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EFFECTIVENESS OF INTRAVENOUS IBUPROFEN COMPARED TO INTRAVENOUS KETOROLAC FOR IMPROVING THE SLEEP QUALITY PATIENTS OF ACUTE NON-SPECIFIC MUSCULOSKELETAL PAINS

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ABSTRACT

Background. Acute musculoskeletal pain is a common health problem. Patients with acute musculoskeletal pain, will experience disturbance sleep. Pain reduction will improve sleep quality. Studies about intravenous Ibuprofen for treating musculoskeletal pain is very limited in Indonesia.
Objective. to compare the sleep quality in patients with non-specific acute musculoskeletal pain between intravenous Ibuprofen versus intravenous Ketorolac
Method. This study uses a quasi-experimental research method with non equivalent, active comparation, and open label study. There were 60 subjects participated in the study and they were divided into 2 groups who received Ibuprofen or Ketorolac, then compared with respect to effectiveness (pain reduction 8, 16, 24 and 48 hours after injection and sleep quality after 48 hours), the possibility of adverse events and rescue medication. Data were analyzed bivariately with Mann Whitney test.
Results. Mean age of subjects 57.00 ± 15.125 years. A total of 60 subjects were divided into 2 groups. Both groups are equal in terms of baseline characteristics. The pain reduction in the Ibuprofen group was significantly greater than the group that received Ketorolac ($p = 0.006$, $p < 0.001$, $p = 0.006$). Sleep quality in the Ibuprofen group was significantly better compared with Ketorolac group ($p < 0.001$). A total of 35 (58.3%) subjects experienced a decrease in pain scale and improvement in sleep quality ($p = 0.022$). There was no significant difference in the use of rescue medication between the two groups ($p = 0.104$). There was a significant difference seen in adverse events (gastrointestinal) between the two groups ($p = 0.004$).
Conclusions. Intravenous Ibuprofen is more effective compared with intravenous Ketorolac for improving sleep quality patients with acute non-specific musculoskeletal pain.

Keywords: acute non-specific musculoskeletal pain, quality of sleep, Ibuprofen, Ketorolac

INTRODUCTION

Based on 2019 IHME (Institute for Health Metrics and Evaluation) data, there is an increase in the ranking of musculoskeletal disorders in the world at DALY (Disability Adjust for Life Years), which in 1990 ranked 4th, and in 2017 ranked 2nd. The DALY figure per 100,000 population in Indonesia, the highest rank is in the Riau Islands, followed by East Java (1).

Patients who experience acute musculoskeletal pain, will experience disruption in sleep such as often waking up at night and others. Various methods are used to reduce pain and have an impact on improving sleep quality, one of them by administering analgesics (2).

This research will compare two analgesics namely Ketorolac and Ibuprofen, which are a group of non-narcotic analgesic drugs that have antipyretic and anti-inflammatory properties. Has a mechanism as inhibiting the biosynthesis of prostaglandine, as well as inhibiting the enzyme cyclooxygenase (COX) including COX-1 and COX

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2. Research on oral Ibuprofen has been extensive in Indonesia, but research on Ibuprofen intravenously as a drug for treating musculoskeletal pain and its effect on sleep quality is still very limited in Indonesia.The aim of this study was to compare the sleep quality in patients with non-specific acute musculoskeletal pain between intravenous Ibuprofen versus intravenous Ketorolac (3).

MATERIAL AND METHODS

Study design

This study uses a quasi-experimental research method with non-equivalent, active comparation, and open label study. This study consisted of two groups, the active comparison group (30 mg Ketorolac) and the experimental group (800 mg Ibuprofen). Subjects studied were acute non-specific musculoskeletal pain patients seeking treatment at Bethesda Hospital Yogyakarta. Therapy is given to patients for 48 hours by giving drugs every 12 hours. Data collection on pain intensity using NPS (Numeric Pain Scale) at 8, 16, 24, 48 hours and data collection on sleep quality using BPI (Brief Pain Inventory) before and after 48 hours of therapy is given. The instrument used has been tested for validity.

Subject selection

The sampling of this research used purposive technique. Purposive technique is to take the population as research subjects who meet the inclusion and exclusion criteria.

