https://doi.org/10.5281/zenodo.4917318 **Research Article**

COMPARISON OF NONSTEROIDAL ANTI-INFLAMMATORY OF COX-1 AND COX-2 REGARDING SIDE EFFECTS IN THE ASTROINTESTINAL TRACT

Healthcare

Keywords: Nonsteroidal anti-infammatory drugs, rheumatoid arthtritis, COX-2, gastrointestinal tract, PPIs.

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Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used to treat symptoms caused by rheumatoid arthritis due to their ability to inhibit prostaglandin synthesis by inhibiting cyclooxygenase (COX). The side effects of NSAIDs are also associated with inhibiting prostaglandin production. Consequently, their application is problematic. NSAID selective COX-2 inhibitors give minor gastrointestinal complications. Our study aims to compare nonsteroidal anti-inflammatory inhibitors of COX-1 and COX-2 regarding side effects in the gastrointestinal tract of patients with rheumatoid arthritis.

Introduction

Non-steroidal anti-inflammatory (NSAID)s drugs are the most commonly utilized medicines proving their efficacy in reducing pain and inflammation. They have analgesic, anti-inflammatory, and antipyretic efficacies, and apart from this, NSAIDs are proved to offer protection against various critical disorders, including cancer[1] and heart attacks[2] (aspirin). The main mechanism of action of NSAIDs is the inhibition of the enzyme cyclooxygenase (COX). COX inhibitors are classified into non-selective non-steroidal anti-inflammatory drugs (NSAIDs), COX-2 selective non-steroidal anti-inflammatory drugs (c2s NSAIDs), and aspirin. The conversion of arachidonic acid into prostaglandin is catalyzed by the cox enzyme. There are two known isoforms, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2)[3].Exist more than 20 COX inhibitors, and each of them varies in the amount they can inhibit each of the isoforms. Prostaglandins (PGs) performed by the enzymatic activity of COX-1 are principally included in regulating homeostatic functions throughout the body, whereas PGs performed by COX-2 essentially mediate pain and inflammation. Based on structural differentiation in the existing sites of COX-1 and COX-2, a new class of drugs has been improved that explicitly inhibits COX-2 but not COX-1 activity. By maintaining the synthesis of homeostatic PGs, these specific inhibitors of COX-2 provide the clinical advantages of nonsteroidal anti-inflammatory drugs and reduce the consequences of nonspecific inhibition of PG synthesis[4].The COX-1 enzyme controls many cellular processes, including platelet aggregation, kidney afferent arteriole vasodilation, and gastric mucosa acid protection. On the other side, the COX-2 enzyme is an inducible enzyme and

progressed while inflammatory processes started. It is evident and present in the brain, bone, kidney, and female reproductive system[5].

Our study aims to compare the side effects that COX-1 and COX-2 have in the gastrointestinal tract in patients diagnosed with rheumatoid arthritis.

Rheumatoid arthritis (RA) is a well-known systemic inflammatory autoimmune disease defined by painful, swollen joints that can seriously cause damage to physical function and quality of life[6]. The main purpose of treatment for RA is to reduce joint inflammation and pain, maximize joint function, and prevent joint destruction and deformity. Treatment regimens consist of combinations of pharmaceuticals, weight-bearing exercise, educating patients about the disease, and rest[7]. The first-line treatment of AR is to decrease pain and reduce inflammation. Medications, examined to be fast-acting, are nonsteroidal anti-inflammatory drugs (NSAIDs), including acetylsalicylate (Aspirin), naproxen, ibuprofen, etodolac, celecoxib etc.NSAIDs act by inhibiting cyclo-oxygenase from preventing the synthesis of prostaglandins, prostacyclin, and thromboxanes[8]. Common side effects are nausea, abdominal pain, ulcers, and gastrointestinal (GI) bleeding. These symptoms can be reduced if taken with food, antacids, proton pump inhibitors, or misoprostol (Cytotec). Celecoxib (Celebrex) is a selective COX-2 inhibitor that has less risk of GI side effects[9].

