JEIMP
E-ISSN: 2980-0617

The Journal of
European Internal Medicine Professionals

JEIMP
The Science

Original Article

Comparison of the Gastrointestinal Side Effects of Selective COX-2 Inhibitor Celecoxib and Indomethacin in Patients With Osteoarthritis

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10.5281/zenodo.11214305

J Eur Int Prof. Year; 2024, Volume: 2, Issue: 2 *Submitted at*: 14.04.2024, *Accepted at*: 05.05.2024, *Published at*: 19.05.2024

JEIMP belongs to "*The Foundation for the Management of Chronic Diseases***" and is supervised by the MKD Digital Publishing.** *www.jeimp.com and digitalmkd.com*

Abstract

Background: Nonsteroidal anti-inflammatory drugs are commonly prescribed for osteoarthritis management but are associated with gastrointestinal (GI) adverse events. This study aimed to compare GI findings in patients receiving indomethacin and celecoxib for osteoarthritis.

Methods: A retrospective analysis was conducted on 50 patients (42 females, 8 males) with osteoarthritis, divided into indomethacin (n=25) and celecoxib (n=25) groups. Clinical data, including age, gender, disease duration, and *H. pylori* status, were collected. Baseline and post-treatment gastroduodenoscopy findings were compared between groups.

Results: No cases of GI bleeding were reported. Indomethacin use was associated with a higher risk of gastroduodenal lesions compared to celecoxib ($p<0.05$). Celecoxib combined with proton pump inhibitors (PPIs) showed a slight improvement in gastric lesions. *H. pylori* prevalence was 86% in the study population.

Conclusion: Despite the absence of GI adverse events, indomethacin use posed a higher risk of gastroduodenal lesions compared to celecoxib. The addition of PPIs appeared to mitigate GI adverse events, particularly in the celecoxib group. Individualized treatment approaches balancing therapeutic benefits and potential adverse effects are essential in osteoarthritis management. Further research with larger sample sizes and longer follow-up durations is warranted to validate these findings.

Keywords: Nonsteroidal anti-inflammatory drugs, gastroduodenal lesions, celecoxib, indomethacin, proton pump inhibitors

INTRODUCTION

Osteoarthritis (OA) is the most common manifestation of arthritis and leading contributor to persistent pain and disability among the elderly (1-3). Obesity and ageing population are the two main factors associated with increasing prevalence of OA (3). World Health Organization reports more than 528 million people worldwide are living with OA; an increase of more tha 100% since 1990 (4). The knee is the most frequently affected joint, followed by the hip and the hand (4).

The treatment of OA includes surgical and non-surgical interventions. It is suggested that pharmacologic treatment should begin with acetaminophen and switch to nonsteroidal anti-inflammatory drugs (NSAIDs) if not responder to acetaminophen in patients with pain (5,6). Exercise is useful to reduce pain and disability, in adjunct to pharmacotherapy (6). Supplements such as glucosamine, chondroitin, collagen hydrolysate, passion fruit peel extract, Curcuma longa extract, Boswellia serrata extract, curcumin, pycnogenol and L-carnitine provided moderate and clinically meaningful treatment effects on pain and function in patients with hand, hip or knee osteoarthritis at short term, although the quality of evidence was very low (7). Corticosteroid injections provide immediate, short-term (four to eight weeks) relief of OA flare-ups of the knee, whereas hyaluronic acid injections provide symptom improvement for longer periods but have a higher cost. Total joint replacement of the hip, knee, or shoulder is recommended for suitable patients with persistent pain and disability despite

maximal medical therapy.

In the realm of OA treatment, NSAIDs have traditionally held a central position. However, recent studies have controversies on the widespread utilization of oral NSAIDs, emphasizing the higher prevalence of upper gastrointestinal (GI) complications and cardiovascular adverse events (CAEs) (8,9). A recent meta-analysis reported that celecoxib was the only NSAID associated with long-term pain improvement, better long-term GI tolerability than nonselective NSAIDs and is not associated with higher risk of CAEs (10). Chan et al. demonstrated 44.0% lower GI bleeding risk with celecoxib compared to naproxen (11).

