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An evaluation of the relationship between the occurrence of chronic kidney disease and the use of NSAIDs

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ABSTRACT

Background: Non-steroidal Anti-Inflammatory Drugs (NSAIDs) are painkillers that Indonesians widely use. Many people use it because it is easy to get and low price. Although, the public does not pay attention to safety in its use. This study aims to determine the relationship and the level of causality between the use of NSAIDs and chronic kidney disease (CKD) events.
Methods: An observational case-control with retrospective retrieval was adopted, and the risk factors between the use of NSAIDs and CKD events were analyzed. Meanwhile, the study was conducted in Makassar city hospital with consecutive sampling from January 2017 until January 2018.
Results: The results showed that 118 patients from a total of 350 used NSAIDs, while 35 of the 175 with CKD had a history of NSAIDs. Furthermore, the data on the use of NSAIDs in these patients was 40% meloxicam and 10% mefenamic acid, and the result of the Chi-square analysis showed a p-value <0.001 and an OR of 0.277. Additionally, the possible incidence of CKD in men and women is 48.55% and 70.72%, respectively, with a history of using NSAIDs for over 3 months. It was further shown that 2 of 118 patients had side effects from CKD due to the long-term use of NSAIDs.
Conclusion: Conclusively, there is no relationship between CKD incidence and the use of NSAIDs in the community. However, some CKD side effects are related to NSAIDs, which implies that NSAIDs do not result in CKD.

Keywords: causality, chronic kidney disease, non-steroidal anti-inflammatory drugs, probability, risk factor.
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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are associated with acute kidney injury in general and progressive ailments that develop into chronic kidney disease (CKD).[1] A further reduction in the volume of renal blood flow in patients with CKD due to decreased prostaglandin synthesis results in acute kidney injury, sodium retention, edema, hypertension, and hyperkalemia.[2] Furthermore, the mechanism of NSAIDs is the inhibition of the cyclooxygenase (COX) enzyme, which is involved in the synthesis of prostaglandins. Additionally, the inhibition of prostaglandin (PG) mediated by NSAIDs explains many kidney complications. PG also plays an important role in maintaining normalcy in renal physiology and stimulating the release of aldosterone, mediated by renin and angiotensin.[3–5]

Furthermore, research on the relationship between the use of NSAIDs and CKD in the Indonesian population is still limited. Meanwhile, genetic polymorphism in enzyme metabolism is considered one of the main causes of inter-individual variation in response to drugs and side effects. Previous research has shown that polymorphism in CYP2C9, which is recorded as a decrease in the hereditary activity of CYP2C9, increases the response to a high-risk drug after the use of NSAIDs. However, the role of genetic variation in CPY2C9 on the risk of CKD due to the use of NSAID is yet to be fully understood.[6]

The population of Sulawesi, the subject of this study, is unique. Meanwhile, Sulawesi is located near the equator line, which marks the zone transition between the continent of Asia and Australia. Due to this, Sulawesi has a variety of flora, fauna, and different ethnicities compared to other islands in Indonesia. Previous research has shown that the frequency allele CYP2C9*3 in Makassar's population is 1.56%.[6] Furthermore, potentially inappropriate prescription (PIP) identification is linked to the use of NSAIDs with some vascular disorders such as heart failure and hypertension than ADR, which results in the hospitalization of patients.[7,8]

Previous studies have shown the presence of CYP2C9, which may increase the risk of adverse drug reaction (ADR) from the NSAIDs used. Various research attempts to determine the relationship between NSAIDs and CKD incidence in Makassar since CKD is one of the reactions associated with the long-term use of NSAIDs. This study, therefore, aims to identify the relationship between the use of NSAIDs and chronic kidney disease.

METHODS

This research was conducted at several hospitals in Makassar, South Sulawesi, Indonesia, from January 2017 until January 2018. Data were collected directly from patients using the questionnaire interview

method and also from their medical reports. Furthermore, data retrieval is done retrospectively by reviewing the medical records.

