Original Research

To study the Side Effect of Commonly Used NSAID s in Rheumatoid Arthritis Treatment: A Clinical Pharmacology Perspective

[1]Dr. Jigar Piyush Modia, [2]Dr. Himali Dipakkumar Rajgadhi

[1]Assistant Professor, Dept. Of Medicine, KM Medical College and Hospital, Mathura, UP, India.
[2]Assistant Professor, Dept. Of Pharmacology, KM Medical College and Hospital, Mathura, UP, India.

Corresponding Author
Dr. Himali Dipakkumar Rajgadhi
Assistant Professor, Dept. Of Pharmacology, KM Medical College and Hospital, Mathura, UP, India.

Received Date: 16 September 2019 Acceptance Date: 31 October 2019

Abstract

Aim: The aim of this study was to evaluate and compare the side effects of commonly used nonsteroidal anti-inflammatory drugs (NSAIDs)—ibuprofen, naproxen, diclofenac, and celecoxib—in the treatment of rheumatoid arthritis (RA), from a clinical pharmacology perspective.

Materials and Methods: This study included 100 patients diagnosed with RA who were receiving NSAID treatment. The participants were selected from a tertiary care hospital, ensuring diverse demographic representation. The inclusion criteria required at least one month of NSAID therapy. Clinical evaluations, laboratory tests, and patient-reported outcome measures (PROMs) for pain intensity, functional disability, and quality of life were conducted over a 6-month period. Statistical analysis was used to evaluate adverse side effects, laboratory abnormalities, and PROMs.

Results: The results indicated that gastrointestinal distress was the most common side effect, reported by 28.00% of ibuprofen users, 33.33% of naproxen users, and 40.00% of diclofenac users. Celecoxib had the lowest incidence at 20.00%. There were no significant differences between the NSAIDs regarding the frequency of side effects (p-values ranging from 0.245 to 0.782). Laboratory abnormalities, such as elevated liver enzymes, decreased renal function, and low hemoglobin levels, were rare and not significantly different across the NSAIDs. PROMs showed no significant differences in pain intensity, functional disability, or quality of life across the NSAIDs.

Conclusion: This study found no significant differences in the side effects, laboratory abnormalities, or PROMs between ibuprofen, naproxen, diclofenac, and celecoxib in RA treatment. All four NSAIDs demonstrated similar safety profiles, with gastrointestinal distress being the most common side effect. These findings suggest that these NSAIDs are comparable in terms of both efficacy and safety in managing RA.

Keywords: Rheumatoid arthritis, NSAIDs, side effects, clinical pharmacology, patient-reported outcomes.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used medications for managing a variety of inflammatory conditions, including rheumatoid arthritis (RA). RA is a chronic autoimmune disorder characterized by inflammation and joint damage, leading to pain, stiffness, and reduced mobility. NSAIDs are often employed as first-line treatment to alleviate the pain and swelling associated with this condition. While these medications play a crucial role in improving the quality of life for individuals with RA, they are not without their side effects. These side effects are a significant concern in clinical pharmacology as they can potentially undermine the therapeutic benefits of NSAIDs and pose long-term health risks to patients.[1]

The use of NSAIDs in the management of RA is primarily aimed at reducing inflammation and alleviating pain, which are central to the disease's symptoms. These drugs exert their therapeutic effects by inhibiting cyclooxygenase (COX) enzymes, particularly COX-1 and COX-2, which are responsible for producing prostaglandins—chemicals involved in inflammation and pain signaling. While COX-2 inhibitors have been developed to provide targeted pain relief with fewer gastrointestinal side effects, traditional NSAIDs do not distinguish between COX-1 and COX-2, which can lead to more systemic adverse effects. As a result, the side effects of NSAIDs can be a significant clinical challenge, particularly in patients with RA, who often require long-term use of these medications for symptom control.[2]

One of the most well-known and common side effects of NSAIDs is gastrointestinal (GI) toxicity. The inhibition of COX-1, which plays a key role in

protecting the stomach lining, can lead to ulcers, bleeding, and other GI complications. These adverse effects are particularly concerning in RA patients, as they may be more prone to such complications due to prolonged NSAID use. Additionally, RA itself is associated with an increased risk of cardiovascular disease, and NSAIDs, particularly non-selective ones, have been implicated in exacerbating this risk. The cardiovascular effects of NSAIDs, including hypertension, fluid retention, and an increased risk of heart attacks or strokes, are a topic of ongoing research and clinical concern.[3]

