Majalah Farmaseutik
ISSN-e: 2614-0064 | ISSN-p: 1410-590x
Volume 20(1) 2025: 30-36

Safety Evaluation of Oral NSAID Treatment on Blood Pressure in Osteoarthritis Patients: Preventive Study to Cardiovascular Events

Intan Adevia Rosnarita[1*], Muhammad Khudzaifi[1], Nindya Priswa[1]
[1] Pharmacy Faculty, Muhammadiyah University of Kudus
Corresponding author: Intan Adevia Rosnarita | Email: intanadevia@umkudus.ac.id
Submitted: 07-01-2025 *Revised: 17-02-2025* *Accepted: 19-02-2025*

ABSTRACT
Osteoarthritis (OA) is a degenerative joint disorder primarily affecting weight-bearing joints, causing pain, stiffness, and reduced mobility. Although there is no cure, symptom management focuses on pain relief and inflammation reduction, often through the use of nonsteroidal anti-inflammatory drugs (NSAIDs). However, NSAIDs are known to increase blood pressure, which poses concerns for long-term use, especially in patients with pre-existing cardiovascular risk factors. Given the chronic nature of OA and the common prescription of long-term NSAID therapy, it is important to assess their impact on blood pressure and cardiovascular health. This study aimed to evaluate the safety of oral NSAID therapy in terms of its effects on blood pressure in osteoarthritis patients at Dr. Moewardi Surakarta Regional General Hospital. An observational descriptive design was used with purposive sampling, analyzing data retrospectively from 35 OA patients receiving outpatient treatment for three months. The Wilcoxon signed-rank test was applied to assess changes in blood pressure, with statistical significance set at $p<0.05$. Results showed a significant increase in both systolic (11.3 ± 7.9 mmHg, $p<0.05$) and diastolic blood pressure (8.9 ± 7.0 mmHg, $p<0.05$) following NSAID use over the 3-month period. These findings highlight the need for careful monitoring of blood pressure in OA patients on long-term NSAID therapy, particularly those at higher cardiovascular risk. Long-term safety assessments are essential when considering NSAID treatment, and alternative therapeutic options should be considered for high-risk patients.
Keywords: *Osteoarthritis, NSAIDs, Blood Pressure*

INTRODUCTION
The American College of Rheumatology defines osteoarthritis (OA) as a degenerative joint disorder marked by the breakdown of cartilage, abnormal bone growth, and inflammation of the synovium. These changes result in symptoms such as pain, stiffness, swelling, and a reduction in normal joint function (Kolasinski et al., 2020). Osteoarthritis is a common degenerative condition closely linked to aging. In Central Java, the prevalence of osteoarthritis is approximately 6.78% among a population of 67,977 individuals (Riskesdas Central Java, 2018). At Dr. Moewardi Regional Public Hospital in Surakarta, osteoarthritis affects 70% of patients, with the majority being over the age of 40 (Nurrahman, 2018)

Pharmacological treatment recommendations for osteoarthritis patients, according to the American College of Rheumatology (ACR) in 2019, include oral NSAIDs (Non-Steroidal Anti-Inflammatory Drugs), topical NSAIDs, corticosteroid injections, paracetamol, tramadol, duloxetine, chondroitin, and topical capsaicin. A meta-analysis of clinical trials has shown a threefold increased risk of vascular diseases in patients using selective NSAIDs compared to those in the placebo group (Marsico et al., 2017). A study by Nussmeier et al. (2005) demonstrated an increased cardiovascular risk within 10 days of using selective NSAIDs. Another study by Levesque et al. (2006) showed an increased risk of myocardial infarction in elderly patients using NSAIDs for 9 days.

Currently, there is no cure for osteoarthritis, so treatment focuses on symptom management, particularly pain and inflammation, with long-term use of NSAIDs being a common approach. Therefore, it is crucial to evaluate the side effects, such as elevated blood pressure due to oral NSAID use, in osteoarthritis therapy, considering the potential cardiovascular risks. This evaluation may serve as a consideration for prescribing oral NSAIDs in osteoarthritis patients and to assess the safety

of oral NSAID analgesic therapy in relation to its side effects on blood pressure in osteoarthritis patients at Dr. Moewardi Regional Public Hospital, Surakarta.

METHODS

Research design, Location, and Duration of study

In this descriptive observational study, researchers aimed to analyze the effects of oral NSAID therapy on blood pressure in osteoarthritis patients. The data collection was retrospective, meaning the researchers did not intervene or manipulate the participants but rather analyzed previously collected data from existing medical records. The study utilized secondary data, which were obtained from the medical records of patients diagnosed with osteoarthritis at Dr. Moewardi Regional Public Hospital in Surakarta. This approach allows for the assessment of historical patient information without the need for new data collection through direct patient interaction. The observation involved a systematic review of relevant clinical data, including patient demographics, medical history, and recorded changes in blood pressure during the treatment period.