Although previous studies reported lower GI adverse events with celecoxib, the most used selective cyclooxygenase-2 inhibitor, celecoxib carries an additional FDA-boxed warning for GI effects, including bleeding, ulceration, and perforation of the stomach and intestines (12).

In this study, we aim to re-discuss "an old story" with updated literature by comparing the GI effects of celecoxib and indomethacin in patients with OA.

METHODS

This prospective study was conducted between 2001-2002 at the Istanbul Prof. Dr. Cemil Taşçıoğlu City Hospital, Departments of Rheumatology, Internal Medicine, and Orthopedics Clinics, where patients presented with knee osteoarthritis. This study was conducted in agreement with the Declaration of Helsinki-Ethical principle for Human researches.

Inclusion: Patients had complaints for at least 6 months, receiving NSAIDs therapy, meeting the American College of Rheumatology clinical criteria for primary knee OA, including functional classes I, II, and III, and were suitable for inclusion if they were aged 50 or older. Patients meeting these criteria were informed about the study and their consent was obtained.

Exclusion: Patients with active duodenal, gastric, or esophageal ulcers, pyloric obstruction, or erosive esophagitis at baseline endoscopy were excluded from the study. Patients who had undergone upper gastrointestinal surgery, had inflammatory bowel disease, serum creatinine levels >2.0 mg/dL, calculated creatinine clearance <30 ml/min, positive occult blood in stool, congestive heart failure, chronic liver disease, a history of malignancy in the last 5 years, cerebral vascular events in the last 2 years, bleeding diathesis, or required anticoagulant therapy, corticosteroids, ticlopidine, or aspirin were also excluded.

Measurements: Detailed medical histories of patients were obtained at baseline, along with physical examinations, complete blood count, erythrocyte sedimentation rate, c-reactive protein (CRP), rheumatoid factor (RF), blood biochemistry, and occult blood in stool were studied before interventions (15 days and monthly for three months). Following baseline assessments, patients underwent physical examination, The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Likert index, and Visual Analog Scale (VAS) were performed. Participants were divided into two groups after a two-week drug "wash-out" period. A group received per os 3x25 mg/day indomethacin, and other group received per os 2x100 mg/day celecoxib. Participants were addressed to the groups according an age and gender matching method manually.

Gastroduedonoscopy: Gastroduedonoscopy was performed at baseline and at the end of treatment. Gastroduedonoscopy was not performed at the end of treatment for patients who discontinued the study due to side effects or inefficacy. The findings included gastric and duodenal ulcers, erosive gastritis, etc. Multiple biopsies were obtained. Pathology and the culture studies were performed. *H. Pylori* presence were noted. Patients with *H. Pylori* positivity were received a 2-3 weeks of treatment for eradication. All individuals received a standard proton pump inhibitor (PPI) regimen during the study.

STATISTICAL ANALYSIS

The data obtained were analyzed using the SPSS version 15 for Windows program. Numerical variables were expressed as mean and ± standard deviation. Independent Samples T-test was used to compare the parametric variables of the two groups. Kolmogorov-Smirnov test was used to determine the distribution types of the variables. Chi-square and Wilcoxon tests were used for comparisons of categorical parameters. $p<0.05$ was considered statistically significant.

RESULTS

Fifty patients were included in the study cohort, comprising 42 females (84%) and 8 males (16%). Twenty females (80%) and 5 males (20%) were assigned to the indomethacin group, while 22 females (88%) and 3 males (12%) were assigned to the celecoxib group. Statistical analysis revealed no significant difference in gender distribution between the two treatment groups ($p=0.782$). The clinical and demogrophical features of the participants were presented in **Table 1**. The mean duration of osteoarthritis was 4.52±2.29 years (range: 1-10) in the indomethacin group and 5.04±1.67 years (range: 2-9) in the celecoxib group, two groups exhibited a similar duration of illness ($p=0.625$).