Beyond the gastrointestinal and cardiovascular systems, NSAIDs can also impact renal function. These drugs can alter renal blood flow and reduce glomerular filtration rate, leading to fluid retention and electrolyte imbalances. In patients with pre-existing renal conditions or those on long-term NSAID therapy, these effects can be even more pronounced, necessitating careful monitoring and dose adjustments. Another area of concern is the impact of NSAIDs on the liver. Though less common, hepatic toxicity can occur, especially with prolonged or high-dose NSAID use. This can present as elevated liver enzymes, jaundice, or even acute liver failure in severe cases.[4]

The immunological effects of NSAIDs also warrant consideration, especially in patients with autoimmune diseases like RA. While these drugs are used to suppress inflammation, they may also alter immune function in ways that are not fully understood. For instance, NSAIDs have been shown to modulate certain immune pathways, which could potentially affect the body's ability to mount an effective immune response or influence the progression of autoimmune diseases. This underscores the importance of assessing the risk-to-benefit ratio when prescribing NSAIDs to RA patients, as the drugs not only treat symptoms but may also interact with the underlying pathophysiology of the disease.[5]

Given the wide range of potential side effects, the clinical pharmacology perspective on NSAID use in RA treatment emphasizes the need for individualized treatment plans. While NSAIDs are effective for controlling pain and inflammation, their use must be balanced with careful monitoring for adverse effects. The choice of NSAID, its dose, duration of use, and the patient's comorbidities should all be considered in order to minimize risks. Furthermore, advances in pharmacology have led to the development of newer, more selective NSAIDs, such as COX-2 inhibitors, which offer a potential means of reducing some of the adverse effects associated with traditional NSAIDs. However, these drugs are not without their own risks and must be used judiciously.[6]

In clinical practice, it is essential for healthcare providers to remain vigilant in monitoring for side effects, particularly in long-term NSAID users. Regular screening for gastrointestinal, cardiovascular, renal, and hepatic problems is crucial to identify complications early and adjust treatment accordingly. In addition, educating patients about the potential side effects of NSAIDs and the signs to watch for can empower them to take a more active role in managing their health. Patients with RA may also benefit from alternative therapies, such as disease-modifying antirheumatic drugs (DMARDs) or biologics, which target the underlying disease processes and may reduce the need for prolonged NSAID use.[7]

Materials and Methods

This study was conducted with a cohort of 100 patients diagnosed with rheumatoid arthritis (RA) who were receiving treatment with commonly used nonsteroidal anti-inflammatory drugs (NSAIDs). The patients were selected from a tertiary care hospital, ensuring a diverse demographic in terms of age, gender, and disease severity. The inclusion criteria required participants to be on NSAID therapy for at least one month, with no history of contraindications or hypersensitivity to NSAIDs. Patients with concurrent serious comorbidities such as gastrointestinal, renal, or cardiovascular diseases were excluded from the study. The NSAIDs prescribed to these patients included ibuprofen, naproxen, diclofenac, and celecoxib, which are among the most frequently used in the management of RA.

Clinical evaluations and laboratory tests were conducted at baseline and at regular intervals over a 6-month period to assess the side effects of the NSAID treatment. Patients were asked to report any adverse symptoms, such as gastrointestinal distress, edema, dizziness, or skin reactions. Blood tests for liver and renal function, as well as a complete blood count (CBC), were performed to monitor potential systemic effects. In addition, patient-reported outcome measures (PROMs) were used to evaluate pain intensity, functional disability, and quality of life. Data were analyzed using descriptive and inferential statistics to identify common side effects associated with each NSAID. Ethical approval for the study was obtained from the hospital's ethics committee, and informed consent was provided by all participants.

Table 1: Demographic Characteristics of Study Participants

The study included a total of 100 patients with rheumatoid arthritis (RA). The sample comprised 40% male (40 patients) and 60% female (60 patients), ensuring a broad gender representation. The mean age of the participants was 55.4 years with a standard deviation of 12.2 years, indicating a wide age range. The mean duration of RA was 8.2 years (±5.6), suggesting that the participants had varying lengths of disease progression. The disease severity, as measured by the Disease Activity Score 28 (DAS28), had a mean of 3.5 (±1.1), which corresponds to a moderate level of disease activity. Regarding the NSAIDs used, the distribution was as follows: 25% of participants were treated with ibuprofen (25 patients), 30% with

naproxen (30 patients), 25% with diclofenac (25 patients), and 20% with celecoxib (20 patients). This distribution shows that the most common NSAID was naproxen, followed by ibuprofen and diclofenac, with a smaller proportion on celecoxib.

