COMPARISON BETWEEN CYCLOOXYGENASE, PROSTAGLANDIN LEVEL, AND PAIN SCORE IN IBUPROFEN AND PARACETAMOL ADMINISTRATION AS PREEMPTIVE ANALGESIA DURING LAPAROTOMY

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Objectives: Preemptive analgesia has potential to be more effective than the same analgesic therapy given after surgery because of its protective effect on the nociceptive system. The purpose of this study was to analyze the comparison of cyclooxygenase levels, prostaglandins and postoperative pain scores 2 hours, 6 hours and 24 hours in the administration of ibuprofen and paracetamol as preemptive analgesia in patients undergoing abdominal surgery under general anesthesia at Integrated Surgery Center (GBPT) of Dr. Soetomo Hospital.

Methodology: Analytical study, quasy experimental, prospective. A total of 60 patients with PS ASA 1-3 aged 18-60 years who underwent laparotomy were recruited in this study. In this study, one of the paracetamol, ibuprofen, or control groups was given a 100 ml PZ placebo in the premedication room before anesthesia was performed. The three groups were treated the same under anesthesia and blood was drawn 1 hour after administration of preemptive analgesia to check cyclooxygenase and prostaglandin levels. After the operation was completed, postoperative pain scores were examined at 2 hours, 6 hours and 24 hours.

Results: In this study there were significant differences in the analysis of cyclooxygenase values, the highest was the control group, followed by paracetamol and the lowest was the ibuprofen group (p value = 0.000). There was a significant difference in the analysis of prostaglandin values, the highest was in the control group, followed by paracetamol and the lowest was in the ibuprofen group (p value 0.000). Significant differences were found in the analysis of postoperative pain scores 6 hours (p value 0.004) and 24 hours (p value 0.043), the highest pain score was in the control group, paracetamol, followed by ibuprofen, while the analysis of postoperative pain scores 2 hours found no significant difference (p value = 0.415).

Conclusion: Patients who received preemptive analgesia (ibuprofen or paracetamol) had lower cyclooxygenase, prostaglandin and postoperative pain scores

Keywords: Preemptive Analgesia, Paracetamol, Ibuprofen, Cyclooxygenase, Prostaglandin, Laparotomy

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INTRODUCTION

Surgical stress is a complex aspect of surgery that involves inflammatory stress leading to catabolism, endothelial dysfunction, fatigue, and gastrointestinal dysfunction. Within surgical stress, hypoxic stress occurs due to vasodilation and extravasation, resulting in increased oxygen demand leading to hypoxemia and hypoperfusion. One way to reduce perioperative surgical stress in elective laparotomy surgery is through minimally invasive surgery, neuraxial blockade using epidural or peripheral blockade with local anesthesia, NSAIDs (Non-Steroidal Anti-Inflammatory Drugs), and glucocorticoids. Neuraxial blockade can reduce surgical stress, postoperative ileus, respiratory complications in elective laparotomy, and decrease pain levels. However, not all cases are suitable for neuraxial blockade, including those involving sepsis, coagulopathy disorders, limited facilities, or lack of expertise (Foss & Kehlet, 2020).

Paracetamol is widely used as an antipyretic and analgesic medication. It acts centrally as a weak inhibitor of prostaglandin synthesis by cyclooxygenase 1 (COX-1), cyclooxygenase 2 (COX-

2) and cyclooxygenase 3 (COX-3). This concept is based on a study conducted by Flower and Vane, which showed that paracetamol was 10 times more sensitive in inhibiting prostaglandin production in the brain compared to the lien. Paracetamol does not suppress the inflammatory process, making it primarily an analgesic. It is a weak inhibitor of COX-1 and an inhibitor of prostaglandins (Hinz & Brune, 2012). Additionally, paracetamol is said to reduce COX-1 cyclooxygenase activity in umbilical vein endothelial cells (Freo et al., 2021).

Ibuprofen is a propionic acid derivative NSAID with anti-inflammatory, antipyretic, and analgesic properties. It is available in oral and intravenous forms and is useful for managing mild, moderate, and severe pain when combined with opioids. Ibuprofen works by inhibiting cyclooxygenase 1 and cyclooxygenase 2. According to a study by Le et al. (2016), ibuprofen used as preemptive analgesia can reduce the prostaglandin stress response in patients undergoing cholecystectomy surgery.

In August 2022, Dr. Soetomo Hospital Surabaya saw 751 cases of patients undergoing surgery under general anesthesia, with 21 cases involving abdominal surgery in patients aged 18-65 years. Among them, 16 cases used paracetamol as postoperative therapy, and 4 cases used ibuprofen as postoperative therapy.

Paracetamol, also known as acetaminophen, is used as an analgesic and antipyretic medication similar to NSAIDs. A study by Hossam (2014) showed that cesarean section patients who received paracetamol as preemptive analgesia experienced reduced opioid consumption during and after surgery (Ciftci et al., 2019).

While research abroad on the effect of ibuprofen and paracetamol exists, there is currently no data specifically discussing their combined effects using prostaglandin and cyclooxygenase markers in abdominal surgery under general anesthesia at Integrated Surgery Center (GBPT) of Dr. Soetomo Hospital (Steinberg et al., 2017).

