study, had surgical procedures > 180 minutes and had emergency cardiac and pulmonary incidence.

➢ *Informed Consent*

After obtaining approval from the ethics committee, the patients received an explanation of the procedure to be undertaken and stated in writing their willingness on the informed consent sheet.

E. The procedure

- This research was carried out under the supervision of an anesthetist consultant who was on duty that day.
- The two groups underwent an elective surgery preparation procedure (fasted for 6 hours, an intravenous line with venocath no. 18G was installed on the back of the hand, the patients were given an infusion of RL 2 cc/kgBW since the fasting in the room).
- After the patients arrived at the operating room waiting room, the patient is re-examined their identity (name, age, gender, weight, height), diagnosis, anesthesia plan, access to infusion (making sure the infusion was installed with 18G venocath, threeway and had smooth flow of infusion).
- The patients were told that they would receive the drug in an infusion of 0.9% NaCl 200 ml 30 minutes before

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the induction of anesthesia in which Group A received Ibuprofen 800 mg and Group B received Ketorolac 30 mg. The patiends were explained about the pain before carrying out operations with a prepared numerical VAS, then checking the VAS, and the initial measurement of blood pressure, pulse frequency, and breathing frequency. (T-0)

- Before the patient entered the operating room, an anesthetic machine was prepared which was connected to an oxygen source. A set of endotracheal tube attachment devices (ETTs), emergency drug injections such as epinephrine, atropine sulfas, ephedrine and dexamethasone were also prepared.
- After the patient entered the operating room, lying on their back, some monitoring devices: an EKG, tensimeter monitor, oxygen saturation were installed on the patients' body
- Both groups were given preload infusion of ringer lactate fluid with 10 ml/kgBW before general anesthesia was performed.
- Both groups were prepared for general anesthesia.
- Premedications with Fentanyl 2 mcg/kgBW, Midazolam 0.05 mg/kgBW, were waited to 5 minutes onset.
- The patients were induced with Propofol 2 mg/kgBW, Rocuronium 1 mg/kgBW muscle relaxant, after onset reached 90 seconds, hemodynamic was administered 1 minute before intubation was measured then direct laryngoscopy was performed with the laryngoscope and trachea intubated with endotracheal tube according to size, hemodynamic was re-measured after intubation.
- The surgery performed.
- The postoperative two groups were treated the same but group A received intravenous ibuprofen 800 mg and group B received intravenous ketorolac 30 mg every 6 hours after the first administration.
- After surgery, the patients were extubated, then observed in the recovery room and transferred to the treatment room if the Aldrette scored 10 points.
- After 4 hours from the first administration of the drug, the vital signs and VAS (T-1) are recorded, then continued on T-2 (6th hour), T-3 (12th hour), T-4 (18th hour) and T-5 (24th hour).
- If the VAS value indicated by the patient showed moderate to severe pain (VAS> 4), then additional analgesics would be given, which was intravenous Fentanyl 1 mcg/kg.
- The study was stopped if the study subjects refused to participate further, the operation was prolonged so that additional general anesthetic drugs were needed and emergency airway, heart, lung, life-threatening brains occurred.
- The patients on vital signs (blood pressure, pulse frequency, breathing frequency) at T-0 (0 hour), T-1 (4th hour), T-2 (6th hour), T-3 (12th hour), T4 (18th hour) and T-5 (24th hour) were recorded and observed after the first drug administration.
- Postoperative VAS scores were assessed by using a VAS table and the patients were asked to show a line that corresponds to the pain perception felt. This assessment was carried out directly by the researcher and volunteers III (Specialist Education Program Students Semester > V who had been trained) who were not involved in administering drugs to these patients at T-0, T-1, T-2, T-3, T- 4 and T-5
- The results of observational data in both groups were compared statistically.

F. Data analysis

Data analysis included descriptive analysis and hypothesis test using the SPSS program for Windows. Numerical data was displayed in mean ± SD (standard deviation) while categorical data was displayed in the % (percentage). The research hypotheses were tested using the Mann Whitney test. The 95% confidence interval with a value of $p < 0.05$ was considered statistically significant.

