

Pain Management in Rheumatoid Arthritis: Clinical Role and Therapeutic Implications of NSAIDs

Faizur Rahman¹, Nalini Kanta Sahoo^{1,*}, Rajesh Nath¹, Alex Martin¹, Asad Jamal Ansari², Ebadurrahman³, Saurabh Kumar Chauhan⁴

Abstract

Rheumatoid arthritis (RA) is a progressive, chronic autoimmune condition that results in swelling in multiple joints. It is estimated to occur in 0.5–1% of the global population and is more common in women. India has an estimated prevalence of 0.75%. RA causes the destruction of joints and a decrease in disabilities and quality of life. It is accompanied by further manifestations and multiple co-occurring conditions that lead to a greater burden of suffering and higher death rates. There has been a lot of progress in therapies that modify diseases; however, the pain of RA remains. A large number of patients who receive biologic denervation treatments for RA experience chronic pain daily. Nonsteroidal anti-inflammatory (NSAIDs) drugs have anti-inflammatory and pain-reducing co-morbidities by inhibiting the cyclooxygenase (COX) enzymes in the stomach and the resulting synthesis of prostaglandins. NSAIDs are loosely classified and divided based on their structures, COX selectivity, how these drugs are cleared from the body, which COX enzyme they inhibit more effectively, and their end-organ safety profiles. The end-effect safety refers to the potential safety of things such as gastrointestinal and potential cardiovascular effects. While NSAIDs can numb the pain, they are not able to prevent the disease from progressing or damaging to the joints. While the NSAIDs and disease-modifying antirheumatic drugs (DMARDs) are used, the biologic treatments and the Janus kinase inhibitors (synthetic agents) are also used. Analgesics, antidepressants, and topical medications are also used. Non-pharmaceutical methods also play a valuable role in a patient's overall care. These include exercise and, to a lesser degree, the role of physical therapy, surgical interventions, and psychological therapies. In summary, mastery of RA management depends on multi-domain strategies that manage inflammatory activity alongside residual inflammatory pain. Improvement of patient quality of life and outcomes hinges on an optimized combination of therapeutic toolsets. While NSAIDs provide fundamental pain relief, treatment strategies must be supported by infusion of targeted interventions of both pharmacological and non-pharmacological pairings.

*Author for Correspondence

Nalini Kanta Sahoo
E-mail: sahoo.nalini@gmail.com

¹Faculty, Department of Pharmaceutical Sciences, Rama University, Kanpur, Uttar Pradesh, India

²Faculty, Department of Pharmacy, Integral University, Lucknow, Uttar Pradesh, India

³Researcher, College of Pharmacy, Integral University, Lucknow, Uttar Pradesh, India

⁴Researcher, Department of Pharmacology, School of Pharmaceutical Education and Research (SPER), Jamia Hamdard, New Delhi, India

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INTRODUCTION

Rheumatoid arthritis (RA) is the most common form of chronic erosive inflammatory arthritis, characterized by symmetrical inflammation of multiple peripheral joints, particularly the small joints of the hands and feet. Worldwide, the prevalence of RA is 0.5–1% of the adult population. RA is more common in women, with reported sex ratios of 2–3:1 [1]. The prevalence of RA in India is 0.75% [2]. Due to the asymmetric and inflammatory nature of RA, it can present with diverse symptoms, both articular and extra-articular. Joint inflammation can result in disability and deformity,

ultimately leading to a diminished quality of life. Active RA can also result in extra-articular manifestations.

Untreated comorbid states can lead to increased healthcare costs, functional disability, impaired quality of life, treatment disruptions, and increased mortality and depression. The increased burden of comorbid states can have economic consequences at the individual and societal levels. The majority of these comorbid states are untreated and recognized [3].

The persistence of pain in patients with RA remains a complex factor. Despite notable achievements in managing synovitis and disease activity, surveys indicate chronic pain. Two-thirds of patients with RA state that they experience a level of pain that is serious, intolerable, and most want to have improved [4, 5]. Longitudinal studies have reported unexplained pain despite the application of biological therapies [6, 7]. This is particularly substantiated in the British Society for Rheumatology Biologics Registry, with 79% of participants experiencing persistent pain. Pain negatively correlates with and affects the quality of life, function, mental health, and level of fatigue in patients with RA [8–11]. Pain in RA is very different from simple nociceptive pain, often due to the presence of chronic pain and associated syndromes/symptoms. The author states that the presence of pain in RA syndromes/symptoms is due to the presence and coexistence of pain in pathways [12], while stating that the presence of pain in RA patients is due to the presence of fibromyalgia [13].

ROLE OF NSAIDS IN PAIN MANAGEMENT OF RHEUMATOID ARTHRITIS

NSAIDs are usually categorized based on their chemical structure, half-life in plasma, and whether they are COX-1 or COX-2 selective inhibitors (Table 1). Most NSAIDs, being organic acids, are categorized by their low pK values, which correspond to their localization in inflamed tissues. In these tissues, the pH is often lower than that of the surrounding tissues.

Table 1. Classification of some of the common NSAIDs.