METHODOLOGY

This study was an analytical, quasi-experimental, prospective study. The sample was divided into three groups: the first group received paracetamol, the second group received ibuprofen in the premedication room before anesthesia, and the control group was given 100 ml of PZ placebo. The treatment assigned to each sample was determined through a Randomized Control Trial (RCT) in a single-blind manner. All three groups received the same treatment during induction, maintenance of anesthesia, and the postoperative period. Cyclooxygenase and prostaglandin levels were measured one hour after the administration of ibuprofen, paracetamol, and PZ 100 ml placebo. This study was conducted at the Integrated Surgery Center (GBPT) of Dr. Soetomo Hospital Surabaya.

The research sample consisted of patients who underwent abdominal surgical procedures using general anesthesia at the Integrated Surgery Center (GBPT) of Dr. Soetomo Hospital Surabaya. The sample of this study was randomly selected based on time-limited criteria and the number of available samples. The sample size for each group was calculated to be 19 patients, rounded up to 20 patients. Since there were 3 groups, the total sample size was 60 patients (Tsagris et al., 2020).

The study's *inclusion* criteria involved patients who underwent abdominal surgical procedures and met the following conditions: they were aged between 18 and 60 years old, classified under PS ASA I-III (American Society of Anesthesiologists Physical Status Classification I-III), were undergoing elective or planned surgeries with a low to moderate expected level of postoperative pain, and received general anesthesia. Additionally, patients or their families were required to express their willingness to participate in the study by signing an informed consent form.

On the other hand, certain *exclusion* criteria were established to exclude specific patient groups from the study. Patients with comorbid hypertension, characterized by a target systolic blood pressure below 140 mmHg, were excluded, as were those with tachycardia, defined as a target heart rate frequency below 100 beats per minute. Individuals with severe cardiac, liver, and renal impairments were also excluded from the study, as were those with known allergies to ibuprofen and paracetamol. Patients with a history of difficult airway management, requiring intubation more than two times, were not included. Similarly, patients with Diabetes Mellitus and those diagnosed with sepsis were excluded from the study.

Pain assessment was conducted by a competent assessor who was also qualified to perform intubation. In this study, the independent variable was preemptive analgesia. The dependent variables were as follows: Cyclooxygenase, Prostaglandins, and the pain score reported by the patients.

To collect data for the study, the research team utilized data collection sheets and employed specific tools and reagents to measure the levels of Cyclooxygenase and Prostaglandins in the patients' blood serum.

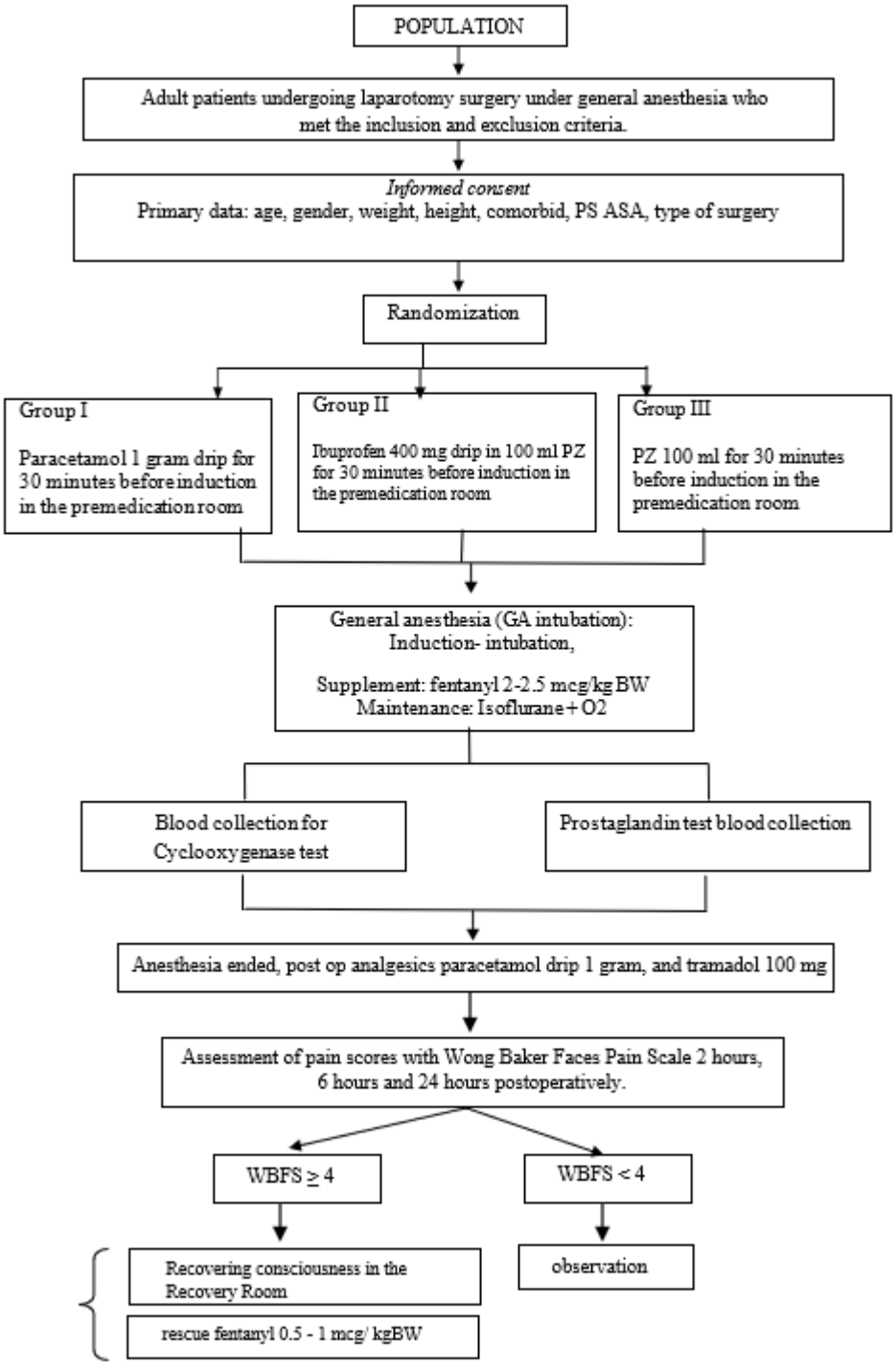

Figure (1) Research Framework

Explanation of the operational framework:

The study's preparation involved several steps. First, one day before surgery, patients underwent a preoperative examination, which included anamnesis, physical examination, and necessary laboratory and radiological tests. Once the patient's condition met the inclusion criteria, informed consent was obtained from the patient and their family, after which the

patient's basic data, such as identity, gender, weight, height, blood pressure, heart rate, breathing frequency, comorbidities, physical status, and type of surgery, were recorded.

Patients were then randomized and grouped into three categories. Group I, the Paracetamol group, received 1 gram of paracetamol through intravenous drip. Group II, the Ibuprofen group, received intravenous ibuprofen 400 mg in 100 ml PZ over 30 minutes. Group III served as the control group and received 100 ml PZ as a placebo. Monitors were set up to measure pulse frequency, blood pressure, and oxygen saturation, while anesthesia machines, anesthetic drugs, and emergency drugs were prepared. Induction of general anesthesia was carried out using specific drugs, and vital signs were continuously monitored.

An hour after the procedure, blood was drawn from all three groups to check cyclooxygenase and prostaglandin levels. During skin suturing, postoperative analgesics were administered, including 1 gram of paracetamol and 100 mg of tramadol in 100 cc NaCl drip for 30 minutes. After the operation, extubation was performed, and the patient was taken to the recovery room and given oxygen with a nasal cannula at 3 lpm. Vital signs and pain scores were continuously monitored in the recovery room for 2 hours, with rescue fentanyl given if the Wong Baker Face Scale pain score was ≥ 4.

The PPDS Anesthesia team assessed pain at 6 and 24 hours postoperatively using the Wong Baker Faces Pain Scale. Data were collected using a special data collection sheet (LPD) and processed using SPSS 22 software. The normality of the data was tested using the Kolmogrov-Smirnov test, and based on the distribution, the Independent t-Test or Mann Whitney U Test was used for analysis accordingly. The research results were presented through tabulations, graphs/diagrams, and explanatory text to provide a clear understanding of the findings.

RESULTS

Description of Research Data

This study was an analytic, quasi-experimental, prospective study. The sample consisted of three groups: the paracetamol group, the ibuprofen group, and the control group. The treatment assigned to each group was determined through a Randomized Control Trial (RCT) in a single-blind manner. All three groups received the same treatment during induction, maintenance of anesthesia, and in the postoperative period. Cyclooxygenase and prostaglandin levels were measured one hour after the administration of ibuprofen, paracetamol, and PZ 100 ml as a placebo.

Characteristics of Research Subjects

The demographic characteristics of the study participants include gender, age, weight, height, BMI (body mass index), length of surgery, and PS ASA (American Society of Anesthesiologists Physical Status Classification). To ensure no significant differences in demographic characteristics among patients in the paracetamol, ibuprofen, and control groups, equality tests were performed. The Chi-Square test was used for nominal data, the Kruskal-Wallis test for non-normally distributed numerical data, and Anova for normally distributed numerical data. Table (1) presents the results of the normality test and the equality of demographic characteristics among the three patient groups: paracetamol, ibuprofen, and control.

Table (1) Normality test of demographic characteristics in paracetamol, ibuprofen and control groups

Demographics	Group	p Shapiro Wilk	Normality / Distribution
Age	Paracetamol	0,464	Normal
	Ibuprofen	0,066	Normal
	Control	0,011	Not Normal
Body Weight	Paracetamol	0,198	Normal
	Ibuprofen	0,250	Normal
	Control	0,006	Abnormal
Height	Paracetamol	0,065	Normal
	Ibuprofen	0,625	Normal
	Control	0,032	Abnormal
BMI (Body Mass Index)	Paracetamol	0,634	Normal
	Ibuprofen	0,784	Normal
	Control	0,160	Normal
Length of Surgery	Paracetamol	0,025	Abnormal
	Ibuprofen	0,044	Abnormal
	Control	0,003	Abnormal

*declared normal if the p value of the Shapiro wilk test> 0.05

Based on the results of Table 1, the normality test using Shapiro-Wilk found that the data on age, weight, and height in the paracetamol and Ibuprofen groups had a p-value > 0.05, indicating normal distribution. However, for the control group, the p-value was < 0.05, indicating abnormal distribution. Additionally, for the demographic data on the length of surgery, all groups were declared abnormal because p < 0.05. Since one group was declared abnormal in the demographic data for age, weight, and height, and all groups were not normal for the length of surgery, the equality test utilized non-parametric methods, specifically the Kruskall-Wallis test. On the other hand, the normality test for BMI data showed that all groups had a p-value > 0.05, indicating normal distribution. Consequently, the equality test employed parametric methods, specifically the ANOVA test.