A case-control design was adopted where the population comprised patients in both hospitals, and the criteria of inclusion that had been established were fulfilled. The inclusion criteria in this study were male or female patients aged ≥ 18 years and < 60 years old, diagnosed with gastric bleeding, acute or chronic kidney disorder, anemia, outpatient or inpatient care, and they have complete medical record data. At the same time, exclusion criteria are patients on chemotherapy therapy, post-traumatic patients, immunosuppressant therapy or patients with impaired consciousness. The subjects in the control and case groups were patients without CKD and those with the disease, respectively. Furthermore, the consecutive sampling method was adopted, and the patients with a history of NSAID use and CKD experience were added to the inclusion criteria. Several variables in this research showed that age was calculated from the patient's date of birth until the time of the study. The dose in this study was the average daily dose of NSAIDs used by patients. The type of NSAIDs was the name of the NSAIDs used. Comorbidity diseases were other diseases outside the admission diagnosis, determined from the results of a doctor's examination and written in the medical record, including the diagnosis as an indication. Use of NSAIDs. Length of service of NSAIDs duration of use of NSAIDs by subjects until the study was conducted.

Respondents in this study were 350 samples consisting of case and control groups of 175 respondents each. The case group had 175 respondents who were interviewed directly to trace the history of using other NSAIDs, the type of NSAID consumed, and the duration. All patients had a duration of NSAID use ranging from 7 to 60 days. Furthermore, data collection from medical records was assessed using WHO causality and some direct questions from patients using the Naranjo algorithm. The statistical analysis used in this study was the bivariate Chi-squared, Mann-Whitney test, and the Multivariate test.

RESULTS

The study was conducted using data from medical records between 2015 and 2017. Moreover, the population consists of 437 patients. However, only 350 met the inclusion criteria. The subject is further divided into 2 groups, the case and control groups of 175 patients. The profile data of the subject is presented in Table 1. Furthermore, from 175 subjects diagnosed with CKD, 121 (58.5%) and 54 (37.8%) were men, and 54 (37.8%) were women, respectively. 59 (54.5%) were geriatric, while 116 (47.9%) were adults. Additionally, the 119 patients diagnosed with CKD (66.1%) had a history of diabetes, hypertension, or both, while the 56 diagnosed with CKD (32.9%) had no history. When analyzed statistically, the result showed a p-value <0.05, which implies that patients with chronic kidney disease who also have a history of diabetes, hypertension, or even both show a significant relationship (Table 1).

Meanwhile, patients who do not use NSAIDs were divided into two groups: the case and the control. The aim is to determine the correlation between the use of NSAIDs and CKD incidence. More detailed data are presented in Table 2.

Furthermore, 140 CKD patients (60.3%) have no history of the use of NSAID, while 35 (29.7%) previously used NSAID. In this case, patients with GFR disorders assessed CKD with <60 ml/min per 1.73 m^2. In addition, the Chi-Square test result showed a p-value <0.001, which implies a significant relationship between the use of NSAIDs and GFR values. The parameters used to determine the strength of the relationship were the OR and 95% CI values. The OR value of 0.277 implies that the patients were 0.277 times more likely to lower GFRs that cause CKD than those who did not. However, the Odds Ratio value, which is less than 1, indicates a very small risk.

Figure 1 shows that in adult subjects with a history of diabetes and/or hypertension using NSAIDs, the probability of CKD

Table 1. Demographic profile and comorbidity in the patients of case and control group (n = 350) with analyzed Mann-Whitney test.

Characteristic		Group		Total	P Value	OR
		Case (n=175)	Control (n=175)			
Sex	Male	121 58.5%	86 41.5%	207 100%	<0.001*	2.319
	Female	54 37.8%	89 62.2%	143 100%		
Age	Geriatrics (>60 years old)	59 54.5%	49 45.4%	108 100%	0.247	1.308
	Adult (18-60 years old)	116 47.9%	126 52.1%	242 100%		
Comorbidity	DM and/or HT	119 66.1%	61 33.9%	180 100%	<0.001*	3.971
	No DM and HT	56 32.9%	114 67.1%	170 100%		
Total		175 50%	175 50%	350 100%		

*significant <0.05

Table 2. **NSAID use among patients in case and control group (n = 350) with analyzed Chi-squared Test.**

Characteristic		Group		Total	P Value	OR (95% CI)	Mean Rank
		Case	Control				
NSAIDs	NSAIDs used	35 29.7%	83 70.3%	118 100%	<0.001*	0.277 (0.172 to 0.445)	211.09
	No NSAIDs	140 60.3%	92 39.7%	232 100%			157.40
Total		175 50%	175 50%	350 100%			

