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Review Article

The Effects of NSAIDs on Patients Diagnosed with Gastroesophageal Reflux Disease (GERD)

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Abstract: Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are a widely used class of medications for managing pain and inflammation. However, long-term use of NSAIDs has been associated with an increased risk of gastrointestinal disorders, including Gastroesophageal Reflux Disease (GERD). This study aims to analyze the impact of NSAID use on GERD patients based on recent research findings. The literature search was conducted through national and international databases such as Elsevier, Google Scholar, and the National Institutes of Health (NIH) National Library of Medicine, using keywords including GERD, NSAID, LES (Lower Esophageal Sphincter), gastric acid, reflux, and regurgitation. A total of 25 journal articles published between 2016 and 2024 were used as data sources. The findings indicate that NSAIDs inhibiting cyclooxygenase-1 (COX-1) can reduce prostaglandin production, which plays a protective role in the gastric mucosa, thereby increasing the risk of irritation and acid reflux. Conversely, selective COX-2 NSAIDs have a lower risk of gastrointestinal side effects, making them a safer alternative for patients with chronic pain and inflammation. This study highlights the importance of selecting the appropriate type of NSAID and monitoring its long-term use to minimize the risk of gastrointestinal disorders, particularly in patients with a history of GERD. By considering these factors, it is hoped that complications related to NSAID use in patients with digestive issues can be reduced.

Keywords: Gastric Acid, GERD, LES, Reflux, Regurgitation

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1. Introduction

The stomach is a fundamental organ within the human digestive system, positioned between the esophagus and the small intestine. It fulfills critical roles in the digestion of food, including the temporary storage of ingested materials and the initiation of the digestive process. Upon the arrival of food in the stomach, it is combined with gastric juices, which consist mainly of hydrochloric acid and digestive enzymes. This mixture not only facilitates the breakdown of complex food substances into simpler, more absorbable components but also plays an essential role in neutralizing harmful pathogens, thereby protecting the integrity of the digestive system. The interior of the stomach is lined with a specialized mucosal layer that serves as a protective barrier against the acidic environment. A healthy stomach depends on a finely tuned equilibrium between gastric mucosal protectors, such as mucus and bicarbonate, and gastric mucosal destroyers, including gastric acid and certain digestive enzymes. Disruptions in this balance can lead to various gastrointestinal conditions, such as gastritis or peptic ulcers. Therefore, maintaining the overall health of the stomach is crucial for effective digestion and optimal nutrient absorption, underscoring its significance within the broader framework of human health (Raehana, 2021).

Stomach disorders are common across all age groups, from infants and children to adolescents, adults, and the elderly. One of the most prevalent stomach conditions is Gastroesophageal Reflux Disease (GERD). GERD is characterized by the persistent

backflow of stomach contents into the esophagus, accompanied by symptoms such as heartburn, a burning sensation in the chest, and other manifestations like regurgitation, epigastric pain, dysphagia, and odynophagia (Saputera & Budianto, 2017).

Gastric fluid comprises various components, including HCl, bile, pepsin, mucin, and rennin. It has an acidic nature, which can damage surrounding tissues. The acidity of gastric fluid is a major contributing factor to esophagitis and reflux symptoms. Unlike the stomach, the esophagus lacks a protective lining against acid, making it more vulnerable to damage from exposure to gastric fluid (Tack & Pandolfino, 2018).

An increase in gastric fluid volume can lead to a decrease in the function of the Lower Esophageal Sphincter (LES). The LES is a barrier between the esophagus and the stomach, preventing gastric reflux. Reflux is when stomach fluid flows back into the esophagus, accompanied by bothersome symptoms. It typically occurs through four main mechanisms: transient lower esophageal sphincter relaxation (tLESR), weakened LES pressure, LES relaxation during swallowing, and increased intra-abdominal pressure (such as during straining) when the LES is weak. Repeated episodes of reflux can damage the LES, contributing to the development of GERD.

Various factors, including medication use, diet, hormonal influences, or structural abnormalities, can cause damage to the LES in GERD. The use of NSAIDs can increase gastric acid production, lower LES pressure, and delay gastric emptying, all of which are closely related to the pathophysiology of GERD (Maradjabessy, Kusadhiani, & Warella, 2023).

The risk factors for GERD are largely associated with lifestyle choices, including obesity, smoking, alcohol consumption, fatty or spicy foods, and the use of NSAIDs (Maradjabessy, Kusadhiani, & Warella, 2023). One significant risk factor for GERD is the use of NSAIDs, a class of drugs commonly prescribed for pain relief, fever, and inflammation. However, NSAID use has been widely reported to cause gastrointestinal side effects, including digestive tract disturbances.

