DOI: 10.4274/tjcd.galenos.2023.2023-3-1
Turk J Colorectal Dis 2023;33:92-102

REVIEW

Systematic Review of the Effect of Non-steroidal Anti-Inflammatory Drugs on the Exacerbation of Inflammatory Bowel Disease

Monia Hayazei[1,2], Manar Abed[1,3], Semra Demirli Atıcı[1,4,5], Shahzaib Ahmad[1,6], Alaa El-Hussuna[1]

[1]OpenSourceResearch Collaboration, Aalborg, Denmark
[2]Southern Jutland Psychiatric Hospital, Department of General Surgery, Aalborg, Denmark
[3]Aalborg University Hospital, Department of General Surgery, Aalborg, Denmark
[4]KRC Private Center for Colorectal Surgery and Peritoneal Surface Malignancies, İzmir, Turkey
[5]Acıbadem Kent Hospital, Department of General Surgery, İzmir, Turkey
[6]King Edward Medical University-Mayo Hospital, Department of General Surgery, Lahore, Pakistan

ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) are generally thought to be associated with an increased risk of inflammatory bowel disease (IBD) exacerbation. The aim of this systematic review is to investigate evidence on the role of NSAIDs in the exacerbation of IBD. Studies were identified by searching the electronic PubMed, EmBase, and Cochrane databases for articles published-up to December 2019. Data on patients, study methodology, study quality, trial setting (single or multicenter, secondary or tertiary center/department, country of origin), duration of follow-up, outcomes assessed, the definition of assessed outcome measures, intervention characteristics (type, dose, duration, mode of administration), and outcome measures were extracted. Due to the heterogeneity of the included studies, no data synthesis was performed. It remains unclear whether there is a consistent association between NSAID use and the risk of Crohn's disease and ulcerative colitis exacerbation and whether NSAIDs are important in triggering IBD relapse.

Keywords: Inflammatory bowel disease, Crohn's disease, ulcerative colitis, non-steroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitor

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are a widely used group of pharmaceutical agents. In addition to being distributed by prescription, NSAIDs are distributed as over-the-counter products and are a component of many different drug formulations. Thus, many patients may unknowingly ingest NSAIDs, which can cause a variety of colonic abnormalities including colitis, ulcers, and strictures.[1]

The mechanisms of damage caused by NSAIDs to the bowel mucosa involve the activities of prostaglandin-endoperoxide synthase 1 [PTGS1 or cyclooxygenase-1 (COX-1)] and PTGS2 (COX-2). Moreover, NSAIDs interact with phospholipids and uncouple mitochondrial oxidative phosphorylation, which initiates biochemical changes that impair the function of the gastrointestinal barrier. The resulting increase in intestinal permeability leads to low-grade inflammation. Furthermore, the NSAID's inhibition of COX enzymes, along with luminal aggressors, results in erosions and ulcers, with the potential complications of bleeding, protein loss, stricture formation, and perforation.[2]

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), refers to chronic inflammatory disorders of the gastrointestinal tract (GIT) identified by episodes of relapse and remission.[3] The two identified subtypes of the disease involve the GIT in different patterns.[3,4] IBD is thought to result from an inappropriate inflammatory response to gut microbial flora in genetically predisposed individuals.[5]

Address for Correspondence: Semra Demirli Atıcı, MD,
Acıbadem Kent Hospital, Department of General Surgery, İzmir, Turkey
E-mail: smrdemirli@hotmail.com **ORCID ID:** orcid.org/0000-0002-8287-067X
Received: 02.04.2023 **Accepted:** 10.09.2023

The NSAID mechanism of action has raised questions over whether these drugs can exacerbate IBD. These questions have been debated in many studies with divergent results.

The aim of this systematic review is to investigate evidence on the role NSAIDs play in the exacerbation of IBD.

Method

Study design: The review was conducted and reported in accordance with the recommendations in the Cochrane Handbook for Reviews of Interventions (http://www.cochrane.org) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (Figure 1).[6]

Outcome measures: The primary outcome is disease exacerbation defined as a flare of disease activity after a period of remission.

The secondary outcome measure is the worsening of disease activity in patients with active IBD. An active IBD is defined as the following: an IBD usually runs a waxing and waning course. When there is severe inflammation, the disease is considered active, and the person experiences a flare of symptoms. When there is less or no inflammation, the person usually is without symptoms and the disease is said to be in remission.[6]

