Gastroduodenal Mucosal Injury Profile in Long-term Low-dose Aspirin Users and Its Influencing Factors

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ABSTRACT

Background: *Low-dose aspirin is the most common drug used for prevention of cardiovascular and cerebrovascular events. Long-term aspirin therapy can induce gastroduodenal mucosal injury, even in a very low dose (10 mg daily). The frequency of gastroduodenal injuries among long-term low-dose aspirin users in Indonesia is currently unknown. The aim of this study is to determine the prevalence of gastroduodenal mucosal injury, endoscopic findings, and influencing factors among long-term low-dose aspirin users in Cipto Mangunkusumo Hospital.*

Method: *This study was a cross-sectional study conducted in Cipto Mangunkusumo Hospital, Jakarta. Subjects were patients aged ≥ 18 years old who had been using low-dose aspirin (75-325 mg) for at least the preceding 28 days. Ninety-five subjects were recruited consecutively in the period of December 2015 – April 2016. History taking, upper endoscopic examination, and histopathology examination for Helicobacter pylori infection were performed in all subjects. Endoscopic findings such as erosions and ulcers were assessed as mucosal injuries. Data were analysed to find prevalence, bivariate analysis (Chi-square test), and multivariate analysis (logistic regression test).*

Results: *Mucosal injury was found in 49 subjects (51.6%; 95% CI: 41.6–61.7%), mucosal erosion in 38 subjects (40%; 95% CI: 30.2–49.9%) and ulcers in 11 subjects (11.6%; 95% CI: 5.2–18.0%). Only 44.9% patients with mucosal injury had dyspepsia symptoms. Double antiplatelet therapy increased the risk of mucosal injury (OR = 3.3; 95% CI: 1.3–8.5). However, proton pump inhibitor (PPI) decreased the risk of mucosal injury (OR = 0,2; 95% CI: 0,04 – 0,60).*

Conclusion: *Gastroduodenal mucosal injury was found in more than half of long-term low-dose aspirin users. Double antiplatelet therapy increased the risk of mucosal injury, while PPI effectively reduced the risk.*

Keywords: *low-dose aspirin, gastroduodenal mucosal injury, endoscopy*

ABSTRAK

Latar belakang: *Aspirin dosis rendah adalah obat profilaksis kejadian kardiovaskular yang paling sering digunakan. Efek samping gastroduodenal sering terjadi pada penggunaan aspirin jangka panjang, bahkan pada dosis yang sangat rendah (10 mg/hari). Saat ini angka kejadian kerusakan mukosa gastroduodenal akibat penggunaan aspirin dosis rendah jangka panjang di Indonesia belum diketahui.*

Tujuan: *Mengetahui besarnya prevalensi dan gambaran endoskopi kerusakan mukosa gastroduodenal pada pengguna aspirin dosis rendah jangka panjang pada pasien yang berobat di Rumah Sakit Cipto Mangunkusumo (RSCM), serta faktor-faktor yang mempengaruhi.*

Metode: *Penelitian ini menggunakan desain potong lintang. Sampel penelitian adalah pasien poliklinik dan ruang perawatan RSCM usia ≥ 18 tahun yang mengkonsumsi aspirin dosis rendah (75-325 mg) lebih dari 28 hari. Didapatkan 95 subjek penelitian melalui metode konsekutif dalam periode Desember 2015 hingga April 2016. Pasien dilakukan anamnesis, pemeriksaan endoskopi saluran cerna atas, dan pemeriksaan histopatologi untuk menilai adanya infeksi Helicobacter pylori. Temuan endoskopi berupa erosi mukosa dan ulkus peptikum dimasukkan ke dalam kelompok kerusakan mukosa. Data diolah untuk memperoleh proporsi, analisis bivariat (uji Chi-square), dan analisis multivariat (uji regresi logistik).*

Hasil: *Kerusakan mukosa gastroduodenal ditemukan pada 49 subjek (51,6%; 95% CI: 41,6-61,7%), dengan gambaran erosi mukosa pada 38 subjek (40%; 95% CI: 30,2-49,9%) dan ulkus peptikum pada 11 subjek (11,6%; 95% CI: 5,2-18,0%). Hanya 44.9% pasien dengan kerusakan mukosa gastroduodenal yang memiliki keluhan dispepsia. Kombinasi antitrombotik meningkatkan risiko terjadinya kerusakan mukosa dengan OR = 3,3 (95% CI: 1,3-8,5). Sedangkan penggunaan obat golongan proton pump inhibitors (PPI) menurunkan risiko kerusakan mukosa (OR = 0,2; 95% CI: 0,04-0,60).*

Simpulan: *Kerusakan mukosa gastroduodenal terjadi pada lebih dari separuh pasien yang menggunakan aspirin dosis rendah jangka panjang. Kombinasi anti-trombotik meningkatkan risiko kerusakan mukosa. Sedangkan penggunaan PPI efektif dalam menurunkan risiko tersebut.*

