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Association Between Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) And *Helicobacter Pylori* Infection on The Incidence Of Peptic Ulcers

Muhammad Zulfitriah¹, Susanto Hendra Kusuma¹, A. Muh. Luthfi Parewangi¹, Syakib Bakri¹, Femi Syahrani¹, Arifin Seweng²

¹Hasanuddin University, Makassar, Indonesia; Department of Internal Medicine, Faculty of Medicine

²Hasanuddin University, Makassar, Indonesia; Department of Public Health and Community Medicine, Faculty of Medicine

Correspondence: Muhammad Zulfitriah

Department of Internal Medicine, Hasanuddin University Hospital A, Tamalanrea, Makassar, South Sulawesi, 90245, Indonesia Phone: +6282296664306 E-mail: Fitrahzulm@gmail.com Orcid : <https://orcid.org/0009-0004-7150-1635>

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Abstrak

Background: Peptic ulcer is defined as damage to the upper gastrointestinal mucosa resulting in ulcer formation that extends to the submucosal layer. *Helicobacter pylori* act by producing various enzymes to damage gastric defenses resulting in chronic inflammation while NSAIDs inhibit the COX-1 enzyme which has a toxic effect on membrane permeability in the gastrointestinal system. This study was conducted to determine the association between the use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and *H. pylori* infection on the incidence of peptic ulcers.

Methods: This study was a cross-sectional study at Dr. Wahidin Sudirohusodo Hospital, Makassar. The samples used patients aged ≥ 18 years, had endoscopy of the upper gastrointestinal tract. Gastrointestinal ulcers diagnosed based on endoscopy findings. *H. pylori* infection diagnosed based on histopathology. NSAID use identified through interviews. Data were analyzed using logistic regression and Chi-square test.

Results: This study involved 151 subjects, history of NSAIDs 135 subjects (89.4%) and *H. pylori* positive 45 subjects (29.8%). Significant association ($p < 0.05$) between NSAIDs and the incidence of gastric and duodenal ulcers. Significant association ($p < 0.05$) also found in subjects with positive *H. Pylori* with the incidence of gastric and peptic ulcers. NSAIDs were found to be an independent risk factor for incidence of gastric ulcer (odds ratio, 6.343; 95% CI, 1.370-29.362) and duodenal ulcer (odds ratio, 5.358; 95% CI, 1.162-24.700).

Conclusion: There is an association between history of NSAIDs and *H. pylori* infection on the incidence of gastrointestinal ulcers. NSAIDs are an independent risk factor for the incidence of gastric and duodenal ulcers.

Keywords: *Helicobacter pylori*, NSAIDs, peptic ulcer, gastrointestinal ulcer

1. Introduction

Peptic ulcer is defined as damage to the upper gastrointestinal mucosa resulting in ulcer formation that extends to the submucosal layer.⁽¹⁾ *Helicobacter pylori* and NSAIDs are the two most common causes of peptic ulcers.⁽²⁾ *H. Pylori* acts by producing various enzymes that can damage the defense of the stomach resulting in chronic inflammation.⁽³⁾ At the same time NSAIDs through the mechanism of inhibiting the COX-1 enzyme which has a toxic effect on membrane permeability in the gastrointestinal system.⁽⁴⁾

NSAID users had a 20–30% prevalence of peptic ulcers, with gastric ulcers occurring almost six times more frequently than duodenal ulcers.⁽⁵⁾ The prevalence of peptic ulcers due to *H. Pylori* infection was 60%, with a higher incidence of duodenal ulcers (66.9%) compared to gastric ulcers (48.5%).⁽⁶⁾

A previous study reported that among 754 patients, there were 472 with duodenal ulcers, 193 with gastric ulcers, and 89 with peptic ulcers. *H. pylori* infection was more common in patients with duodenal ulcers, and NSAID use was more common in patients with gastric ulcers.⁽⁷⁾ We conducted a study on the effects of *H. pylori* and NSAIDs on the incidence of peptic ulcers because gastrointestinal ulcers remain a public health concern, particularly when complications arise in the form of gastrointestinal bleeding.

Materials and Methods

This study was a cross-sectional study at Dr. Wahidin Sudirohusodo Central General Hospital, Makassar from December 2023 until the minimum sample size was reached. Our minimum sample size was 83 patients. The study sample was patients aged ≥ 18 years who underwent endoscopic examination of the upper gastrointestinal tract at the gastroenterology department and were diagnosed with peptic, duodenal, and gastric ulcers regardless of the degree of ulcer, degree of activity, and form (primary or recurrent).