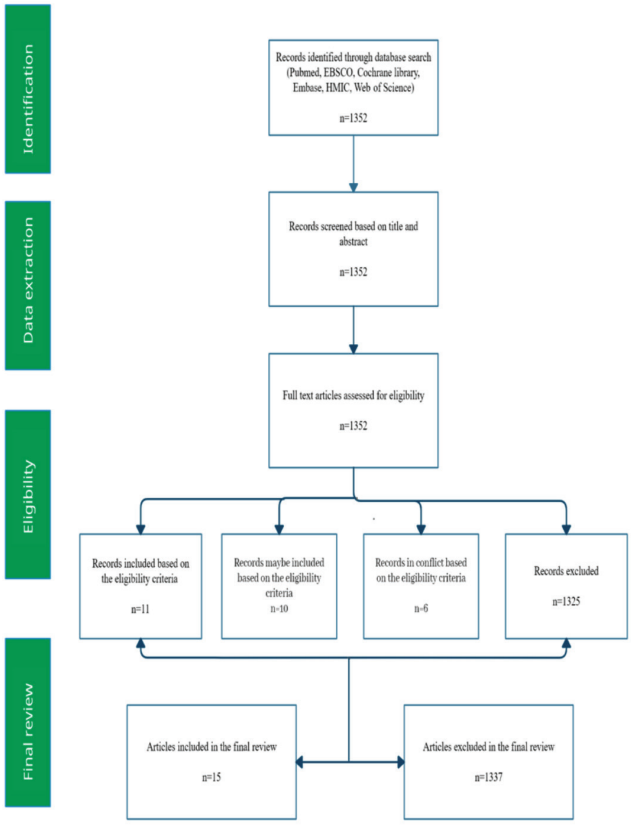

Figure 1. Preferred reporting items for systematic reviews and Preferred Reporting Items for Systematic Reviews and Meta-Analyses[6] flow diagram

Eligibility criteria:

1. Patients with IBD, including CD and UC in addition to microscopic colitis and collagen colitis.
2. No age limits.
3. All known NSAIDs, including non-specific COX inhibitors (such as aspirin, paracetamol, and ibuprofen) and COX-2 inhibitors (such as celecoxib, etoricoxib, and parecoxib). Rofecoxib and valdecoxib, which were withdrawn from the market in 2004 and 2005, respectively, because they excessively increased the risk of heart attacks and strokes with long-term use, are also included in the review, when found, as they may have caused an inflammatory effect while prescribed to patients.
4. Duration of using NSAIDs.
5. Oral, intravenous, or other methods of drug intake.
6. All observational studies (case-control and cohort studies), interventional studies [blinded or non-blinded randomized controlled trials (RCTs)], and other reviews (narrative and systematic reviews).

Studies on humans published between 2000 and 2020 were included to ensure up-to-date data. No language limit was used.

Studies were identified by searching the electronic PubMed, EmBase, and Cochrane databases. The reference lists in relevant papers were also screened for any additional studies. Additional trials were identified through the World Health Organization search portal (www.who.int/trialsearch).

The search was conducted by two authors (MH, AE). The last search date was December 6, 2019.

The search thread used was as follows:

((((((((((“anti-inflammatory agents, non-steroidal”[MeSH Terms] OR “nonsteroidal anti inflammatory”[Text Word]) OR “non steroidal anti inflammatory”[Text Word]) OR “non steroidal antiinflammatory”[Text Word]) OR “nonsteroidal antiinflammatory”[Text Word]) OR “NSAID”[Text Word]) OR “cyclooxygenase inhibitor*”[Text Word]) OR “cox inhibitor*”[Text Word]) OR “anti inflammatory analgesi*”[Text Word]) OR “anti inflammatory agent*”[Text Word]) AND (((((“Inflammatory Bowel Diseases”[MeSH Terms] OR “inflammatory bowel dis*”[Text Word]) OR “crohn*”[Text Word]) OR “colitis”[Text Word]) OR “irritable bowel dis*”[Text Word]) OR “irritable bowel syn*”[Text Word])) NOT ((((“Animals”[Mesh]) OR (mice[Text Word] OR rats[Text Word] OR rabbit*[Text Word])) NOT (((“Animals”[Mesh]) OR (mice[Text Word] OR rats[Text Word] OR rabbit*[Text Word])) AND (“Humans”[Mesh])))) AND ((((((((((“anti-inflammatory agents, non-steroidal”[MeSH Terms] OR “nonsteroidal anti inflammatory”[Text Word]) OR “non steroidal anti inflammatory”[Text Word]) OR “non steroidal antiinflammatory”[Text Word]) OR “nonsteroidal

antiinflammatory"[Text Word]) OR "NSAID"[Text Word]) OR "cyclooxygenase inhibitor*"[Text Word]) OR "cox inhibitor*"[Text Word]) OR "anti inflammatory analgesi*"[Text Word]) OR "anti inflammatory agent*"[Text Word]) AND (((((("Inflammatory Bowel Diseases"[MeSH Terms] OR "inflammatory bowel dis*"[Text Word]) OR "crohn*"[Text Word]) OR "colitis"[Text Word]) OR "irritable bowel dis*"[Text Word]) OR "irritable bowel syn*"[Text Word]))))) AND ((("Systematic Review"[Publication Type] OR "Systematic Reviews as Topic"[Mesh] OR systematic[sb] OR "Meta-Analysis as Topic"[Mesh] OR "Meta-Analysis" [Publication Type] OR metaanalys*[Title] OR meta-analys*[Title])) OR ((((((("Controlled Clinical Trial"[Publication Type] OR "Controlled Clinical Trials as Topic"[Mesh])) OR (((random*[Text Word] OR controlled[Text Word] OR crossover[Text Word] OR cross-over[Text Word] OR blind*[Text Word] OR mask*[Text Word])) AND (trial[Text Word] OR trials[Text Word] OR study[Text Word] OR studies[Text Word] OR analys*[Text Word] OR analyz*[Text Word]))) OR rct[Text Word]) OR (((singl*[Text Word] OR doubl*[Text Word] OR tripl*[Text Word])) AND (blind[Text Word] OR mask[Text Word]))) OR placebo[Text Word]))