1. Target population: All non-specific acute musculoskeletal pain patients
2. Affordable population: All non-specific acute musculoskeletal pain patients in Bethesda Hospital Yogyakarta in November 2019

Inclusion criteria were :

1. Male or female (> 18 years)
2. Moderate to severe acute musculoskeletal pain in Bethesda Hospital Yogyakarta (NPS> 4)

Exclusion Criteria were :

1. Unwilling to join research
2. Subjects with Ibuprofen or Ketorolac hypersensitivity
3. Subjects who are incompetent in giving consent and answering questionnaires
4. Pregnant and nursing patients
5. Subjects who receive other analgesics within 24 hours

Statistical analysis

This study uses a non-parametric test for trends (Mann withney test and chi-squared test) with SPSS version 21 licensed for data analysis. The test will compare the average improvement in sleep quality in both groups of patients with acute non-specific musculoskeletal pain given intravenous Ibuprofen and intravenous Ketorolac.

Research ethics

This research has been registered in the Indonesian Disease Register of Center of Health Resources and Services Research and Development titled Comparison of Intravenous Ibuprofen and Ketorolac for Acute Musculoskeletal Pain from Various Etiologies, and has been approved by the UKDW FK Yogyakarta Research Ethics Committee with EC 1101/C.16/FK/2019. Respondents were given informed consent before the study was conducted. The respondent's identity and address will be kept confidential. Data is taken entirely only for research purposes and not others.

RESULTS

There were 60 research subjects, divided into 30 subjects in the Ibuprofen group and 30 subjects in the Ketorolac group. There is no subject drop out in this study. Figure 1 shows the systematic research process, the subject has signed an informed consent sheet. Each subject was assessed 5 times (before therapy, 8 hours, 16 hours, 24 hours, 48 hours). Data collection on pain intensity using NPS (numeric pain scale) before and at 8, 16, 24, 48 hours after therapy is given. Retrieval of sleep quality data using BPI (brief pain inventory) before and after 48 hours of therapy is given.

In this study, 60 subjects with non-specific acute musculoskeletal pain with an average age of 57.00 ± 15,125 years were randomly divided into 2 groups who were given IV Ketorolac therapy or Ibuprofen (men 55%). Table 1 shows the initial characteristics of patients in two groups. Both groups were in comparable condition in terms of age ($p = 0.448$), sex ($p = 0.604$), initial pain intensity ($p = 0.107$),