Class	Subclass	Drugs
Enolic acids	Pyrazolones	Phenibutazone
	Oxicams	Piroxicam
		Meloxicam
Cox-2 selective	Sulphonamides	Celecoxib
	Sulfonylurea	Etoricoxib
	Non-acid	Lumiracoxib
Carboxylic acids	Salicylic Acids	Acetylsalicylic acid
		Trisalicylate
		Salsalate
	Acetic Acids	Diclofenac
		Etodolac
		Indomethacin
		Sulindac
		Tolmetin
		Ketorolac
	Propionic Acids	Flurbiprofen
		Ketoprofen
		Oxaprozin
		Ibuprofen
		Naproxen
		Fenoprofen
	Fenamic acids	Meclofenamate

Usually, low pK values are accompanied by short half-lives; however, an exception is nabumetone, which is non-acidic. Classifying NSAIDs based on their plasma half-lives is not entirely correct because they tend to accumulate in synovial tissues, where the concentration is higher than that in plasma. Therefore, they could be administered at lower frequencies than their plasma half-lives. NSAIDs with longer half-lives take longer to reach steady-state levels in the plasma. Drugs with half-lives longer than 12 h can be administered once or twice daily. The plasma concentrations would continue to rise and subsequently remain constant after a few days to several weeks, assuming a half-life of several days. NSAIDs with longer half-lives take longer to equilibrate, and synovial concentrations of the drug will be higher; however, the concentrations of the drug in synovial fluid will be lower than in plasma because of lower albumin levels in synovial fluid.

Extended-release formulations and NSAIDs with longer half-lives are associated with an increased risk of adverse side effects [14]. When determining the relative risk of NSAIDs in the gastrointestinal and cardiovascular systems, some of the most important factors to be considered, aside from most of the other pharmacologic properties of each NSAID, would be the selectivity of the COX isozymes [15].

Any nearly ubiquitous NSAID will be bound to plasma proteins to the extent of over 90%. If the concentration of the drugs in the blood plasma or other body fluids exceeds the concentration that the proteins in the plasma must bind to them, the free concentration of the drugs, which are biologically active, becomes, in principle, an incremental function of concentration, in contrast to the concentration bound to proteins. NSAIDs are mostly eliminated by the liver, transforming them into inactive byproducts, which are moved to the bile and, subsequently, to urine. Most of them are eliminated by the microsomal mixed-function oxidase system of the cytochrome P450. NSAIDs are eliminated most frequently by the oxidation reactions of P450 of the CYP3A and CYP2C subfamilies, although some are eliminated by the other hepatic cytosolic enzymes. Different individuals may exhibit diverse responses to the same NSAID; the mechanisms underlying such variability are poorly characterized. Multiple drug-related factors may be responsible for this variability, including differences in dose-response relationships, plasma half-life, enantiomeric properties, urinary elimination, and pharmacologic effects [16]. Drug-related factors include affinity for binding to proteins, the drug's metabolism, and the proportion of the drug existing in the free (active) S form. These factors are independent of the pharmacokinetics of NSAIDs, which can also be affected by hepatic and renal dysfunction as well as aging.

THERAPEUTIC ACTION OF NSAIDS IN RHEUMATIC DISEASES

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to address inflammation associated with a range of medical disorders. In clinical research where some form of arthritis was provoked, NSAIDs were assessed against a placebo, aspirin, and one another using randomized and controlled blind methods. Upon studying the efficacy of NSAIDs in RA and osteoarthritis (OA), the most used research design asks participants to withdraw from their current NSAID regimen, with symptom flare or worsened quality of life as a study entry requirement. Although there is some variation in the primary outcome measures, most include parameters that are part of the ACR-20. Within studies involving the RA population, NSAIDs demonstrating improved efficacy beyond the placebo effect commonly do so in cases where the trial participants are not receiving corticosteroids or other anti-inflammatory agents [17]. The comparisons between traditional NSAIDs and selective COX-2 agents across these studies rarely differ in their reported outcomes. While analgesia and stiffness are improved with these agents, they do not reduce inflammation or modify the study. The anti-inflammatory effects of NSAIDs in OA spectrum, rheumatic fever, juvenile RA, ankylosing spondylitis, gout, and systemic lupus erythematosus are evident. Although their efficacy is not precisely documented in research, they are widely accepted for treating reactive arthritis, psoriatic arthritis, various subtypes of acute and chronic bursitis, and tendinitis.

All NSAIDs have an analgesic effect that, theoretically, means they can painlessly deliver doses much slower than the doses required to inhibit inflammation related to these disorders. The analgesic effect

of NSAIDs occurs as a result of their ability to inhibit the production of prostaglandins in peripheral tissues and the central nervous system.