III. RESEARCH RESULTS

➢ *Demographic Characteristics of Subjects*

This study was participated by 50 subjects to see whether there was a difference in mean postoperative pain visual analogue scale (VAS) after being treated with non-steroidal anti-inflammatory drugs. The subjects were divided into 2 groups, group A received intravenous ibuprofen 800 mg and group B received intravenous ketorolac 30 mg.

The mean age in group A and B was 42.52 years old and 42 years old, respectively. based on education, the majority of subjects in both groups completed high school education, 68% in group A and 72% in group B.

In group A the most cases occurred were ovarian cysts and uterine myoma with 36%. While in group B, uterine myoma was the most case found (52%). Based on anthropometric characteristics (weight, height, and BMI) and duration of surgery, no significant mean difference was found ($p > 0.05$). The full data is presented in table 4.1.

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Characteristic	IV Ibuprofen 800 mg group (n=25)	IV Ketorolac 30 mg group (n=25)	P
Age, mean (SD), years old	42.52 (9,5)	42 (8,15)	0.836[a]
Education, n (%)			
Elementary school	5 (20)	2 (8)	0.328[b]
High school	17 (68)	18 (72)	
D3	1 (4)	4 (16)	
Bachelor Degree	2 (8)	1 (4)	
ASA PS, n (%)			
1	18 (72)	19 (76)	0.747[b]
2	7 (28)	6 (24)	
Body weight, mean (SD), kg	55.44 (4,65)	55.68 (8.25)	0.905[c]
Body Height, mean (SD), m	1.56 (0,05)	1.57 (0.08)	0.841[c]
BMI, mean (SD), kg/m2	22.72 (1,5)	22.47 (1.76)	0.710[c]
Duration of surgery, mean (SD), minute	122 (21,6)	122.6 (20.52)	0.920[a]

Table 1:- Demographic characteristics

[a]T Independent, [b] Chi Square, [c] Mann Whitney

➢ *VAS mean difference*

VAS	IV Ibuprofen 800 mg group (n=25)	p*
4th hour	3.14 (1.94)	<0.001
6th hour	3.04 (0.18)	
12th hour	2.88 (0.18)	
18th hour	2.72 (0.17)	
24th hour	2.53 (0.18)	

Table 2:-VAS mean difference in the IV Ibuprofen 800 mg group

*Friedman

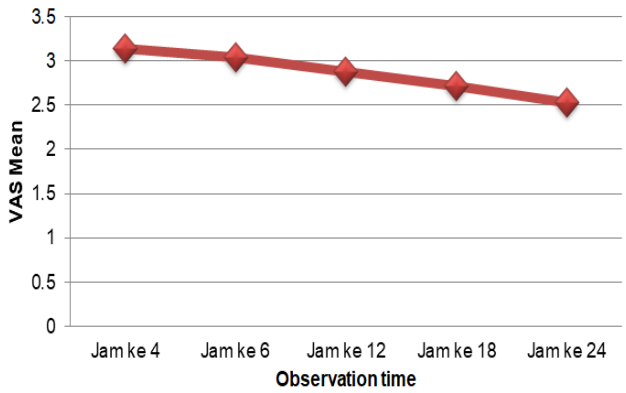

Fig 1:- Chart of VAS changes in the IV Ibuprofen 800 mg group

These Results were not much different from the mean VAS scores in the group receiving intravenous ketorolac 30 mg. The highest mean VAS score occurred at the 4th hour. The VAS score continued to decline until the 24th hour with a mean of 3.2 (0.19). The analysis with the Friedman test concluded that there were differences in the mean VAS scores from the 4th to 24th observation.

VAS	IV Ketorolac 30 mg group (n=25)	p*
4th hour	3,98 (0,73)	<0,001
6th hour	3,59 (0,23)	
12th hour	3,44 (0,23)	
18th hour	3,31 (0,21)	
24th hour	3,2 (0,19)	