Kata kunci: *aspirin dosis rendah, kerusakan mukosa gastroduodenal, endoskopi*

INTRODUCTION

Low-dose aspirin (acetylsalicylic acid or ASA) (75-325 mg) is the most frequently used prophylactic drugs for cardiovascular and cerebrovascular events.[1,2,3] Use of aspirin can decrease 10-20 per 1,000 cardiovascular events and also mortality rates due to vascular diseases.[1] Administration of this drug increases globally as the rate of life expectancy improves.[4] In clinical setting, the most important and frequent side effects of aspirin administration is gastrointestinal side effects, ranging from mucosal erosion to bleeding which may lead to death.[5] Even the very low-dose aspirin (10 mg per day) can decrease gastric mucosal prostaglandin level which causes significant injury to gastric mucosa.[6]

Based on previous studies, mucosal erosion took place in approximately 60% of aspirin users, while peptic ulcer was found in 11-19% patients.[7,8] However, more studies associated the use of aspirin with gastrointestinal bleeding.[9-14] In a large study involving 27,694 patients, upper gastrointestinal bleeding was found in 2.6% of aspirin users.[15] But, clinical symptom does not always present in mucosal injury due to aspirin administration.[7,16] Therefore, endoscopic examination of upper gastrointestinal tract should be performed in long-term low-dose aspirin users regardless of the presence of clinical complaints.

Incidence of non-variceal gastroduodenal bleeding in Indonesia is quite high. Among 4,154 patients who underwent endoscopic examination of upper gastrointestinal tract in year 2001 to 2005 in Cipto Mangunkusumo Hospital, it was found that 837 patients (20.15%) suffered from upper gastrointestinal bleeding and most of them were non-variceal (66.6%).[17] The same researcher in year 2008 reported higher incidence of gastric and duodenal ulcer in non-steroidal anti-inflammatory drugs (NSAIDs) users compared to control group.[18] Meanwhile, there is no available data regarding prevalence of gastroduodenal mucosal injury in long-term low-dose aspirin users in Indonesia yet.

METHOD

This study used cross-sectional design. Samples of this study were polyclinic and hospitalized patients in Cipto Mangunkusumo Hospital aged ≥ 18 years old who consumed low-dose aspirin (75-325 mg) for more than 28 days without considering the presence of dyspepsia symptoms. We obtained 95 study subjects through consecutive sampling method in the period of December 2015 – April 2016. Patients who underwent coronary stent placement in the last 6 months, those who had undergone gastrectomy, or those who refused endoscopic examination were excluded from this study. Patients' data were collected through direct history taking with patients included in the study. Endoscopic examination was performed in Gastrointestinal

Endoscopy Centre, Cipto Mangunkusumo Hospital. Histopathology examination was performed in Anatomy Pathology Laboratory, Cipto Mangunkusumo Hospital.

Endoscopic findings in the form of mucosal erosion and peptic ulcer were included in mucosal injury group. Independent variables which were being analysed include age, antithrombotic combination, combination with anticoagulant, combination with other NSAIDs, *Helicobacter pylori (H pylori)* infection, diabetes mellitus, and PPI administration. Data was analysed to obtain the proportion, bivariate analysis (Chi-square test), and multivariate analysis (regression logistic test). This study had received approval from ethical committee and all research subjects had signed written informed consent.

RESULTS

Based on the endoscopy results of upper gastrointestinal tract, gastroduodenal mucosal injury was found in 49 patients (51.6%; 95% CI: 41.6-61.7%), with erosive gastritis appearance in 38 patients (40%; 95% CI: 30.2-49.9%) and peptic ulcer in 11 patients (11.6%; 95% CI: 5.2-18.0%). Through Kolmogorov Smirnov test, we found normal distribution data of age, with average of 63.5 ± 7.7 years old. Majority patients were male 61 patients (64.2%). There were 49 patients (51.6%) who suffered from dyspepsia complaints while the remaining 46 patients were asymptomatic. In the group of patients whose upper gastrointestinal endoscopic results revealed mucosal injury appearance, we found 57.1% patients whose age were above 65 years old; 40.8% used antithrombotic combination; 4.1% used warfarin; 8.2% used NSAIDs; 8.2% suffered from *H. pylori* infection; and 38.8% suffered from diabetes mellitus. Description of characteristics of research subjects was shown in Table 1.

In this study, there were 6 risk factors which were analysed as risk factors of gastroduodenal mucosal injury in patients who consumed low-dose aspirin for more than 28 days, including age, use of antithrombotic combination, use of warfarin, use of NSAIDs, *H. pylori* infection, and diabetes mellitus. Proportion of independent variables in gastric mucosal injury group and normal mucosa group can be seen in Table 2. There was one statistically significant variable, which was the use of antithrombotic combination OR = 3.3 (95% CI: 1.3-8.5). The group of patients who used PPI drugs before endoscopy was performed had lower incidence of gastric mucosal injury OR = 0.2 (95% CI: 0.1-0.7).

Based on bivariate analysis, there was 3 independent variables had $p < 0.25$, which were age, antithrombotic combination, and use of proton pump inhibitor (PPI). Furthermore, we performed multivariate analysis to those variables. After multivariate analysis of those three variables had been performed, they were then included in the results as the most influencing factors in the occurrence of gastroduodenal mucosal injury. Age factor was still included in the final multivariate model, although statistically the p value > 0.05, as it was the most important factor in gastroduodenal mucosal injury. The final model of multivariate analysis could be seen in Table 3.