Peripherally, prostaglandins (PGs) are not, themselves, pain-inducing, though they, along with other mediators, sensitize peripheral nociceptors, such as those affected by histamine or bradykinin [18]. Peripherally, PGs released during inflammation or trauma lower the activation threshold of tetrodotoxin-resistant sodium channels present on sensory neurons. PGs sensitize neurons in the central nervous system (CNS), where NSAIDs and acetaminophen also have their analgesic action, and as such, also sensitize neurons in pain perception [19, 20]. Beyond COX-1, COX-2 also has a strong presence in the spinal cord dorsal horn, and its presence is increased during inflammation. PGE₂ released from the back, in the spinal cord, activates pain perception neurons and activates glia in the neuropathic pain mechanisms [21]. Both COX-1 and COX-2 are involved in nociception, as evidenced by the reduction of experimental pain in mice lacking either COX-1 or COX-2 [22].

OTHER TREATMENT STRATEGIES FOR THE MANAGEMENT OF RHEUMATOID ARTHRITIS

In clinical practice, management strategies for RA pain include both pharmacological and non-pharmacological interventions. Pharmacological interventions include the use of nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GCs), and disease-modifying antirheumatic drugs (DMARDs). DMARDs include biologics and targeted synthetics. Targeted synthetic Janus kinase (JAK) inhibitors are among the most widely used targeted DMARDs [23]. Recent studies have shown that the monoclonal antibody tandolumab has the potential to be an effective analgesic [24]. The targeted synthetics have the advantage of being administered orally, having rapid-acting chances of action, and of inhibiting intracellular pathways of inflammation. Drugs that are used for pain management in RA include gabapentin, pregabalin, tricyclic antidepressants (e.g., amitriptyline), and topically applied NSAIDs, including diclofenac gel or patches [25]. Complement inhibitors, including anti-C5a, have reached the stage of clinical trials. Non-pharmacological interventions comprise surgical and psychological interventions along with physical therapy and rehabilitation [26]. Therapeutic exercises that include low-impact, low-intensity, and aerobic exercises should be used. Swimming and cycling are examples of exercises with a low-impact and low-intensity.

Patients with RA who suffer from significant loss of joint function or severe joint deterioration undergo synovectomy, joint replacement surgery, and tendon repair surgery [26]. Cognitive and behavioral therapy has proven to be effective in the management and rehabilitation of chronic pain. While still in the experimental stages, several other treatment avenues have opened up through the use of emerging therapies and research modalities, such as neural therapy, stem cell therapy, and bioregulatory medicine. Subsequently, bioregulatory methods and new-generation biopharmaceuticals have shown exceptional clinical potential for the treatment of RA and are in various phases of research and development.

RESULT

The literature shows that RA leads to chronic pain, disability, and reduced quality of life, regardless of the advancement in disease-modifying treatment. A significant number of patients with RA report pain that persists despite disease-modifying therapies targeting inflammatory disease activity, including the use of biologics [27].

NSAIDs have been found to provide pain relief and reduce stiffness that may occur after disease flares. Clinically, the analgesic effects are peripheral and central, with the cyclooxygenase (COX) enzyme and prostaglandin, which are known pain mediators, inhibited.

Traditionally, COX-2 selective and non-selective NSAIDs provide comparable pain relief. However, COX-2-selective NSAIDs may be associated with an increased risk of cardiovascular events, although

they generally have a lower risk of gastrointestinal adverse effects than traditional NSAIDs. There may be a higher risk of adverse NSAID effects, including in the elderly and patients with comorbid illnesses, associated with the use of NSAID single daily sustained-release formulations and those with a longer half-life [28].

The findings demonstrate that NSAIDs are not a substitute for DMARDs and biologics because of the limited effects of NSAIDs on inflammatory disease activity and radiographic outcomes.

The literature also suggests that it is necessary to have multiple layers of pain management methods, such as the utilization of gabapentinoids, antidepressants, and other types of pain management, such as physical therapy, exercise, and psychological help. Combining different monoclonal antibodies and other types of improvements and technologies will yield improved outcomes and pain management.

The information from this study indicates that multiple types of pain management through different layers, as well as calling factors such as anti-inflammatory management, will yield the best outcomes for users of NSAIDs and for RA [29].

CONCLUSION

RA is a condition that focuses on the user's quality of life and uncontrollable factors, such as pain. It causes inflammation, joint damage, and chronic pain. Although there have been significant improvements in disease-modifying therapies, pain remains a challenge for many patients whose inflammation is controlled and whose RA is under management to reduce inflammation and destruction of the joints.

The use and management of pain through NSAIDs seems to be the go-to treatment for RA. The management of pain through the use of NSAIDs is speedy and effective, as it targets the pain in a way that reduces and manages the inflammation of the joints through the synthesis of a protein called cyclooxygenase.

Unfortunately, through the use of NSAIDs, many different things will be controlled through pain, and many of the effects of RA, such as destruction and damage to the joints, will continue to progress. There are also some adverse effects, such as those experienced in the gastrointestinal, cardiovascular, and renal tracts. This is all provided to the patient after the use of NSAIDs, and this is also the reason why there is a lot of caution that is evident in many different places.

RA management has advanced to an integrated and individualized framework of 'multidisciplinary layering', combining NSAIDs with DMARDs, Biologics, and targeted DMARDs, to attain a better level of disease control. Extensive care interventions can include adjunct pharmacological and non-pharmacological interventions such as physical rehabilitation, lifestyle changes, and psychological care.

Competing Interests

The author states no conflict of interest.

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