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The Effect of Loperamide on Pain Intensity and IL-6 Levels in Patients Undergoing Hysterectomy With Spinal Anesthesia

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Abstract

Background: Hysterectomy is the most common gynecological surgical procedure performed in various countries. Spinal anesthesia has become a popular technique for surgery on the lower abdomen, pelvis, and lower extremities. Loperamide, an opioidergic drug used to treat non-bacterial diarrhea by decreasing intestinal motility and has been reported to produce analgesic effects. However, research related to the effect of loperamide use on IL-6 levels after surgery has never been conducted before.

Objective: To determine the effect of loperamide on pain intensity and IL-6 levels in patients undergoing hysterectomy under spinal anesthesia.

Subject and Method: This research was a single-blind, randomized clinical trial conducted at Wahidin Sudirohusodo Hospital and Hasanuddin University Hospital. The population of this study were all patients who underwent a hysterectomy procedure under spinal anesthesia. The sample used in this research was 30 patients. The patients were randomly divided into two groups: treatment group (patients were given the analgesic adjuvant loperamide tab 2 mg) and control group (patients were not given the analgesic adjuvant loperamide).

Results: There were no significant differences in age and BMI ($p>0.05$) between the group given loperamide compared with the control group during hysterectomy so the data could be said to be homogeneous. There was no significant difference between VAS 2, 8, 12, and 24 hours after hysterectomy in the group given loperamide and controls, but there was a significant difference in the 4 hour VAS. In this study, no post-surgical rescue opioids were found in either group, nor were any serious post-surgical side effects found in either group. There was no difference between IL-6 levels before surgery and 2 hours after surgery in the group given loperamide and controls who underwent hysterectomy. The correlation between IL-6 levels after surgery compared to the VAS value 2 hours after surgery showed that there was no significant correlation between IL-6 levels and VAS with the r value at 8 hours -0.204 meaning there was no relationship between the group given loperamide and the control group. The correlation between the post-surgical VAS scores in the loperamide and control groups from the VAS 2, 4, 8, 12, and 24 hours showed that there was no significant correlation between the post-surgical VAS scores in the loperamide and control groups.

Conclusion: Loperamide 2 mg can be used as an analgesic adjuvant in hysterectomy surgery because it can reduce post-surgical pain scores compared to the control group at the 4th hour post-surgery.

Keywords: Loperamide, hysterectomy, spinal anesthesia, IL-6, VAS.

Introduction

Hysterectomy is the most common gynecological surgical procedure performed in various countries. Although the majority of patients who undergo hysterectomy are satisfied with the results of the procedure, many patients report chronic pain after hysterectomy. The prevalence of chronic pain after hysterectomy in benign gynecology is approximately 5-32%. The causes of chronic pain after hysterectomy include psychological factors, pelvic pain before surgery or pain elsewhere, hysterectomy technique and acute pain after surgery.[1]

Pain is a biological process that arises due to damage or disease in the body.[2]Uncontrolled post-surgical pain can result in widespread negative impacts in the form of increased morbidity, long hospital stays and a high incidence of persistent chronic pain. Pain can alter the patient's endocrine response by increasing catecholamine and cortisol levels and can amplify autonomic reflexes, triggering a hypertensive crisis or vagal syndrome that can result in severe complications during and after surgery. Adequate pain management in major gynecological surgery is a key factor in reducing postoperative morbidity and increasing patient satisfaction where the use of opioid medications is often required.[3]

Spinal anesthesia has become a popular technique for surgery on the lower abdomen, pelvis, and lower extremities.[4]Spinal anesthesia produces intense sensory and motor blockade as well as sympathetic blockade.[4] Parasympathetic stimulation increases gastrointestinal motility, but sympathetic control inhibits intestinal motility tone so that gastrointestinal motility is balanced by sympathetic and parasympathetic nervous control.[5]Thus, sympathetic nerve blockade or spinal anesthesia causes increased intestinal motility.