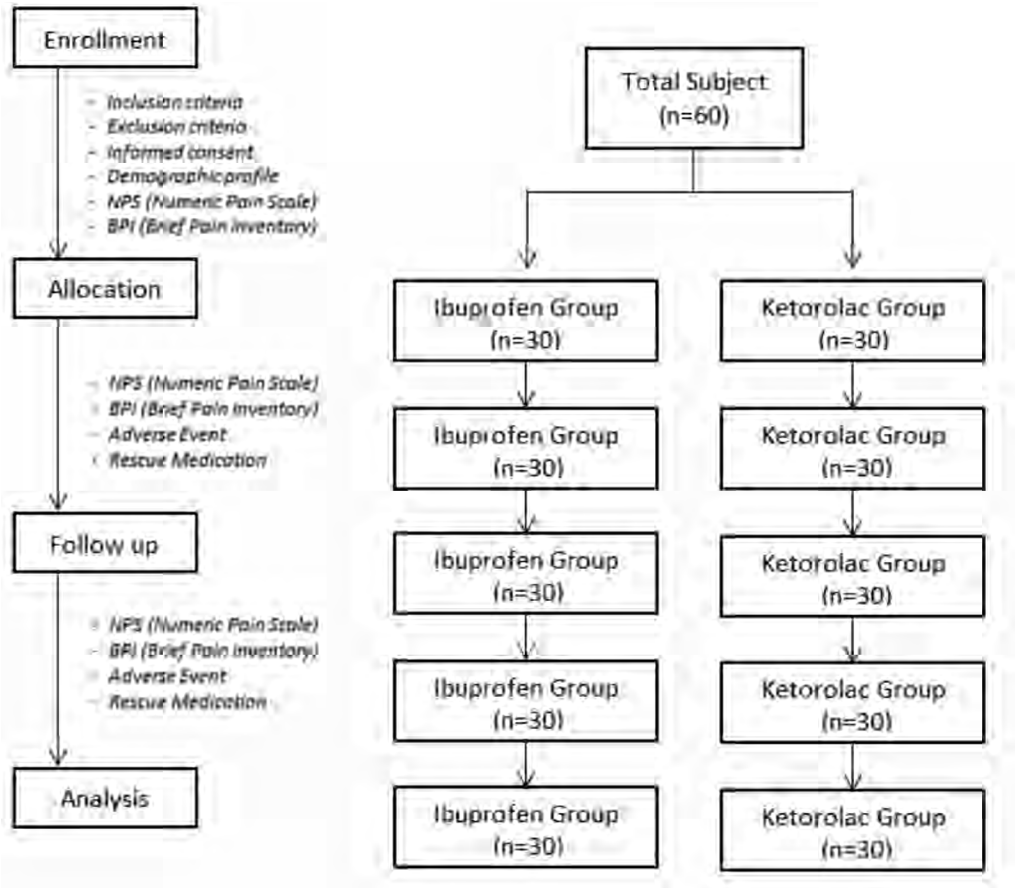

FIGURE 1. *The flow diagram of research*

early sleep quality (p = 0.064), comorbid disease (p = 1,000), comedication (p = 0.796).

The results after administration of intravenous Ibuprofen or intravenous Ketorolac are summarized in table 2. The reduction in pain intensity in the Ibuprofen group was significantly greater than the group receiving Ketorolac (p 16 hours = 0.006, p 24 hours <0.001, p 48 hours = 0.006). Table 3

TABLE 1. *Baseline characteristics*

Characteristics of Respondents		**Ibuprofen group (n = 30)**	**%**	**Ketorolac group (n = 30)**	**%**	**p value**
Gender	Male	18	60.0%	15	50.0%	0.604
	Female	12	40.0%	15	50.0%	
Age, Mean±SD		58.50±10.487		55.50±18.730		0.448
Location of pain	Back	14	46.7%	18	60.0%	0.438
	Knee	7	23.3%	4	13.3%	0.505
	Neck	9	30.0%	5	16.7%	0.360
Initial pain intensity, Mean±SD		63.33±8.841		59.33±12.847		0.107
Initial sleep quality, Mean±SD		56.33±13.515		59.00±10.289		0.064
Comorbid	Hypertension	13	43.3%	8	26.7%	1.000
	Diabetes mellitus	1	3.3%	5	16.7%	
	Cardiovascular disease	14	46.7%	4	13.3%	
	Gastrointestinal disease	9	30.0%	5	16.7%	
Comedication	Antihypertensive drug	13	43.3%	7	23.3%	0.796
	Antidiabetic drugs	1	3.3%	4	13.3%	
	Antiplatelet drug	13	43.3%	4	13.3%	
	Proton pump inhibitor/ H2 blocker	17	56.7%	5	16.7%	
	Vitamin	16	53.3%	2	6.7%	
	Steroid	7	23.3%	0	0.0%	

TABLE 2. *Decreased pain intensity between two groups*

Assessment time	Ibuprofen group Mean±SD	Ketorolac group Mean±SD	p value
Baseline	63.33±8.841	59.33±12.847	0.107
8 hours	38.67±10.417	42.67±8.277	0.061
	Δ 24.67±10.080	Δ 16.67±7.581	0.001
16 hours	31.67±11.769	38.00±7.144	0.006
	Δ 31.67±12.888	Δ 21.33±9.371	0.002
24 hours	24.33±13.047	34.67±7.303	<0.001
	Δ 39.00±12.959	Δ 24.67±11.366	< 0.001
48 hours	17.33±13.880	26.67±7.581	0.006
	Δ 46.00±16.316	Δ 32.67±10.148	0.001

TABLE 3. *Improvement of sleep quality between two groups*

Assessment time	Ibuprofen group Mean±SD	Ketorolac group Mean±SD	p value
Baseline	56.33±13.515	59.00±10.289	0.064
48 hours	25.00±13.065	37.33±8.683	<0.001
	Δ 30.00±19.652	Δ 22.67±9.072	0.363

Table 4. Comparison of adverse event (gastrointestinal) between the two groups

Adverse event	**Ibuprofen group (N = 30)**	**%**	**Ketorolac group (N = 30)**	**%**	**p value**
The patient experiences an adverse event	0	0.0%	9	30.0%	0.004

shows that intravenous Ibuprofen or intravenous Ketorolac can significantly reduce pain intensity and can improve the subject's sleep quality ($p < 0.001$).