Table 1. Characteristics of research subjects

Characteristics	Erosive gastritis or peptic ulcer (49 subjects) n (%)	Normal gastric mucosa (46 subjects) n (%)
Age (year old)	63.8 ± 7.7	63.2 ± 7.8
Age classification (year old)	3 (50)	3 (50)
< 50	18 (41.9)	25 (58.1)
50-64	28 (60.9)	18 (39.1)
≥ 65		
Sex		
Male	33 (54.1)	28 (45.9)
Female	16 (47.1)	18 (52.9)
Dyspepsia complaints		
Present	22 (44.9)	27 (55.1)
Absent	27 (58.7)	19 (41.3)
Antithrombotic combination		
Yes	20 (71.4)	8 (28.6)
No	29 (43.3)	38 (56.7)
Warfarin use		
Yes	2 (66.7)	1 (33.3)
No	47 (51.1)	45 (48.9)
NSAIDs use		
Yes	4 (66.7)	2 (33.3)
No	45 (50.6)	44 (49.4)
Diabetes Mellitus		
Yes	19 (54.3)	16 (45.7)
No	30 (50)	30 (50)
Helicobacter pylori Infection		
Present	4 (66.7)	2 (33.3)
Absent	45 (50.6)	44 (49.4)
PPI administration		
Yes	36 (45.6)	43 (54.4)
No	13 (81.3)	3 (18.7)

PPI: proton pump inhibitor; NSAIDs: non-steroidal anti-inflammatory drugs

DISCUSSION

In this study, we found that the average age of research subjects was 63.5 ± 7.7 years old, from which 43.2% patients were more than 65 years old. Similar result was reported in a study performed in Australia with average age of 61 years old.[7] A meta-analysis also obtained similar average age of research subjects with this study, which was 63.3 years old.[19] A study in Japan described that most patients' age were more than 65 years old, with average age of 68.9 ± 10.3 years old.[8] This was caused by the use of low-dose aspirin to prevent cardiovascular and cerebrovascular diseases which increased with the increase of age.

Table 2. Bivariate analysis

Variables	Erosive gastritis or peptic ulcer n (%)	Normal gastric mucosa n (%)	P	OR (95% CI)
Age				
≥ 65 years old	28 (60.9)	18 (39.1)	0.121	2.1 (0.91 – 4.7)
< 65 years old	21 (42.9)	28 (57.1)		
Antithrombotic combination				
Yes				
No	20 (71.4)	8 (28.6)	0.023	3.3 (1.3 – 8.5)
	29 (43.3)	38 (56.7)		
Warfarin use				
Yes	2 (66.7)	1 (33.3)	0.524	1.9 (0.2 – 21.9)
No	47 (51.1)	45 (48.9)		
NSAIDs use				
Yes	4 (66.7)	2 (33.3)	0.369	2.0 (0.3 – 11.2)
No	45 (50.6)	44 (49.4)		
Diabetes mellitus				
Yes	19 (54.3)	16 (45.7)	0.849	1.2 (0.5 – 2.7)
No	30 (50)	30 (50)		
H. pylori infection				
Present	4 (66.7)	2 (33.3)	0.369	2.0 (0.3 – 11.2)
Absent	45 (50.6)	44 (49.4)		
PPI Administration				
Yes	36 (45.6)	43 (54.4)	0.020	0.2 (0.1 – 0.7)
No	13 (81.3)	3 (18.7)		

NSAIDs: non-steroidal anti-inflammatory drugs; PPI: proton pump inhibitor

Table 3. Multivariate analysis

Variable	P	OR	95% CI
Age	0.059	2.4	0.97 – 5.82
Antithrombotic combination	0.009	3.8	1.40 – 10.49
PPI Administration	0.008	0.2	0.04 – 0.60

PPI: proton pump inhibitor

Forty-six patients (48.4%) did not have dyspepsia complaints during the administration of long-term low-dose aspirin. However, gastroduodenal mucosal injury was found in 58.7% patients who had no dyspepsia complaints. This showed that the absence of dyspepsia symptoms did not exclude the possibility of gastroduodenal mucosal injury. This was in accordance with previous studies. Yoemans et al identified that only 20% patients with peptic ulcer had clinical symptoms of dyspepsia (nausea, regurgitation, bloating). The study also stated that that there was no significant difference of clinical symptoms of dyspepsia in ulcer and non-ulcer group.[7] Niv et al conducted an oesophagoduodenoscopy study in 46 patients who used long-term low-dose aspirin (more than 3 months) and were asymptomatic and revealed that 22 patients (47.8%) had mucosal injury in the form of erosion or peptic ulcer.[16]

Diabetes mellitus is a disease which is commonly found as a risk factor of cardiovascular and cerebrovascular diseases.[20] In this study, we found 35 patients (36.8%) suffered from diabetes mellitus. This rate was higher in comparison to the population without cardiovascular or cerebrovascular incidence. A report from *Badan Penelitian dan Pengembangan Kesehatan Kementrian Kesehatan (RISKESDAS)* in year 2013 reported that the prevalence of diabetes mellitus was gained by interview, which was 1.5% in the year 2013. Meanwhile, the prevalence of diabetes mellitus based on doctors' diagnosis in Indonesia was 2.1%.[21] Proportion of diabetes mellitus patients with coronary heart disease alone varied, which was 15.1–21.4% patients based on registry data.[22] In contrast, data of patients in India showed a rate similar to the results of this study, which was 30.4% and 39.1%.[22] It showed that diabetes mellitus as an important risk factor of cardiovascular disease.

