TREATMENT STRATEGY FOR NSAID GASTROPATHY IN OSTEOARTHRITIS: A NEW APPROACH IN THERAPY

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Abstract. *This article reviews the treatment strategy for nonsteroidal anti-inflammatory drugs (NSAID) gastropathy in patients with osteoarthritis, presenting a new approach in the therapy of this condition. The authors discuss recent research and clinical data related to the use of drug combinations, including selective NSAIDs and proton pump inhibitors, as well as the role of zinc in improving treatment efficacy and reducing the risk of complications.*

Keywords: *osteoarthritis/osteoarthritis nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase (COX), NSAIDs-gastropathy, gastric mucosa, proton pump inhibitors, esomeprazole, zinc.*

Osteoarthritis/Osteoarthrosis (OA) is a common degenerative joint disease that affects at least 20% of the world's population [28]. OA primarily occurs due to the damage of joint cartilage [21]. Its incidence increases with age, and it is one of the top ten causes of disability in developed countries. Risk factors for developing OA include an unhealthy lifestyle, lack of physical activity, joint overloading, decreased bone mineral density, excess weight, metabolic disorders, genetic predisposition, and injuries [12,17,8]. Individuals with rheumatic diseases of the musculoskeletal system and connective tissue, most of which have a chronic and progressive course, are particularly susceptible, especially if diagnosed late and treated ineffectively [28]. Heavy physical labor is also associated with an increased risk of developing OA. In various countries worldwide, the prevalence of OA among people aged over 60 is, on average, 9.6% in men and 18.0% in women [21].

The main symptom of OA that significantly impairs the quality of life for patients is pain. The pain experienced by OA patients does not always correspond to the degree of changes in the joint. It has been observed that patients often experience pain almost constantly, as inflammation is at the core of the disease. However, the level of pain varies widely due to numerous factors and does not always directly correlate with the severity of joint changes. On average, patients rate their pain as 35.3 mm (maximum 54.4 mm) on a 100-mm Visual Analog Scale (VAS) [3].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used by healthcare professionals to alleviate pain, including those dealing with OA [1]. Approximately 30 million people take NSAIDs on a daily basis [27]. They account for about 5–10% of all prescriptions issued annually and are among the most commonly prescribed drugs for the elderly population [21]. The use of NSAIDs in general medical practice among patients over 65 years old reaches 96%, and 7.3% of patients over 60 years old have taken at least one drug from this group within a year, indicating a significant need for such medications in this patient demographic [18].

The pharmacological group of NSAIDs can be divided into selective (s-NSAIDs) and non-selective (n-NSAIDs). The primary mechanism of action of these drugs is associated with the blockade of cyclooxygenase isoforms (COX-1 and COX-2). These enzymes are the target for

NSAIDs. COX-1 plays a crucial role in maintaining the mucous membrane of the stomach's resistance to external aggressive factors by participating in the synthesis of prostaglandins, which increase the secretion of mucus and bicarbonates, maintain normal blood flow, and support platelet hemostasis. COX-2 is found in small amounts in normal tissues but is present in larger quantities during inflammation. In therapeutic doses, n-NSAIDs block both COX-2 and COX-1, determining a significant difference between s-NSAIDs and n-NSAIDs in terms of the extent of their negative impact on the gastrointestinal tract (GIT) [19].

Studies show that the use of NSAIDs can cause damage to the GIT. This can lead to the risk of developing a gastroenteropathy known as "NSAID-induced gastropathy," along with other adverse effects [27]. Pathological damage to the GI tract often occurs in patients with joint diseases who are treated with NSAIDs, reducing their quality of life, leading to financial expenses for expensive treatment, and ultimately, may result in disability [28]. Research indicates that the likelihood of developing ulcers with the use of n-NSAIDs is 16%, while with s-NSAIDs, it is 5.2%, and this probability increases with age [10].

When using NSAIDs, the most common side effects include:

• Gastrointestinal toxicity, manifested as dyspeptic reactions, gastroduodenal ulcers, bleeding, and perforations.