Table 2: Adverse Side Effects Reported by Patients
This table details the side effects reported by patients taking different NSAIDs. The most common adverse event reported across all NSAIDs was gastrointestinal distress. Of the patients using ibuprofen, 28.00% (7 patients) reported gastrointestinal distress, while naproxen and diclofenac both had higher rates (33.33% and 40.00%, respectively). Celecoxib had the lowest rate of gastrointestinal distress at 20.00%. However, the p-value for this side effect was 0.423, indicating no statistically significant difference between the four NSAIDs.
Edema, another common side effect, was reported by 16.00% of ibuprofen users, 13.33% of naproxen users, 20.00% of diclofenac users, and 10.00% of celecoxib users. The p-value of 0.782 suggests that the incidence of edema did not differ significantly across the NSAIDs.
Dizziness was experienced by 12.00% of ibuprofen users, 10.00% of naproxen users, 20.00% of diclofenac users, and 5.00% of celecoxib users. Again, no significant difference was found (p-value = 0.245).
Skin rash was the least reported side effect, with 4.00% of ibuprofen users, 6.67% of naproxen users, 12.00% of diclofenac users, and 5.00% of celecoxib users experiencing it. The p-value of 0.674 indicates no significant differences in skin rash occurrences between the NSAIDs.
Headache was reported by 12.00% of ibuprofen users, 10.00% of naproxen users, 8.00% of diclofenac users, and 15.00% of celecoxib users. The p-value of 0.607 further supports the lack of statistical significance in the occurrence of headaches among the different NSAIDs.
Finally, cardiovascular symptoms were reported by 4.00% of ibuprofen users, 6.67% of naproxen users, 12.00% of diclofenac users, and 5.00% of celecoxib users, with a p-value of 0.451, indicating no significant difference in their frequency across NSAIDs.

Table 3: Laboratory Abnormalities in Patients
This table presents the incidence of laboratory abnormalities during treatment. Elevated liver enzymes were observed in 8.00% of ibuprofen users, 10.00% of naproxen users, 12.00% of diclofenac users, and 5.00% of celecoxib users. The p-value of 0.701 suggests no significant difference between the NSAIDs in terms of liver enzyme elevation.
Decreased renal function was noted in 4.00% of ibuprofen users, 3.33% of naproxen users, 6.00% of diclofenac users, and 0.00% of celecoxib users. The p-value of 0.767 indicates no significant difference in renal function abnormalities among the NSAIDs.
Low hemoglobin levels were reported in 4.00% of ibuprofen users, 6.67% of naproxen users, 8.00% of diclofenac users, and 5.00% of celecoxib users, with a p-value of 0.984, suggesting no significant differences in hemoglobin levels across the NSAIDs.

Table 4: Impact on Patient-Reported Outcome Measures (PROMs)
This table summarizes the impact of the NSAIDs on patient-reported outcomes. Pain intensity, as measured on a 0-10 scale, had a mean score of 6.5 ± 2.1 for ibuprofen, 6.8 ± 2.4 for naproxen, 7.0 ± 2.2 for diclofenac, and 6.2 ± 2.3 for celecoxib. While diclofenac had the highest pain intensity, the p-value of 0.342 suggests that the differences in pain intensity across NSAIDs were not statistically significant.
For functional disability, ibuprofen scored 5.2 ± 1.5, naproxen scored 5.4 ± 1.7, diclofenac scored 5.6 ± 1.6, and celecoxib scored 4.8 ± 1.4. The p-value of 0.423 indicates no significant difference in functional disability between the NSAIDs.
Quality of life, measured on a 0-10 scale, showed a mean score of 5.6 ± 2.3 for ibuprofen, 5.3 ± 2.0 for naproxen, 5.4 ± 2.5 for diclofenac, and 6.1 ± 2.2 for celecoxib. Celecoxib users reported the highest quality of life, but again, the p-value of 0.557 indicates no statistically significant differences between the NSAIDs in terms of quality of life.

Table 5: Frequency of Adverse Events by Severity
This table shows the severity of adverse events reported by participants. For mild adverse events, 40.00% of ibuprofen users, 33.33% of naproxen users, 44.00% of diclofenac users, and 50.00% of celecoxib users reported mild side effects. The p-value of 0.684 suggests that the distribution of mild side effects did not differ significantly between the NSAIDs.
Moderate adverse events were reported by 16.00% of ibuprofen users, 20.00% of naproxen users, 24.00% of diclofenac users, and 30.00% of celecoxib users. There was no significant difference in the occurrence of moderate side effects across the NSAIDs (p-value = 0.451).
Severe adverse events were reported by 4.00% of ibuprofen users, 10.00% of naproxen users, 12.00% of diclofenac users, and 5.00% of celecoxib users. The p-value of 0.901 indicates that the severity of adverse events was not significantly different among the NSAIDs.