Table (2) Distribution of demographic characteristics and equivalence test between paracetamol, ibuprofen and control groups

Demographic Characteristics	Group			Total	p value
	Paracetamol (n=20)	Ibuprofen (n=20)	Control (n=20)		
Gender					
Male	8 (40,0%)	7 (35,0%)	6 (30,0%)	21 (35,0%)	0,803 [a]
Female	12 (60,0%)	13 (65,0%)	14 (70,0%)	39 (65,0%)	
Age					
Median (range)	26-60 (49,00)	21-60 (47,50)	24-59 (48,50)	21-60 (48,00)	0,867 [c]
Body Weight					
Median (range)	40-74 (52,00)	37-75 (51,50)	40-86 (55,00)	37-86 (54,00)	0,347 [c]
Height					
Median (range)	145-166 (155,00)	144-178 (157,00)	145-182 (156,50)	144-182 (155,00)	0,481 [c]
BMI					
Mean ± SD	22,02 ± 3,20	21,48 ± 3,88	22,63 ± 2,96	22,04 ± 3,35	0,560 [b]
The length of surgery (minute)					
Median (range)	90-150 (110,00)	90-140 (120,00)	90-130 (100,00)	90-150 (110,00)	0,222 [c]
PS ASA					
1	1 (5,0%)	0 (0%)	0 (0%)	1 (1,7%)	0,229 [c]
2	16 (80,0%)	13 (65,0%)	16 (80,0%)	45 (75,0%)	
3	3 (15,0%)	7 (35,0%)	4 (20,0%)	14 (23,3%)	

[a]Chi Square test, [b]Anova test, [c]Kruskal Wallis test, declared equal / homogeneous if the p value> 0.05

Types of Surgery	Paracetamol	Ibuprofen	Control	Total
Herniotomy hernioplasty	4 (6,4%)	4 (6,4%)	2 (3,2%)	10 (16%)
Repair of umbilical hernia	3 (4,8%)	3 (4,8%)	3 (4,8%)	9 (14,4%)
Sigmoidostomy	3 (4,8%)	3 (4,8%)	3 (4,8%)	9 (14,4%)
Stoma closure	3(4,8%)	2 (3,2%)	3 (4,8%)	8 (12,8%)
Laparotomy myomectomy	3 (4,8%)	3 (4,8%)	2 (3,2%)	8 (12,8%)
Herniotomy hernioraphy	3(4,8%)	4 (6,4%)	3 (4,8%)	10 (16%)
Double colonoscopy attach stoma cap	3 (4,8%)	2 (3,2%)	1 (1,6%)	6 (9,6%)

Based on the results from Table 2, the distribution of demographic characteristics for gender in the paracetamol, ibuprofen, and control groups was predominantly female, comprising 60.0%, 65.0%, and 70.0%, respectively. The male subjects constituted 40.0%, 35.0%, and 30.0% in the respective groups. Regarding age, the median (range) for the paracetamol, ibuprofen, and control groups were 26-60 (49), 21-60 (47.5), and 24-59 (48.5), respectively. Based on weight, the median (range) for the paracetamol, ibuprofen, and control groups were 40-74 (52), 37-75 (51.5), and 40-86 (55), respectively. For height, the median (range) for the paracetamol, ibuprofen, and control groups were 145-166 (155), 144-178 (157), and 145-182 (156.5), respectively.

Regarding BMI (Body Mass Index), the mean and standard deviation for the paracetamol, ibuprofen, and control groups were 22.02 ± 3.20, 21.48 ± 3.88, and 22.63 ± 2.96, respectively. For the length of surgery, the median (range) for the paracetamol, ibuprofen, and control groups were 90-150 (110), 90-140 (120), and 90-130 (100), respectively. Furthermore, based on the PS ASA (Physical Status according to the American Society of Anesthesiologists) for the paracetamol, ibuprofen, and control groups, the distribution was as follows: PS ASA1 - 1 (5.0%), 0 (0%), and 0 (0%); PS ASA2 - 16 (80.0%), 13 (65.0%), and 16 (80.0%); PS ASA3 - 3 (15.0%), 7 (35.0%), and 4 (20.0%).

Moving on to the results from Table 1, which focused on the equality test or homogeneous test for demographic characteristics between the paracetamol, ibuprofen, and control groups based on various subject characteristics, such as gender, age, body weight, height, BMI, length of surgery, and PS ASA, all p-values obtained were > 0.05. This implies that there were no significant or meaningful differences between the three groups based on demographic characteristics. Consequently, it can be concluded that the demographic characteristics of the three groups were homogeneous or equivalent.

Laboratory Characteristics

The laboratory characteristics in this study include systolic and diastolic blood pressure, mean arterial pressure (MAP), pulse rate, respiratory rate, and pain levels. These characteristics were tested among the three groups: paracetamol, ibuprofen, and control. The aim was to ensure that there were no significant differences in laboratory characteristics between patients using paracetamol, ibuprofen, and the control group.

To achieve this, an equality or homogeneous test was conducted between the three groups based on their laboratory characteristics. For numerical data that were found to have abnormal distribution, the Kruskal-Wallis test was utilized. On the other hand, numerical data that were found to have a normal distribution were analyzed using the ANOVA test. The following table presents the results of the normality test and the equality test conducted for laboratory characteristics across the three patient groups:

Table (3) Normality test of laboratory characteristics in paracetamol, ibuprofen and control groups

Demography	Group	p Shapiro Wilk	Distribution
Systole BP	Paracetamol	0,148	Normal
	Ibuprofen	0,300	Normal
	Control	0,462	Normal
Diastole BP	Paracetamol	0,742	Normal
	Ibuprofen	0,412	Normal
	Control	0,897	Normal
MAP	Paracetamol	0,629	Normal
	Ibuprofen	0,087	Normal
	Control	0,679	Normal
Pulse	Paracetamol	0,692	Normal
	Ibuprofen	0,441	Normal
	Control	0,366	Normal
Breath	Paracetamol	0,001	Abnormal
	Ibuprofen	0,003	Abnormal
	Control	0,000	Abnormal

* declared normal if the Shapiro wilk test p value> 0.05

Based on the results of Table 3, the normality test using Shapiro-Wilk found that for Systole BP, Diastole BP, MAP, and Pulse data in all groups, the p-

value > 0.05, indicating normal distribution. Therefore, the equality test used parametric methods with ANOVA as the selected test.