• Cardiovascular effects, such as edema, hypertension, heart failure, myocardial infarction, stroke, and other thromboembolic complications.

• Nephrotoxic effects, including electrolyte imbalances, hypernatremia, edema, reduced glomerular filtration rate, nephrotic syndrome, acute interstitial nephritis, renal papillary necrosis, and chronic kidney diseases.

• Complications affecting the ENT organs, respiratory system, and skin, such as rhinorrhea, nasal congestion, the risk of developing rhinosinusitis, nasal cavity polyps, and exacerbation of respiratory diseases during NSAID use [21].

Various factors increase the risk of developing gastropathies when using NSAIDs. According to a 2002 study by the American Rheumatology Association, in patients with two or more risk factors for developing gastropathies while taking NSAIDs, the probability of experiencing such complications is very high and is not dependent on the specific mechanism of action of the NSAIDs [23]. Despite the potential risks associated with NSAID use, GIT complications do not always manifest. It is essential to consider factors such as age (over 65 years), the presence of gastrointestinal pathology (peptic ulcer disease, gastroesophageal reflux disease, esophageal stricture), serious comorbidities (systemic sclerosis, liver cirrhosis, cardiovascular diseases), high doses of NSAIDs, and their combination with other medications that may increase the risk of gastropathy [30]. Paying attention to reducing the negative impact of NSAIDs in the elderly and in individuals with GIT, cardiovascular, or renal issues is crucial [22]. In elderly patients, the number of medications taken increases, leading to an elevated risk of drug interactions and side effects. When NSAIDs are used in conjunction with angiotensin-converting enzyme inhibitors, the risk of elevated blood pressure rises due to a reduction in the antihypertensive effects of the medication. Additionally, combining NSAIDs with antiplatelet drugs, selective serotonin reuptake inhibitors, and glucocorticoids increases the risk of gastrointestinal bleeding [19]. It is known that the risks of gastrointestinal complications are always present in the group of patients taking NSAIDs overall, and they are higher in the group taking n-NSAIDs compared to s-NSAIDs [5].

When using NSAIDs to treat rheumatic diseases in patients, upper GIT disorders are observed much more frequently (12%) compared to lower GIT disorders (1%) [4]. About 40% of patients taking NSAIDs for more than 7 days report complaints of pain in the epigastric region, and half of them experience dyspeptic disorders. Individuals regularly taking NSAIDs are also at risk of developing acid reflux from the stomach into the esophagus, stomach or duodenal ulcers, esophagitis, and GIT bleeding [24]. Примерно Approximately 40% of patients taking NSAIDs experience symptoms related to the upper GIT tract, such as dyspepsia, heartburn, bloating, spasms, nausea, and vomiting. It should be noted that 50–60% of patients taking NSAIDs may have GIT complications without clinical symptoms [9]. As a result, the symptoms of NSAID-induced gastropathies do not always correspond to the detected changes during gastroscopy [27]. Studies show that dyspeptic symptoms can occur both in the presence of erosive-ulcerative changes and without them [30]. It is worth noting that patients at high risk are more likely to develop NSAID-related gastropathies, even with concurrent use of proton pump inhibitors (PPIs) [4].

Endoscopic changes associated with the use of NSAIDs typically manifest in the antral part of the stomach and occasionally in the duodenal bulb, indicating their adverse effects on the GIT mucosa. Damage from NSAIDs can affect any part of the GIT. This type of gastropathy is usually characterized by eosinophilic infiltration of the mucosa, sometimes with foveolar hyperplasia and an increase in smooth muscle cells, but their sensitivity as gastropathy markers is not high. Enhanced proliferation is usually absent, possibly due to the high prevalence of Helicobacter pylori infection. Endoscopic signs include hyperemia, edema, bleeding, erosions, ulcers, and the absence of a periulcerative rim typical of peptic ulcer disease. To assess changes in the upper GIT due to NSAID use, the modified Lanza F.L. scale is applied, along with grading the condition of the esophageal, gastric, and duodenal mucosa. When ulcerative-erosive damage to the mucosa of the upper GIT is detected, it is crucial to evaluate the likelihood of complications such as gastrointestinal bleeding and perforation resulting from NSAID use [30].