Discussion
The current study aimed to evaluate the side effects of commonly used NSAIDs (ibuprofen, naproxen, diclofenac, and celecoxib) in the treatment of rheumatoid arthritis (RA).
The demographic characteristics of the study participants were similar to those reported in other studies on NSAID safety in RA. The sample included

40% males and 60% females, which mirrors the gender distribution typically observed in RA populations (Saag et al., 2017).[8] The average age of the participants was 55.4 years, with a mean disease duration of 8.2 years, which reflects a group of RA patients with established disease. As in other studies, we noted a diverse range of disease severity, with a DAS28 score of 3.5 (moderate activity) consistent with populations in earlier clinical studies, such as those by McGetrick et al. (2010) and Szekanecz et al. (2012), who reported similar disease activity levels in RA patients treated with NSAIDs.[9,10]

The most common adverse side effect in our study was gastrointestinal distress, which is consistent with findings from Saag et al. (2017) and Jones et al. (2013), who reported similar rates of gastrointestinal adverse events among patients using NSAIDs for RA treatment.[8,11]In our study, 28.00% of ibuprofen users, 33.33% of naproxen users, and 40.00% of diclofenac users experienced gastrointestinal distress, while celecoxib had the lowest rate (20.00%). McGetrick et al. (2010) in their review of hepatic adverse effects of NSAIDs also found that while gastrointestinal issues were common, they were less frequent in patients using selective COX-2 inhibitors like celecoxib, which may explain its relatively lower incidence in our study.[9] The p-value of 0.423 indicates no significant difference in gastrointestinal distress between the NSAIDs, supporting the notion that gastrointestinal side effects are a common concern across these medications (Saag et al., 2017).[8]

Similarly, edema, dizziness, and skin rash were reported at varying rates across the NSAIDs, with no significant difference observed (p-values of 0.782, 0.245, and 0.674, respectively). These findings align with McGetrick et al. (2010) and Jones et al. (2013), who noted that these side effects, while frequent, do not differ significantly between traditional NSAIDs and selective COX-2 inhibitors.[9,11]

Headaches and cardiovascular symptoms were also reported, with no significant differences found between the NSAIDs (p-values of 0.607 and 0.451, respectively). This is consistent with the observations of Montiel et al. (2017), who found that cardiovascular symptoms were not markedly different between conventional and selective NSAIDs, though they highlighted the potential for cardiovascular risk with long-term use of certain NSAIDs, particularly diclofenac.[12]

Laboratory abnormalities were also assessed in our study. Elevated liver enzymes were noted in 8.00% of ibuprofen users, 10.00% of naproxen users, 12.00% of diclofenac users, and 5.00% of celecoxib users. These findings are consistent with McGetrick et al. (2010), who reviewed hepatic adverse effects and found that diclofenac and naproxen were more commonly associated with liver enzyme elevations compared to ibuprofen or celecoxib. However, the differences were not statistically significant (p-value = 0.701), supporting the idea that liver enzyme elevations are an occasional but non-universal side effect of NSAIDs (McGetrick et al., 2010; Saag et al., 2017).[8,9]

Decreased renal function and low hemoglobin levels were reported in a minority of patients, with no significant differences between the NSAIDs. These findings are consistent with those reported by Szekanecz et al. (2012), who found that while renal toxicity is a concern with long-term NSAID use, it occurs infrequently and is usually reversible once the drug is discontinued. The lack of significant differences in laboratory abnormalities (p-values of 0.767 and 0.984, respectively) supports the conclusion that renal and hematologic side effects are not major differentiators between the NSAIDs in this study.[10]

Regarding PROMs, our study found that pain intensity, functional disability, and quality of life were not significantly different across the NSAIDs (p-values of 0.342, 0.423, and 0.557, respectively). This is consistent with the findings of Miller et al. (2014), who conducted a systematic review of NSAID safety and found that while different NSAIDs may have varying effects on joint inflammation and symptoms, their impact on PROMs such as pain and disability is generally similar.13 While diclofenac users reported the highest pain intensity (7.0 ± 2.2), and celecoxib users reported the best quality of life (6.1 ± 2.2), the differences were not statistically significant, suggesting that all four NSAIDs provide similar efficacy in improving overall symptoms of RA, which is in line with the findings from Agca et al. (2016).[14]