From 95 research subjects, gastroduodenal mucosal injury was found in 49 patients (51.6%; 95% CI: 41.6-61.7%), from which erosive gastritis was found in 38 patients (40%; 95% CI: 30.2 – 49.9%) and peptic ulcer in 11 patients (11.6%; 95% CI: 5.2 – 18.0%). Yeomans et al also reported similar incidence rate, which was 10.7% peptic ulcer and 63.1% erosion.[7] Other study in India stated similar results, which revealed mucosal lesions in 28 from 47 patients (60%) with ischemic stroke and transient ischemic attacks who received long-term low-dose aspirin.[23] In a study in Japan, it was found that 61.4% long-term low-dose aspirin users suffered from gastroduodenal mucosal injury and in 18.8% patients, ulcers were identified.[8] However, there was no association between the duration of aspirin use with the frequency of mucosal injury.[8]

The dose of aspirin being used in the study performed by Nema et al was 80-100 mg.[8] While, in the study

conducted by Yeomans et al was 144 ± 9 mg. Subjects in this study also used the similar dose of aspirin, which was 80-160 mg. A study which used patients' data in England concluded that there was no significant difference of gastroduodenal mucosal injury in patients who used aspirin with the dose of 75 mg up to 300 mg.[24] Mucosal injuries could even happen in aspirin administration with the dose of 10 mg for more than 3 months.[25]

The occurrence of gastroduodenal mucosal injury in aspirin users is through the similar mechanism of mucosal injury due to NSAIDs, which is systemic inhibition of endogen prostaglandin synthesis in the mucosa and direct irritation to gastric mucosa epithelial.[26,27] During 6 years period of aspirin administration, it was reported that there was an increased incidence of upper gastrointestinal bleeding from 15 to 18, and further increased to 27 events in 100,000 population. Conversely, there was no significant increase in long-term NSAIDs users group.[28] This is because aspirin has particular characteristic compared to other NSAIDs group, including its acidic property and irreversible bond with cyclooxygenase (COX) enzyme, which both pathophysiology may worsen gastroduodenal mucosal injury.[27,29]

Based on bivariate analysis, it was found that patients with age group more than 65 years old had higher risk in the occurrence of gastroduodenal mucosal injury with OR = 2.1 (95% CI: 0.91-4.7). Yeomans et al reported more significant result, which was increased risk of 3.32 fold in age group more than 70 years old.[7] Other studies in the United States revealed significant mean difference of age in group of patients who were low-dose aspirin users with gastrointestinal bleeding (70.9 ± 12.2 years old) with group without bleeding (66.5 ± 12.8 years old).[30] Using data of low-dose aspirin users in England and Spain, Hernandez-Diaz et al identified that the incidence of gastrointestinal complication was 10-20 cases per 1,000 patients per year and was higher in group with age more than 70 years old, affecting more than 100 patients per 1,000 patients per year.[31] In this study, age factor was included in the final model of multivariate analysis with adjusted OR = 2.4 (95% CI: 0.97-5.82).

Elderly patients who use long-term low-dose aspirin have a higher absolute risk of gastrointestinal complication compared to young aged patients because elderly patients have a baseline condition which is more prone to the incidence of gastrointestinal complication.[32] In old age, there are alterations in the gastrointestinal tract in the form of gastric mucosa atrophy and longer gastrointestinal transit time, therefore increases the risk of gastrointestinal complication in aspirin users.[33] Additionally, in old age, there is also sensory nerve disturbance, which causes the absence of clinical symptoms and delay in diagnosis.[34]

The study results suggested that antithrombotic combination increased the risk of gastroduodenal mucosal injury with OR = 3.3 (95% CI:1.3-8.5). Antithrombotic combination which was used in patients in this study was aspirin and clopidogrel. From the results of multivariate analysis, we also showed that antithrombotic combination, along with other risk factors including age more than 65 years old were important risk factors in the occurrence of gastroduodenal mucosal injury with OR = 3.8 (95% CI: 1.4-10.49).