The principles of long-term NSAID therapy for OA are based on research findings. It is advisable to first check for the presence of peptic ulcers or GIT bleeding and assess the potential impact of other medications on the GIT. Treatment is recommended to commence with less toxic NSAIDs after meals, considering potential adverse effects from other drugs. Additionally, an esophagogastroduodenoscopy is recommended before starting therapy and should be repeated 30 days after the initiation of treatment. In the case of detecting ulcerative lesions in the GIT, it is recommended to either discontinue NSAID use or reduce their dosage, switching to safer alternatives. Furthermore, a combination of selective NSAIDs and PPIs is recommended for patients at high risk of GIT complications with NSAID use [14].

Recent studies have shown the benefits of using a combination of s-NSAIDs and PPIs in the treatment of NSAID-induced gastropathy, either alone or in combination with other drugs [20]. The efficacy of this combination has been confirmed by clinical trials, including VENUS and PLUTO. Within these studies, involving 1469 patients at high risk of gastrointestinal complications who took n-NSAIDs or COX-2 inhibitors in combination with esomeprazole or a placebo for 6 months, it was found that the use of the PPI esomeprazole at doses of 20 and 40 mg/day has an effective impact [14]. Due to its isomeric composition, esomeprazole possesses higher efficacy, faster onset of action, and longer duration of impact compared to omeprazole [30].

The combination of s-NSAIDs and PPIs demonstrates a lower likelihood of NSAID-induced gastropathy compared to the combination of COX-2 inhibitors and PPIs [14].

The following study, involving 441 patients with a history of gastrointestinal bleeding, was divided into two groups: one group was prescribed celecoxib at a dose of 400 mg/day, while patients in the second group received celecoxib 400 mg/day along with esomeprazole 20 mg for one year. The results showed that recurrence of bleeding occurred in 8.9% of patients in the first group, whereas those receiving combination therapy did not experience recurrences ($p<0.001$). These findings suggest that the combination of s-NSAIDs and PPIs is an optimal treatment method for patients at high risk of gastrointestinal bleeding [6].

In recent years, scientific literature has been increasingly enriched with a greater number of articles dedicated to the anti-ulcer properties of zinc [15,26]. The cytoprotective mechanisms of zinc on the GIT may be attributed to various factors, including lipid peroxidation, apoptosis processes, nucleic acid synthesis, and prostaglandin synthesis [25,29]. Studies indicate the necessity for a more in-depth exploration of the relationship between inflammatory and destructive processes in the mucous membranes of the gastrointestinal tract and the levels of zinc in the human body. This, overall, contributes additional insights to the therapy of NSAID-induced gastropathies.
Conclusion: Considering the fact that NSAIDs have remained the first choice for pain and inflammation treatment for many years, complete discontinuation becomes a challenging task in practice, especially for patients with chronic musculoskeletal disorders, including OA. Therefore, physicians need to exercise caution when prescribing NSAIDs to ensure maximum treatment effectiveness and minimize side effects. Assessing the patients' condition and identifying risk factors before initiating NSAID therapy can significantly reduce the risk of NSAID-induced gastropathy [7,16]. Periodic gastroscopic monitoring is recommended, especially in the early stages of treatment (first 2 months), for effective control and prevention of serious complications, particularly for those with one or several risk factors [27].

Currently, there are several international and regional guidelines that doctors follow in the treatment of GIT complications induced by NSAID use [2,11,13]. However, none of these guidelines adequately focuses on the management of patients with NSAID-induced gastropathy. This emphasizes the need for specialized clinical guidelines for physicians dealing with NSAID-induced gastropathy, especially in developing countries.

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