However, for the normality test of group breathing data, a p-value < 0.05 was obtained, indicating non-normal distribution. Therefore, the equality test used parametric methods with the Kruskal-Wallis test as the appropriate choice. Lastly, for the normality test of pain scores, the Chi-Square test was used.

Table (4) Distribution of laboratory characteristics and equivalence test between paracetamol, ibuprofen and control groups

Laboratory Characteristics	Group			p value
	Paracetamol (n=20)	Ibuprofen (n=20)	Control (n=20)	
Systole BP				
				0,722[a]
Mean ± SD	123,75 ± 10,92	121,25 ± 12,09	121,45 ± 9,41	
Diastole BP				
				0,676[a]
Mean ± SD	78,50 ± 8,06	76,85 ± 7,52	79,10 ± 9,23	
MAP				
				0,417[a]
Mean ± SD	96,25 ± 9,14	92,35 ± 10,68	93,35 ± 8,91	
Pulse				
				0,761[a]
Mean ± SD	84,35 ± 10,94	82,05 ± 10,15	83,10 ± 9,09	
Breath				
Median (range)	18-22 (20,00)	18-22 (20,00)	18-22 (20,00)	0,134[b]
Pain Score				
Median (range)	0-1 (0,00)	0-1 (1,00)	0-1 (1,00)	0,420[c]
No Pain	20 (100%)	20 (100%)	20 (100%)	

[a]Anova test, [b]Kruskal Wallis test, [c]Chi Square is declared equal / homogeneous if the p value> 0.05

Based on the results of Table 4, the laboratory characteristics based on Systole BP in the paracetamol, ibuprofen, and control groups showed the following mean and standard deviation values: 123.75 ± 10.92, 121.25 ± 12.09, and 121.45 ± 9.41, respectively. For laboratory characteristics based on Diastolic BP, the paracetamol, ibuprofen, and control groups had mean and standard deviation values of 78.50 ± 8.06, 76.85 ± 7.52, and 79.10 ± 9.23, respectively.

Regarding laboratory characteristics based on MAP, the paracetamol, ibuprofen, and control groups had mean and standard deviation values of 96.25 ± 9.14, 92.35 ± 10.68, and 93.35 ± 8.91, respectively. As for laboratory characteristics based on pulse, the paracetamol, ibuprofen, and control groups obtained mean and standard deviation values of 84.35 ± 10.94, 82.05 ± 10.15, and 83.10 ± 9.09, respectively.

The laboratory characteristics based on breathing in

all three groups had a median of 20, with a range of 18-22. Furthermore, laboratory characteristics based on pain scores in all three groups had a median of 0.00, with a range of 0-1, indicating that all groups fell into the category of no pain.

Analysis of Cyclooxygenase Test

The comparison test for Cyclooxygenase in the paracetamol, ibuprofen, and control groups was conducted using the ANOVA test when the data was normally distributed, and the Kruskal-Wallis test when the data was not normally distributed. The normality test was performed using the Shapiro-Wilk test since the amount of data in all three groups (paracetamol, ibuprofen, and control) was less than 30. The results of the normality test and the Cyclooxygenase comparison test are presented in the following table.

Table. 5. Cyclooxygenase normality test in the paracetamol, ibuprofen and control groups.

Cyclooxygenase	Group	p Shapiro Wilk	Distribution
Cyclooxygenase	Paracetamol	0,132	Normal
	Ibuprofen	0,005	Abnormal
	Control	0,014	Abnormal

*declared normal if the Shapiro wilk test p value> 0.05

Based on the results of Table 5, the normality test using Shapiro-Wilk found that the Cyclooxygenase data in the paracetamol group had a p-value > 0.05, indicating normal distribution. However, for the Ibuprofen and control groups, the p-value was < 0.05, indicating non-normal distribution. As two groups were declared to be abnormal, the comparison test for Cyclooxygenase among the paracetamol, ibuprofen, and control groups was performed using non-parametric methods with the Kruskal-Wallis test as the selected test.

Table. 6 Comparative test of systole and diastole in the paracetamol and ibuprofen groups

Group	Cyclooxygenase	p value		p value Between Groups	
	Median (range)		Paracetamol vs Ibuprofen	Paracetamol vs Control	Ibuprofen vs Control
Paracetamol	39,28 -73,74 (50,90)	0,000[a]	0,000[b]	0,000[b]	0,000[b]
Ibuprofen	21,09-58,98 (31,43)				
Control	73,71-111,88 (85,18)				

*****declared significantly different if the p value <0.05, [a]Kruskal Wallis Test, [b]MannWhitney

Based on the results of Table 6, the Cyclooxygenase comparison test found that the median for the paracetamol group was 39.28-73.74 (50.90), for the ibuprofen group it was 21.09-58.98 (31.43), and for the control group it was 73.71-111.88 (85.18). The statistical analysis using the Kruskal-Wallis test yielded a p-value of 0.000, which is less than 0.05, indicating a significant difference among the groups. From the diagram, it can be observed that the control group had the highest Cyclooxygenase value, while the ibuprofen group had the lowest value among the three groups.