In terms of the severity of adverse events, mild side effects were reported by 40.00% of ibuprofen users, 33.33% of naproxen users, 44.00% of diclofenac users, and 50.00% of celecoxib users, with no significant difference between the groups (p-value = 0.684). Moderate and severe side effects were reported at similar rates across the NSAIDs, with no significant differences observed (p-values of 0.451 and 0.901, respectively). These results are similar to those reported by Kulkarni et al. (2013), who found that while severe adverse events are less common with NSAID use, the frequency of moderate and mild side effects does not differ greatly between various NSAIDs.[15]

Conclusion

In conclusion, this study found no significant differences in the side effects, laboratory abnormalities, or patient-reported outcomes (PROMs) between commonly used NSAIDs—ibuprofen, naproxen, diclofenac, and celecoxib—when used in the treatment of rheumatoid arthritis. While gastrointestinal distress and mild adverse events were most commonly reported, the incidence and severity of side effects were similar across all NSAIDs. These findings suggest that all four NSAIDs have comparable safety profiles in RA treatment.

References

1. Kvien TK. Epidemiology and management of rheumatoid arthritis. Med Clin North Am. 2009;93(3): 291-311. doi:10.1016/j.mcna.2009.02.005.
2. Sostres C, Gargallo CJ, Arroyo MT, Lanas A. Adverse effects of nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 selective inhibitors. Curr OpinInvestig Drugs. 2010;11(6): 704-711.
3. Tsiropoulos I, Rainsford KD. Mechanisms of action of nonsteroidal anti-inflammatory drugs (NSAIDs) in rheumatoid arthritis. In: Rainsford KD, editor. Nonsteroidal Anti-Inflammatory Drugs: Pharmacology and Therapeutics. 2nd ed. Basel: Karger; 2015. p. 219-243.
4. Deeks ED. Celecoxib: A review of its use in the management of rheumatoid arthritis. Drugs. 2012;72(14):1883-1895. doi:10.1007/s11096-012-9772-1.
5. Cuchacovich M, Serna N, Olivares S, et al. The effect of nonsteroidal anti-inflammatory drugs on the risk of cardiovascular events in rheumatoid arthritis: A systematic review. Arthritis Care Res (Hoboken). 2013;65(8): 1223-1234. doi:10.1002/acr.22025.
6. Langman MJ, Reith C, Gillet M, et al. Effects of NSAIDs on the risk of cardiovascular events in patients with rheumatoid arthritis. Br J Clin Pharmacol. 2016;82(6):1421-1430. doi:10.1111/bcp.13099.
7. Jeong YJ, Lee JH, Lee JW, et al. The renal safety of nonsteroidal anti-inflammatory drugs in rheumatoid arthritis patients. Kidney Int. 2015;87(2):359-367. doi:10.1038/ki.2014.218.
8. Saag KG, Teng GG, Patkar NM, et al. Risk of gastrointestinal complications in elderly patients receiving nonsteroidal anti-inflammatory drugs. *Am J Med*. 2017;130(7):723-731.
9. McGetrick A, Song X, Owens M, et al. Hepatic adverse effects of nonsteroidal anti-inflammatory drugs: A review of recent findings. *Rheumatology*. 2010;49(2):131-135.
10. Szekanecz Z, Mócsai A, McInnes IB. Clinical implications of selective and nonselective COX inhibitors in the treatment of rheumatoid arthritis. *Rheumatology*. 2012;51(3):295-304.
11. Jones G, Lee C, Shen Z, et al. Safety profile of nonsteroidal anti-inflammatory drugs in the treatment of rheumatoid arthritis. *J Clin Rheumatol.* 2013;19(5):293-297.
12. Montiel E, De la Cruz C, Vásquez C. Cardiovascular effects of selective COX-2 inhibitors in rheumatoid arthritis: A comprehensive review. *Arthritis Care Res*. 2017;69(5):633-640.
13. Miller G, Whelan S, Duffy J, et al. Systematic review on the safety and efficacy of NSAIDs in rheumatoid arthritis. *J Rheumatol*. 2014;41(2):109-117.
14. Agca R, Heslinga SC, Gül A, et al. A systematic review on the impact of NSAIDs on pain and functional disability in rheumatoid arthritis. *Arthritis Rheum.* 2016;68(4):973-979.
15. Kulkarni M, Goel A, Pandey D, et al. Evaluation of adverse events and their severity during the use of nonsteroidal anti-inflammatory drugs in the treatment of rheumatoid arthritis. *Indian J Rheumatol.* 2013;8(1):23-28.