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Evaluation of Pain Scale Decrease and Adverse Effects of Ketorolac Injections: An Observational Study in Patients with Postoperative Pain

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ABSTRACT

The use of ketorolac injections in Indonesia is restricted with the provision of 2-3 ampoules per day with a maximum of two days even though the literature states that ketorolac could be used for no more than five days. This study aimed to determine the decrease in pain scale as well as gastrointestinal and renal adverse effects of ketorolac injections in two days of use. This study was an observational study with a one-group pre-test post-test design conducted prospectively. The group was a group of patients with postoperative pain who received ketorolac injections and were treated during January till April 2018 in an academic hospital in Yogyakarta. The results showed that ketorolac injections did not provide a statistically significant decrease in pain scale in two days of use compared to before surgery (median [range] = 2.0[0.0-9.33] vs 1.33[0.0-8.33]; p=0.32). Ketorolac injections decreased the kidney function of subjects in two days of use compared to before surgery based on creatinine values (0.76mg/dL vs 0.80mg/dL; p=0.024) and GFR (96.13mL/min/m^2 vs 87.52mL/min/m^2; p=0.023), and as many as 31 subjects (43.06%) experienced complaints that were suspected to be the gastrointestinal adverse effects of ketorolac injections with the three most complaints were bloating (18.06%), nausea (16.67%), and heartburn (15.28%). Those three results support the use of ketorolac injections following what has been regulated in the Indonesian National Formulary.

Keywords: Pain scale, gastrointestinal adverse effects, renal adverse effect, ketorolac injections, postoperative.

INTRODUCTION

Postoperative pain is an unexpected subjective complaint. Data on the prevalence of postoperative pain in Indonesia is still not well documented, but in other countries such as studies conducted in Barcelona, it had shown that the prevalence of orthopedic postoperative pain and trauma was around 28% with mild pain of 15% and moderate to severe pain by 13% (Robleda *et al*., 2014). Another study showed that moderate to severe pain in the first 24h and the first 48h after surgery were 13% and 11.7%, respectively (Mwaka *et al*., 2013). Ketorolac is one of the drugs of choice for postoperative pain management. A study showed that 89.7% of patients with postoperative pain in one hospital in Indonesia were treated using ketorolac (Permata, 2014).

The results of several other studies showed that ketorolac could provide better postoperative pain management than placebo, tramadol (Shah *et al*., 2013), diclofenac (Mony *et al*., 2016), and significantly reduced pain intensity 30 minutes after surgery (Eftekharian and Pak, 2017). However, the risk of gastrointestinal bleeding due to ketorolac was known to be quite high and relatively higher than other NSAIDs. The results of a study showed that nonselective NSAIDs increased the relative risk of bleeding, but ketorolac could increase the risk of bleeding much even higher (Gonza´lez *et al*., 2010). A study that examined the association between NSAIDs and chronic kidney disease (CKD) showed that ketorolac increased the risk of CKD by 2.54 times in less than 3 months (Ingrasciotta *et al*., 2015) and acute renal failure by 2.08 times if given for more than 5 days (Feldman *et al*., 1997). In addition, other studies that have been conducted showed that in addition to gastrointestinal bleeding, the

adverse effects that may arise in 48 hours of ketorolac injections use in postoperative patients were; nausea/vomiting 37.5%; dizziness 25%; dyspepsia 8.7%; pruritus 6.2%; and constipation 3.1% (Siribumrungwong *et al*., 2015).

The use of ketorolac injections is generally restricted for no more than five days (Grosser *et al*., 2018; Strom *et al*., 1996), but the use of ketorolac injections in Indonesia is restricted with the provision of 2-3 ampoules per day with a maximum of two days by the Indonesian National Formulary (Kementerian Kesehatan, 2016). This certainly raises the question whether ketorolac influences the decrease in pain scale adequately and whether gastrointestinal and renal adverse effects will indeed appear in just two days. Therefore, this study aimed to determine the decrease in pain scale along with gastrointestinal and renal adverse effects of ketorolac injections in two days of use.