Non-steroidal anti-inflammatory drugs (NSAIDs) hold the potential to produce unfavorable events through their actions on the cyclo-oxygenase (COX)-1 and COX-2 enzymes, including gastrointestinal ulcers and bleeding (COX-1), cardiovascular (CV) events like myocardial infarction and stroke (COX-2 > COX-1) hypertension and kidney injury (COX-1 and COX-2)[10]. Selective cyclooxygenase-2 inhibitors (coxibs) look to be correlated with a lower incidence of GI adverse reactions when compared to classical NSAIDs. Certainly, some clinical trial has confirmed fewer GI complications in coxib group compared to classical NSAIDs[11]. There have been done several studies of the pathogenesis of NSAID-induced gastrointestinal illness. NSAIDs are able to inhibit prostaglandin-endoperoxide synthase 1 (PTGS1 or COX-1) and COX-2, which have been thought to mediate gastrointestinal trouble[12,13.14]. NSAID-induced reductions in mucosal levels of prostaglandins correlate with gastric and small bowel damage[15,16,17], which can be attenuated by the administration of exogenous prostaglandins[18]. COX-2 is not constitutively manifested in the gastrointestinal tract COX-2 selective inhibitors are perceived as safer than conventional NSAIDs[19]. Suggested mechanisms of damage to the gastrointestinal tract include prostaglandin mediated enhanced gastric acid secretion, reduced mucus and bicarbonate secretion, diminished cell proliferation and mucosal blood flow[20]. NSAIDs can usually cause gastrointestinal symptoms like dyspepsia, nausea, vomiting, and abdominal pain in up to 40 % of patients[21].

Two fundamental strategies have been improved to prevent the increase of gastrointestinal mucosal injury in patients using NSAID: co-therapy with a gastro-protective agent or replacement of a common NSAID with a COX-2 inhibitor. The gastro-protective agents may include a

histamine-2 receptor antagonist (H2RA), misoprostol, or a proton-pump inhibitor (PPI). Systematic reviews have shown that these strategies are variably effective to reduce the risk of NSAID-related ulcers and complications[19.]

Methods

This is a retrospective study that aims to assess and compare the gastrointestinal complications of COX-1 and COX-2 in patients diagnosed with rheumatoid arthritis. There are 250 patients with AR diagnosis evaluated in the hospital at QSUNT during 2018-2019. Two hundred patients are treated with naproxen 500 mg / 1 time per day and omeprazole 20 mg / 1 time per day; 50 patients are treated with celecoxib 200 mg / 1 per day. For all patients, the duration and treatment were eight weeks. We investigated gastrointestinal side effects like abdominal pain, indigestion (dyspepsia), vomiting, heartburn, andgastric ulcers (when they were confirmed by fibrogastroscopy).

Results

We evaluated 250 patients (the year 2019) with rheumatoid arthritis diagnose who have been used NSAIDs COX-1 and COX-2 and understand what side effects and complications they have after using for eight weeks naproxen 500mg and omeprazole 20 mg per day (in this group, there are 200 patients) in comparison with patients (n=50) who have been treated with celecoxib 200mg per day for eight weeks.

Table 1

Clinical Signs	Patients treated with naproxen 500mg + omeprazole 20 mg for 8 weeks (n=200)	Patients treated with celecoxib 200mg for 8 weeks (n=50)	Total	P-value
Dyspepsia	40 (20.0)	2 (4.0)	42 (16.8)	0.007
Vomiting	20 (10.0)	1 (2.0)	21 (8.4)	0.068
Heartburning	30 (15.0)	4 (2.0)	31 (12.4)	0.013
Gastric ulcers (Fibrogastroscopy)	18 (9.0)	1 (2.0)	19 (7.6)	0.095

Tab. 1 explains a version of the results obtained from the clinical signs that rheumatoid arthritis patients have shown during treatment with naproxen 500mg + omeprazole 20 mg for 8 weeks and patients treated with celecoxib 200mg in a period of 8 weeks.

Forty-two patients (16.8%) had dyspepsia, of which forty patients were treated with naproxen + omeprazole and two patients treated with celecoxib (p = 0.007), and the conclusion is statistically significant. Twenty-one patients (8.4%) had vomiting; from them, only one patient was treated with the celecoxib (p = 0.068). Thirty-one patients (12.4%) complained of heartburning; 30 patients were treated with naproxen + omeprazole and one patient with celecoxib

(p = 0.013). The result is statistically significant. Gastric ulcer was confirmed endoscopically in 19 (7.6%) cases, where 18 treated with naproxen + omeprazole, and one was treated with celecoxib (p = 0.095).