The opioid crisis in North America emerged when inadequate regulation in the pharmaceutical and healthcare industries led to a fourfold increase in the number of profit-driven opioid prescriptions. Hundreds of thousands of people overdose on prescription opioids, and millions more become addicted or harmed in other ways, including disability, family breakdown, crime, unemployment, and loss. In response to the large number of individuals addicted to prescription opioids, the heroin market expanded, further increasing morbidity and mortality rates. As the heroin market becomes saturated with illegal synthetic opioids such as fentanyl, an already dire situation is brought to public attention. a health disaster that has worsened since the start of the COVID-19 pandemic. Since 1999, more than 600,000 people in the United States and Canada have died from opioid overdoses, and the death toll in each country exceeds the death toll from opioid overdoses. worst of the HIV/AIDS epidemic.[6]

Loperamide, an opioidergic drug used to treat non-bacterial diarrhea by decreasing intestinal motility and has been reported to produce analgesic effects. Loperamide given systemically has less effect on the central nervous system because it is a permeability glycoprotein (P-gp) substrate which blocks entry into the blood brain barrier, but when administered or at high doses, loperamide is reported to be able to cross it.[2]

Cytokines play a role in pain mechanisms. Cytokines have a significant influence on sensory neurons. Cytokines in particular interleukin (IL)-6 can act directly on nociceptors or more commonly indirectly stimulate the release of agents such as prostaglandins increasing the activation of Transient receptor potential (TRP) and sodium voltage (Nav) channels and that this activation leads to sensitization of nociceptor neurons .[7]During the acute phase, cytokines induce sensitization through receptor-associated kinases and ion channel phosphorylation whereas in chronic inflammation through regulation of receptor transcription and secondary signals.[8]Other immune cells, such as macrophage cells, play a role in receptor sensitization where it is reported that after activation, macrophage cells release IL-6 and cause pain sensitivity in nociceptors which contributes to chronic pain.[7]Research related to the effect of loperamide use on IL-6 levels after surgery has also never been conducted before. Therefore, this study was interested in

examining the effect of loperamide on pain intensity and IL-6 levels in patients undergoing hysterectomy under spinal anesthesia.

Research methods

This research was a single-blind, randomized clinical trial conducted at Wahidin Sudirohusodo Hospital and Hasanuddin University Hospital. The population of this study were all patients who underwent a hysterectomy procedure under spinal anesthesia. The sample used in this research was 30 patients. The patients were randomly divided into two groups: treatment group (patients were given the analgesic adjuvant loperamide tab 2 mg) and control group (patients were not given the analgesic adjuvant loperamide).

The inclusion criteria in this study were patients who were planned to undergounderwent a hysterectomy under spinal anesthesia, aged 18 - 60 years, nutritional status for age in the normal category, physical status ASA I and II, and agree to take part in the research. The exclusion criteria in this study were patients who refused spinal anesthesia or who had contraindications to spinal anesthesia, patients with a history of heart and cardiovascular disease, patients with a history of consuming drugs such as: Amiodarone, chlorpromazine, haloperidol, methadone, moxifloxacin, pentamidine, procainamide, quinidine , sotalol, thioridazine, and ziprasidone, a history of allergy to loperamide, as wellpatients who refused to take part in the study. The drop out criteria in this study were patients who experienced complications during the study and patients withdrew from the study.

All subjects underwent anamnesis, physical examination and support to determine physical status and anesthesia plan. Patients who met the inclusion criteria were collected in order of arrival until the sample size was met. The collected patients were randomly divided into 2 groups: Group I: patients were given the analgesic adjuvant loperamide tab 2 mg and Group II (control): patients were not given the analgesic adjuvant loperamide.

Blood samples were taken to check IL-6 levels before sub-arachnoid block anesthesia was carried out. In the intervention group, loperamide was given at a dose of 2 mg 2 hours before surgery. In the control group, loperamide was not administered before surgery. Both groups were givenpremedication ranitidine 50mg/IV, ondansetron 8mg/kg, dexamethasone 5mg/IV,ketorolac 30 mg/IV, paracetamol 1 g/IV. The patient enters the supine position, an 18G IV catheter is attached to the back of the hand. Standard monitors (blood pressure, heart rate, electrocardiography (ECG) waves) and O2 saturation are attached. Loading colloid fluid 250 cc. Position the patient on the operating table in the left lateral decubitus (LLD) position. Identification of the 3-4th lumbar vertebra interspace, disinfection with 70% alcohol and 10% povidone iodine, skin wheal with 2% lidocaine 40 mg, 25G spinocan insertion with positive paramedian approach cerebral spinal liquor (CSF), flowing clear, blood negative, barbotage positive . Spinal bupivacaine injection 0.5% 12 mg. Position supine, check the height of the autonomic block with a cold test: at the level of the 6th thoracic vertebra, check the height of the sensory block with a prick test at the level of the 8th thoracic vertebra, check the motor block: bromage score 3/3. Maintenance with O2 2-4 lpm via nasal cannula.