MATERIAL AND METHODS

Study design

This study was an observational study with a one-group pre-test post-test design conducted prospectively. This study only consisted of one group, namely the group of patients who received ketorolac injections. The study was conducted in the surgical ward of an academic hospital in Yogyakarta since January till April 2018. The design of this study was approved by the Research Ethics Committee of the Faculty of Medicine (now is the Faculty of Medicine, Public Health, and Nursing) of the Universitas Gadjah Mada with number KE/FK/1033/EC/2017.

Population and samples of study

The population of this study was all surgical patients hospitalized in the surgical ward of the study hospital, while the study samples were all patients aged ≥18 years with postoperative pain who received ketorolac injections during hospitalization in the surgical ward and were not included in the exclusion criteria specified in the study. The exclusion criteria of this study consisted: 1) Patients who were unconscious after completing surgery; 2) Patients with a history of peptic ulcer, chronic kidney disease, or were experiencing nausea, vomiting, diarrhea, and constipation before undergoing surgery.

Data collection

The collection of study subjects involved physicians who treated the patients and it was performed using consecutive sampling method. The physicians asked the patients to participate in the study by signing an informed consent sheet before undergoing surgery. After the patients agreed to participate as study subjects, the patients' pain scale was assessed using a numeric rating scale (NRS) instrument (Hawker *et al*., 2011) and determined as the baseline pain scale. The patients' pain scale was reassessed on the first and second day after surgery. Complaints or symptoms that were thought to be ketorolac adverse effects were monitored during treatment. Suspected adverse effects were adverse effects that lead to gastrointestinal and renal. Identification of gastrointestinal adverse effects of ketorolac injections use was performed using the Naranjo adverse drug reaction probability questionnaire (Belhekar *et al*., 2014), whereas the identification of renal adverse effects was carried out by examining the patients' serum creatinine and Blood Urea Nitrogen (BUN) values.

Data analysis

Numerical data were processed in decimal form with the central tendency of data in the form of mean ± SEM (Standard Error of Mean) if the data is normally distributed statistically, or in the form of median if the data were not normally distributed. Patient data that were categorized were processed in the form of proportions. Both types of data were then presented in the form of tables or figures.

The analysis of decrease in pain scale was done by comparing the pain scale before surgery with the pain scale on the day one and day two after surgery, whereas the analysis of decrease in kidney function was done in two ways, namely by comparing creatinine values before undergoing surgery with creatinine values on day two after surgery, and by comparing values of GFR before undergoing surgery with GFR on day two after surgery. Measurement of the value of GFR was done using the MDRD4 formula (Levey *et al*., 2000). Before analyzing the decrease in the pain scale and kidney function, the investigators conducted a data distribution normality test using the Shapiro-Wilk test. Then, the significance of the decrease in pain scale and kidney function (creatinine and GFR) was tested using paired t-test if the data were normally distributed or the Wilcoxon test if the data were not normally distributed statistically. The p-value of <0.05 showed that the pain scale or kidney function before undergoing surgery were significantly different from day one or two after surgery.

Table I. Characteristics of study subjects

Characteristics		Mean $\bar{x}$ ± SEM (N=72)	Proportion n (%) (N=72)
Age (years)		46.76±1.90	
Baseline blood pressure (mmHg)		124.67±1.95/77.25±0.99	
Baseline pain scale		2.13±0.28	
Baseline BUN (mg/dL) (N=43[a])		25.70±1.57[a]	
Baseline creatinine (mg/dL) (N=43[a])		0.84±0.03[a]	
Baseline GFR (mL/min/1.73 m^2) (N=43[a])		95.34±3.39[a]	
Age groups	-19-35 years		17 (23.6)
	-36-45 years		15 (20.8)
	-46-60 years		24 (33.3)
	-61-75 years		14 (19.4)
	-76-90 years		2 (2.8)
Gender	-Male		32 (44.4)
	-Female		40 (55.6)
Smoking status	-Yes		13 (18.1)
	-No		59 (81.9)
Types of surgery	-general surgery		32 (44.44)
	-digestive surgery		27 (37.5)
	-orthopedic surgery		13 (18.1)
Comorbid	-hypertension		11 (15.28)
	-diabetes		9 (12.5)
	-asthma		4 (0.06)
	-vertigo		2 (0.03)
Ketorolac dose	-30mg every 8h		70 (97.2)
	-30mg every 12h		2 (2.8)

a=measured from only 43 patients who had complete BUN, creatinine, and GFR values on the day before undergoing surgery.