Table 4 shows that the adverse event (gastrointestinal) only occurred in the Ketorolac group, with 9 people (30.0%) with $p = 0.004$ indicating that there were significant differences in the two groups.

DISCUSSION

In this study, the characteristics of subjects who were non-specific acute musculoskeletal pain patients at Bethesda Hospital in Yogyakarta were 33 male (55%), female subjects were 27 (45%) of the total 60 subjects person. The same research results can be found in research conducted by Uribe et al. (2012) at The Ohio State University Wexner Medical Center, United States, with subjects who underwent arthroscopic knee surgery with general anesthesia as many as 35 people (68.6%) were male and 16 people (31.4%) were female (4).

Paller et al. (2009) suggest that neurophysiological mechanisms, sex hormones, endogenous opioid function and physical activity contribute to differences in pain sensitivity between men and women. In neurophysiological mechanisms, three opioid receptors, μ, κ, and δ are significantly involved in pain modulation. Women have a higher pain prevalence than men due to male-female differences in opioid pharmacodynamics, and human postmortem analysis shows a greater concentration of opioid receptors in women. In addition to neurophysiological mechanism factors, differences in pain sensitivity between men and women are influenced by gonadal hormone. Smith et al. (2006) found that women with high estrogens (eg, those using transdermal patches) showed an increase in the number of regional μ-opioid receptors and increased pain activation associated with endogenous neurogenic μ-opioid transmission compared with women with low estrogen states. In the study of Hoy et al. (2012), women have a higher prevalence of musculoskeletal pain associated with exposure to musculoskeletal burden due to pregnancy, child care, and work. In addition, physiological characteristics such as less muscle and bone mass and psychological factors can contribute to the prevalence of musculoskeletal pain (5,6,7).

The mean age of the subjects in this study was 57.00 ± 15.125. This is similar to the study con-

ducted by Uribe et al. (2012) in which the average age of patients who experience musculoskeletal pain is 43.7 ± 12.7 years. Based on the study by Smeltzer et al. (2012), the elderly (elderly) responding to pain can be different from how to respond to younger people (4,8).

The highest frequency of location and type of pain in this study were back injuries of 35 people (58.3%). The same research results can be found in research conducted by Amako et al. (2018) regarding the epidemiological pattern of injury or musculoskeletal disorders, the highest prevalence of non-traumatic musculoskeletal disorders due to lumbar disorder was 4,548 subjects (27.7%). This is also similar to the research conducted by Taanila et al. (2009) regarding the type and anatomic location of the most common musculoskeletal disorders is LBP 106 subjects (20%). Based on the study by Fitriningsih et al. (2011), the high prevalence of LBP might be related to occupational and household exposure which burdens the lower back together with the degenerative articular process shown after age 30. In addition, the back muscles play a role to hold the burden of the upper limbs who are doing work. As a result, the workload rests on the lumbar region and causes the lumbar muscles to hold the main burden will easily experience pain (9-11).

Adverse event in this study only occurred in the Ketorolac group, as many as 9 subjects (30.0%). In the Ketorolac group, 9 of these patients had gastrointestinal disorders, including abdominal pain and gastrointestinal bleeding. This is consistent with the theory by Orlando et al. (2015) that the rate of inhibition of COX-1 and COX-2 in Ketorolac is 330: 1, which explains the high risk of side effects, some deaths have been reported due to side effects of gastrointestinal bleeding. The level of inhibition of COX-1 and COX 2 in Ibuprofen is 2.5:1, which indicates a lower risk of bleeding or digestive problems compared to Ketorolac. This is similar to the study conducted by Singer et al. (2003) in which several deaths have been reported due to side effects of gastrointestinal bleeding in the use of Ketorolac. Ketorolac has been shown to increase the incidence of intraoperative blood loss and postoperative bleeding when given before or during surgery (12,13).