Histopathologic techniques were used to diagnosis *H. pylori* from ulcer samples, and the results were documented. Through interviews, NSAID use was verified. The variety and length of NSAID use were not differentiated in this study. A logistic regression test and a Chi-square test were used to assess the data. If the p value for a statistical test was less than 0.05, the results were deemed significant.

The study was approved by the Ethics Committee for Biomedical Research on Humans at the Faculty of Medicine, Hasanuddin University, Makassar, Indonesia. Based on the letter of recommendation Number: 920/UN.4.6.4.5.31/PP36/2023 with protocol number: UH23110823.

2. Results

There were 151 subjects who met the criteria; the mean age in this study was 55.8 ± 13.0 years. NSAID was found in 135 subjects (89.4%), infected with *H. pylori* 45 subjects (29.8%). Gastric ulcer 65 subjects (43%), duodenal ulcer 60 subjects (39.7%), and peptic ulcer 26 subjects (17.2%).

Table 1. Subjects' characteristics.

Variabel	n (151)	%
Sex		
Male	88	58.3
Female	63	41.7
Age		
	57.17 + 13.01	
History of NSAID		
Yes	135	89.4
No	16	10.6
H. Pylori infection		
Yes	45	29.8
No	106	70.2
NSAID + H. Pylori		
Yes	40	26.5
No	111	73.5
Ulcer Location		
Gaster	65	43.0
Duodenum	60	39.7
Peptic	26	17.2

NSAID: *Nonsteroidal Anti-inflammatory Drugs*, HP: *Helicobacter pylori*;

Based on the location of gastrointestinal ulcers, subjects with a history of NSAIDs and positive *H. pylori* had the most duodenal ulcers at 35% (21/60), and negative *H. pylori* was found in gastric ulcers at 76.9% (50/65). Subjects without a history of NSAIDs with positive *H. pylori* found in duodenal ulcers were 5% (3/60), and negative *H. pylori* found in duodenal ulcers were 10% (6/10).

Table 2. Prevalence of gastrointestinal ulcers based on etiology and ulcer locations.

Variables	GU	DU	PU	Total
	n (%)	n (%)	n (%)	
NSAID (+)/ HP (+)	13 (20)	21 (35)	6 (23.1)	40
NSAID (+) /HP (-)	50 (76.9)	30 (65)	15 (57.7)	95
NSAID (-) /HP (+)	0 (0)	3 (5)	2 (7.7)	5
NSAID (-) /HP (-)	2 (3.1)	6 (10)	3 (11.5)	11
Total	65	60	26	151

NSAID: Nonsteroidal Anti-inflammatory Drugs, HP: *Helicobacter pylori*; GU: Gastric Ulcers;
DU: Duodenal Ulcers; PU: Peptic Ulcers.

This study analyzed the relationship between NSAIDs and *H. pylori* with gastrointestinal ulcers. Gastric ulcers were found in 63 subjects (41.7%) with a history of NSAIDs and 13 subjects (8.6%) with positive *H. pylori*. Duodenal ulcers were found in 58 subjects (38.4%) with a history of NSAIDs and 13 (8.6%) with positive *H. pylori*. Peptic ulcers were found in 26 subjects (17.2%) with a history of NSAIDs and 3 (2%) with positive *H. pylori*. This study found a significant ($p < 0.05$) correlation between Gastric and duodenal ulcers with NSAID. Subjects with gastric and peptic ulcers who confirmed positive for *H. pylori* also had significant results ($p < 0.05$).

Table 3. Association between NSAIDs and *H. pylori* with gastrointestinal ulcers

Variables	NSAID			<i>H. pylori</i>		
	(+)	(-)	p*	(+)	(-)	p*

Gastric Ulcer	Yes	63	2	0.009	13	52	0.022
	No	72	14		32	54	
Duodenal ulcer	Yes	58	2	0.019	13	47	0.076
	No	77	14		32	59	
Peptic ulcer	Yes	26	0	0.054	3	23	0.025
	No	109	16		42	83	

*Chi square (p<0.05)

NSAID: *Nonsteroidal Anti-inflammatory Drugs*

Patients with History of NSAID had a higher risk of duodenal ulcer (OR, 5.358; 95% CI, 1.16–24.70; p<0.05) and gastric ulcers (OR, 6.343; 95% CI, 1.37–29.36; p<0.05) in multivariate analysis (Table 4).