The study period was from 2023 to 2024, with 54 osteoarthritis patients being treated during this 3-month timeframe. Out of this population, a sample size of 35 patients was selected based on statistical power analysis or other criteria to ensure that the sample was representative of the population while maintaining statistical validity. The sample size was chosen to achieve a balance between feasibility and the ability to detect significant findings related to the research question. By using retrospective data, the study aimed to assess the safety of NSAID therapy in terms of its impact on blood pressure in real-world clinical settings, providing valuable insights into the risks associated with prolonged use of NSAIDs in osteoarthritis patients.

Statistical Analysis

Quantitative data included blood pressure measurements for each NSAID used by osteoarthritis patients. The data were analyzed with SPSS 21 at a 95% confidence level ($\alpha = 0.05$). Normality was tested using Kolmogorov-Smirnov (for $n > 50$) or Shapiro-Wilk (for $n < 50$). Paired t-tests were used for normally distributed data, and Wilcoxon tests for non-normal data to compare pre- and post-NSAID blood pressure. A p-value < 0.05 indicated a significant difference. Blood pressure changes across NSAID groups were analyzed using one-way ANOVA or Kruskal-Wallis tests, with $p < 0.05$ indicating significant differences.

RESULTS AND DISCUSSION

The gender distribution of the 35 patients in this study indicated a predominance of female participants, with 31 patients (88.6%), while 4 patients (11.4%) were male. The detailed gender data can be found in Table 4.1. This finding is in line with the study by Minratno et al. (2022), which reported a higher incidence of osteoarthritis in women compared to men, with 34 out of 43 subjects being female. The significant decline in estrogen levels following menopause leads to a reduction in chondrocyte synthesis within the bone matrix, which contributes to the increased prevalence of osteoarthritis in women (Sangadah & Kartawidjaja, 2020).

The age range of osteoarthritis patients in this study was between 30 and 65 years. This age range was chosen because, around the age of 30, there is a notable decrease in bone density and a reduction in proteoglycan size, which causes a decline in chondroitin sulfate and an increase in keratan sulfate, resulting in reduced cartilage flexibility (Fadhilah, 2016). The upper age limit of 65 was set to minimize bias due to age-related decline in organ function.

NSAID Therapy Safety Analysis

Patterns of Oral NSAID Therapy in Osteoarthritis Patients

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for a variety of inflammatory conditions due to their ability to alleviate pain and reduce inflammation. These conditions include osteoarthritis, rheumatoid arthritis, axial spondyloarthritis, migraines, and both acute and chronic mild to moderate pain (Kolasinski et al., 2020; NICE, 2013). NSAIDs are particularly significant in the management of osteoarthritis, a condition that primarily affects the joints, leading to chronic pain and functional impairment. The use of NSAIDs, when prescribed for long durations,

Table I. Characteristics of Patients Based on Gender

Gender	Amount	Percentage (%)
Laki-laki	4	11,4
Perempuan	31	88,6
Total	35	100

is categorized as chronic NSAID therapy, which is generally defined as the intake of NSAIDs more than three times per week for a period exceeding three months. Chronic use of NSAIDs is a prevalent practice in managing conditions like osteoarthritis, with recent studies indicating that more than 29 million adults in the United States engage in regular, long-term NSAID use (Huang et al., 2023). This widespread usage underscores the necessity for ongoing evaluation of the safety profile of NSAIDs, particularly their impact on various physiological systems.

The pharmacological action of NSAIDs is primarily mediated through the inhibition of cyclooxygenase (COX) enzymes, which play a pivotal role in the arachidonic acid metabolic pathway. This pathway is responsible for the conversion of arachidonic acid into a range of bioactive lipids, including prostaglandins and thromboxanes, which are key mediators of inflammation, pain, and fever. By inhibiting COX enzymes, NSAIDs reduce the production of these inflammatory mediators, thereby providing symptomatic relief for conditions like osteoarthritis. However, the selective inhibition of COX enzymes is critical to understanding the varied side-effect profiles of different NSAIDs.

There are two main isoforms of the COX enzyme: COX-1 and COX-2. COX-1 is constitutively expressed in most tissues and is involved in the maintenance of normal physiological functions, such as gastric mucosal protection and platelet aggregation. In contrast, COX-2 is inducible and primarily responsible for the production of prostaglandins at sites of inflammation. The structural differences between the COX-1 and COX-2 isoforms, particularly in the substrate binding channel, allow for selective inhibition by specific NSAIDs. Some NSAIDs are designed to selectively inhibit COX-2, thereby minimizing gastrointestinal side effects associated with COX-1 inhibition, which can lead to ulcers and bleeding (White & Cruz, 2011). This selectivity is crucial for optimizing the therapeutic benefits of NSAIDs while minimizing adverse outcomes, especially with long-term use in chronic conditions like osteoarthritis.