Prostaglandin Test Analysis

The comparison test for prostaglandin levels in the paracetamol, ibuprofen, and control groups was performed using ANOVA if the data was normally distributed, and the Kruskal-Wallis test if the data was not normally distributed. The normality test was conducted using the Shapiro-Wilk test due to the sample size being less than 30 in all three groups (paracetamol, ibuprofen, and control). The results of the normality test and the prostaglandin comparison test are presented in the following table.

Table (7) Normality test of prostagladin in paracetamol, ibuprofen and control groups

Prostagladin	Group	p Shapiro Wilk	Distribution
Prostagladin	Paracetamol	0,052	Normal
	Ibuprofen	0,647	Normal
	Control	0,000	Abnormal

*declared normal if the Shapiro wilk test p value> 0.05

Based on the results of Table 7, the normality test using Shapiro-Wilk found that the p-values for prostaglandin data in the paracetamol and ibuprofen groups were all > 0.05. This indicates that the prostaglandin data in the paracetamol and ibuprofen groups were declared normally distributed. However, for the control group, the prostaglandin data had a p-value < 0.05, suggesting that it was declared as not normally distributed or abnormal.

Since there is one group (the control group) that is not normally distributed, the comparison test for prostaglandin among the paracetamol, ibuprofen, and control groups uses a non-parametric method, with the Kruskal-Wallis test being the selected test.

Table (8) Comparative test of prostagladin in paracetamol, ibuprofen and control groups

Kelompok	Prostagladin	p value	p value Between Groups		
	Range (Median)		Paracetamol vs Ibuprofen	Paracetamol vs Control	Ibuprofen vs Control
Paracetamol	81,95 -132,43 (99,18)	0,000[a]	0,000[b]	0,000[b]	0,000[b]
Ibuprofen	49,23-98,80 (68,23)				
Control	126,50-335,37 (170,85)				

[a]Kruskal Wallis Test, [b]MannWhitney

Based on the results of Table 8, the prostaglandin comparison test found that the median for the paracetamol group was 81.95-132.43 (99.18), for the ibuprofen group it was 49.23-98.80 (68.23), and for the control group it was 126.50-335.37 (170.85). Based on these results, it can be observed that the prostaglandin levels in the control group tended to be higher than those in the paracetamol and ibuprofen groups.

Pain Analysis

The comparison test for pain in the paracetamol, ibuprofen, and control groups was conducted using the Chi-Square test. This choice of test was made because the pain data was in ordinal/categorical form. The results of the pain comparison test are presented in the following table.

Table (9) Comparative test of pain in paracetamol, ibuprofen and control groups

Pain	Group			p value
	Paracetamol (n=20)	Ibuprofen (n=20)	Control (n=20)	
Pain at 2 hours				
No Pain	13 (65,0%)	15 (75,0%)	11 (55,0%)	0,415
Mild Pain	7 (35,0%)	5 (25,0%)	9 (45,0%)	
Pain at 6 hours				
No Pain	3 (15,0%)	8 (40,0%)	0 (0%)	0,004
Mild Pain	17 (85,0%)	12 (60.0%)	20 (100%)	
Pain at 24 hours				
No Pain	0 (0%)	3 (15,0%)	0 (0%)	0,043
Mild Pain	20 (100%)	17 (85,0%)	20 (100%)	

*declared significantly different if the p value <0.05

Based on the results of Table 9 for the pain comparison test at 2 hours, it was observed that in the paracetamol group, 13 (65.0%) subjects reported no pain, while 7 (35.0%) subjects experienced mild pain. In the ibuprofen group, 15 (75.0%) subjects had no pain, and 5 (25.0%) subjects had mild pain. For the control group, 11 (55.0%) subjects had no pain, and 9 (45.0%) subjects experienced mild pain.

Moving on to the pain comparison test at 6 hours, the

findings were as follows: In the paracetamol group, 3 (15.0%) subjects reported no pain, and 17 (85.0%) subjects had mild pain. In the ibuprofen group, 8 (40.0%) subjects experienced no pain, while 12 (60.0%) subjects had mild pain. However, in the control group, all 20 (100%) subjects reported mild pain, and none had no pain.

Finally, examining the pain comparison test results at 24 hours: In the paracetamol group, all 20 (100%) subjects experienced mild pain, and none reported no pain. For the ibuprofen group, 3 (15.0%) subjects had no pain, and 17 (85.0%) subjects had mild pain. Similarly, in the control group, all 20 (100%) subjects reported mild pain, and none had no pain.

Analysis of Cyclooxygenase Values with Normal

Values

The chi-square test was employed to analyze the relationship between cyclooxygenase values and normal values. The results of the comparison test are presented in the following table:

Table (10) Cyclooxygenase Values with Normal Values

Cyclooxygenase	Group			p value
	Paracetamol (n=20)	Ibuprofen (n=20)	Control (n=20)	
Normal levels				
50-200 pg/ml	11 (55,0%)	1 (5,0%)	20 (100,0%)	0,000
Abnormal levels < 50 pg/ml, atau >200 pg/ml	9 (45,0%)	19 (95,0%)	0 (0,0%)	

*declared significantly different if the p value <0.05

From the analysis test of cyclooxygenase values with normal values, a p-value of 0.000 was obtained, where $p < 0.05$. This indicates that there is a significant difference between cyclooxygenase values in the control group, paracetamol, and ibuprofen with normal values.