Repeated gastroduedonoscopy was performed 3 months later in 19 cases of the indomethacin. In 13 (68.4%) cases, no change was observed in the findings of gastroduedonoscopy, while worsening was observed in

Table 1. The clinical and laboratory of th participants and the comparison of thw two groups

	Indomethacin, n=25	Celecoxib, n=25	P value
Age, years	52.92±4.68	55.48±4.82	0.055
Male, female, n	5/20	3/22	0.782
Disease duration, years	4.52±2.29	5.04±1.67	0.625
H. Pylori positivity, n	23	20	0.522
Cases stopped to receive medicine, n **Causes of stopping medicine, n**	6 Ineffective (2)* Refused to continue (3 cases refused the next gastroduedonoscopy) Adverse reactions (1 case of edema)	6 Ineffective (2)* Refused to continue (2 cases refused the next gastroduedonoscopy) Adverse reactions (1 case of allergy and 1 case of coronary bypass operation)	1.000

*Evaluations based on the VAS index, Likert index, and WOMAC scale were taken into account to determine medication ineffectiveness.

6 (30%). Number of cases with gastroduodenal erosion increased folowing indomethacin treatment (p=0.014).

In the celecoxib group, 19 out of 25 patients (76%) completed the treatment and underwent repeated gastroduedonoscopy. There was no change in 17 patients (84%), while finding got worsened in 2 individuals (16%). Pretreatment and posttreatment GI findings did not exhibit a significant change (p=0.157) in the celecoxib group (Table 2). The prevalence of *H. Pylori* was 86% (43 of 50 patients).

Following indomethacin treatment 3 of 4 patients with normal gastroduedonoscopy findings developed pangastritis, while in the celecoxib group 3 patient with pangastritis recoverd to normal gastrocopy findings (Table 3). However, in the celecoxib group one patient developed duodenal ulcer. Beside, celecoxib group had less tendency to develop duodeneal erosive lesions (1 case vs 4 cases and p=0.005).

DISCUSSION

This study demonstrates a comparison of gastrointestinal findings in indomethacin and celecoxib users. Despite there being no cases of GI bleeding with selective and nonselective NSAIDs in this study, indomethacin exhibited a significant risk increase for gastroduodenal lesion development compared to celecoxib use. Further, in the celecoxib users, a slight improvement in gastric lesions was observed under the PPI use.

Pain is the main symptom and indication in the treatment of OA. Guidelines recommend the use of NSAIDs, a group of medicines that inhibit the production of prostaglandins and thromboxane A by blocking cyclooxygenase (COX) (6,13,14). Traditional NSAIDs target the COX-1 and COX-2 isozymes to varying degrees and play a significant role in the symptomatic treatment of pain in musculoskeletal disorders (15,16). However, their prolonged use raises concerns regarding toxicity, especially cardiovascular, gastrointestinal, and renal issues. Furthermore, previous studies have indicated a lower risk of gastrointestinal bleeding or intolerance with selective COX-2 inhibitors, at least in the short term (6-12 months) (16-18). In this study, there was no cases of GI bleeding or dyspepsia, which the leading causes of premature discontinuation of the drug (19). This outcome is likely linked to the use of PPIs alongside NSAIDs, as suggested by Bakriansyah et al. Their study demonstrated that selective COX-2 inhibitors with PPIs, as well as selective COX-2 inhibitors and conventional NSAIDs with PPIs, were associated with a reduced risk of gastrointestinal adverse events compared

Table 2. Pre and posttreatment gastroduedonoscopy findings

	Indomethacin, n=19	Celecoxib, n=19	P value
Baseline; n •Pangastrit, •Nonerosive duodenitis •Antral erosvive lesions	 25 (6 were excluded) 5 0	 25 (6 were excluded) 1 0	1.00
Posttreatment; n •Pangastrit, •Nonerosive duodenitis •Antral erosive lesions •Normal	 13 5 7 1	 15 2 1 3	<0.05