Given the widespread and prolonged use of NSAIDs, particularly in older populations who are at increased risk for cardiovascular and gastrointestinal complications, understanding the molecular mechanisms of action, as well as the selective inhibition profiles of these drugs, is essential for ensuring their safe use in clinical practice.

Based on the data in Table II, the oral NSAID therapies administered to osteoarthritis patients at Dr. Moewardi Regional General Hospital include diclofenac sodium, celecoxib, and meloxicam. These NSAIDs have distinct mechanisms of action, particularly in terms of their selectivity for inhibiting cyclooxygenase (COX) enzymes.

Diclofenac sodium and meloxicam are classified as semi-selective NSAIDs, meaning they primarily increase the affinity for COX-2 inhibition while still retaining some activity against COX-1. In contrast, celecoxib is a selective NSAID, specifically inhibiting COX-2 activity (Zahra & Carolia, 2017).

The Effect of NSAID Use on Blood Pressure in Osteoarthritis Patients

This study evaluated blood pressure changes in 35 osteoarthritis patients following NSAID therapy. The analysis involved comparing blood pressure measurements before and after a 3-month period of NSAID treatment. Additionally, the study examined differences in blood pressure changes among patients using different NSAID therapies, specifically diclofenac sodium, celecoxib, and meloxicam.

The Wilcoxon test results for assessing the difference in blood pressure before and after 3 months of NSAID therapy showed statistically significant changes in both systolic and diastolic blood pressure among osteoarthritis patients, with a p-value of 0.000 ($p < 0.05$). This indicates that oral NSAID therapy in osteoarthritis patients significantly affects blood pressure, leading to an increase

Table II. Patterns of Oral NSAID Therapy Usage

NSAID	Quantity	Percentage (%)
Celecoxib	13	37,1
Natrium Diklofenak	17	48,6
Meloxicam	5	14,3
Total	35	100

Table III. Wilcoxon Test Results for Systolic Blood Pressure Before and After NSAID Use

Sistolik Post – Sistolik Pre	
Z	-4,901
Asymp Sig.(2-tailed)	,000

a. Wilcoxon signed Ranks Test; b. Based on negative ranks

Table IV. Results of the Wilcoxon Test on Diastolic Blood Pressure Before and After Using NSAIDs."

Sistolik Post – Sistolik Pre	
Z	-1,862
Asymp Sig.(2-tailed)	,000

in systolic blood pressure (11.3 ± 7.9 mmHg) and diastolic blood pressure (8.9 ± 7.0 mmHg) over the 3-month treatment period.

The results of this study indicate that osteoarthritis patients at Dr. Moewardi Regional General Hospital in Surakarta experienced an average increase of 11.3 mmHg in systolic blood pressure and 8.9 mmHg in diastolic blood pressure after 3 months of NSAID therapy. These findings are consistent with a meta-analysis conducted by Snowden & Nelson (2011), which demonstrated an increase in systolic blood pressure by 14.3 mmHg and diastolic blood pressure by 2.3 mmHg after 4 weeks of NSAID use. Additionally, the findings are aligned with the MEDAL (Multinational Etoricoxib and Diclofenac Arthritis Long-term) program, which evaluated the long-term use of NSAIDs. This program reported an increase in blood pressure among patients with rheumatoid arthritis and osteoarthritis who were treated with etoricoxib or diclofenac sodium (Krum et al., 2009).

The increase in blood pressure caused by NSAIDs is due to the metabolism of arachidonic acid into prostaglandins and thromboxanes, with the enzymes involved being known as key contributors to the production of prostacyclin (Prostaglandin I2), which has cardioprotective effects. When the metabolism of arachidonic acid is inhibited by NSAIDs, prostacyclin plays a significant role in the pathophysiology of cardiovascular disorders associated with NSAIDs (Zahra & Carolia, 2017). Thus, it is possible that long-term use of NSAIDs in osteoarthritis patients may increase the risk of higher blood pressure."

The results of the comparison analysis of diastolic blood pressure using the Kruskal-Wallis test revealed no statistically significant difference among users of sodium diclofenac, celecoxib, and meloxicam, with a p-value of 0.201 ($p>0.05$). Similarly, the comparison of blood pressure differences among the three therapeutic groups indicated no significant disparity. However, from a theoretical perspective, celecoxib, a selective COX-2 inhibitor NSAID, is associated with a higher risk of elevating blood pressure compared to sodium diclofenac and meloxicam, which are semi-selective NSAIDs. This effect is attributed to COX-2 inhibition, which reduces prostaglandin E2 synthesis, thereby decreasing daily sodium excretion by 30-50% (Zahra & Carolia, 2017).