Gracia et al informed that the risk of upper gastrointestinal bleeding in the administration of combination of aspirin and clopidogrel was 3.7 fold with an annual incidence of 1.4-2.7 per 1,000 patients.[35] This bleeding risk was also higher in comparison to patients who consumed aspirin only with RR = 2.08 (95% CI: 1.34-3.21).[35] Hallas et al in their study in Denmark also reported increased risk of upper gastrointestinal bleeding in aspirin and clopidogrel users was 7.4 (95% CI: 3.5-15) compared to aspirin only group, which was 1.8 (95% CI: 1.5-2.1).[10] Through this study, we may conclude that administration of combination of clopidogrel and aspirin had increased risk of gastroduodenal mucosal injury, not only gastrointestinal bleeding. This showed that there was possibility of antithrombotic combination was not only associated with the severity of gastroduodenal mucosal injury, but also the earlier onset of injury. Nonetheless, this needs to be proven in a study with prospective (cohort) design.

Three out of 95 research subjects (3.2%) consumed warfarin as co-medication with aspirin. We found no significant increased risk of gastroduodenal mucosal injury statistically in warfarin users as co-medication, although we obtained OR = 1.9 (95% CI: 0.2 – 21.9). Warfarin alone could increase major bleeding risk almost 4 times compared to aspirin.[36] Most studies also reported increased risk of gastrointestinal bleeding in aspirin and warfarin co-medication group compared to aspirin only group.[10,35-39] Only two studies showed results that combination with warfarin did not increase the risk.[40,41] In this study, there was also no significant difference of the occurrence of gastroduodenal mucosal injury between aspirin and warfarin co-medication group and aspirin only group. However, statistically significance of proportion difference between these two groups was difficult to analyse due to the small number of research subjects who used warfarin as co-medication.

Six research subjects (6.3%) consumed NSAIDs in a

period of more than 7 days before upper gastrointestinal endoscopy procedure was performed. There was no significant increased risk of gastroduodenal mucosal injury statistically in NSAIDs combination group (OR = 2.0; 95% CI: 0.3-11.2). Statistical significance in this study was difficult to attain due to the small number of subjects who used NSAIDs as comedication (6.3%).

A study in England identified an increased risk in patients with NSAIDs and aspirin co-medication (RR = 6.8; 95% CI: 4.5-10.3) compared to aspirin only group (RR = 2.9; 95% CI: 2.3-3.6).[24] Hallas et al also reported higher proportion of NSAIDs users (36.2%) in upper gastrointestinal bleeding group in aspirin users compared to control group (10.7%).[10] A cohort study with large sample size (27,694 subjects) also found an increased risk of upper gastrointestinal bleeding in NSAIDs and aspirin combination group (RR = 5.6; 95% CI: 4.4-7.0) compared to aspirin only (RR = 2.6; 95% CI: 2.2-2.9).[15]

Diabetes mellitus is an important risk factor of cardiovascular diseases and is considered equal to coronary heart disease.[20] Thirty-five patients (36.8%) in this study suffered from diabetes mellitus. Diabetes was an independent risk factor of peptic ulcer bleeding with HR = 1.44 (1.11-1.86).[42] Incidence of gastrointestinal complication was found to be higher in diabetic population patients. A prevalence study in Taiwan revealed that the incidence of peptic ulcer was higher in diabetic patients (14.8%) compared to non-diabetic patients (8.5%) and was significantly different in statistics (p = 0.002).[43] This study found low rate of gastrointestinal complaints in diabetic group (30.3 vs. 35.4%; p = 0.006). This was due to autonomic nerves disturbance which leads to the absence of clinical symptoms during mucosal injury.[43] Animal study also showed that the slow rate of gastric ulcer healing and increased risk of mucosal injury due to ulcerogenic drugs or stress in diabetic rats.[42]

There is no study to identify diabetes mellitus as risk factor of mucosal injury in long-term low-dose aspirin users yet. Although diabetes mellitus is an independent risk factors of peptic ulcer bleeding, this study did not find significant difference in proportion of patients with diabetes mellitus in the group with gastroduodenal mucosal injury compared to normal mucosal group (38.8 vs. 34.8; p = 0.849).

H. pylori infection was an independent risk factor of gastrointestinal ulcer bleeding with increased risk OR = 6.5 (95% CI: 3.4-12.6).[44,45] In this study, there was 6 patients with *H. pylori* infection based on histopathology examination. Proportion of *H. pylori* infection in mucosal injury group was higher compared to normal mucosa group (OR = 2.0; 95% CI: 0.3-11.2), although it was not statistically significant (p = 0,369). Lanas et al described that *H. pylori* infection increased the risk of gastrointestinal bleeding in low-dose aspirin users with OR = 4.7 (95% CI: 2.0-10.9).[20] In that study, patients suffering from *H. pylori* infection reached up to 40% from all research subjects.[46] Meanwhile, Gracia Rodriguez reported different result, in which there was no difference of gastrointestinal bleeding risk in low-dose aspirin users with or without *H. pylori* infection (RR = 2.5 vs. 3.0).[24] Yeomans et al identified that *H. pylori* infection increased the risk of duodenal ulcer in low-dose aspirin users (OR = 18.5; 95% CI: 2.3-149.4), but not for gastric ulcer (OR = 2.3; 95% CI: 0.7–7.8).[7] It seemed that although *H. pylori* infection was independently associated with increased risk of gastrointestinal bleeding, its role in low-dose aspirin users is still controversial. In this study, the low incidence of *H. pylori* infection (6.3%) also became a reason to find significant association statistically.