Table 3:- VAS mean difference in the IV Ketorolac 30 mg group

*Friedman

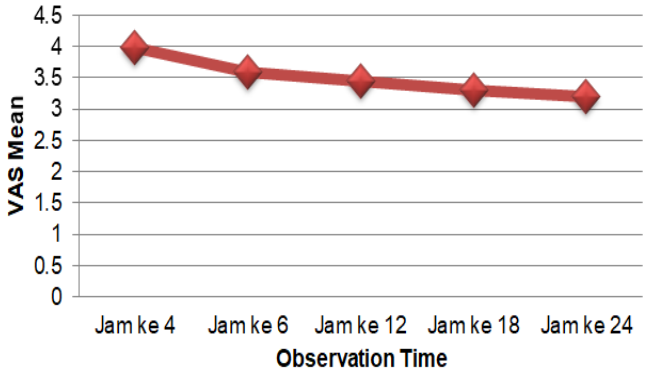

Fig 2:- Chart of VAS changes in the IV Ketorolac 30 mg group

Assessment of pain score (VAS) was carried out at 4th hour, 6th hour, 12th hour, 18th hour and 24th hour. Table 4.2 below shows the mean and standard deviation (SD) of VAS scores from each observation in group A and group B. The results showed that the average VAS score between groups A and B differed significantly from observation of the 4th hour to the 24th hour (p<0.001).

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VAS	IV Ibuprofen 800 mg group (n=25)	IV Ketorolac 30 mg group (n=25)	p*
0th hour	0	0	
4th hour	3.14 (1.94)	3.98 (0.73)	<0.001
6th hour	3.04 (0.18)	3.59 (0.23)	<0.001
12th hour	2.88 (0.18)	3.44 (0.23)	<0.001
18th hour	2.72 (0.17)	3.31 (0.21)	<0.001
24th hour	2.53 (0.18)	3.2 (0.19)	<0.001

Table 4:- VAS mean difference between IV Ibuprofen 800 mg group and IV Ketorolac 30 mg group
*Mann Whitney

In group A, the VAS mean at the 4th-hour observation was 3.04 (SD = 0.18) which was the highest VAS mean and showed a declining trend until the 24th hour. The mean at the 24th hour was 2.53 (SD = 0 .18) which was the lowest VAS mean in the group of subjects who received intravenous ibuprofen 800 mg. The results of the analysis using the Friedman test showed that there were significant differences in VAS from the observation of the 4th hour to the 24th hour in subjects of the group A (p<0.001).

	IV Ibuprofen 800 mg group (n=25)	IV Ketorolac 30 mg group (n=25)	p*
Rescue analgesia, n (%) Yes	0	6 (24)	0,011
No	25 (100)	19 (76)	

Table 5:- Provision of rescue analgesia

* Fisher's Exact

There were no subjects in group A who received rescue analgesia, whereas in group B there were 6 subjects (24%) who received rescue analgesia (RA). All RA in subjects of group B were given at the 4th observation post-surgery. The results of the analysis using the Fisher's Exact test showed that there were significant differences in the provision of rescue analgesia in the two study groups (p=0.011).

IV. DISCUSSION

This study compared the analgesic effect that occurred in postoperative preemptive analgesia of intravenous ibuprofen 800 mg with intravenous ketorolac 30 mg 30 minutes before the induction of anesthesia. 30 minutes before the induction of anesthesia was to reach the onset of the drug when the surgical incision began, this was aimed to prevent the occurrence of central sensitization and reduce the subsequent pain.

This study was devoted to the treatment of postoperative pain which is still the main problem for patients because after the anesthetic effect is gone, the patient will experience pain. Pain that is not handled properly will cause chronic pain, which is actually difficult to handle. Adequate postoperative pain relief is an important component so that the patient's postoperative condition is more comfortable and emotionally pleasing. Quality pain relief is very important to help the healing process faster.

50 samples who had met the inclusion criteria participated in this study. The group was divided into two, 25 samples received intravenous Ibuprofen 800 mg (group A) and 25 samples received intravenous Ketorolac 30 mg (group B). From the general data, the characteristics of the sample showed that age, weight, body mass index, education level, ASA physical status and duration of surgery (table 4.1) between the two groups had no statistically significant differences. It meant that the samples taken were relatively homogeneous and suitable to be compared (p> 0.05)

Likewise, in the preoperative visual analogue scale (VAS) value characteristics (table 4.2) between the two groups, there were no statistically significant differences. It meant that the samples taken were relatively homogeneous and suitable to be compared (p>0.05).