All studies identified by the search were screened for inclusion, primarily based on title and abstract. Eligible studies were retrieved in full text. Three authors (MH, MA, SDA) performed the inclusion/exclusion phase of the study. Any disagreement was resolved by discussion among the three authors or involvement of a senior author (AE).

A Rayyan intelligent systematic review was used for the inclusion/exclusion phase.[7]

This web-based application allows a blinded inclusion/exclusion of studies to be conducted and then disagreements to be resolved.

Data extraction: Three authors (M.H., M.A., and S.D.A.) independently extracted data based on the pre-defined study protocol's inclusion criteria. Differences were resolved by consulting senior author (A.E.H.).

Data on patients, study methodology, study quality [case-control and cohort studies, interventional studies (blinded or non-blinded RCTs), narrative and systematic reviews], trial setting (single or multicenter, secondary or tertiary center/department, country of origin), duration of follow-up, outcomes assessed, definition of assessed outcome measures, intervention characteristics (type, dose, duration, mode of administration), and outcome measures were extracted.

No data synthesis was performed due to the heterogeneity of the included studies and inherent qualitative differences among studies.

Risk of bias in individual studies: The quality of bias control in the included studies was assessed by three authors independently of each other. The Cochrane risk-of-bias tool can be used for randomized trials and the Newcastle-Ottawa Scale to assess bias in observational studies. To assess bias (MH, MA, and SDA) in the included randomized trials, we used the Cochrane risk-of-bias tool for RCTs (RoB 2.0),[8] which focuses on random sequence generation (selection bias), allocation concealment (selection bias), the blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). The Newcastle-Ottawa Scale is used to assess the quality of non-randomized studies included in a systematic review.[9] Each study was assigned a number of stars based on the selection of patients (maximum 4 stars), the comparability of cohorts (maximum 2 stars), and the ascertainment of the outcome (maximum 3 stars). The lower the number of stars is, the greater the risk of bias.

Results

In total, 1,352 articles were selected, with 11 included based on the inclusion criteria, 1,325 excluded based on the exclusion criteria, 6 disputed, and 10 that might be included. The final review included 15 articles after reading the full research text. These 15 studies were undertaken between 2000 and 2020: 1 double-blind placebo-controlled study, 1 prospective randomized placebo-controlled pilot study, 1 prospective open-label trial, 1 prospective open-label monocentric trial, 1 retrospective case-control trial, 1 prospective case-control trial, 7 systematic reviews, and 2 meta-analyses published before December 2019.[10-24] The number of participants per study ranged from 11 to 217 for the prospective and retrospective case-control, randomized, and placebo-controlled studies. The number of studies included in the meta-analyses varied between 2 and 21. The study characteristics are summarized in Table 1, 2.

Quality assessment results

Studies involving the relationship between NSAID use and IBD disease exacerbation, disease exacerbation after the IBD remission period, and the worsening of disease activity in patients with active IBD are described in Table 1, 2. The number of studies included in the meta-analyses varied between 2 and 21. The number of participants per study ranged from 11 to 217 for the prospective and retrospective case-control, randomized, and placebo-controlled studies. Using RoB 2.0, we assessed the risk of bias in the randomized trials (Table 3), and quality was assessed using the Newcastle-Ottawa Scale due to inherent qualitative differences between studies (Table 4).

Table 1. Observational studies (prospective and retrospective cohorts) and randomized controlled trials included in this systematic review