In this study, majority of patients (83.2%) had received therapy of PPI drugs before gastrointestinal endoscopy procedure was performed. From 79 patients who consumed PPI, only 57% patients who actually complained of dyspepsia. This denoted the doctors' concern when prescribing low-dose aspirin was probably the reason of high proportion of patients receiving PPI. From 79 patients consuming PPI, most patients consumed lansoprazole (93.7%) and the others had omeprazole (6.3%). In bivariate analysis, the use of PPI was proven to be protective to gastroduodenal mucosal injury in low-dose aspirin users with OR = 0.02 (95% CI: 0.1-0.7). Multivariate analysis also showed the use of PPI as significant protective factor OR = 0.2 (95% CI: 0.04 – 0.60).

Many studies supported PPI as a protection for gastroduodenal mucosal injury. Ibanez et al described that PPI administration in low-dose aspirin users would decrease the risk of gastrointestinal bleeding from 4.0 (3.2-4.9) to 1.1 (0.5-2.6).[13] Study by Lanas A et al also revealed that PPI decreased the risk of upper gastrointestinal bleeding with OR = 0.09 (95% CI: 0.01-0.69).[46] Gracia et al reported that PPI administration for less than 1 month did not significantly decrease the risk of upper gastrointestinal bleeding (OR = 2.9; 95% CI: 2.1-4.2); however, this became significant if administered for more than 1 month with OR = 0.6 (95% CI: 0.4-1,0).[24] Other studies exhibited that esomeprazole decreased risk of peptic ulcer.[14,47,48]

In comparison to other gastric acid anti-secreting drugs (H_2 receptor antagonist), PPI had stronger

protection effect. Ng FH et al identified higher gastrointestinal bleeding in famotidine group compared to pantoprazole in aspirin users (20 *vs*. 0%).[49] Lanas et al also reported that PPI administration was more effective compared to H_2 receptor antagonist (OR = 0.009 *vs*. 0.41).[46] Other study by Gracia et al also exhibited that PPI was more superior compared to H_2 receptor antagonist (OR = 0.6; 95% CI: 0.4-1.0) *vs*. 1.7 (95% CI: 1.2-2.4).[24] Other studies by Chan et al compared the recurrence rate of peptic ulcer bleeding due to aspirin use in clopidogrel and placebo combination group with aspirin and esomeprazole combination group. In that study, they found lower recurrence rate in aspirin and esomeprazole combination group (1 vs. 13 patients). This study concluded that PPI administration (esomeprazole) was superior compared to aspirin and clopidogrel combination group.[50]

Limitation of this study was this study used a cross-sectional design; thus, direct causal relationship could not be concluded. This study used OR value as an output to describe the different possibility of mucosal injury in groups with and without exposure. However, due to the quite high prevalence being obtained (51.6%), the OR value became overestimated. Further studies with cohort or case-control design are needed to confirm causal relationship between risk factors with the occurrence of mucosal injury.

CONCLUSION

To sum up, gastroduodenal mucosal injury happened in more than half patients who used long-term low-dose aspirin. Antithrombotic combination increased the risk of mucosal injury. Meanwhile, PPI administration was effective in decreasing the aforementioned risk. Elderly aged group, combination with warfarin, use of NSAIDs as co-medication, and evidence of *H. pylori* infection had higher risk in the occurrence of gastroduodenal mucosal injury in long-term low-dose aspirin; although it was not statistically significant. Diabetes mellitus did not increase the risk of gastroduodenal mucosal injury in long-term low-dose aspirin users.

Further studies with cohort or case-control design are needed to confirm the causal relationship of influencing factors with the occurrence of gastroduodenal mucosal injury in long-term low-dose aspirin users. Studies comparing patients who consumed long-term low-dose aspirin to control groups (not aspirin users) may also be performed.