Given the significant impact of NSAIDs on the gastrointestinal tract, further investigation is needed to assess the relationship between NSAID use and the occurrence of Gastroesophageal Reflux Disease (GERD).

2. Preliminaries Literature Review

Research on the mechanism of action of NSAIDs and their relationship with gastric mucosal injury, as well as their impact on GERD patients has been extensively conducted with various findings highlighting the strong association between NSAID use and gastrointestinal disorders. The study by Bindu, Mazumder, & Bandyopadhyay (2020) emphasizes the effectiveness of NSAIDs in managing pain and inflammation but does not delve deeply into their significant gastrointestinal side effects. Meanwhile, research by Qorib, Purba, & d'Arqom (2022) classifies NSAIDs based on their inhibition of COX-1 and COX-2 enzymes, reinforcing that COX-1 inhibition plays a major role in gastric mucosal injury due to the reduction of protective prostaglandins. Studies by Syahroni (2021) and Soekaryo, Setyahadi, & Simanjuntak (2017) highlight that COX-1 found in the gastric mucosa, has a protective role, and its inhibition disrupts the acid-mucus balance, increasing the risk of gastric ulcers. Other studies, such as those by Sohail et al. (2023) and Tai & McAlindon (2021), compare the side effects of selective COX-2 and non-selective NSAIDs showing that while selective NSAIDs are safer for the gastric mucosa, they carry an increased cardiovascular risk. Regarding the relationship between NSAIDs and GERD, studies by Ajjah, Mamfaluti, & Putra (2020) and Saputera & Budianto (2017) explain that GERD results from lower esophageal sphincter (LES) dysfunction, which NSAIDs further exacerbate by increasing gastric acid secretion, reducing LES contraction, and impairing esophageal motility, as described by Saod & Albhbah (2024). Research by Sohail et al. (2023) further confirms that NSAIDs prolong reflux duration, decrease mucus secretion, and increase acid regurgitation, contributing to esophagitis progression. Additionally, studies by Mungan & Şimşek (2017) and Masuda et al. (2017) suggest that long-term NSAID use correlates with increased regurgitation frequency and GERD complications, such as chronic esophagitis and even esophageal cancer.

3. Proposed Method

A comprehensive literature review was conducted using systematic methods to identify relevant references. This study focused on primary data from national and international

journals published over the past nine years (2016–2024). The data collection process involved thorough searches of reputable online databases, including Elsevier, Google Scholar, and the National Institutes of Health (NIH) National Library of Medicine. Keywords used in the search included "GERD", "NSAIDs", "LES", "gastric acid", "reflux" and "regurgitation".

4. Results and Discussion

NSAIDs and Its Mechanism of Action

NSAIDs represent a widely utilized category of medications recognized for their effectiveness in managing pain and inflammation. These agents are commonly prescribed for a variety of conditions, including chronic pain disorders such as osteoarthritis and rheumatoid arthritis, which significantly impact joint function and overall quality of life (Bindu, Mazumder, & Bandyopadhyay, 2020). The mechanism of action of nonsteroidal anti-inflammatory drugs (NSAIDs) is categorized into two types based on their inhibition of the cyclooxygenase (COX) enzyme. COX enzymes play a crucial role in converting arachidonic acid into thromboxane, prostaglandins, and prostacyclin. There are two main isoenzymes of COX: COX-1 and COX-2 (Qorib, Purba, & d'Arqom, 2022).

Nonselective NSAIDs work by inhibiting the COX-1 and COX-2 enzymes. The COX-1 enzyme is found in gastrointestinal cells, gastric mucosa, endothelium, brain, platelets, and kidneys (Syahroni, 2021 and Soekaryo, Setyahadi, & Simanjuntak, 2017). The COX-1 enzyme plays a role in the synthesis of bicarbonate, increased blood flow, and mucosal protection under normal physiological conditions. COX-1 is directly involved in synthesising prostaglandins, which help maintain physiological functions in the body, particularly in gastric mucosal protection and platelet function. Inhibition of the COX-1 enzyme, which plays a vital role in the synthesis of prostaglandins can have significant consequences for the gastrointestinal (GI) mucosa. Prostaglandins are essential compounds that help maintain the integrity of the GI lining by promoting several protective mechanisms. They enhance blood flow to the gastric mucosa, ensuring that the cells receive adequate oxygen and nutrients. Additionally, prostaglandins stimulate the production of gastric mucus, which forms a protective barrier that shields the gastric wall from the corrosive effects of stomach acid. When COX-1 is inhibited, the production of these protective prostaglandins decreases significantly. This reduction compromises the natural defense mechanisms of the GI tract, leaving it vulnerable to damage from factors such as excessive acid secretion or irritating substances. NSAIDs are widely utilized for their analgesic and anti-inflammatory properties. However, they are associated with several potential side effects that warrant careful consideration. A primary concern is the possibility of damage to the gastrointestinal mucosa, which can lead to complications such as ulcers or gastrointestinal bleeding. Additionally, the use of these medications may result in constipation, which can cause discomfort and exacerbate digestive issues (Sohail et al., 2023).