Author	Study type	Published year	Disease	Drugs used	Duration of medication	Aim	No. of participating patients	Conclusion
El Miedany et al.[10]	(Prospective) double-blind placebo-controlled study	2006	IBD	Etoricoxib tablets of 60-120 mg once a day	1 and 3 months	Gastrointestinal safety and effect on disease activity of etoricoxib, a selective COX-2 inhibitor in IBD	76 patients: UC (38) and (CD) (38). The control group included 70 patients known to have UC (35) and CD (35)	Etoricoxib therapy is safe and beneficial in most patients with IBD. Treatment with etoricoxib was not associated with the exacerbation of the underlying IBD-related and gastrointestinal-related complications.
Sandborn et al.[11]	(Prospective) randomized placebo-controlled pilot study	2006	UC	200 mg of oral celecoxib or placebo twice daily for 14 days	14 days	Safety of celecoxib in patients with UC in remission: A randomized placebo-controlled pilot study	217 patients (110 celecoxib, 107 placebo)	Therapy with celecoxib for up to 14 days did not have a greater relapse rate than placebo in patients with UC in remission who had a present or past history of non-specific arthritis, arthralgia, or other condition amenable to NSAIDs.
Biancone et al.[12]	(Prospective) open-label trial	2004	IBD	Rofecoxib (12.5 mg/day)	3 days to 3 months	Rofecoxib and early relapse of IBD	IBD group included 45 inactive patients (CD activity index <150 or UC [Mayo score <4]; 25 patients with CD and 20 with UC) with associated arthralgia. The control group included 30 patients with dyspepsia	Rofecoxib appears to control arthralgia in almost two-thirds of patients with IBD. Side effects requiring drug discontinuation are observed but only in one-quarter of patients (during the first few days of treatment).
Reinisch et al.[13]	(Prospective) open-label monocentric trial	2003	IBD (UC, CD, indeterminate colitis)	Rofecoxib (12.5 mg/day) Rofecoxib (25 mg/day)	20 days	To evaluate the safety and efficacy of rofecoxib in patients with IBD with associated peripheral arthropathy and/or arthritis	Rofecoxib (12.5 mg/day) (n=6) Rofecoxib (25 mg/day) (n=26) Total patients=32	No IBD flares occurred during the treatment phase. The CD activity index decreased; in patients with UC, the changes in the clinical disease activity index were non-significant throughout the study. The risk of aggravating intestinal symptoms by the administration of COX inhibitors may be low and mainly restricted to patients with signs of active disease.
Mahadevan et al.[14]	(Retrospective study) retrospective review chart	2002	IBD, UC, CD, pouchitis	Celecoxib or rofecoxib	9 months (range 1 week to 22 months)	Safety of selective COX-2 inhibitors in IBD	11 patients were treated with celecoxib (median dose 200 mg/day) and 16 with rofecoxib (median dose 25 mg/day)	The preliminary results suggest that COX-2 inhibitors may be safe and beneficial in most patients with IBD, but the safety of COX-2 inhibitors in patients with IBD needs to be prospectively assessed in a placebo-controlled trial.

Table 1. Continued

Author	Study type	Published year	Disease	Drugs used	Duration of medication	Aim	No. of participating patients	Conclusion
Beaugerie et al.[15]	(Prospective) case-control study	2001	Patient with rheumatoid arthritis without diarrhea (patient underwent a surveillance colonoscopy)	NSAIDs (type unspecified)	3 months	Identify alterations in the colonic mucosa of patients without diarrhea receiving NSAIDs, with the focus on intraepithelial lymphocyte count, epithelial apoptosis, and immunobiological features of immune cell activation	Group 1: Patient with rheumatoid arthritis without diarrhea and taking NSAIDs. Group 2: Patient with rheumatoid arthritis without diarrhea and NOT taking NSAIDs. Group 3: Surveillance colonoscopy due to benign polyps or colectomy colorectal cancer	The chronic use of NSAIDs does not result in constant inflammatory changes in colonic mucosa in humans. No changes in the colon mucosa were observed in patients with non-diarrhea rheumatoid arthritis on long-term NSAID therapy.

IBD: Inflammatory bowel disease, UC: Ulcerative colitis, CD: Crohn's disease, COX-2: Cyclooxygenase-2, NSAID: Non-steroidal anti-inflammatory drug

The publication year of the studies, subtype of inflammatory disease, type and dose of NSAIDs used in treatment, duration of NSAID drug use, and results were reviewed.

Summary of the study findings: The results of the included studies are summarized in Table 1, 2.[10-24] Three of the observational studies included in this review investigated the impact of rofecoxib in flares of IBD, reporting no flares.[12-14] Similarly, a study reported that etoricoxib was safe in cases of IBD.[10] Two studies determined that celecoxib was unrelated to IBD flares and could be used for the management of inflammatory symptoms where indicated,[11,14] as detailed in Table 1.[10-15]

Five out of 9 review studies (systematic reviews and meta-analyses) documented that NSAIDs induce relapse in IBD as a result of unknown mechanisms and induce colitis in previously asymptomatic patients. However, some studies reinforced the safety of selective COX-2 inhibitors.[20,21] The evidence synthesis in these reviews was weak, and studies with a greater sample size were recommended.[22-24]

Discussion

Active infection such as amoeba, parasite, bacterial, and viral infections in blood smear and/or stool cultures, presence of cytomegalo-virus pp65 and clostridium difficult toxin a and b antigens, use of NSAIDs, drug compliance, and type of current treatment (corticosteroid, salicylates, immunosuppressive drugs, and anti-tumor necrosis factor) were considered causes of exacerbation.[12,25,26]

Regarding the administration of NSAIDs, according to consensus guidelines from the British Society of Gastroenterology, individuals with UC (including those with extensive disease) should be given a mix of oral and enema 5-ASA, and those who do not respond well to oral 5-ASA should also receive topical medication.[27] Even in patients with pancolitis, oral and topical 5-ASA therapy is preferable to monotherapy. Despite the clear advantages of enema therapy, patients continue to find the administration and maintenance of enemas difficult, and support and education in this area are urgently required.[26]