During the operation, blood pressure and pulse frequency were recorded at the 1st, 5th, 15th and 30th minutes followed every hour. Systolic blood pressure, diastolic blood pressure, mean arterial pressure, pulse rate, body temperature are monitored during the operation. In both groups, post-operative pain management was given with Ketorolac 30 mg/8 hours/IV and Paracetamol 500 mg/6 hours/oral (first day) followed by Ibuproven 400 mg/8 hours/oral and

Paracetamol 500 mg/6 hours/oral, given rescue with fentanyl 0.5-1 mcg/ kgBW/ IV (dose titration) if VAS >4. Blood samples were taken for IL-6 examination at 2 hours after surgery and assessment of pain intensity at 2 hours, 4 hours, 8 hours, 12 hours and 24 hours after surgery. The amount of opioid consumption, the incidence of post-surgical side effects, pain intensity, blood pressure, pulse frequency and rhythm at 2 hours, 4 hours, 8 hours, 12 hours and 24 hours after surgery were recorded.

Analysis of research data using SPSS Version 26 for Mac. Test data normality using the Shapiro-Wilk test. The test to determine differences between groups and each group uses the independent sample t-test and paired t-test if the data is normally distributed, while the Mann-Whitney U and Wilcoxon Z tests if the data is not normally distributed. To determine the difference between variables and all categorical data, the chi-square test is used (if there is no expected calculated value <5). For expected calculated values <5, data were tested with the Fisher-exact test.

The ethical feasibility (ethical clearance) of the research was obtained from the Ethics Committee for Biomedical Research on Humans, Faculty of Medicine, Hasanuddin University with recommendation number 353/UN4.6.4.5.31/ PP36/ 2024.

Research result

Sample Characteristics

The characteristics of the research samples for the two groups can be seen in Table 1.

Table 1. Characteristics of the research sample

Characteristics	Loperamide	Control	P
	Mean ± SD	Mean ± SD	
Age (years)	46.60 ± 7.98	45.20 ± 5.37	0.227ns
BMI (kg/m2)	22.25 ± 1.22	21.96 ± 1.61	0.278ns

Based on table 1, it shows that there is no significant difference in age and BMI (p>0.05) between the group given loperamide compared to the placebo group during hysterectomy so that the data can be said to be homogeneous.

Pain Score

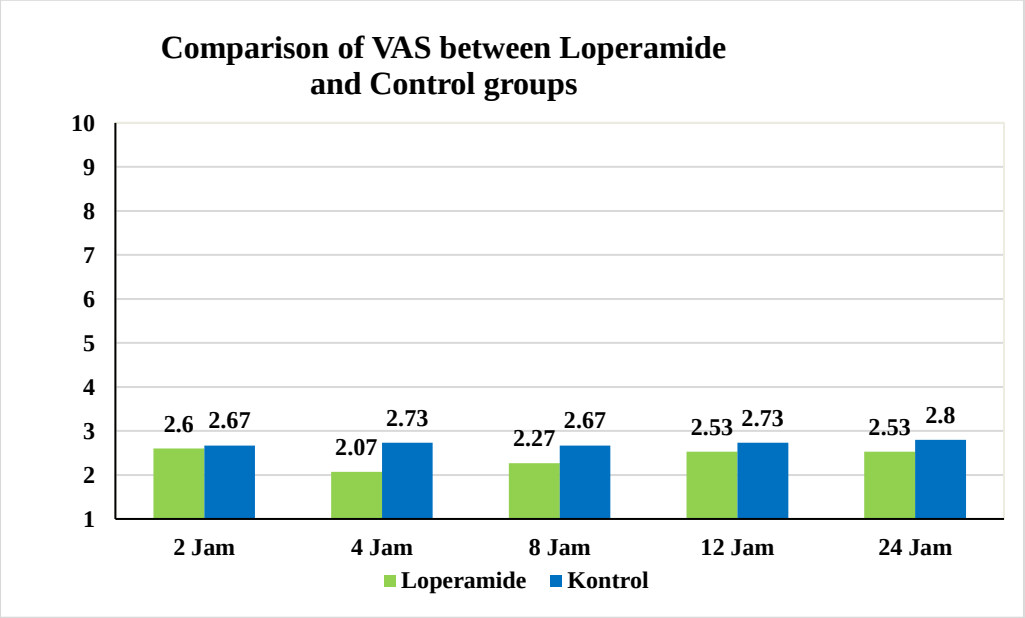
The results of comparative VAS measurements between the loperamide administration group and the control group can be seen in Table 2.