Analysis of Prostaglandin Values with Normal Values

The chi-square test was utilized to analyze the relationship between prostaglandin values and normal values. The results of the comparison test are presented in the following table:

Table (11) Prostaglandin Values with Normal Values

Prostaglandin	Group			p value
	Paracetamol (n=20)	Ibuprofen (n=20)	Control (n=20)	
Normal levels				
35-115 pg/ml	17 (85,0%)	20 (100,0%)	0 (0,0%)	0,000
Abnormal levels < 35 pg/ml or >115 pg/ml	3 (15,0%)	0 (0,0%)	20 (0,0%)	

From the analysis test of prostaglandin values with normal values, a p-value of 0.000 was obtained, where $p < 0.05$. This indicates that there is a significant difference between prostaglandin values in the control group, paracetamol, and ibuprofen with normal values.

DISCUSSION

Analysis of Subject Characteristics

A total of 60 patients who met the inclusion and exclusion criteria were observed in this study. The types of surgery selected included stoma closure, umbilical hernia repair, herniotomy hernioplasty, sigmoidostomy, and laparotomy myomectomy. These surgeries are expected to have low to moderate postoperative pain.

In this study, most patients in the control, paracetamol, and ibuprofen groups were female. The median (range) age in the paracetamol group was higher than in the control and ibuprofen groups. The median (range) body weight in the control group was higher than in the paracetamol and ibuprofen groups. The median (range) height in the ibuprofen group was higher than in the control and paracetamol groups.

From the general data of sample characteristics, it was found that gender, age, weight, height, Body Mass Index (BMI), length of surgery, type of surgery, and PS ASA obtained p-values > 0.05. Statistically, there was no significant difference between the three groups, indicating that the samples of the ibuprofen, paracetamol, and control groups were considered homogeneous or equivalent. This finding aligns with previous research conducted by Ciftci et al. (2019), where the proportion of women was higher than men, at 74%. The median age in this group is almost the same as the research conducted by Le et al. (2016), which reported a median age range of 21-60 (48.00) years. The study conducted by Uribe et al. (2018) stated that there was no difference in age between the control and treatment groups.

In this study, most of the samples in the paracetamol, ibuprofen, and control groups were classified as PS

ASA 2. This is in accordance with a study conducted by Ciftci et al. (2019), where the highest proportion of PS ASA in the control and treatment groups was PS ASA 2. The duration of surgery between the control, paracetamol, and ibuprofen groups was not significantly different, which was also found in the study conducted by Ciftci et al. (2019).

Based on the results of table 1 for the equality test or homogeneous test for demographic characteristics between the paracetamol, ibuprofen, and control groups based on subject characteristics (gender, age, body weight, height, BMI, length of surgery, and PS ASA), all p-values > 0.05 were obtained. This means that there were no significant or meaningful differences between the paracetamol, ibuprofen, and control groups based on demographic characteristics. Consequently, it can be concluded that the demographic characteristics of the three groups are homogeneous or equivalent.

Laboratory Analysis

Based on the results of table 4 for the equality test or homogeneous test for laboratory characteristics between the paracetamol, ibuprofen, and control groups, namely Systolic BP, Diastolic BP, MAP, Pulse, Breath, and Pain, all p-values > 0.05 were obtained. This indicates that there are no significant or meaningful differences between the paracetamol, ibuprofen, and control groups in terms of laboratory characteristics, and it can be concluded that the laboratory characteristics of the three groups before treatment are homogeneous or equivalent.

In this study, there were no significant differences in systolic blood pressure, diastolic blood pressure, MAP, pulse, breathing, and pain. However, the mean systolic blood pressure and pulse of the paracetamol group were higher than those of the ibuprofen and control groups.

Analysis of Cyclooxygenase Test

Based on the results of table 6 for the cyclooxygenase comparison test, it was found that in the paracetamol group, the median cyclooxygenase levels in control patients tended to be higher than in the paracetamol and ibuprofen groups. According to the Kruskal-Wallis statistical test, the p-value is 0.000, where the value is < 0.05. This means that there is a difference in cyclooxygenase levels between patients who use paracetamol, ibuprofen, and control, and the difference is declared to be significantly different. The diagram shows that the control group has the highest cyclooxygenase value, while the ibuprofen group has the lowest.

The results of this study are in accordance with the study conducted by Kaye et al. (2008), which found that ibuprofen given as preemptive treatment can reduce cyclooxygenase levels in gynecological, dental, orthopedic, and thoracic surgery.

Other studies (Hinz & Brune, 2012) have shown that paracetamol is an inhibitor of COX-1 and prostaglandins. Paracetamol is said to reduce COX-1 cyclooxygenase activity in umbilical vein endothelial cells (Freo et al., 2021). However, in another study on impacted tooth surgery, patients who were given 1 gram of paracetamol before surgery experienced increased levels of inflammation, as measured by COX-1 and COX-2.

Furthermore, a study by Orlando et al. (2015) suggested that ibuprofen inhibits COX-2 more than COX-1. However, another study by Gundogdu-Hizliates et al. (2014) reported that ibuprofen has a higher COX-1 binding affinity than COX-2. Both act as analgesics, antipyretics, and strong anti-inflammatories.

Prostaglandin Test Analysis

Based on statistical tests using the Kruskal-Wallis test, the p-value is 0.000, where the value is < 0.05. This indicates that there is a difference in prostaglandin levels between patients using paracetamol, ibuprofen, and the control group, and the difference is declared to be significantly different. The diagram shows that the control group has the highest prostaglandin value, followed by the paracetamol group, and the lowest value is in the ibuprofen group.