Table 3. All cases are given with their gastroduedonoscopy findings

Cases and Groups	Gender	Age	Disease Duration	H.Pylori	Baseline Gastroduedonoscopy	Posttreatment Gastroduedonoscopy
1-Indomethacin	Female	60	4	-	PG	PG + NED
2-Indomethacin	Male	57	5	+	N	PG
3-Indomethacin	Female	72	9	-	PG	PG (ae)
4-Indomethacin	Female	56	5	-	PG	PG(ae)
5-Indomethacin	Male	63	3	+	PG	PG (ae) + NED
6-Indomethacin	Female	64	4	+	PG	PG (ae)
7-Indomethacin	Female	42	1	-	PG + NED	PG
8-Indomethacin	Male	66	5	+	N	PG
9-Indomethacin	Female	68	4	+	PG	PG
10-Indomethacin	Female	53	3	+	N	PG
11-Indomethacin	Female	50	5	+	PG + NED	PG
12-Indomethacin	Female	49	3	+	PG	PG (ae)
13-Indomethacin	Female	45	1	+	N	N
14-Indomethacin	Female	70	10	+	PG	PG
15-Indomethacin	Female	55	6	+	PG + NED	PG
16-Indomethacin	Female	62	5	+	PG	PG
17-Indomethacin	Female	53	4	+	PG +NED	PG (ae) + NED
18-Indomethacin	Female	46	1	+	PG	PG (ae) + NED
19-Indomethacin	Female	52	3	+	PG + NED	PG
20-Indomethacin	Female	71	9	+	PG	
21-Indomethacin	Male	66	5	+	PG	PG + NED
22-Indomethacin	Female	52	4	-	PG	
23-Indomethacin	Female	59	5	+	PG	
24-Indomethacin	Female	67	6	+	PG	
25-Indomethacin	Male	52	3	+	PG	
1-Celeocoxib	Female	48	2	+	PG	Duodenal Ulcer
2- Celeocoxib	Female	52	4	+	PG	PG
3- Celeocoxib	Female	66	3	+	PG	PG
4- Celeocoxib	Male	41	3	+	PG	N
5- Celeocoxib	Female	60	5	+	PG	PG
6- Celeocoxib	Female	55	6	+	PG	PG (ae)
7- Celeocoxib	Female	53	5	+	PG + NED	PG + NED
8- Celeocoxib	Female	56	5	+	PG	N
9- Celeocoxib	Female	47	5	+	PG	N
10- Celeocoxib	Male	59	6	+	PG	
11- Celeocoxib	Female	52	4	+	PG	PG + NED
12- Celeocoxib	Female	53	7	-	PG	PG
13- Celeocoxib	Female	63	7	-	PG	
14- Celeocoxib	Female	71	9	+	PG	
15- Celeocoxib	Female	61	6	+	PG	PG
16- Celeocoxib	Male	65	7	+	PG	PG
17- Celeocoxib	Female	52	3	+	PG	
18- Celeocoxib	Female	50	6	+	PG	PG
19- Celeocoxib	Female	62	5	+	PG	PG
20- Celeocoxib	Female	57	4	+	PG	
21- Celeocoxib	Female	67	7	+	PG	
22- Celeocoxib	Female	60	4	+	PG	PG
23- Celeocoxib	Female	53	3	+	PG	PG
24- Celeocoxib	Female	54	4	+	PG	PG
25- Celeocoxib	Female	67	6	+	PG	PG

PG; pangastritis, NED; nonerosive duodenitis, ae; antral erosive lesion

to conventional NSAIDs (17). However, celecoxib showed a lower incidence of nonerosive duodenitis and antral erosive lesions. Moreover, three cases exhibited a transition to normal gastric findings with celecoxib combined with PPI usage, whereas only one case showed a similar improvement with indomethacin combined with PPI. It's worth noting that most patients had a prolonged history of NSAID use before being enrolled in the study. Despite a short "drug wash-out" period, prior NSAID exposure might have influenced the outcomes.