*significant <0.05

Table 3. **Analysis of Naranjo Scale and Causality (n=25).**

NSAIDs Name	Patient	Naranjo	Causality
Meloxicam	9	1 Definite, 1 Probable, 7 Possible	1 Certain 5 Possible 2 Unlikely 1 Unclassified
Mefenamic acid	6	2 Probable, 4 Possible	4 Possible 1 Unlikely 1 Unclassified
Diclofenac sodium	2	1 Definite, 1 Probable	1 Certain 1 Probable
Etoricoxib	1	1 Probable	1 Possible
Celebrex	1	1 Probable	1Possible
Ketorolac	4	4 Possible	2 Unlikely 1 Unclassified 1 Unassesable
Herbal Medicine	2	1 Probable 1 Possible	1 Probable 1 Possible

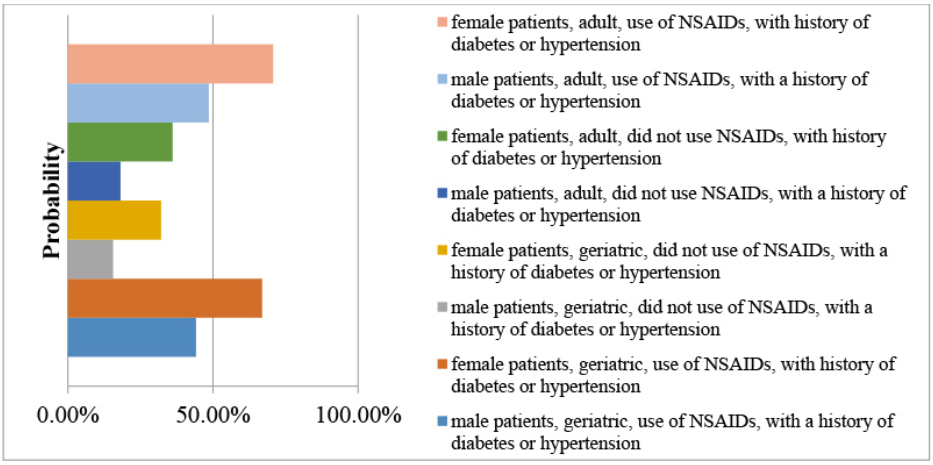

Figure 1. The probability of occurrence of CKD with analyzed Multivariate test.

increases to 48.55% and 70.72 in men and women, respectively.

Patients were interviewed based on the Naranjo algorithm and assessed using WHO causality, the result obtained from evaluating patients' data. On the other hand, Naranjo's score is the results obtained from interviewing the patients, and both were conducted to increase the accuracy of the research data. This data is shown in Table 3.

DISCUSSION

Risk factors in developing kidney disease are gender, diet, kidney and glomerular function, hemodynamic differences, and sexual hormonal effects.[9–11] age also significantly affects the increase or decrease of CKD incidence, which is strongly influenced by glomerular filtration rate (GFR) associated with diabetes and hypertension that triggers the progressive increase in the severity of CKD.[12] Other studies have shown that patients between 18 to 65 years are at high risk of decreasing GFR to <60 ml/min. The factors that increase the risk include the presence of cardiovascular disease and diabetes.[12,13] Additionally, the development of the disorder appears to be slow In geriatric patients. However, most of them have entered the dialysis stage.[2,7] Surprisingly, the value of the GFR tends to decline in adults, which is related to the influence of the disease and the patient's lifestyle. Furthermore, diabetes and other cardiovascular diseases are some of the factors that cause a decrease in GFR.[13,14]

Furthermore, considering the risk of using NSAIDs from the result of the Odds Ratio, which is less than 1 (0.277), it was confirmed that there was no relationship between the use of NSAIDs and CKD incidence in South Sulawesi. Additionally, the CKD events may have been caused by other factors such as the worsening of comorbid illnesses, diabetes, and hypertension. In this study, two patients with renal impairment were found due to the use of NSAIDs. The mechanism of inhibition of prostaglandins and prostacyclin by NSAIDs results in vasoconstriction with an unpredictable rate of events because of its non-specific nature, so NSAIDs may not always have a role and vasoconstriction of blood vessels in the kidney.

Meanwhile, an illustration was made to show the relationship between kidney disease disorder and other variables, such as gender and comorbidities. The results showed that women had a greater risk

of developing CKD than male subjects. Previous research mentioned that severity development is faster in men than women. However, female subjects might experience CKD earlier than males.[4,15] After linking and statistical calculations, women were more susceptible to CKD than men.