REFERENCES

1. Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009;373:1849-60.
2. Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas JL, et al. International prevalence, recognition and treatment of cardiovascular risk factors in outpatients with atherothrombosis. JAMA 2006;295:180-9.
3. Schellack N. An overview of gastropathy induced by non-steroidal anti-inflammatory drugs. S Afr Pharm J 2012;79:12-18.
4. Yuji S, Akihito N, Hojo M, Asaoka D, Sasaki H, Ueyama H, et al. Upper gastrointestinal mucosal injury and symptoms in elderly low-dose aspirin users. Gastroenterol Res Pract 2015; 2015:252963.
5. Lanas A, Perez-Aisa MA, Feu F, Ponce J, Saperas E, Santolaria S, et al. A nationwide study of mortality associated with hospital admission due to severe gastrointestinal events and those associated with non-steroidal anti-inflammatory drug use. Am J Gastroenterol 2005;100:1685-93.
6. Cryer B, Bhatt DL, Lanza FL, Dong J, Lichtenberger LM, Marathi UK. Low-dose aspirin-induced ulceration is attenuated by aspirin – phosphatidylcholine: a randomized clinical trial. Am J Gastroenterol 2011;106:272-7.
7. Yeomans ND, Lanas AI, Talley NJ, Thomson AB, Daneshjoo R, Eriksson B, et al. Prevalence and incidence of gastroduodenal ulcers during treatment with vascular protective doses of aspirin. Aliment Pharmacol Ther 2005;22:795-801.
8. Nema H, Kato M, Katsurada T, Nozaki Y, Yotsukura A, Yoshida I, et al. Endoscopic survey of low-dose aspirin-induced gastroduodenal mucosal injuries in patients with ischemic heart disease. J Gastroenterol Hepatol 2008;23:S234-S236.
9. Lanas A, Bajador E, Serrano P, Fuentes J, Carreño S, Guardia J, et al. Nitrovasodilators, low-dose aspirin, other non-steroidal anti-inflammatory drugs, and the risk of upper gastrointestinal bleeding. N Engl J Med 2000;343:834–9.
10. Hallas J, Dall M, Andries A, Andersen BS, Aalykke C, Hansen JM, et al. Use of single and combined antithrombotic therapy and risk of serious upper gastrointestinal bleeding: population based case-control study. BMJ 2006;333:726.
11. Soylu A, Dolapcioglu C, Dolay K, Ciltas A, Yasar N, Kalayci M, et al. Endoscopic and histopathological evaluation of acute gastric injury in high-dose acetaminophen and non-steroidal anti-inflammatory drug ingestion with suicidal intent. World J Gastroenterol 2008;14:6704-10.
12. Sakamoto C, Sugano K, Ota S, Sakaki N, Takahashi S, Yoshida Y, et al. Case-control study on the association of upper gastrointestinal bleeding and non-steroidal anti-inflammatory drugs in Japan. Eur J Clin Pharmacol 2006;62:765-72.
13. Ibanez L, Vidal X, Vendrell L, Moretti U, Laporte JR. Upper gastrointestinal bleeding associated with antiplatelet drugs. Aliment Pharmacol Ther 2006;23:235-42.
14. Garcia Rodriguez LA, Hernandez-Diaz S, de Abajo FJ. Association between aspirin and upper gastrointestinal complications: systematic review of epidemiologic studies. Br J Clin Pharmacol 2001;52:563-71.
15. Sorensen HT, Mellemkjaer L, Blot WJ, Nielsen GL, Steffensen FH, McLaughlin JK, et al. Risk of upper gastrointestinal bleeding associated with use of low-dose aspirin. Am J Gastroenterol 2000;95:2218-24.
16. Niv Y, Battler A, Abuksis G, Gal E, Sapoznikov B, Vilkin A. Endoscopy in asymptomatic minidose aspirin consumers. Dig Dis Sci 2005;50:78-80.