RESULTS AND DISCUSSION

This study aimed to: 1) to determine the adequacy of the decrease in the patients' pain scale given by injections of ketorolac on day one and day two after surgery, 2) to determine the effect of ketorolac injections on kidney function on day two after surgery, and 3) to investigate complaints suspected of being an adverse effect of ketorolac injections. This study was beneficial as a basis for evaluating the restrictions on the use of ketorolac injections according to the Indonesian National Formulary, which states that ketorolac injections are only given in a maximum of two days with a dose of 2-3 ampoules per day (Kementerian Kesehatan, 2016) even though Vadivelvu *et al*. (2017) states that ketorolac use may be used for not more than five days (Grosser *et al*., 2018; Vadivelu *et al*., 2017).

Characteristics of study subjects

The subjects of this study were surgical patients who were hospitalized and received ketorolac injections as a postoperative analgesic since February to April 2018 in the study site hospital. The types of surgery included in this study were general surgery, digestive surgery, and orthopedic surgery.

The subject collection was carried out by a consecutive sampling method and this study finally obtained a total of 72 patients. In general, the characteristics of the subjects in this study were general surgical patients aged 46-60 years with a mean age of 46.76±1.90 years, female gender, not smoking, with comorbid of hypertension and received ketorolac injection dose of 30mg every 8h during treatment (Table I). Also, the study subjects admitted the hospital with a pain scale of 2.13±0.28 and normal kidney function which was seen through normal BUN, creatinine, and GFR values.

The decrease in pain scale

This study was conducted with a one group pre-test post-test design so that the statistically

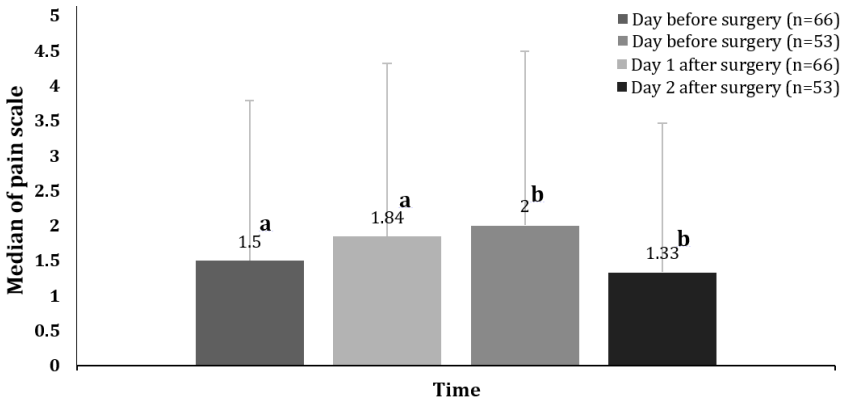

Figure 1. Median of pain scale from the day before surgery until day two after surgery. a=not significantly different with a Z score of -1.02 between before the surgery and the day one after surgery (p=0.31). b=not significantly different from the Z score of -0.994 before the surgery and day two after surgery (p=0.32).

tested data were only the completely paired data. This caused the number of subjects analyzed on the comparison of pain scale on the day before surgery with the day one after surgery was not the same as in the analysis on the comparison of the pain scale on the day before surgery with the day two after surgery.