Interestingly, as shown in Figure 1, when men and women (adult subjects) with a history of diabetes and/or hypertension use NSAIDs, the probability increases to 48.55% and 70.72, respectively. This finding also suggests that women are at higher risk and more vulnerable to a decrease in GFR <60 mL/min than men when using NSAIDs.

Furthermore, the kidney is an organ with a widespread estrogen receptor and has a strong modulation effect on the complex and functional metabolic processes in the glomerulus and the tubule.[11] It may be explained by hormonal factors in women, resulting in a higher risk of CKD.

Identification Probability with Naranjo Scale and Causality

The result from the Naranjo algorithm showed that 2 NSAID users (1.69%) were identified to have adverse drug reactions in the form of CKD with a definite ADR category. Meanwhile, 6 NSAID users (5.08%) were identified in the probable ADR category. However, the causality of certain ADR categories is greatly influenced by certain factors, as shown in the statistical analysis table. These include sex and comorbidities with a history of using NSAIDs.

NSAIDs and Renal Relationship

Chronic Kidney Disease is a serious health problem globally, and its resuscitation has continued to increase in the past decades. Furthermore, the main factor influencing enhancement progressions in the global prevalence of CKD is the presence of comorbidities such as diabetes or hypertension. Furthermore, some NSAID drugs widely used by the public may affect kidney function.[16]

NSAIDs results in acute kidney injury (AKI) with various mechanism, accounting for 16% of used drugs in conjunction with renal impairment.[3,17] Also, PG inhibition mediated by NSAID explains many kidney complications, and it has an important role in maintaining normalcy in renal physiology. Furthermore, renal vasodilation is an essential PG effect in maintaining adequate kidney perfusion.[9,18,19] It is believed that the renal impairment caused by NSAIDs is due to prostaglandins' inhibition, which activates RAAS, leading to a decreased blood flow to the kidney reduced.[2,4] Additionally, patients with long-term use (> 3 months) or high doses (> 1 daily) tend to have a higher risk of CKD. It is in comparison with the use of NSAIDs <3 months and a small dose (1 daily).[10] In the type of reaction pharmacology, the side effects of CKD in using these NSAIDs are categorized as type D since it depends on the duration and doses used. Therefore, overdose with long-term use is not recommended, especially for geriatric patients. It is in line with Beers Criteria, which states that NSAIDs are not recommended for geriatric patients.[20]

The use of drugs that act on prostaglandin inhibition, specifically on COX-2, has a lower risk of causing vascular side effects compared to NSAIDs that act randomly on the cyclooxygenase cycle. It is related to the random inhibition of prostaglandins that will have an indirect effect, especially on the renin-angiotensin-aldosterone (RAAS) mechanism in maintaining glomerulotubular equilibrium.[16,19,21,22]

Providing information related to the use of painkillers, both benefits and disadvantages in therapy, is an absolute choice that health workers must make to avoid patient risks.[23,24] Furthermore, several studies have shown that there is a risk of CKD when using NSAIDs in some cases. It is evident from the result of this study, which showed that there is a risk of CKD associated with NSAIDs. It was proven with causality and Naranjo's assessment and the statistical test that showed a p-value<0.05. However, this does not imply that there is a relation between the use of NSAIDs and the incidence of CKD (odd ratio = 0.27), which means that the risk is small. Other factors that are more likely to cause CKD include gender and comorbidity.

Furthermore, the result showed that patients who use NSAIDs have no risk of having CKD. Therefore, the use of NSAIDs in the Makassar population has no relationship to CKD events.

This study was limited to retrospective data collection, so many variables were unlikely to interfere because they were based on patient memory. It would be very good if this research is continued into a prospective design.

CONCLUSION

Conclusively, there is no relation between the use of NSAIDs and CKD incidence in the population, which is reflected by the odds ratio of only 0.277 or below 1, indicating a low risk. Furthermore, it is evident from the results of WHO causality and the Naranjo algorithm that only 5 subjects are likely to experience the side effects of CKD due to NSAIDs. Therefore, the low degree of causality indicates that NSAIDs do not result in the side effects of CKD.

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ETHICAL CLEARANCE

Informed consent was obtained from all respondents before the start of the study, and this study has received ethical approval from The Committee of the Faculty of Medicine, Universitas Hasanuddin, Indonesia, with number 1626/H4.8.4.5.31/PP36-KOMETIK/2016.

CONFLICT OF INTERESTS

The author declares no conflict of interest in this research.

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AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript's preparation and approved the final version for publication.

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