Patients who received rescue medication in this study were 7 people (23.3%) in the Ibuprofen group and 14 people (46.7%) in the Ketorolac group, with a p value = 0.104. This indicates that there were no significant differences in the two groups because p > 0.05. In this study, after administration of intravenous Ibuprofen or intravenous Ketorolac, the results were obtained in the form of a decrease in the intensity of the patient's pain at 8 hours, 16 hours, 24 hours and 48 hours. The decrease in pain intensity in the Ibuprofen group was significantly greater than the group that received Ketorolac, with a comparison of the decrease in pain intensity in both groups also statistically significant in bivariate analysis (p 16 hours = 0.006, p 24 hours < 0.001, p 48 hours = 0.006) This result is similar to a study conducted by Forouzanfar et al. (2019) that colic renal pain patients were randomly divided into 2 groups who received IV Ibuprofen or IV Ketorolac and after 60 minutes, the number of cases with VAS = 0 reached 0 (0.00%) patients in the Ketorolac group and 8 (26.67%) patients in the Ibuprofen group. This is consistent with the theory by Bushra et al. (2010) that intravenous Ibuprofen has a maximum levels in plasma of 1 hour, analgesic duration of 6-8 hours. Intravenous Ketorolac has a analgesic peak is reached in 2 hours, analgesic time is 4-6 hours (14,15).

Intravenous Ibuprofen and intravenous Ketorolac can significantly reduce pain intensity and can improve the subject's sleep quality (p 48 hours < 0.001), these results are statistically significant marked with $p < \alpha$ ($\alpha = 0.05$). Analysis of the relationship of pain intensity with improvement in sleep quality after therapy showed a significant relationship. This study is in line with research conducted by Indri, Karim and Elita (2014) about the relationship between pain, anxiety and the environment with sleep quality in postoperative appendicitis patients. The results of research conducted on 54 respondents showed that there was a significant relationship between pain and anxiety with sleep quality in patients with postoperative appendicitis (2).

This is supported by theory by Ødegård et al. (2010), which is a population-based study in Norway reporting that pain sufferers are 17 times more likely to suffer from sleep disorders than painless individuals. Theory by laboratory-based sleep studies shows that lack of sleep causes increased sensitivity to dangerous stimuli (noxious stimuli) and

decreased endogenous pain inhibition processes, this explains the relationship between poor sleep quality and an increased prevalence of musculoskeletal pain. The above theory is also confirmed by the study of Chun et al. (2018) showing a correlation between multi-site musculoskeletal pain experienced in 48.4% of participants with sleep duration disorders (16,17).

Stress, pain and sleep quality, often referred to as trias of pain, are three interrelated things. Based on research by Fauziyah et al. (2018), the relationship between stress and sleep is stronger than the relationship between pain and sleep. Episodes of acute stress cause the release of catecholamines and cortisol associated with a "fight or flight" response. Cortisol is produced in a daily pattern by the adrenal glands to deal with stressors, under normal circumstances the body benefits from cortisol production. However, when the stress response is persistent, problems related to health and well-being tend to increase because prolonged exposure to cortisol causes a number of unfavorable biological events such as inflammation and changes in appetite. Based on research by Finan et al. (2013) the mechanism of sleep and pain is in dopaminergic signaling (DA). DA receptors are widely available in the ascending reticular activating system (ARAS) including the raphe nucleus in the brain stem, the sleep modulation region. Based on research by Foo and Mason (2003), serotoninergic raphe cells alert markers can become irregular (inhibited formation) when there is pain, causing disruption of sleep duration and disruption of sleep continuity (18-20).

The cost of treatment (cost of treatment) of intravenous Ibuprofen is greater than intravenous Ketorolac, i.e. intravenous Ibuprofen (800 mg) USD $4.89 and intravenous Ketorolac (30 mg) USD $0.17. When viewed from the price, of course intravenous Ketorolac is more affordable, but it should be noted also about side effects that may arise, especially gastro intestinal side effects, based on this study, gastrointestinal side effects appear more in the Ketorolac group. Of course, in dealing with side effects, additional treatment costs for these patients are needed, based on data obtained from the Bethesda Hospital Yogyakarta, initial treatment costs with H2 blockers (ranitidin injection) of USD $0.21. So it can be seen that the cost of intravenous Ibuprofen is greater, but it is more effective and safer to use. Study limitation was not randomized and not blind assessment.

CONCLUSION

Intravenous Ibuprofen is more effective compared with intravenous Ketorolac for improving sleep quality patients with acute non-specific musculoskeletal pain.

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