Ketorolac injections did not decrease the pain scale on day one after surgery but were able to decrease the pain scale on day two after surgery (Figure 1). However, the decrease in the pain scale on day two after surgery produced by ketorolac injection was not significant. This indicated that the problem of postoperative pain was still unresolved using ketorolac injections as is presented in the pain management guidelines published by the American Pain Society (2016) which states that less than half of patients with postoperative pain report adequate postoperative pain relief (Chou *et al*., 2016).

A similar study was conducted by Eftekharian and Pak (2017) in which the study investigated the effects of intravenous ketorolac on postoperative pain in patients with mandibular fractures, but the pain measured was early postoperative pain. One study showed that ketorolac did not provide a pain scale that was different significantly with the placebo group in the first 4h after surgery (pain intensity 1.08±0.49 vs 1.04±0.68; p=0.135; scores on Visual Analog Scale (VAS) >1=16% compared to 24%, p=0.725) (Eftekharian and Pak, 2017). There is still no agreement of opinion in the definition of relieving or control of pain although O'neil (2016) states that one example of pain management in patients with acute pain is pain with a scale of less than 3 (O'Neil, 2016).

The decrease in renal function

The study subjects included in the analysis of the decrease in kidney function in this study were subjects with complete creatinine level data before undergoing surgery and on day two after surgery so that the number of subjects analyzed amounted to only 23 patients. This study analyzed the decline in kidney function of the study subjects using serum creatinine and GFR parameters.

The results showed that ketorolac injections caused an increase in serum creatinine levels on day two after surgery (Figure 2). Although the increase in the value was slight (0.4mg/dL), the results of statistical tests showed that the increase in the value was statistically significant. The GFR parameter was used to ensure that changes in kidney function occur because creatinine is a less specific parameter of kidney function. Creatinine is the end-product of nitrogen metabolism which is excreted in the urine. Creatinine production reflects total body muscle mass (Rae *et al*., 2018) so that the same creatinine levels among subjects could show different kidney function due to different muscle mass in different ages and genders.
Therefore, this study used GFR which is a more specific kidney function parameter. The results of the study also showed that the decline in kidney function in the subjects of the study consistently occurred when viewed using the GFR parameter (Figure 3).

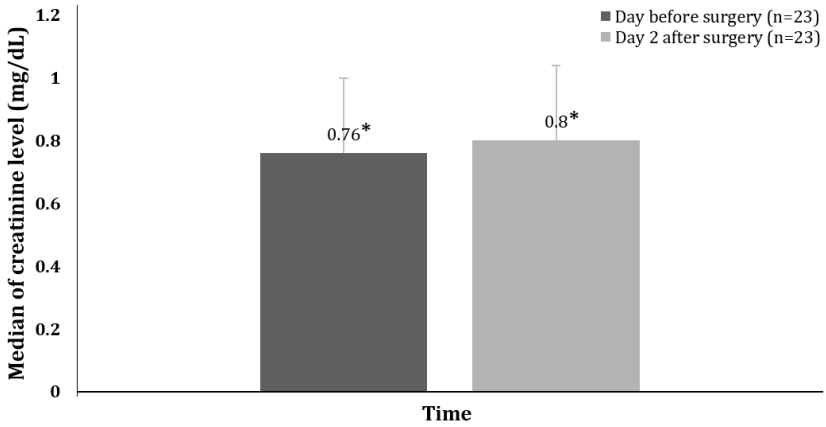

Figure 2. Median serum creatinine value from the day before undergoing surgery and day two after surgery. The study subjects included in this analysis of the increase in creatinine serum value were subjects with complete creatinine level data before surgery and on day two after surgery (n=23) so that it was different with the number of subjects in the table of study subjects' characteristics (n=43) (Table I). Therefore, the serum creatinine value between this figure 2 and table I was also different. *=Statistically significant difference with a Z score of -2.25 of creatinine levels before undergoing surgery with day two after surgery (p=0.024).

