

## Original Article

**EFFECTIVENESS OF KETOPROFEN SUPPOSITORIA AS PREEMPTIVE ANALGESIA FOR POSTOPERATIVE PAIN IN PATIENTS UNDERGOING ELECTIVE SURGERY WITH GENERAL ANESTHESIA**Lupi Lestari<sup>1</sup>, Elizeus Hanindito<sup>2</sup>, Arie Utariani<sup>2a</sup><sup>1</sup> Resident of Department of Anesthesiology and Reanimation, Faculty of Medicine Universitas Airlangga, Dr Soetomo Academic Hospital, Surabaya, Indonesia<sup>2</sup> Consultant of Department of Anesthesiology and Reanimation, Faculty of Medicine Universitas Airlangga, Dr Soetomo Academic Hospital, Surabaya, Indonesia<sup>a</sup>Corresponding Author: [arieutariani1955@gmail.com](mailto:arieutariani1955@gmail.com)**ABSTRACT**

**Introduction:** Effective postoperative pain management provides improved patient comfort and satisfaction, earlier mobilization, fewer pulmonary and cardiac complications, reduced risk deep vein thrombosis, fast recovery, and reduced cost of care. Preemptive analgesia, initiated before the surgical procedure to prevent pain in the early postoperative period, has the potential to be more effective than a similar analgesic treatment initiated after surgery. As a part of multimodal analgesia, the use of NSAIDs should always be considered for acute postoperative pain management. NSAIDs can be used preoperatively as a part of the preemptive regimen and for postoperative pain control to increase the efficacy of opioids and reduce its side effects. **Material and Method:** This research was experimental research with a case-control design of the study. The samples separated into two groups, the first group got ketoprofen suppository before the induction, and the second group didn't get the ketoprofen suppository. The intensity of pain measured with the Numeric Rating Scale (NRS) or Wong-Baker Faces Pain Scale was the variable studied at different postoperative times (30 min, 60 min, 120 min, 2-6 hours, 6-12 hours). The total amount of rescue analgesics (fentanyl) and side effects were other variables of this study. **Result and Discussion:** The result is ketoprofen suppository as preemptive analgesia administrations can reduce postoperative pain. Numeric Rating Scale was significantly lower in the ketoprofen group compared to the control group ( $p < 0,05$ ) at 30 min, 60 min, 230 min, 2-6 hours, 6-12 hours. The number of postoperative analgesics needed in the recovery room was significant differences among both groups ( $p < 0,05$ ). **Conclusion:** Preemptive analgesia in patients who underwent an operation with general anesthesia with ketoprofen suppository was effectively in blocking noxious stimuli and central sensitization, with subsequent prevention of acute postoperative pain.

**Keywords:** Postoperative Analgesia; General Anesthesia; Ketoprofen Suppository; Preemptive Analgesia**ABSTRAK**

**Pendahuluan:** Manajemen nyeri postoperatif yang efektif akan dapat meningkatkan kepuasan dan kenyamanan pasien, mobilisasi dini, komplikasi pulmoner dan kardiovaskuler yang rendah, menurunkan resiko deep vein thrombosis, pemulihan lebih cepat dan menurunkan biaya perawatan. Preemptive analgesia yang diberikan sebelum prosedur pembedahan untuk mencegah nyeri diawal periode postoperatif lebih efektif dibandingkan dengan terapi analgesik yang sama diberikan di akhir pembedahan. Konsep multimodal analgesia diajukan dan direkomendasikan bila memungkinkan. Sebagai bagian dari multimodal analgesia, penggunaan NSAID dapat dipertimbangkan sebagai bagian dari manajemen nyeri akut postoperatif. NSAID sapat digunakan sebagai regimen preemptive dan mengendalikan nyeri postoperatif untuk menurunkan penggunaan opioid dan mengurangi resiko. **Bahan dan Metode:** Penelitian ini merupakan penelitian eksperimental dengan desain studi case control. Sample dibedakan menjadi dua kelompok, kelompok pertama mendapat ketoprofen suppositoria sebelum induksi dan kelompok kedua tidak mendapatkan ketoprofen suppositoria. Intensitas nyeri postoperatif diukur dengan skala Numeric Rating Scale (NRS) atau Wong Baker Faces Pain Scale (pada menit ke 30, 60, 120, dan jam ke 2-6, 6-12). Pemberian rescues analgetics dan efek samping juga diteliti. **Hasil dan**