The most common indications of the use of NSAIDs in IBD are extraintestinal manifestations, such as IBD-associated arthralgia, ankylosing spondylitis, sacroiliitis, and arthritis. However, the use of these drugs in the management of extraintestinal symptoms may lead to the exacerbation of the disease itself.[28] Hence, it is important to consider the side effects of such medications for extraintestinal manifestations because of their potential role in disease exacerbation. According to the American College of Gastroenterology, the use of NSAIDs is a possible trigger for disease exacerbation in patients with diagnosed IBD.[29] Similarly, Evans et al.[30] noted that NSAIDs play a role in relapse in patients with IBD. Therefore, patients with IBD are encouraged to avoid using NSAIDs because of concerns relating to their potential

Table 2. Published reviews on the effects of NSAIDs on IBD exacerbation

Author	Study type	Published year	Disease	Drugs used	Duration of medication	Aim	No. of studies involved	Conclusion
Forrest et al.[16]	Systematic review	2004	IBD	NSAIDs + paracetamol	Ranged from 2 hours to 6 weeks	To assess whether ingestion of paracetamol or NSAIDs is associated with IBD exacerbation	17 related to NSAIDs	NSAIDs may precipitate a relapse in some patients with IBD. This may be an idiosyncratic reaction. The published evidence does not support the view that NSAIDs are key to inducing IBD relapse. There is weak evidence that paracetamol may be more crucial
Ballinger[17]	Systematic review	2008	IBD (all types)	NSAIDs (all types)	Not mentioned	Adverse effects of NSAIDs on the colon	17	NSAIDs can induce colitis in a previously normal bowel, and symptoms can be indistinguishable from idiopathic IBD. Limited evidence suggests that NSAIDs may exacerbate preexisting IBD and should be prescribed cautiously to patients with IBD. NSAID ingestion is also associated with the development of collagenous colitis
Kefalakes et al. [18]	Systematic review	2009	IBD (all types)	NSAIDs (conventional and selective COX-2)	Not mentioned	Exacerbation of IBD associated with the use of NSAIDs	21	The available data remain contradictory and confusing, and it remains uncertain whether COX-2 inhibitors are safer than conventional NSAIDs. Further randomized double-blind trials should be performed
Singh et al.[19]	Systematic review	2009	IBD	NSAIDs (type unspecified)	Not mentioned	Whether NSAIDs, infection, antibiotics, or stress trigger flares in IBD	7 related to NSAIDs	The evidence to date does not support NSAID use as an initiator. Methodological difficulties and ambiguities were identified in the study results, limiting the ability to draw firm conclusions. To date, there is insufficient evidence to warrant NSAID avoidance in IBD among patients who require them for joint-related symptoms
Paiotti et al.[20]	Systematic review	2012	IBD (all types)	NSAIDs and COX-2 inhibitors	Not mentioned	The role of NSAIDs and COX-2 inhibitors in experimental colitis	13 studies (controlled trials, original articles, case reports, and reviews)	More studies should be conducted using a broader spectrum of cases of colitis to verify that patients with a history of IBD should avoid using NSAIDs. The relative role of COX-2 selective inhibitors in human and experimental colitis remains to be explored
Lanas et al.[21]	Systematic review	2014	IBD (UC, CD)	NSAIDs (all types), low-dose aspirin, paracetamol	Not mentioned	Safe prescription recommendations for NSAIDs: Consensus document elaborated by nominated experts of three scientific associations	7	In patients suffering from IBD, the use of NSAIDs should be avoided. NSAIDs should be used in quiescent phases of the disease, the use of COX inhibitors is recommended at low doses for a short time

Table 2. Continued

Author	Study type	Published year	Disease	Drugs used	Duration of medication	Aim	No. of studies involved	Conclusion
Miao et al.[22]	Systematic review	2014	IBD with rheumatological manifestations	COX-2 inhibitors, etoricoxib (60 to 120 mg/day) OR celecoxib (200 mg twice daily), and placebo	2-12 weeks	Evaluate the tolerability and safety of COX-2 inhibitors used for the treatment of rheumatological manifestations of IBD	Two randomized controlled trials comparing COX-2 inhibitors with placebo	Celecoxib and etoricoxib do not exacerbate IBD symptoms. However, both studies had relatively small sample sizes and short follow-up durations
Ribaldone et al.[23]	Meta-analysis	2015	IBD (UC, CD)	COX-2 inhibitors and placebo	3 days to 3 months	To show whether COX-2 inhibitors are associated with an increased risk of IBD exacerbation compared with placebo	7 studies (including patients with IBD that had to stop COX inhibitor therapy because IBD activity deteriorated)	COX inhibitors are safe in most patients with IBD (no difference in gastrointestinal adverse events in the COX inhibitor and placebo groups)
Moninuola et al.[24]	Meta-analysis	2018	IBD	NSAIDs and acetaminophen	15 days to 48 weeks	To examine the association between acetaminophen and NSAIDs, including COX-2 inhibitor use, and risk of CD and UC exacerbation	18 studies	No consistent association between NSAID use and the risk of CD and UC exacerbation. No consistent evidence for an association with acetaminophen