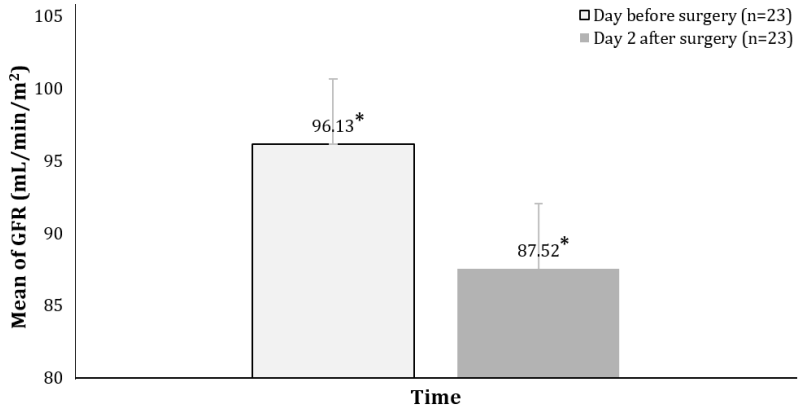

Figure 3. Mean GFR from days before undergoing surgery and day two after surgery. The number of study subjects included in this analysis of the decrease in GFR value (n=23) was different with the number of subjects in the table of study subjects' characteristics (n=43) (Table I) because the subjects were subjects with complete creatinine level data before surgery and on day two after surgery. Therefore, the GFR value between this figure and table I was also different. *=statistically significant with a difference in the mean GFR of 8.61±3.51mL/min/1.73 m^2 compared to the GFR value on the day before surgery (p=0.023).

Authors found that it is difficult to find relatively new studies of ketorolac, but because ketorolac is a drug belonging to the group of Nonsteroidal Anti-inflammatory Drugs (NSAIDs) (Candido *et al*., 2017) and because studies of NSAIDs generally included various types of NSAIDs including ketorolac, then a discussion of NSAID adverse effects on the kidneys could apply to ketorolac. Candido *et al*. (2017) mentioned that NSAIDs only caused a temporary mild decrease in kidney function on day one after surgery. The decrease was measured using creatinine clearance parameters in 1,450 healthy adults with a yield of 16 mL/min [5-28 mL/min] which was not significant compared to the placebo group (Candido *et al*., 2017). A systematic review study conducted by Zhang *et al*. (2017) showed that patients who were exposed to NSAIDs had an increased risk of Acute Kidney Injury (AKI) (OR 1.73 [1.44-2.07]) (Zhang *et al*., 2017).

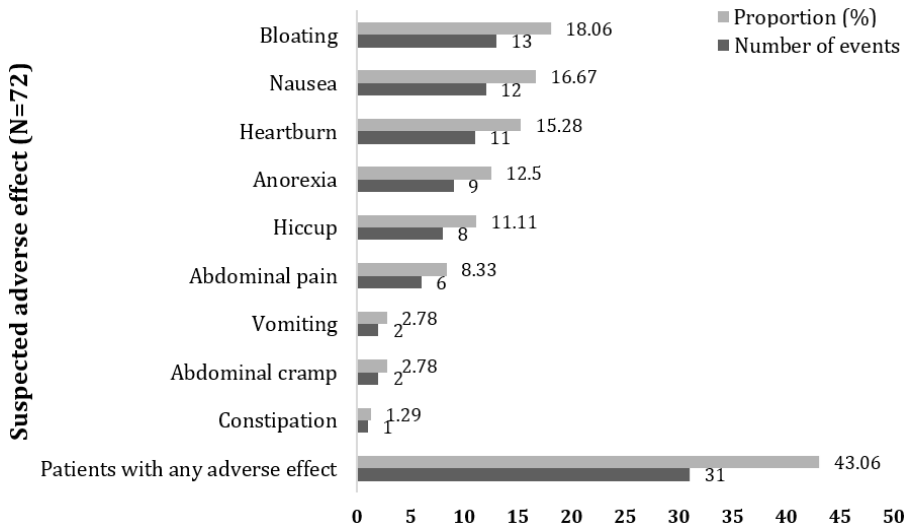

Figure 4. Events and proportions of each adverse effect suspected caused by ketorolac injections.