Table 2. Comparison of VAS between Loperamide and Control groups.

Measurement Time	Group	Mean ± SD	P
2 hours	Loperamide	2.60 ± 0.737	0.562ns
	Control	2.67 ± 0.488	
4 hours	Loperamide	2.07 ± 0.704	0.007ns
	Control	2.73 ± 0.458	
8 hours	Loperamide	2.27 ± 0.704	0.101ns
	Control	2.67 ± 0.488	
12 hours	Loperamide	2.53 ± 0.516	0.264ns

Measurement Time	Group	Mean ± SD	P
	Control	2.73 ± 0.458	
24 hours	Loperamide	2.2 ± 0.516	0.128ns
	Control	2.80 ± 0.414	

From the summary of the analysis results in table 2, it was found that there was no significant difference between VAS 2, 8, 12, and 24 hours after hysterectomy in the group given loperamide and the control. Meanwhile, in the 4 hour VAS, a significant difference was found in the group given loperamide and the control with a value of ($p < 0.05$). In this study, no post-surgical rescue opioids were found in either group, nor were there any post-surgical side effects in either group.



IL-6 levels

The results of comparative measurements of IL-6 levels between the group given loperamide and the control group can be seen in Table 3.

Table 3. Comparison of IL-6 levels between Loperamide and Control groups.

Measurement Time	Group	IL-6 levels Mean± SD	P
Before surgery	Loperamide	100.73±74,182	0.242ns
	Control	143.65±160,981	
2 hours post surgery	Loperamide	91.17 ± 64.345	0.243 ns
	Control	136.03 ± 149.791	

From the summary of the analysis results in table 3, it was found that there was no difference between IL-6 levels before surgery and 2 hours after surgery in the group given Loperamide and controls who underwent hysterectomy. The correlation between IL-6 levels and post-operative VAS scores in the loperamide group can be seen in table 6 below.

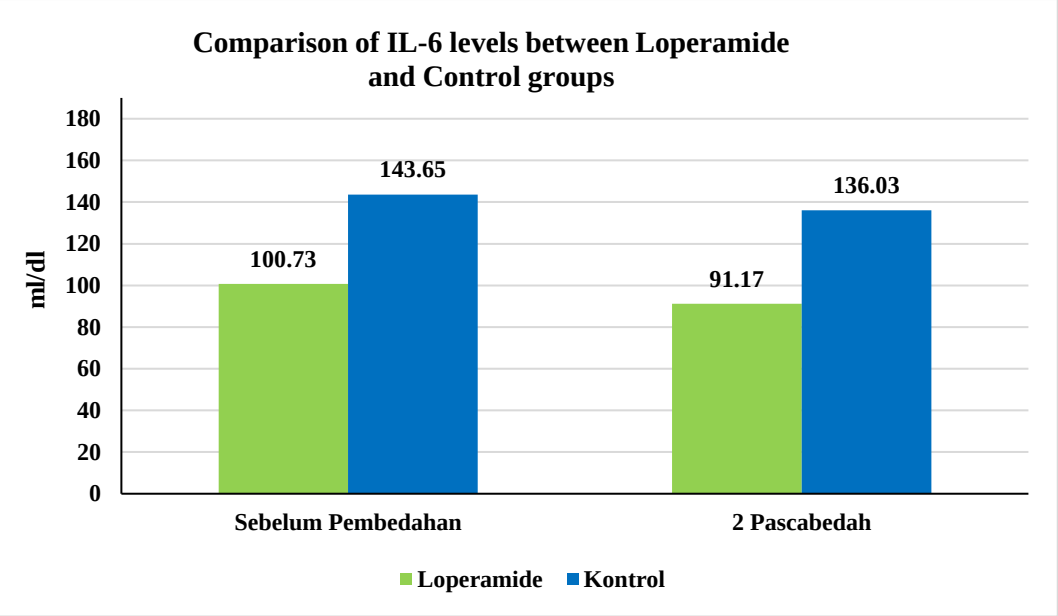


Table 4.Correlation of IL-6 Levels and Post-operative VAS Score in the Loperamide group.