**Pembahasan:** Hasil penelitian yakni pemberian ketoprofen suppositoria sebagai preemptive analgesia dapat menurunkan intensitas nyeri postoperatif. NRS postoperatif pada kelompok ketoprofen suppositoria lebih rendah dibandingkan kelompok kontrol ( $p < 0,05$ ) dimana pada 30 menit ( $p = 0,005$ ), 60 menit ( $p = 0,002$ ), 120 menit ( $p = 0,001$ ) dan 2-6 jam ( $p = 0,005$ ). Jumlah penggunaan analgetik durante dan postoperatif di ruang pulih sadar berbeda secara signifikan diantara dua kelompok ( $p < 0,05$ ). Ketoprofen suppositoria sebagai preemptive analgesia efektif dalam memblokir stimulus noxius dan sensitisasi sentral pada pasien yang menjalani operasi dengan pembiusan secara general anestesi untuk menurunkan nyeri akut postoperatif.

**Kata Kunci:** Analgesia Postoperatif; General Anestesi; Ketoprofen Suppositoria; Preemptive Analgesia

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## INTRODUCTION

Pain is an unpleasant experience, both sensory and emotional, due to the damage of tissue, which is described in the form of its destruction.<sup>1</sup> The great challenge for the anesthesiologist is the pain management of postoperative. The postoperative pain is a part of acute pain which is predictively occurring. If it is not done well, it will cause physiological changes, causing negative impacts in the organ system, producing adverse outcomes in the postoperative period, even it can develop into chronic pain syndrome in the individuals both adult and children.<sup>2,3</sup>

Tissue trauma caused by the surgery can cause afferent sensitization, which will stimulate the Central Nervous System, but it can be prevented by giving antinociceptive (preemptive analgesia) that will reduce the acute pain of post-operative.<sup>2,3</sup> Preemptive analgesia is an action to mitigate or avert mediator production, which is responsible for nerve stimulation and aims to block pain receptors and release inhibitory effect toward pain neurotransmitters so that it can avoid hyperalgesia and allodynia. Several preemptive analgesia drugs used until now including ibuprofen, celecoxib, ketorolac, gabapentin orally. All are given a single dose of pre-operative.<sup>4,5</sup>

Ketoprofen is a propionic acid group of NSAID (Nonsteroidal Anti-Inflammatory Drugs) It is very beneficial for pain management of post-operative because it gives analgesic effect, anti-inflammatory, and antipyretic by blocking cyclooxygenase (COX) activity and reduces prostaglandin and thromboxane.<sup>1,6,7</sup> Besides, NSAID will not cause side effects such as opioids, causing breath depression, sedatives and nausea, and vomiting.

In September up to October 2015, the number of patients who did elective surgery with general anesthesia was 1124 in Dr. Soetomo Hospital → 731 patients (65.03%) aged 18-65 years old and 375 patients (50%-61%) were given ketorolac (intravenous) at the end of surgery as anti-pain of post-operative. In the research done by Ismar Lima C, et al., rescue analgesics such as opioid analgesic like paracetamol, dipyron, tenoxicam or ketoprofen were used to handle post-operative pain with the level of moderate pain up to severe in the oncology patients undergoing surgery in the head and neck areas who used oxycodone as an anti-pain.<sup>8</sup>

## MATERIAL AND METHOD

This research was an experimental research with a case-control study design.