The COX-2 enzyme is predominantly found in macrophages, leukocytes, fibroblasts, and endothelial cells (Syahroni, 2021). Selective NSAIDs work by specifically inhibiting the COX-2 enzyme. Inhibiting COX-2 has a lower potential for causing gastrointestinal damage than COX-1 inhibition (Tai & McAlindon, 2021).

COX-2 plays a key role in inflammation and pain perception. It actively produces prostaglandins in response to inflammation, which interact with the nervous system to transmit pain signals to the brain. Prostaglandins produced by COX-2 are primarily involved in pain induction and inflammation. COX-2 expression increases during gastric ulcer formation and decreases as the healing progresses. Inhibiting COX-2 helps alleviate inflammation and pain in inflammatory conditions. Selective COX-2 NSAIDs provide analgesic and anti-inflammatory effects without causing gastric irritation or damage (39). Therefore, COX-2 selective NSAIDs have a lower risk of gastrointestinal damage compared to COX-1 inhibition (Tai & McAlindon, 2021). However, their use is associated with an increased risk of myocardial infarction due to thrombosis, as thromboxane A2, responsible for platelet aggregation and vasoconstriction, is produced by COX-1 and remains uninhibited.

Gastroesophageal Reflux Disease (GERD)

Gastroesophageal reflux disease represents one of the most prevalent chronic conditions within the community. This disorder is characterized by the weakening of the

Lower Esophageal Sphincter (LES), which facilitates the recurrent reflux of gastric contents into the esophagus. The condition is associated with several symptoms, including heartburn (a burning sensation in the epigastric region), acid regurgitation (a bitter taste in the mouth), nausea, and dysphagia (difficulty swallowing). Prolonged exposure to these symptoms may lead to significant damage to the esophageal mucosa (Ajjah, Mamfaluti, & Putra, 2020 and Saputera & Budianto, 2017).

GERD occurs due to an imbalance between aggressive and protective factors in the esophageal defence system and gastric contents. The LES is a ring of muscle located between the oesophagus and the stomach. Under normal conditions, LES pressure decreases during swallowing, allowing food to pass from the oesophagus into the stomach. However, in GERD, LES function is impaired, causing the digestive flow to reverse from the stomach back into the oesophagus. LES dysfunction can result from medication use, certain types of food, hormonal factors, or structural abnormalities (Saputera & Budianto, 2017).

Mechanism of NSAIDs in Causing Gastric Mucosal Injury

Gastric mucosal damage is a medical condition that involves the deterioration of the stomach lining, which can occur in two distinct forms. The first is partial mucosal loss, commonly referred to as erosion, where localized areas of the lining are compromised. The second form is characterized by complete loss of the mucosal layer, affecting its entire thickness. Such damage can give rise to various complications, including gastrointestinal bleeding, ulcer development, and disruptions in normal digestive processes (Sohail et al., 2023). NSAIDs can adversely affect the gastric mucosa through both local and systemic mechanisms. Certain NSAIDs are characterized by a high pKa value, indicating they are weakly acidic compounds. In the acidic environment of the stomach, these medications predominantly exist in a non-ionized form. This non-ionized state is crucial, as it facilitates the diffusion of the drug across lipid membranes. Consequently, NSAIDs can move alongside hydrogen ions (H+) into the epithelial cells that line the gastric mucosa. Once within the gastric epithelium, the environment becomes more neutral, resulting in the retention of these drugs within the epithelial cells. This accumulation can lead to several negative outcomes. Primarily, it increases the risk of developing gastric ulcers by irritating the protective mucosal layer. In addition, NSAIDs can inhibit the synthesis of prostaglandins (PGs), which are essential for maintaining gastric mucosal integrity. Prostaglandins contribute to mucus production and help regulate gastric acid secretion, and their reduction compromises the mucosal defense mechanisms, making the gastric lining more vulnerable to injury (Putri, Apriliany, & Praja, 2024 and Syahroni, 2021).