According to studies conducted by Przybyła et al. (2021), paracetamol possesses characteristics of COX-3, which has a similar structure to COX-1 but produces other polypeptides that act as antipyretics and analgesics, with weak anti-inflammatory effects. This is attributed to COX-3 retaining intron 1 in the mRNA more than COX-1, resulting in the inclusion of two amino acids to the signal peptide. However, the exact mechanism of COX-3's mRNA conversion into an active peptide with enzyme activity is still unclear. The study also mentioned that COX-3 can trigger remission in chronic inflammatory conditions, such as cervical, ovarian, leukemia, and colon cancer. Due to its weak anti-inflammatory effect, paracetamol may not be as potent as ibuprofen in surgical conditions that cause inflammatory stress.

Another study by Hinz & Brune (2012) stated that paracetamol functions as a COX-2 inhibitor, leading to weak peroxidase concentrations that do not significantly suppress platelet activity and inflammation.

The results of the above-mentioned studies are in

accordance with a study conducted by Freo et al. (2021), which indicated that paracetamol could reduce prostaglandin and cyclooxygenase levels. Additionally, a study conducted by Le et al. (2016) showed that ibuprofen, as preemptive analgesia, was effective in reducing the prostaglandin stress response in patients undergoing cholecystectomy surgery.

Further, studies by Wnek (2004) suggested that the use of ibuprofen as preemptive analgesia could significantly reduce prostaglandin levels compared to the group that did not receive ibuprofen in spinal surgery (p-value < 0.003).

Analysis of Pain Score Test at 2 hours, 6 hours, and 24 hours

Based on the results of table 9, the statistical tests using the Chi-square test obtained a p-value of 0.415, where the value is > 0.05. This means that there is no significant difference in pain at 2 hours between patients using paracetamol, ibuprofen, and the control group.

However, for the 6-hour pain score, based on statistical tests using the Chi-square test, the p-value is 0.004, which is < 0.05. This indicates that there is a significant difference in pain at 6 hours between patients using paracetamol, ibuprofen, and the control group.

Similarly, for the 24-hour pain score, based on statistical tests using the Chi-square test, the p-value is 0.043, which is < 0.05. This implies that there is a significant difference in pain at 24 hours between patients using paracetamol, ibuprofen, and the control group.

Studies conducted by Freo et al. (2021) suggest that paracetamol has strong analgesic and antipyretic effects, but weak anti-inflammatory effects. This can lead to a lack of analgesic effect of paracetamol compared to ibuprofen in patients undergoing surgery, where inflammation occurs due to surgical incisions. According to Kissin & Weiskopf (2000), inflammation occurs during the surgery process, and for nociception protection, preemptive analgesia needs to be continued until the postoperative period to relieve the inflammatory phase. In this study, all samples received the same postoperative analgesic administration, namely paracetamol 1 g drip and tramadol 100 mg drip. However, postoperative pain scores at 6 hours and 24 hours were still better with the administration of ibuprofen compared to paracetamol.

Additional studies by Karaca et al. (2019) showed that preemptive ibuprofen reduces postoperative opioid consumption in cholecystectomy surgery, while Ciftci et al. (2019) reported that intravenous ibuprofen reduces opioid consumption in the first 24 hours after gastrectomy surgery, especially in the first 2 hours post gastrectomy surgery. A randomized control trial conducted by Kaye et al. (2008) indicated that the use of COX2 inhibitors in knee replacement surgery can reduce opioid use, vomiting, and sleep disturbances by 35%.

According to Masigati & Chilonga (2014), the Wong Baker Faces Pain Scale cut-off point ≥ 4 is used as a threshold pain score where clinical intervention is required. Studies by Hudyarisandi & Hanindito (2016) show that preemptive administration of paracetamol and tramadol is significant in reducing postoperative pain scores (p=0.03).

This study does have some limitations. First, monitoring for the last postoperative pain score check was only carried out at 24 hours postoperatively, while postoperative pain can persist up to 48 hours. Second, the administration of postoperative analgesics to patients in the room was found to be undisciplined in the time of administration, which could affect the 6-hour and 24-hour postoperative pain scores. The results of this study are expected to be used as a reference for further research on preemptive analgesia.

CONCLUSION

Based on the statistical analysis and discussion in this study, the researchers concluded that there are significant differences in cyclooxygenase levels among patients undergoing abdominal surgery under general anesthesia at Integrated Surgery Center (GBPT) of Dr. Soetomo Hospital Surabaya when administered ibuprofen, paracetamol as preemptive analgesia, and the control group. Additionally, there were significant differences in prostaglandin levels in the same groups. Furthermore, postoperative pain scores at 6 hours and 24 hours showed significant differences between patients administered ibuprofen, paracetamol as preemptive analgesia, and the control group at RSUD Dr. Soetomo. However, the 2-hour postoperative pain score did not show any significant difference among the three groups. To improve patient care, the researchers suggest considering the results of this study and exploring the use of alternative drugs for postoperative analgesic administration that may effectively reduce pain scores up to 24 hours. Moreover, they recommend adhering to strict time discipline in administering postoperative drugs according to the schedule in the inpatient room.

AUTHORS' CONTRIBUTION

AJ, PSA and CS: Concept and design, data acquisition, interpretation, drafting, final approval,

and agree to beaccountable for all aspects of the work. AJ and PSA: Data acquisition, interpretation,drafting, final approval and agree to be accountable for all aspects of the work.

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