The number of samples was as many as 60 adult patients aged 18-65 years old who underwent elective surgery with the estimation of moderate up to severe post-operative pain. From all the samples, the samples were divided into two groups covered the first (case) group as many as 30 patients were given ketoprofen suppository after induction and the second (control) group as many as 30 patients were not given ketoprofen suppository.

Both groups were given the same treatment during induction, anesthesia maintenance, and in the postoperative period during the surgery. In the recovery room, both groups were measured toward the level of pain by using Numeric Rating Scale (NRS), Wong-Baker Faces Pain Scale, and vital parameter signs in the recovery room at the 30, 60, 90, 120 and 180 minutes if  $NRS \geq 4$  then post-rescue analgesia (fentanyl 1-2 mcg/kg) post-operative.

This research was done at the Integrated Central Surgery of RSUD Dr. Soetomo, Surabaya, in December 2016 up to January 2016.

## RESULT AND DISCUSSION

### Demographic Characteristics of Research Samples

The demographic characteristics of the patients in this research included gender, age, weight, height, BMI, surgery duration, surgery type, number of bleeding, and PS ASA. After data of demographic characteristics of the patient were collected, then different test in the case and control groups were conducted.

**Table 1.** Demographic Characteristics of Age, Gender, PS ASA, Weight, Height, BMI, Surgery Duration, Hemorrhage

Variable	Group		P-Value
	Case (Ketoprofen Suppositoria)	Control	
<b>Gender</b>			
Male	12 (40.0)	4 (13.3)	0.041
Female	18 (60.0)	26 (86.7)	
Age (year)	41.1 ± 13,1	45.2 ± 11.2	0.202
PS ASA 1	5 (16.7%)	5 (16.7%)	
PS ASA 2	25(83.3%)	25(83.3%)	1.000
Weight (kg)	60.7 ± 11.3	57.1 ± 9.0	0.2
Height (cm)	157.8 ± 9.2	155.1 ± 7.4	0.5
BMI	24.2 ± 2.7	23.8 ± 2.8	0.567
Duration of surgery (minute)	197.7 ± 91.9	209.2 ± 84.5	0.622
Hemorrhage (ml)	223.3 ± 189.3	263.3 ± 154.2	1.47

Based on Table 1, there was a significant difference in the gender of the patients between ketoprofen suppository and control groups. Based on the results of the different test, it obtained the result of the P-value is 0.41 or  $<0.05$  so that it could be said to be significant, or there was a significant difference between the two groups. It possibly to happen because of the randomization system so that the difference of gender between men and women among the treatment and control groups were different.

The characteristics of the patients were also examined based on the surgery types done. The different test Results of both groups as in the following table:

**Table 2.** Demographic Characteristics of Surgery Types of Each Research Group

Surgery	Case (Ketoprofen Suppositoria)	Control	P-Value
Oncological Surgery	8 (26.7%)	7 (23.3%)	0.922
Head-neck Surgery	15 (50%)	16 (53.3%)	
General Surgery	1 (3.3%)	1 (3.33%)	
Oral Surgery	3 (10.0%)	3 (10.0%)	
Otolaryngology	2 (6.7 %)	0 (0%)	
Obstetric and Gynecology	1 (3.3%)	3 (10.0%)	

On Table 2, it was known that the types of surgery of two research groups. In the research of ketoprofen suppository and control groups obtained, most of the patients were from head-neck surgery while the least patients found was otolaryngology surgery. The statistics analysis result showed there was no significant difference between those two groups in which the P-value > 0.05 (p = 0.922).

### The Influence of Ketoprofen Suppository Giving on the Value of NRS/Wong-Baker Faces Pain Scale in Post-Operative

The measurement of The NRS/Wong-Baker Faces Scale aimed to know the response of postoperative pain in adult patients who had elective surgery under general anaesthesia. The data collected in this research included the NRS pain scale, or Wong-Baker Faces Pain Scale in pre-operative, in the conscious recovery room at 30, 60, 60, 90, 120 minutes, 2-6 hours, 6-12 hours in the room.