In the context of systemic conditions, nonsteroidal anti-inflammatory drugs (NSAIDs) play a significant role in alleviating inflammation and pain through the inhibition of the cyclooxygenase enzyme. This enzyme is integral to the synthesis of prostaglandins, which are lipid compounds involved in various physiological processes, including the modulation of inflammatory responses, the sensation of pain, and the maintenance of gastrointestinal mucosal protection. The inhibition of COX-1 by NSAIDs results in a marked reduction in prostaglandin production. While this can effectively alleviate symptoms such as pain and swelling, it is essential to recognize that decreased levels of prostaglandins may compromise the protective mechanisms of the gastrointestinal lining. Prostaglandins are critical for sustaining the integrity of the mucosal barrier, as they promote mucus secretion, enhance blood flow to the gastric lining, and stimulate bicarbonate production to neutralize gastric acid (Tai & McAlindon, 2021). The inhibition of prostaglandin production diminishes the protective effects on the gastric mucosa, resulting in a reduction of protective mucus secretion within the digestive tract. This decrease can lead to varying degrees of irritation, ranging from mild discomfort to severe lesions of the gastric mucosa (Idacahyati, Nofianti, Aswa, & Nurfatwa, 2020 and Bjarnason et al., 2018).

Effects of NSAID Use on the Stomach

Table 1. Effects of NSAID Use on the Stomach

Drugs Name	Effect on the Stomach	References
Aspirin	Mucosal injury due to ROS (Reactive Oxygen Species) (Rifzian, 2021), Increased gastric acid production (Farhan, Oktora, & Hasni, 2022)	Rifzian, 2021 and Farhan, Oktora, & Hasni, 2022
Diclofenac	Gastric ulcer, Increased ROS (Reactive Oxygen Species)	Syahroni, 2021
Ibuprofen	Induction of gastric ulcer, Gastrointestinal perforation	Arfania et al., 2023
Naproxen	Gastric Ulcer	Isnenia, 2020
Mefenamic Acid	Increased gastric acid production, decreased mucus secretion	Parhan & Gulo, 2019
Meloxicam	Gastric Intestinal Metaplasia (GIM)	Aulia & Subarnas, 2024
Ketoprofen	Gastric Ulcer	Isnenia, 2020
Piroxicam	Gastroenteritis, Erosion of the gastric mucosa (Hssoni & Salman, 2019), Gastric Ulcer (Nugroho, Hakim, & Satoto, 2019)	Hssoni & Salman, 2019) and (Nugroho, Hakim, & Satoto, 2019
Ketorolac	Gastric Ulcer	Nugroho, Hakim, & Satoto, 2019
Celecoxib	Gastric Ulcer	Isnenia, 2020
Dexketoprofen	Gastric mucosal damage	Nugroho, Hakim, & Satoto, 2019
Etoricoxib	Gastric Ulcer	Isnenia, 2020

[1] Tables may have a footer.

NSAIDs that inhibit both COX-1 and COX-2, such as aspirin, ibuprofen, diclofenac, naproxen, mefenamic acid, ketoprofen, piroxicam, ketorolac, and dexketoprofen, have a higher potential for causing severe gastric damage compared to selective COX-2 inhibitors like etoricoxib, meloxicam, and celecoxib. NSAIDs that inhibit both COX enzymes can slow gastric ulcer healing and have a higher risk of gastrointestinal toxicity (Nugroho, Hakim, & Satoto, 2019).

Effect of NSAIDs on GERD Patients

Various studies have shown the use of NSAIDs is significantly more common in NSAID users compared to GERD patients who do not use NSAIDs. NSAIDs can cause gastric mucosal injury, increase gastric acid production, nausea, epigastric pain, and vomiting (Saod & Albhbah, 2024), Additionally, NSAID use has been associated with prolonged reflux duration, reduced mucus secretion, lower LES contraction, and delayed gastric emptying, all of which contribute to the pathophysiology of GERD.

Additionally, NSAIDs can worsen gastroesophageal reflux symptoms, characterized by epigastric pain, cough, and regurgitation (Mungan & Şimşek, 2017). Regurgitation is a primary symptom of GERD, in which stomach contents flow back into the esophagus (Sohail et al., 2023 and Masuda et al., 2018). NSAIDs can cause the gastroesophageal sphincter to relax and reduce esophageal peristaltic movement (Sohail et al., 2023). Moreover, NSAIDs increase gastric acid production, leading to a higher frequency and volume of acid reflux into the esophagus. Continuous regurgitation can result in esophageal mucosal damage, esophagitis, and even esophageal cancer (Sohail et al., 2023).

Long-term NSAID use can further aggravate GERD symptoms, such as epigastric pain, heartburn, and a sour taste in the mouth, which are hallmark signs of GERD.

Conclusions

The use of NSAIDs in GERD patients must be approached with caution, as their side effects can trigger and worsen GERD symptoms. Selective COX-2 NSAIDs tend to have fewer gastrointestinal side effects compared to non-selective NSAIDs. Therefore, COX-2 selective NSAIDs can serve as an alternative treatment for inflammatory conditions or

chronic pain, especially in patients at high risk of gastrointestinal complications, such as gastric ulcer or GERD.

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