17. Syam AF, Abdullah M, Makmun D, Simadibrata MK, Djojoningrat D, Manan C, et al. The Causes of upper gastrointestinal bleeding in the national referral hospital: evaluation on upper gastrointestinal tract endoscopic result in five years period. Indones J Gastroenterol Hepatol Dig Endosc 2005;6:71-4.
18. Syam AF, Abdullah M, Makmun D, Kolopaking MS, Djojoningrat D, Manan C, Daldiyono. Gastroduodenal lesion in chronic NSAID users: a case control study. Digestion 2008;77:60.
19. Valkhoff VE, Sturkenboom MCJM, Hill C, Van Zanten SV, Kuipers EJ. Low-dose acetylsalicylic acid use and the risk of upper gastrointestinal bleeding: a meta-analysis of randomized clinical trials and observational studies. Can J Gastroenterol 2013;27:159-67.
20. Expert panel on detection, evaluation and treatment, of high blood cholesterol in adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood pressure in adults. (Adult treatment panel III). JAMA 2001;285:2486-97.
21. Badan Penelitian dan Pengembangan Kesehatan Kementerian Kesehatan RI. Riset Kesehatan Dasar (RISKESDAS) 2013. Jakarta. 2013.
22. Ali MK, Narayan V, Tandon N. Diabetes & coronary heart disease: current perspectives. Indian J Med Res 2010;132:584-97.
23. Chowdhury A, Ganguly G, Chowdhury D, Santra A, Gupta JD, Roy T. Gastro-duodenal mucosal changes associated with low-dose aspirin therapy: a prospective, endoscopic study. Indian J Gastroenterol 2001;20:227-9.
24. Garcia Rodríguez LA, Hernandez-Diaz S. Risk of uncomplicated peptic ulcer among users of aspirin and non-aspirin non-steroidal anti-inflammatory drugs. Am J Epidemiol 2004;159:23-31.
25. Cryer B, Feldman M. Effects of very low dose daily, longterm aspirin therapy on gastric, duodenal, and rectal prostaglandin levels and on mucosal injury in healthy humans. Gastroenterology 1999;117:17-25.
26. Berardi RR, Fugit RV. Peptic ulcer disease. In: DiPiro JT, Talbert RL, Yee GC, eds. Pharmacotherapy: a pathophysiologic approach. 8th ed. New York: The McGraw-Hill Companies 2011.
27. Wallace JL. Prostaglandins, NSAIDs, and gastric mucosal protection: why doesn't the stomach digest itself? Physiol Rev 2008;88:1547-65.
28. Iwamoto J, Saito Y, Honda A, Matsuzaki Y. Clinical features of gastroduodenal injury associated with long-term low-dose aspirin therapy. World J Gastroenterol 2013;19:1673-82.
29. Sinha M, Gautam L, Shukla PM, Kaur P, Sharma S, Singh TP. Current Perspectives in NSAID-Induced Gastropathy. Mediators Inflamm 2013;2013:258209.
30. Alli O, Smith C, Hoffman M, Amanullah S, Katz P, Amanullah AM. Incidence, predictors, and outcomes of gastrointestinal bleeding in patients on dual antiplatelet therapy with aspirin and clopidogrel. J Clin Gastroenterol 2011;45:410-4.
31. Hernandez-Diaz S, Rodriguez LA. Cardioprotective aspirin users and their excess risk of upper gastrointestinal complications. BMC Medicine 2006;4:22.
32. Laine L. Review article: gastrointestinal bleeding with low-dose aspirin – what's the risk? Aliment Pharmacol Ther 2006;24:897–908.
33. Newton JL, Johns CE. May FEl 2004 review article: the ageing bowel and intolerance to aspirin. Aliment Pharmacol Ther 2004;19:39-45.
34. Hirasawa T, Satoh K, Sugano K. The present state and problem of gastric ulcer caused by low-dose aspirin. Nippon Rinsho 2010;68:1983–86.
35. Garcia Rodríguez LA, Lin KJ, Hernandez-Diaz S, Johansson S. Risk of upper gastrointestinal bleeding with low-dose Acetylsalicylic Acid alone and in combination with Clopidogrel and other medications. Circulation 2011;123:1108-15.
36. Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin or both after myocardial infarction. New Engl J Med 2002;347:969-74.
37. Lanas A, Scheiman J. Low-dose aspirin and upper gastrointestinal damage: epidemiology, prevention and treatment. Curr Med Res Opin 2007;23:163-73.
38. The Medical Research Council's General Practice Research Framework. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. Lancet 1998;351:233-41.
39. Johnson WC, Williford WO. Benefits, morbidity and mortality associated with long-term administration of oral anticoagulant therapy to patients with peripheral arterial bypass procedures: a prospective randomized study. J Vasc Surg 2002;35:413-21.
40. Meschengieser SS, Fondevila CG, Frontroth J, Santarelli MT, Lazzari MA. Low-intensity oral anticoagulation plus low-dose aspirin versus high-intensity oral anticoagulation alone: a randomized trial in patents with mechanical prosthetic heart valves. J Thorac Cardiovasc Surg 1997;113:910-6.
41. Gullov AL, Koefoed BG, Petersen P. Bleeding during warfarin and aspirin therapy in patients with atrial fibrillation: the AFASAK 2 study. Atrial fibrillation aspirin and anticoagulation. Arch Intern Med 1999;159:1322-8.
42. Li YW, Aronow WS. Diabetes Mellitus and Cardiovascular Disease. J Clinic Experiment Cardiol 2011;2:1.
43. Tseng PH, Lee YC, Chiu HM, Chen CC, Liao WC, Tu CH, et al. Association of diabetes and HbA1c levels with gastrointestinal mani-festations. Diabetes Care 2012;35:1053–60.
44. Simmons DL, Botting RM, Hla T. Cyclooxygenase isozymes: the biology of prostaglandin synthesis and inhibition. Pharmacol Rev 2004;56:387-437.
45. Udd M, Miettinen P, Palmu A, Heikkinen M, Janatuinen E, Pasanen P, et al. Analysis of the risk factors and their combinations in acute gastroduodenal ulcer bleeding: A case-control study. Scand J Gastroenterol 2007;42:1395-403.
46. Lanas A, Fuentes J, Benito R, Serrano P, Bajador E, Sainz R. *Helicobacter pylori* increases the risk of upper gastrointestinal bleeding in patients taking low-dose aspirin. Aliment Pharmacol Ther 2002;16:779-86.
47. Yeomans N, Lanas A, Labenz J, van Zanten SV, van Rensburg C, Racz I, et al. Efficacy of esomeprazole (20 mg once daily) for reducing the risk of gastroduodenal ulcers associated with continuous use of low-dose aspirin. Am J Gastroenterol 2008;103:2465-73.
48. Scheiman JM, Devereaux PJ, Herlitz J, Katelaris PH, Lanas A, Veldhuyzen van Zanten S, et al. Prevention of peptic ulcers with esomeprazole in patients at risk Iwamoto J et al. Low-dose aspirin-induced gastroduodenal injury of ulcer development treated with low-dose acetylsalicylic acid: a randomised, controlled trial (OB ERON). Heart 2011;97:797-802.
49. Ng FH, Wong SY, Lam KF, Chu WM, Chan P, Ling YH, et al. Famotidine is inferior to pantoprazole in preventing recurrence of aspirinrelated peptic ulcers or erosions. Gastroenterology 2010;138:82-8.
50. Chan FK, Ching JY, Hung LC, Wong VW, Leung VK, Kung NN, et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. N Engl J Med 2005;352:238-44.