Figure 1

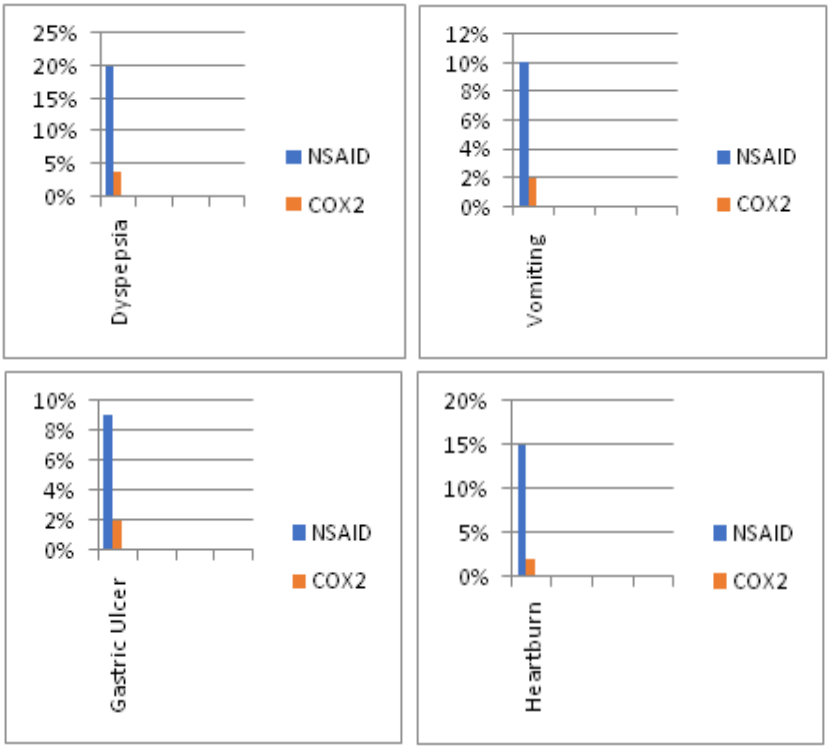

Fig. 1 shows us a simple graphical illustration of how the side effects are manifested in patients treatment with naproxen 500mg + omeprazole 20 mg and in patients treated with celecoxib 200mg for a period of 8 weeks.

Discussion

Non-steroidal anti-inflammatory drugs (NSAIDs) are generally prescribed and recommended to treat pain in arthritis rheumatoid. While measured to have a good effect on pain in arthritis rheumatoid, NSAIDs have been connected with wide-ranging adverse events affecting the gastrointestinal. Our study has a significant meaning in helping with therapeutic decisions on the appropriate choice of medications for patients with AR by having the minimum side effect in the gastrointestinal tract. Gastrointestinal complications are found with all NSAIDs, but recent studies have found that gastric events may be reduced by taking the suitable NSAID, which probably is COX-2 (celecoxib). However, celecoxib presented significant reductions in the risk for several outcomes compared with other commonly used NSAIDs (naproxen 500mg + omeprazole 20 mg)[22]. Rheumatoid arthritis is a chronic disease that has no remedy. Rheumatoid arthritis is a

chronic disease that has no remedy. However, the drugs used to treat rheumatoid arthritis also have potential side effects, which often are not well-tolerated. Still, future approaches are focus on improving medical therapies that offer a better quality of life. The ideal NSAID as a medical treatment is more selective for COX-2 than COX-1.

Strategies to reduce the risk for damage to the gastrointestinal tract have introduced the transition to other types of drugs; lower dose systemic NSAIDs, and topical NSAIDs. In addition, there are other strategies include the joining of prostaglandin analogs, H2 receptor antagonists, or proton pump inhibitors as concomitant therapies. Immediate diagnosis and intervention are fundamental for the prevention of serious damage and loss of essential bodily functions[23]. Moreover, early referral to a specialist can improve to guarantee better treatment outcomes. Traditional treatment modalities have been optimized, and new ones have been produced.

Conclusion

COX-2 selective, present fewer gastrointestinal side effects than NSAIDs (COX-1) associated with PPIs. It is essential to underline that COX-2 are more expensive. Physicians need to balance the reduced risk of gastrointestinal side effects and higher costs arising from selective COX-2 inhibitors.

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