The effect of the anti-pain drug in this study was based on the VAS (Visual Analog Scale) assessment at the 0th-hour observation until the 24th hour after administration of non-steroidal anti-inflammatory drugs (NSAIDs). According to William and Hoggart (2005), VAS is a reliable, valid and sensitive pain measurement technique for both children and adults. VAS measurement is easy, fast and commonly used in research and clinical studies. VAS scores are subjective feelings of patients that are represented by 0-10.

VAS values before surgery are determined to be only 0-1 to eliminate the possibility of bias caused by the pain before surgery. Because the pain that will be assessed is surgical pain, not the pain due to the disease before surgery. Therefore VAS data obtained from both groups can be used as a measure to compare the effects of both drugs in postoperative pain management.

Based on statistical tests on VAS assessment it was found that there were significant differences in VAS values between group A and group B at the 4th observation hour (T1), 6th hour (T2), 12th hour (T3), 18th hour (T4) to 24th hour (T5) (p<0.001). In observations at T1 to T5, it appeared that the mean of VAS value in the intravenous ibuprofen 800 mg group (A) was lower than the intravenous ketorolac 30 mg group (B). On the observation of T1 the mean of VAS value in group A was 3.14 while in group B it was 3.98. Similarly, from the observation of T5,

the mean of VAS value in group A was 2.53 and in group B it was 3.2.

The results of the study of VAS values between the two groups (table 2) showed that VAS values were significantly different at the 4th to 24th hour ($p<0.05$). VAS assessment continued to decline since the observation of the 4th hour to the 24th hour. This is in accordance with the statement of Stoelting RK, 2006 which stated that severe pain will be felt on the first day and decreases after 24 hours and usually the pain is minimal after 3-4 days, it means that VAS scores will always decrease over time (Stoelting, 2006)

This study used an opioid drug called Fentanyl for the rescue analgesia. The main requirement of rescue analgesia is to have a fast start of action, so that patients with VAS values >4 were considered to be in moderate to severe pain that made them uncomfortable and in need of rescue analgesia (Rawal, 2008).

Based on the presence or absence of rescue analgesia in table 4.5, a statistically significant difference was found ($p = 0.011$), in group A there were no research subjects who received rescue analgesia, whereas in group B there were 6 subjects who received rescue analgesia at the 4th hour (T1). This showed that intravenous ibuprofen 800 mg provides sufficient analgesia for postoperative pain management compared to intravenous ketorolac 30 mg. This is in accordance with a study conducted by Singla in 2010 about the benefits of giving preemptive analgesia of intravenous ibuprofen 800 mg in reducing the opioid analgesic needs (Singla, 2010).

With no use of rescue analgesia in the intravenous ibuprofen 800 mg group, it can indirectly avoid the side effects of opioid use such as respiratory depression, sedation, nausea, vomiting, and pruritus (Kurihara, 2008).

Fentanyl is known to induce immunosuppression at certain doses. Sacerdote et al's 2007 study showed that continuous infusion of fentanyl can suppress activation of natural killer (NK) cells. But on the other hand, the administration of certain doses of fentanyl is also known to induce immunosuppression (Sacerdote, 2007).

Major surgeries such as laparotomy cause excessive amounts of pro-inflammatory cytokines which can cause undesirable complications such as postoperative complications, suppression of the immune system, and end-organ injury, which in turn will cause multiple organ failure and death (Roussabrov, 2008).

With no use of rescue analgesia in the intravenous ibuprofen 800 mg group, we indirectly, based on Sacerdote and Anjangsari's study, avoid drug that can induce immunosuppression, which can cause undesirable complications such as slow wound healing.

This study did not assess the incidence of side effects that occurred from both drugs, it only assessed acute pain in the first 24 hours without assessing its effect on postoperative chronic pain. In further research, the incidence of side effects that may occur from the drugs and their effects on chronic pain may be further studied.

V. CONCLUSIONS

1. The administration of intravenous Ibuprofen 800 mg had a lower VAS value compared to intravenous Ketorolac 30 mg as preemptive analgesia after abdominal gynecological surgery from the 4th hour to the 24th hour.
2. The administration of intravenous Ibuprofen 800 mg can reduce the use of opioid as rescue analgesia compared to intravenous Ketorolac 30 mg.

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