IBD: Inflammatory bowel disease, NSAID: Non-steroidal anti-inflammatory drug, COX-2: Cyclooxygenase-2, UC: Ulcerative colitis, CD: Crohn's disease

Table 3. Risk-of-bias assessment using Revised Cochrane risk-of-bias for randomized trials software

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
El Miedany et al.[10]	?	?	+	?	+	+	+
Sandborn et al.[11]	+	+	+	+	+	+	+

Risk-of-bias assessment: +: Low, ?: Unclear

Table 4. Risk-of-bias assessment (Newcastle-Ottawa Quality Assessment Scale Criteria) for case-control and cohort studies

Study	Selection				Comparability	Outcome			Quality score
	Representativeness of exposed cohort	Selection of the non-exposed cohort from the same source as the exposed cohort	Ascertainment of exposure	Outcome of interest was not present at the start of the study	Comparability of cohorts	Assessment of outcomes	Follow-up long enough for outcomes to occur (median duration of follow-up ≥6 months)	Adequacy of follow-up	
Biancone et al.[12]	Prospective open-label trial★	Yes★	Yes★	Yes★	The IBD group included 45 inactive patients (25 CD; 20 UC) with associated arthralgia. The control group included 30 patients with dyspepsia★	Rofecoxib and early relapse of IBD★	No	3 days to 3 months	Good
Reinisch et al.[13]	Prospective open-label monocentric trial★	Yes★	IBD (UC, CD, indeterminate colitis)	Yes★	To evaluate the safety and efficacy of rofecoxib in patients with IBD with associated peripheral arthropathy and/or arthritis★	No IBD flares occurred during the treatment phase. The CD activity index decreased; in patients with UC, changes in the clinical disease activity index were non-significant throughout the study. The risk of aggravating intestinal symptoms by the administration of COX inhibitors may be low and mainly restricted to patients with signs of active disease★	No	20 days	Fair
Mahadevan et al.[14]	Retrospective study, retrospective review chart★	No	IBD, UC, CD, pouchitis	Yes★	Retrospective review	Safety of selective COX-2 Inhibitors in IBD★	No	9 months (range 1-22 weeks) months)★	Fair

Table 4. Continued

Study	Selection			Comparability	Outcome			Quality score
Beaugerie et al.[15]	Patient with rheumatoid arthritis without diarrhea (patient underwent surveillance colonoscopy)★	Yes★	Patient with rheumatoid arthritis without diarrhea and taking NSAIDs. Group 2: Patient with rheumatoid arthritis without diarrhea and NOT taking NSAIDs. Group 3: Surveillance colonoscopy due to benign polyps or colectomy for colorectal cancer★	Yes★	Group 1: Patient with rheumatoid arthritis without diarrhea and taking NSAIDs. Group 2: Patient with rheumatoid arthritis without diarrhea and NOT taking NSAIDs. Group 3: Surveillance colonoscopy due to benign polyps or colectomy for colorectal cancer★	Chronic use of NSAIDs does not result in constant inflammatory changes in colonic mucosa in humans. No changes in the colon mucosa were observed in patients with non-diarrhea rheumatoid arthritis on long-term NSAID therapy★	Yes★	3 months	Good

Good quality: 3 or 4 stars (★) in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome domain, Fair quality: 2 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome/exposure domain, Poor quality: 0 or 1 star in the selection domain OR 0 stars in the comparability domain OR 0 or 1 stars in the outcome/exposure domain. CD: Crohn's disease, UC: Ulcerative colitis, IBD: Inflammatory bowel disease, NSAID: Non-steroidal anti-inflammatory drug, COX-2: Cyclooxygenase-2

adverse effects on disease activity. In addition, Takeuchi et al.[31] reported that non-selective NSAID intake is associated with the frequent and early clinical recurrence of IBD, as measured using the Harvey-Bradshaw Clinical Disease Activity Index.

Regarding the possible mechanism involved in the pathophysiology of gastrointestinal damage, several mechanisms have been proposed.[2] COX-1 and COX-2, when used concomitantly, cause damage to gastric mucosa by reducing blood flow and increasing the tendency of leukocytes to adhere to the blood vessels of the GIT, thus decreasing GIT defense.[32] Although this is not the only manner in which NSAIDs can harm the gastrointestinal mucosa, the inhibition of prostaglandin synthesis is crucial in the development of mucosal injury.[33,34]

Moreover, NSAIDs cause gastrointestinal damage by interacting with cellular phospholipids and oxidative phosphorylation.[35] These drugs frequently uncouple mitochondrial oxidative phosphorylation processes, leading to changes associated with a weakened gastrointestinal barrier. These biochemical changes are important in the pathophysiology of the disease, causing intestinal permeability to rise, which then causes low-grade inflammation. Erosion and ulceration are the outcomes of the NSAID suppression of COX enzymes in conjunction with luminal aggressors, with the possibility of perforation, hemorrhage, stricture development, and protein loss as sequelae.[2,34,36]

The aforementioned processes might be used to account for the biological plausibility of IBD exacerbation with NSAID use. Because the major therapeutic objective of medicinal interventions for IBD is intestinal mucosal repair, non-selective COX inhibitors may cause GIT mucosal injury, which could delay healing. Similarly, NSAID use may lead to frequent relapses, as revealed by Forrest et al.[16]. However, the possible safety of selective COX-2 inhibitors may be explained by their lower interaction with the gastrointestinal barrier.