Variable	R	P
IL-6 vs VAS 2 hours post surgery	-0.204	0.466

Table 4 shows the correlation between levelsPost-surgical IL-6 compared to VAS values 2 hours post-surgery showed that there was no significant correlation between IL-6 and VAS levels with the r value at 8 hours -0.204 meaning there was no relationship between the group given loperamide and the control group.

Table 5.Correlation of IL-6 levels and post-surgical VAS scores in the control group.

Variable	R	P
IL-6 vs VAS 2 hours post surgery	-0.065	0.817

Table 5 shows the correlation between levelsPost-surgical IL-6 compared to VAS values 2 hours post-surgery showed that there was no significant correlation between IL-6 levels and post-surgical VAS.

Discussion

In this study, a total of 30 patients were studied, 15 patients were given the adjuvant analgesic loperamide at a dose of 2 mg, 2 hours before surgery and 15 patients were not given the adjuvant analgesic loperamide during hysterectomy operations with spinal anesthesia. From the characteristics of the research sample, it shows that there are no significant differences in the age and BMI variables ($p>0.05$) between the group given loperamide and the control group in hysterectomy operations with spinal anesthesia so that the data can be said to be homogeneous and further suitable for comparison tests.

In comparing the VAS scores between the group given loperamide and the control group, there was no significant difference between the VAS 2, 8, 12 and 24 hours after hysterectomy in the group given loperamide and the control, whereas in the VAS 4 hours there was a significant difference after hysterectomy surgery in groups given loperamide and controls.

In this study, no post-surgical opioid rescue was found in either group, nor were there any post-surgical side effects in either group. Serious side effects caused by loperamide such as obstructive ileus and heart rhythm disturbances caused by lengthening of the QRS complex such as ventricular dysrhythmia, ventricular tachycardia, ventricular fibrillation and even cardiac arrest were not found in this study which were evaluated intraoperatively and during observation in the post anesthesia care room. units. Other side effects including dizziness, stomach cramps,

constipation and more severe allergic skin reactions such as Stevens-Johnson syndrome and TEN were also not observed in this study during 24 hours post-surgical observation.

This study also showed that administration of loperamide provided a significant difference in reducing pain compared to the control group on VAS 4 hours after hysterectomy surgery. This could be indicated that loperamide 2 mg has a strong analgesic effect on the 4 hour VAS compared to the control group in the context of pain after hysterectomy surgery with spinal anesthesia.

This is in line with research conducted by Anagha Gadepali et al, which investigated the effects of loperamide as a peripherally acting mu-opioid receptor agonist. Loperamide treatment significantly attenuated mechanical and cold hypersensitivity and produced significant place preference behavior in neuropathic mice indicating its potential for treating both stimulated and spontaneously elicited pain. Loperamide treatment of mice without intervention did not result in a preference for the drug-paired chamber which demonstrated non-addictive analgesic potential. These findings suggest that activation of peripheral mu-opioid receptors contributes to the improvement of stimulated and spontaneous pain by downregulating TRP channels and VGSCs along with suppressing nitro-oxidative stress and the neuroinflammatory cascade. 48

In a study by Ying Wu et al., loperamide was identified as a sodium channel blocker (Nav). Inhibition of Nav channels can reduce neural activity associated with pain transmission, providing an analgesic effect. 47 The existence of cross-interactions between sodium channels and opioid receptors in pain processing implies that the effects of loperamide may be more complex. The combined effects of sodium channel blocking and opioid receptor activation may produce an optimal analgesic response in specific post-hysterectomy surgical conditions.

The results of the study showed a significant difference in the 4-hour VAS score between the group receiving loperamide and the control group. Meanwhile, in VAS 2, 8, 12, and 24 hours there was no significant difference, this could be caused by the half-life of loperamide which is around 11 hours and the time to reach peak concentration is around 2.5-5 hours where the average duration of surgery around 2 hours so that the assessment at the 8th hour onwards had passed the half-life of loperamide, even though research conducted by Kumar et al said that loperamide was much better than morphine at 42 and 49 hours after surgery but at a larger dose.2