The results of the study are supported by a study conducted by Chou *et al*. (2016) whose results showed that the use of NSAIDs increased the risk of AKI (OR 2.73 [2.28-3.28] in patients with current NSAID use and with OR 1.17 [1.01-1.35] in patients with NSAID use 30 days beforehand) (C.-I. Chou *et al*., 2016). NSAIDs do not only increase the risk of AKI but also End-Stage Renal Disease (ESRD) as in the results of a study conducted by Chang *et al*. (2015) (OR 2.72 [2.60-2.82]) (Chang *et al*., 2015).

Two mechanisms of NSAIDs-induced AKI in children have been estimated. Both mechanisms may also apply to cases of AKI induced by NSAIDs in adults. The two mechanisms are the mechanism of hemodynamic changes and Acute Interstitial Nephritis (AIN). The first mechanism causes around 78% of AKI cases to occur, while the second mechanism is around 22% (Misurac *et al*., 2013). In the first mechanism, NSAIDs inhibit cyclooxygenase (COX) so that prostaglandin synthesis is inhibited. Prostaglandin acts as a vasodilation regulator that maintains adequate renal perfusion. The inhibition of prostaglandin synthesis causes uncontrolled vasoconstriction in afferent arterioles so that GFR decreases and causes acute ischemia and acute tubular necrosis. The AKI case in the second mechanism is also caused by NSAIDs which also inhibit COX, but the effect of this is the shift in arachidonic acid metabolism towards the pathway that synthesizes more leukotrienes, whereas leukotrienes are involved in the activation of the inflammatory response (Faught *et al*., 2015).

Complaints which suspected as adverse effects of ketorolac injections

The two instruments generally used to measure adverse effects are Naranjo and the WHO-UMC scale (Belhekar *et al*., 2014), but the measurement of adverse effects in this study used a questionnaire developed by Naranjo. This questionnaire uses a scoring system that is divided into five probability categories consisting of definite, probable, possible and doubtful. Most of the complaints issued as the adverse effects of ketorolac injections in this study were categorized as probable category with a score of 5-8 (max. 13).

The results showed that the most and least common adverse effects of ketorolac injections were bloating (18.06%) and constipation (1.29%) (Figure 4). The overall incidence of complaints suspected of being an adverse effect of ketorolac injections was high because complaints occurred in almost half of the study subjects (43.06%). The results of this study were slightly different from the results of a study conducted by Siribumrungwong *et al*. (2015) which, in that study the most common ketorolac adverse effects were nausea/vomiting (37.5%), while the least was constipation (3.1%) (Siribumrungwong *et al*., 2015). However, in this study, nausea was the second most common complaint suspected as an adverse effect of ketorolac injections with a proportion of 16.67%.

Another important adverse effect to note was that ketorolac could increase the risk of gastrointestinal bleeding the highest compared to other NSAIDs (OR 14.54 [5.87-36.04]) (Gonza´lez *et al*., 2010) based on adverse effect conducted by Gonzalez *et al*. (2010).

This study certainly had limitations. This study was an observational study that did not provide intervention to study subjects such as temporary stopping the ketorolac injections and re-challenging it after being stopped so that the measurement of the adverse effects of ketorolac injections in this study did not produce adverse effects that could reach definite degree. Complaints with probable degree still leave the possibility that the complaint was not due to ketorolac injections, but due to other factors such as patient comorbidities so that further studies with the interventional design conducted prospectively could improve the results of this study.

CONCLUSION

The conclusion that could be drawn from the results and discussion of this study is that two days of ketorolac injections use was not able to significantly decrease the postoperative pain scale statistically. Also, gastrointestinal adverse effects occurred with the two most common forms of bloating and nausea. The study also showed that the use of ketorolac injections for two days decreased kidney function as seen from an increase in serum creatinine levels and a decrease in GFR in the study subjects. Those three things can be the basis for consideration of the use of ketorolac injections for only two days following as regulated in the Indonesian National Formulary.

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