**Table 3.** The Average of NRS/Wong-Baker Faces Pain Scale Value in each group

Variable	NRS≥4 Control	NRS<4 Control	NRS≥4 Ketoprofen	NRS<4 Ketoprofen
Pre Anesthesia	0	30	0	30
30th minute	8	22	0	30
60th minute	0	21	0	30
120th minute	10	20	0	30
2-6th hour	12	18	2	28
6-12th hour	13	17	2	28

Based on Table 3, it was known that the NRS value of the control and the ketoprofen suppository (case) groups had significant difference at 30, 60, 120 minutes, 2-6 hours and 2-12 hours, while at pre-anesthesia did not show a significant difference of NRS value. The results of statistics test to show p-value in the differences of NRS values of each time, at the 30 minutes with P-Value of 0.005 (p<0.05), at the 60 minutes with P-value of 0.002 (p<0.05), at the 120 minutes with P-value of 0.001 (p<0.05), at the 2-6 hours with P-value of 0.005 (p<0.05) and at the 6-12 hours with P-value of 0.002 (p<0.05).

This research analyzed the effectivity of ketoprofen suppository (*Non-Steroid AntiInflammatory Drug/ NSAID* type), which was a very beneficial analgesic in the pain management of post-operative because it was able to reduce the pain and inflammation. NSAID was effective in the pain management of mild and moderate postoperative. In severe pain which needed opioid giving, the giving of NSAID added analgesia and opioid-sparing effect. For optimal outcome, the time given was very important because NSAID required time to block prostaglandin synthesis and inhibit the

pain way. The giving of pre-operative as preemptive analgesia became essential to get a good postoperative effect.<sup>9-12</sup>

It could be concluded from this research that the effectivity of ketoprofen suppository as preemptive analgesia seen in the ketoprofen suppository group compared with the control group and it obtained the significant difference with P-value < 0.05, in which the score of postoperative pain measured by the value of NRS or Wong-Baker Faces Pain Scale in the ketoprofen group was lower than the control group.

Theoretically, due to “protective” effect toward the system of nociceptive, preemptive analgesia was potentially more effective than the similar analgesic therapy given after surgery because the giving of preemptive analgesia was able to prevent central sensitization which was triggered by the incision and inflammatory trauma happened during the surgery and at the beginning of postoperative period.

### The Influence of Ketoprofen Suppository on the Need of Rescue Analgesic (Fentanyl)

**Table 4.** The Needs of Rescue Analgesic (Fentanyl) during the Induction, Durante Operation and Post-Operative in the Recovery-Room

Fentanyl Use	Ketoprofen	Control	P-Value
<b>Induction Fentanyl</b>	73.3 ± 19.6	70.0 ± 23.1	0.541
<b>Durante Operation Fentanyl</b>	40.0 ± 44.3	62.5 ± 50.7	0.048
<b>Post Operation Fentanyl</b>	0.00 ± 0.00	14.2 ± 26.8	0.003

According to table 4, it showed that the differences in the use of fentanyl in the ketoprofen and control groups could be seen through the use of fentanyl during Durante operation with P-value of 0.048 (P<0.05) and post-operative in the recovery room with P-value of 0.003 (P<0.05). The use of fentanyl during the induction did not show any significant differences in the ketoprofen and control groups with P-value of 0.541 (p> 0.05).

The needs of opioid fentanyl suppository during Durante operation and post-operative was much lower compared to control group, and this is in line with the theory stating that preemptive analgesia (in this case was ketoprofen suppository) reduced the amount of intravenous sedation and general anesthetic agents during the surgery due to the loss of patients’ central nervous system reaction to the pain stimuli. The ability to recover from anesthesia was faster with lower analgesic side effects if it was given before onset stimulus noxious and pre-operative, it gave the reaction of blocking the pain receptors and released inhibitory effects on pain with the mechanism on neurotransmitters in which it affected the central nervous system and peripheral nervous system by processing noxious stimuli and significantly reduced hyperalgesia and allodynia before it even occurred. However, on analgesia pharmacological perspective, the needs of analgesia also relied on the patients’ pain response, while pain referred to a very complex cause coming from family factor, culture, environment, previous pain experience greatly determined the patients’ needs for analgesia.