Study Limitations

This study has several limitations, such as the heterogeneity of the included studies. Even well-designed studies on NSAID use and IBD exacerbation risk have significant limitations in defining outcomes. Although some studies have defined the exacerbation of the disease as a subjective criterion, such as emergency admission to the hospital, there are also more objective studies using the "disease activity index."

Conclusion

The published data remain contradictory and confusing. No consistent association between NSAID use and the risk of CD

and UC exacerbation has been established, and it remains uncertain whether NSAIDs are key to inducing IBD relapse.

Peer-review: Externally peer-reviewed.

Acknowledgement: OpenSourceResearch collaboration is an international independent organization with special focus on implementing information technologies and artificial intelligence in clinical research. More about the organization and its projects can be found on its website: OSRC.network

Authorship Contributions

Concept: A.E.H., Design: M.H., A.E.H., Data Collection or Processing: M.H., M.A., S.D.A., Analysis or Interpretation: S.A., Literature Search: M.H., M.A., S.D.A., S.A., A.E.H., Writing: M.H., M.A., S.D.A., S.A., A.E.H.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Goldstein NS, Cinenza AN. The histopathology of nonsteroidal anti-inflammatory drug-associated colitis. Am J Clin Pathol 1998;110:622-628.
2. Bjarnason I, Scarpignato C, Holmgren E, Olszewski M, Rainsford KD, Lanas A. Mechanisms of damage to the gastrointestinal tract from nonsteroidal anti-inflammatory drugs. Gastroenterology 2018;154:500-514.
3. Rogler G, Singh A, Kavanaugh A, Rubin DT. Extraintestinal manifestations of inflammatory bowel disease: current concepts, treatment, and implications for disease management. Gastroenterology 2021;161:1118-1132.
4. Mansour-Ghanaei F, Haghkerdar M, Joukar F, Aminian K, Yousefi Mashhour M, Shafaghi A, Fakhriyeh Asl S, Ghanavi Z. Epidemiologic Features of inflammatory bowel disease in guilan province, North of Iran, during 2002-2012. Middle East J Dig Dis 2015;7:69-74.
5. Eremin O, Sewell H, (eds). Essential Immunology for Surgeons. Oxford, 2011; Oxford Academic. URL: https://doi.org/10.1093/med/9780199586875.001.0001
6. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 2009;6:e1000097.
7. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev 2016;5:210.
8. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.
9. Stang A. Critical evaluation of the Newcastle-Ottawa Scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603-605.
10. El Miedany Y, Youssef S, Ahmed I, El Gaafary M. The gastrointestinal safety and effect on disease activity of etoricoxib, a selective cox-2 inhibitor in inflammatory bowel diseases. Am J Gastroenterol 2006;101:311-317.
11. Sandborn WJ, Stenson WF, Brynskov J, Lorenz RG, Steidle GM, Robbins JL, Kent JD, Bloom BJ. Safety of celecoxib in patients with ulcerative colitis in remission: a randomized, placebo-controlled, pilot study. Clin Gastroenterol Hepatol 2006;4:203-211.
12. Biancone L, Tosti C, Geremia A, Fina D, Petruzziello C, Emerenziani S, Pallone F. Rofecoxib and early relapse of inflammatory bowel disease: an open-label trial. Aliment Pharmacol Ther 2004;19:755-764.
13. Reinisch W, Miehsler W, Dejaco C, Harrer M, Waldhoer T, Lichtenberger C, Vogelsang H. An open-label trial of the selective cyclo-oxygenase-2 inhibitor, rofecoxib, in inflammatory bowel disease-associated peripheral arthritis and arthralgia. Aliment Pharmacol Ther 2003;17:1371-1380.
14. Mahadevan U, Loftus EV Jr, Tremaine WJ, Sandborn WJ. Safety of selective cyclooxygenase-2 inhibitors in inflammatory bowel disease. Am J Gastroenterol 2002;97:910-914.
15. Beaugerie L, Berenbaum F, Berrebi D, Gendre JP, Prier A, Kaplan G, Chatelet FP. Chronic use of non-steroidal anti-inflammatory drugs does not alter colonic mucosa of patients without diarrhoea. Aliment Pharmacol Ther 2001;15:1301-1306.
16. Forrest K, Symmons D, Foster P. Systematic review: is ingestion of paracetamol or non-steroidal anti-inflammatory drugs associated with exacerbations of inflammatory bowel disease? Aliment Pharmacol Ther 2004;20:1035-1043.
17. Ballinger A. Adverse effects of nonsteroidal anti-inflammatory drugs on the colon. Curr Gastroenterol Rep 2008;10:485-489.
18. Kefalakes H, Stylianides TJ, Amanakis G, Kolios G. Exacerbation of inflammatory bowel diseases associated with the use of nonsteroidal anti-inflammatory drugs: myth or reality? Eur J Clin Pharmacol 2009;65:963-970.
19. Singh S, Graff LA, Bernstein CN. Do NSAIDs, antibiotics, infections, or stress trigger flares in IBD? Am J Gastroenterol 2009;104:1298-1313; quiz 1314.
20. Paiotti AP, Marchi P, Miszputen SJ, Oshima CT, Franco M, Ribeiro DA. The role of nonsteroidal antiinflammatory drugs and cyclooxygenase-2 inhibitors on experimental colitis. In Vivo 2012;26:381-393.
21. Lanas A, Benito P, Alonso J, Hernández-Cruz B, Barón-Esquivias G, Perez-Aísa A, Calvet X, García-Llorente JF, Gobbo M, Gonzalez-Juanatey JR. Safe prescription recommendations for non steroidal anti-inflammatory drugs: Consensus document ellaborated by nominated experts of three scientific associations (SER-SEC-AEG). Gastroenterol Hepatol 2014;37:107-127.
22. Miao XP, Li JS, Ouyang Q, Hu RW, Zhang Y, Li HY. Tolerability of selective cyclooxygenase 2 inhibitors used for the treatment of rheumatological manifestations of inflammatory bowel disease. Cochrane Database Syst Rev 2014;CD007744.
23. Ribaldone DG, Fagoonee S, Astegiano M, De Angelis C, Smedile A, Caviglia GP, Petrini E, Greco A, Pellicano R. Coxib's safety in patients with inflammatory bowel diseases: a meta-analysis. Pain Physician 2015;18:599-607.
24. Moninuola OO, Milligan W, Lochhead P, Khalili H. Systematic review with meta-analysis: association between acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) and risk of Crohn's disease and ulcerative colitis exacerbation. Aliment Pharmacol Ther 2018;47:1428-1439.
25. Smale S, Tibble J, Sigthorsson G, Bjarnason I. Epidemiology and differential diagnosis of NSAID-induced injury to the mucosa of the small intestine. Best Pract Res Clin Gastroenterol 2001;15:723-738.
26. Wehkamp J, Götz M, Herrlinger K, Steurer W, Stange EF. Inflammatory bowel disease. Dtsch Arztebl Int 2016;113:72-82.
27. Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, Hayee B, Lomer MCE, Parkes GC, Selinger C, Barrett KJ, Davies RJ, Bennett C, Gittens S, Dunlop MG, Faiz O, Fraser A, Garrick V, Johnston PD, Parkes M, Sanderson J, Terry H; IBD guidelines eDelphi consensus group; Gaya DR, Iqbal TH, Taylor SA, Smith M, Brookes M, Hansen R, Hawthorne AB. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut 2019;68(Suppl 3):s1-s106.