Table 4. Multivariate analysis of NSAIDs and *H. pylori* on the incidence of gastrointestinal ulcers

variables	p	Odds ratio	95% CI.	
Gastric Ulcer				
NSAID	0.018	6.343	1.370	29.362
<i>H. pylori</i>	0.022	0.411	0.192	0.881
Duodenal Ulcer				
NSAID	0.031	5.358	1.162	24.700
<i>H. pylori</i>	0.077	0.503	0.235	1.077
Peptic Ulcer				
NSAID	0.998	3789.2	0.000	0.000
<i>H. pylori</i>	0.034	0.254	0.072	0.901

NSAID: *Nonsteroidal Anti-inflammatory Drugs*

3. Discussion

There were 151 subjects who fulfilled the criteria, the mean age of the study subjects was 55.8 ± 13.0 years. Male gender was 88 subjects (58.3%), female 63 subjects (41.7%). NSAID history was found in 135 subjects (89.4%), 45 subjects (29.8%) were infected with *H. pylori*. The same results were found by Djumhana et al, about the prevalence of NSAIDs and *H. Pylori* in

Indonesia on the incidence of gastrointestinal ulcers, H. Pylori infection 15% and NSAIDs 87.5% (Table 1).⁽⁸⁾

Previous investigations performed by Hamid et al found the prevalence of peptic ulcers in patients who were taking NSAIDs and H. Pylori positive was most prevalent in duodenal ulcers, 67% (16/24). H. Pylori infection without a history of NASID was mostly found in duodenal ulcers 70% (123/175). History of NSAIDs with negative H. Pylori was most common in duodenal ulcers 46% (13/28).⁽⁹⁾ Research by Kim et al. found a significant reduction in blood flow through the gastric antral mucosa (as determined by a laser doppler flowmeter) in subjects taking NSAIDs and significantly associated with an increased risk of gastric ulcers. These results are similar to our study which found subjects taking NSAIDs with positive H. pylori in duodenal ulcers 35% (21/60) and negative H. pylori in gastric ulcers 76.9% (50/65). Subjects without a history of NSAIDs with positive H. pylori were found in duodenal ulcers 5% (3/60) and negative H. pylori were found in duodenal ulcers 10% (6/10) (Table 2).⁽¹⁰⁾

This study found that NSAIDs were significantly associated with gastric and duodenal ulcers ($p < 0.05$) while *Helicobacter pylori* infection was associated with the incidence of gastric ulcers and peptic ulcers. These results also confirmed the most common causes of gastrointestinal ulcers, where NSAIDs and H. pylori are the two independent factors that play the most role in gastrointestinal ulcer disease (Table 3). Previously Salit et al in a retrospective study in Turkey reported NSAIDs were associated with the incidence of gastric and duodenal ulcers while H. pylori was significantly associated with the incidence of gastric ulcers.⁽¹¹⁾ A study by Taha et al reported that NSAIDs were significantly associated with gastric metaplasia, gastritis and duodenal ulceration.⁽¹²⁾

In multivariate analysis, NSAIDs were found to be an independent risk factor for gastric ulcer and duodenal ulcer (OR, 6.343: 5.358; 95% CI, respectively). This result is not much different from previous studies that reported NSAIDs as an independent risk factor for gastrointestinal ulcers (OR: 1.34; 95% CI) (Table 4).⁽¹³⁾

Different results were found for *helicobacter pylori* infection on the incidence of gastric ulcer and peptic ulcer (OR, 0.411: 0.254; 95%CI, respectively). Some factors that are thought to affect these results are (1). The small number of subjects detected *helicobacter pylori*, (2). The method of diagnosis of *helicobacter pylori* which only uses the histopathology method of biopsy, (3). This study was conducted at a tertiary healthcare facility where most of the subjects had

received eradication therapy at the primary healthcare facility. The clinical implication of this study is the need for careful consideration and close monitoring in prescribing NSAIDs to avoid the occurrence of peptic ulcers and complications.

4. Conclusions

NSAIDs and *H. pylori* infection are linked to an increased risk of gastrointestinal ulcers. NSAID use has been found to be an independent risk factor for the development of duodenal and gastric ulcers.

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