The American Heart Association (AHA) scientific statement recommends using selective COX-2 NSAIDs at the lowest effective dose to minimize the risk of cardiovascular events until more extensive long-term safety data becomes available. Furthermore, the duration of NSAID therapy should be individualized based on the patient's clinical profile. If no therapeutic benefit is observed after three weeks, it is advisable to consider alternative agents (Magni et al., 2021). Consequently, the management of musculoskeletal symptoms in patients with cardiovascular disease should adopt a stepwise approach, prioritizing agents with the lowest cardiovascular risk, such as paracetamol,

Table V. Results of the One-Way ANOVA Test on the Difference in Systolic Blood Pressure Among Users of Sodium Diclofenac, Celecoxib, and Meloxicam

NSAID	n	Mean ± SD	*p-value*
Natrium Diklofenak	17	13,6 ± 7,3	
Celecoxib	13	10,7 ± 8,5	0,093
Meloxicam	5	5,0 ± 5,0	

Table VI. Results of the Kruskal-Wallis Test on the Difference in Diastolic Blood Pressure Among Users of Sodium Diclofenac, Celecoxib, and Meloxicam

	The difference in diastolic blood pressure
Chi Square	3,206
df	2
Asymp Sig.(2-tailed)	,201

a. Kruskal Wallis Test; b. Grouping Variable: NSAID types

aspirin, tramadol, and non-acetylated salicylates. Second-line therapy includes non-selective NSAIDs, with selective COX-2 inhibitors recommended as third-line options (Patrono & Baigent, 2014).

Currently, there is no definitive cure for osteoarthritis. The management of osteoarthritis primarily aims to control and alleviate pain, requiring long-term therapeutic interventions. However, prolonged use of NSAIDs, while effective in symptom management, can lead to elevated blood pressure, thereby increasing the risk of developing hypertension. Therefore, for osteoarthritis patients who have an elevated cardiovascular risk, careful consideration must be given when selecting the most appropriate treatment regimen to prevent the exacerbation of blood pressure elevation and associated cardiovascular complications.

NSAIDs can induce hypertension through several mechanisms, including the inhibition of cyclooxygenase (COX) enzymes, which disrupts the balance of prostaglandins that play a key role in regulating vascular tone and sodium excretion. This disruption may lead to sodium retention, fluid accumulation, and vasoconstriction, all of which can elevate blood pressure. Chronic use of NSAIDs, particularly in higher doses or over extended periods, can thus contribute to the development or worsening of hypertension, a risk factor for cardiovascular diseases such as heart attack, stroke, and heart failure.

As a result, the use of NSAIDs in osteoarthritis patients requires careful consideration, particularly in those with existing cardiovascular risk factors. Patients with a history of hypertension, diabetes, or other cardiovascular conditions may be particularly vulnerable to the blood pressure-raising effects of NSAIDs. In such cases, it is crucial to balance the benefits of pain relief with the potential risks of exacerbating cardiovascular conditions. Healthcare providers must exercise caution when selecting an appropriate therapeutic regimen for these patients, ensuring that they choose medications that do not compromise cardiovascular health. Alternative pain management strategies, such as the use of acetaminophen, opioid analgesics (for short-term use), or topical treatments, may be considered to minimize the risk of elevating blood pressure. Additionally, regular monitoring of blood pressure should be conducted in patients on long-term NSAID therapy, and adjustments to the treatment plan should be made as necessary to mitigate the risks of hypertension.

NSAIDs also exert antagonistic effects on certain antihypertensive classes, specifically ACE inhibitors (Angiotensin Converting Enzyme Inhibitors) and ARBs (Angiotensin Receptor Blockers). In contrast, calcium channel blockers (CCBs) do not interfere with the effectiveness of NSAIDs and can effectively control blood pressure in patients with a history of hypertension who are undergoing NSAID therapy. In osteoarthritis patients with a history of cardiovascular disease, NSAID therapy may be replaced with alternatives such as paracetamol or short-term narcotics (Imananta & Sulistiyaningsih, 2018). Additionally, patient education on non-pharmacological therapies for osteoarthritis, as well as proper medication usage, is essential to optimize treatment outcomes and minimize unwanted side effects.

SUMMARY

The use of NSAID therapy in osteoarthritis patients for a period of 3 months results in a significant increase in both systolic and diastolic blood pressure. Therefore, long-term safety considerations must be taken into account when selecting osteoarthritis therapy, particularly in patients with cardiovascular disease.

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