A meta-analysis of 410.879 participants from 73 countries across six continents revealed an overall *H. Pylori* prevalence of 44.3% worldwide. This rate varied, with developing countries showing a higher prevalence of 50.8% compared to 34.7% in developed countries. Globally, the *H. pylori* infection rate was 42.7% in females and 46.3% in males. Furthermore, the prevalence in adults (≥18 years) was significantly higher than in children, with rates of 48.6% and 32.6%, respectively (20). The prevalence of *H. Pylori* in Turkey was found 82.5% according to the TURHEP study

(21). Our study reveals a high prevalence, with 86% of participants testing positive for *H. Pylori*, a figure close to the data presented in TURHEP. Despite NSAIDs and *H. Pylori* share a number of similar pathogenic mechanisms, there is no evidence to argue a significant synergistic action between these two risk factors for GI bleeding or dyspepsia. Lazzaroni et al. reported that neither short- nor long-term NSAID administration definitively poses a major risk of gastric and duodenal injury or, more importantly, ulcer-related complications such as bleeding or perforation in *H. Pylori*-positive patients (22). Similarly, despite the high prevalence of *H. Pylori* in this study population, no GI adverse events were observed.

COX-2 selective NSAIDs have been associated with electrolyte imbalance including hyponatremia and hyperkalemia (23,24). However, in this study we did not observe any case of electrolyte imbalance.

NSAIDs are effective agents in the treatment of osteoarthritis and a recent study revealed that topical NSAIDs can demonstrate comparable efficacy to oral NSAIDs in treating osteoarthritis, with both forms effectively reducing pain and enhancing physical function among OA patients (25). Therefore, topical treatment approaches may reduce GIS side effects at high risk patients.

Limitations of the Study

The relatively small sample size in this study may limit the generalizability of our findings to broader populations. A larger sample size would enhance the statistical power of the analysis and provide more robust conclusions. The brief period between cessation of prior NSAID use and study enrollment may not have adequately mitigated the lingering effects of previous NSAID exposure. This could influence the interpretation of outcomes, particularly regarding the comparison between indomethacin and celecoxib. The relatively short follow-up duration may have precluded the detection of long-term GI complications associated with NSAID use. Extended monitoring periods could provide a more comprehensive understanding of treatment-related adverse events. The recruitment of participants from a single center may introduce selection bias and limit the diversity of the study population. Including participants from multiple centers or employing a multicenter study design could mitigate this limitation. Detailed information regarding the duration, frequency, and types of prior NSAID use was not consistently available for all participants. This lack of comprehensive data may have influenced the analysis of treatment outcomes and adverse events. While efforts were made to control for potential confounding variables, such as concomitant medication use and comorbidities, the presence of unmeasured confounders could impact the validity of our results. Our study focused primarily on GI findings associated with indomethacin and celecoxib use, neglecting other potential adverse events and long-term outcomes. A broader assessment encompassing systemic effects and patient-reported outcomes would provide a more holistic understanding of treatment safety and efficacy.

CONCLUSION

Our findings underscore the importance of considering both the efficacy and safety profiles of NSAIDs in clinical decision-making for osteoarthritis treatment. While traditional NSAIDs like indomethacin remain effective in pain management, their use may necessitate careful monitoring for gastrointestinal complications. In contrast, celecoxib, a COX-2 selective inhibitor, offers a potentially safer alternative with a reduced risk of gastric lesions, particularly when combined with PPI therapy.

DECLERATIONS

Ethics Committee Approval: This manuscript is retrieved from the graduation thesis of Sibel ADA, MD (Istanbul, 2003).

Financial Disclosure: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions: S.A.; Project design, writing, and submitting, the other researchers equally contributed to data collection and analyzing the final version of the article. All authors read and approved the final manuscript.

Conflict of interest: None

Informed consent form: Not available

Funding source: No funding was received for the research

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