### The Effect of Ketoprofen Suppository on Post-Operative Side Effects

**Table 5.** The Effect of Ketoprofen Suppository on Post-Operative Side Effects

Side Effect		Ketoprofen	Control	P Value
Dizziness	Yes	3 (10%)	14 (46.7%)	0.004
	No	27 (90.0%)	16 (53.3%)	
Nausea	Yes	0 (0%)	7 (23.3%)	0.011
	No	30 (100%)	23 (76.7%)	
Gag	Yes	0 (0%)	4 (13.3%)	0.112
	No	30 (100%)	26 (86.7 %)	

The table 5 showed that the difference of the side effects of fentanyl usage in both groups could be seen in the forms of dizziness with p-value of 0.004 ( $p < 0.05$ ) and nausea with p-value of 0.011 ( $p < 0.05$ ). The side effects of fentanyl usage in the form of nausea did not give the difference to the ketoprofen and control groups with p-value of 0.112 ( $p > 0.05$ ).

Some literatures state that the use of inhalation and opioid drugs stimulate the center of nausea indirectly through this Chemoreceptor Trigger Zone/ CTZ, similarly sore is a factor that influences the occurrence of postoperative nausea and vomiting because those give effects indirectly through higher cerebral cortex towards the center of chemotactic (Chemoreceptor Trigger Zone/ CTZ located on the area of Postrema that is the base of ventricle IV) and triggers the release of katekolamin.<sup>12</sup> As it was known, the center of nausea could be activated directly as a result of irritant or indirectly as a result of the input from the main Four areas: gastrointestinal tract, cerebral cortex and thalamus, vestibular region and chemoreceptor trigger zone

(CTZ). CTZ located between the medulla and the base of the fourth ventricle.

### The Effect of the Total Amount of Opioid toward the Emersion of Side Effects

**Table 6.** The Total usage of Opioid (Morphine and Fentanyl) toward the Emersion of Side Effects.

Variables	The Side Effects		
	B	P-value	OR (CI 95%)
<b>Ketoprofen suppository</b>	-2, 744	<0,0001	0,064 (0,02- 0,26)
<b>Fentanyl</b>	-0,003	0,568	0,997 (0,989- 1,006)
<b>Morphine</b>	0,189	0,629	1,208 (0,562-2,597)

Based on the results of Table 6 of statistical analysis to the side effects of dizziness, nausea, and vomiting in post-operative, in the Ketoprofen suppository group was lower than in the control group (B= -2.744), however the amount of morphine and fentanyl usage gave no effect toward the emersion of the side effects with the value of  $p > 0.05$  ( $p = 0.629$  and  $p = 0.568$ ).

Some literature showed that the use of opioid as monomodal caused complications and side effects such as inhalation depression, drowsiness, pruritus, skin rash, urine retention, inhibited gastrointestinal motility and postoperative vomiting and nausea. The vomiting and nausea induced by opioids were caused by direct stimulation from chemoreceptor trigger zone in the base of the fourth ventricle. This reflected the agonist role of opioid as partial dopamine agonist to dopamine receptor in the

chemoreceptor trigger zone; moreover, morphine also caused nausea and vomiting with the incline of gastrointestinal secretion and the deceleration of gastrointestinal flow. However, if it was used together with NSAID, then the group of non-opioid added analgesia, supported opioid efficacy with opioid sparing-effect and decreased the side effect of opioids.

## CONCLUSION

Ketoprofen suppository was more effective as preemptive analgesia in handling post-operative sore. The giving of rescue analgesia (fentanyl) in the Durante operation and post-operative in the ketoprofen suppository group was lower than in the control group. The side effects of dizziness and nausea in the ketoprofen group were lower than in the control group.

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