28. Peluso R, Manguso F, Vitiello M, Iervolino S, Di Minno MN. Management of arthropathy in inflammatory bowel diseases. Ther Adv Chronic Dis 2015;6:65-77.
29. Kornbluth A, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol 2010;105:501-523.
30. Evans JM, McMahon AD, Murray FE, McDevitt DG, MacDonald TM. Non-steroidal anti-inflammatory drugs are associated with emergency admission to hospital for colitis due to inflammatory bowel disease. Gut 1997;40:619-622.
31. Takeuchi K, Smale S, Premchand P, Maiden L, Sherwood R, Thjodleifsson B, Bjornsson E, Bjarnason I. Prevalence and mechanism of nonsteroidal anti-inflammatory drug-induced clinical relapse in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2006;4:196-202.
32. Takeuchi K. Pathogenesis of NSAID-induced gastric damage: importance of cyclooxygenase inhibition and gastric hypermotility. World J Gastroenterol 2012;18:2147-2160.
33. Soreide K. Damage to the Gastrointestinal tract from nonsteroidal anti-inflammatory drugs: what about perforations and the healing intestine? Gastroenterology 2018;155:1271-1272.
34. Kareva EN. NSAID enteropathy. Ter Arkh 2020;92:85-92.
35. Leite AZ, Sipahi AM, Damião AO, Coelho AM, Garcez AT, Machado MC, Buchpiguel CA, Lopasso FP, Lordello ML, Agostinho CL, Laudanna AA. Protective effect of metronidazole on uncoupling mitochondrial oxidative phosphorylation induced by NSAID: a new mechanism. Gut 2001;48:163-167.
36. Sostres C, Gargallo CJ, Lanas A. Nonsteroidal anti-inflammatory drugs and upper and lower gastrointestinal mucosal damage. Arthritis Res Ther 2013;15(Suppl 3):S3.