The complexity of the mechanism of action of loperamide is not directly or strongly enough to influence post-hysterectomy pain at the time of measurement in this study, where as an opioid agonist, binding to opioid receptors will activate G protein, especially the Gai subunit, showing a preference for opioid receptors, resulting in a decrease in cAMP levels. intracellularly, inhibiting calcium currents through closing Voltage-gated calcium channels (VGCC) such as TRPA1, TRPM8 and increasing extracellular potassium currents, causing a decrease in neuronal excitation and inhibition of the release of neurotransmitters and/or neuropetides as well as inhibition of the expression of voltage-gated sodium ion channels (VGSCs).) such as NaV 1.7 and Nav 1.8. However, at a dose of loperamide 2 mg orally with low bioavailability, plasma levels are insufficient to influence the inhibitory effect of calcium channels and the interaction between opioid receptors and sodium channels to provide measurable analgesic effects in specific clinical conditions over a longer duration.

In this study, it was found that there was no significant difference between IL-6 levels in the group given loperamide 2 hours after surgery and the control group in hysterectomy operations with spinal anesthesia. Loperamide is known to have the ability to modulate immune responses, including decreasing the production of proinflammatory cytokines such as IL-6 through blockade of intracellular calcium channels. However, in a post-surgical context involving an inflammatory process, this effect may not be dominant enough to significantly reduce IL-6 levels at a dose of 2 mg and/or within 2 hours post-surgery.

Research conducted by Orosz et al. showed that IL-6 levels increased significantly in the first few hours after surgery but began to decrease after 24 hours. This suggests that the acute

inflammatory response may be more related to surgical trauma than to drug modulation over a short period of time.53 Laterresearch conducted by Catarci et al. discussed how regional anesthesia, including spinal anesthesia, can reduce the inflammatory response and post-surgical pain. 54 These effects may mask or reduce the potential effect of loperamide 2 mg on IL-6 levels.

However, no differences were found between IL-6 levels in the administration groupsloperamide 2 mg and controls who underwent hysterectomy with post-operative spinal anesthesia. This means that before the hysterectomy operation with spinal anesthesia the IL-6 levels between the two groups can be considered the same and after the hysterectomy operation with spinal anesthesia at 2 hours the IL-6 levels in the two groups did not experience a significant difference.

This is different from research conducted by Juárez E et. al. which states that loperamide is known to have effects on calcium channels and opioid receptors that can influence the immune response. Blockade of intracellular calcium influx by loperamide can reduce the production of proinflammatory cytokines such as IL-6, TNF-α, MCP-1, and IFN-γ. Reduction of these proinflammatory cytokines could potentially reduce inflammatory pain, but this effect may not be strong enough at a dose of 2 mg to significantly reduce IL-6 levels post-hysterectomy.[42]Akel T and Bekheit S. said that the bioavailability of loperamide is very low when consumed orally, namely <2%, so administration with a dose of 2 mg loperamide may not reach sufficient plasma concentrations to affect IL-6 levels.

In this study, the level of correlation between levels was also measuredIL-6 and VAS values 2 hours after surgery. However, there was no correlation between IL-6 levels and VAS scores 2 hours after surgery in the loperamide group. This means, when IL-6 levels increase, the VAS score tends to decrease or vice versa, but this relationship is very weak with a p value > 0.05, which means the relationship between IL-6 and VAS 2 hours after surgery in the loperamide group does not have a significant relationship. statistically. In other words, there is not enough evidence to state that there is a real relationship between these two variables. Then the correlation coefficient in the control group 2 hours after surgery with an r value of -0.065 shows that the relationship between IL-6 levels and VAS values 2 hours after surgery in the control group after surgery is very weak. The negative sign (-) indicates the opposite direction of the relationship between the two variables, although the strength is very low with a p value >0.05, which means the relationship between IL-6 and VAS 2 hours after surgery in the control group does not have a statistically significant relationship.

Conclusion

Loperamide 2 mg can be used as an analgesic adjuvant in hysterectomy surgery because it can reduce post-surgical pain scores compared to the control group at the 4th hour post-surgery. Loperamide 2 mg orally could not reduce IL-6 levels at 2 hours after hystectomy surgery. No side effects were found when administering Loperamide 2 mg orally. There was no relationship between the group given loperamide as an analgesic adjuvant and changes in IL-6 levels. There was no relationship between the control group as an analgesic adjuvant and changes in IL-6 levels.

Conflict of Interest

The author declares that there is no conflict of interest in writing this article.

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