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Relationship between continuous use of low-dose enteric-coated aspirin and gastrointestinal injuries in patients with gastrointestinal hemorrhage

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Background/aims: *Gastrointestinal disorders are important side effects of aspirin therapy, even if the low-dose enteric-coated form is administered. The aim of the current study was to present the upper and lower endoscopic features of patients with gastrointestinal hemorrhage using low-dose enteric-coated aspirin.* ***Materials and Methods:*** *This prospective study was conducted among 633 consecutive patients with gastrointestinal hemorrhage who admitted to our tertiary referral hospital for endoscopy assessment. Patients were divided into two groups as low-dose aspirin users (n=168) and non-aspirin users (n=495). Aspirin users included those who were taking 80-100 mg of enteric-coated aspirin per day.* ***Results:*** *Ulcer lesions were found in 78 patients in the aspirin user group and in 113 patients in the control group. Prevalence of duodenal ulcer was statistically similar between the two groups; however, gastric ulcer was seen more in the aspirin-user group. The use of low-dose aspirin could strongly predict gastric ulcers in the patients examined by endoscopy (p<0.001). Overall prevalence of peptic ulcer disease in those with confirmed Helicobacter pylori infection was significantly higher than in non-infected ones (p<0.001). The presence of this infection was strongly associated with peptic ulcer disease in the aspirin-user group (p<0.001). Multivariable analysis also demonstrated that the use of aspirin had a main triggering effect on short-term mortality following gastrointestinal endoscopy (p=0.003).* ***Conclusions:*** *Low-dose enteric-coated aspirin causes significant gastric endoscopic lesions and even predicts mortality due to progression of gastrointestinal disorders.*

Key words: Low-dose enteric-coated aspirin, gastrointestinal lesions, endoscopic findings, gastrointestinal bleeding

Gastrointestinal kanamalı hastalarda düşük doz enterik kaplı aspirinin devamlı kullanılması ve gastrointestinal hasar arasındaki ilişki

Amaç: *Gastrointestinal bozukluklar, düşük doz enterik-kaplı formu kullanılsa bile aspirin tedavisinin hayati yan etkilerindendir. Bu çalışmanın amacı, gastrointestinal kanamalı hastalarda düşük doz enterik-kaplı aspirine bağlı üst ve alt endoskopik bulguları sunmaktır.* ***Gereç ve Yöntem:*** *Bu prospektif çalışma, üçüncü basamak referans merkezimize endoskopik değerlendirme için gastrointestinal kanama ile başvuran ardışık 633 hastada yapılmıştır. Hastalar iki gruba ayrılmıştır; düşük doz aspirin kullananlar (n=168) ve aspirin kullanmayanlar (n=495). Aspirin kullananlar günde 80-100 mg enterik-kaplı aspirin alanlardan oluşmaktaydı.* ***Bulgular:*** *Ülser lezyonları aspirin kullanan grupta 78 hastada ve kontrol grubunda 113 hastada bulundu. Duodenal ülser prevalansı iki grup arasında istatistiksel açıdan benzerdi; ancak gastrik ülser aspirin kullanan grupta daha fazla görüldü. Düşük doz aspirin kullanımı endoskopi yapılan hastalarda gastrik ülser riskini artırıyordu (p < 0.001). Konfirme edilmiş Helikobakter pilori infeksiyonu olan hastalarda, olmayanlara göre genel peptik ülser prevalansı anlamlı şekilde yüksekti (p < 0.001). Bu infeksiyonun varlığı aspirin kullanan grupta peptik ülser hastalığı ile kuvvetli şekilde ilişkili bulundu (p < 0.001). Çok değişkenli analizde ayrıca aspirinin gastrointestinal endoskopi sonrası kısa dönem mortaliteyi belirleyen ana tetikleyici etmen olduğu görüldü (p = 0.003).* ***Sonuç:*** *Düşük doz enterik-kaplı aspirin, belirgin gastrik endoskopik lezyonların oluşmasına ve gastrointestinal hastalığın ilerlemesi sonucunda mortalitenin artmasına neden olmaktadır.*

Anahtar kelimeler: Düşük doz enterik kaplı aspirin, gastrointestinal lezyonlar, endoskopik bulgular, gastrointestinal kanama

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INTRODUCTION

Low-dose aspirin is a commonly applied drug worldwide to prevent both cardiovascular and cerebrovascular diseases. Because the number of people, especially younger people, who suffer from these diseases is increasing dramatically, the need for a low-dose aspirin treatment regimen is expected to also increase in the near future. The functional mechanisms of aspirin in protecting vital organs have been clearly determined. This drug can inhibit the synthesis of cyclooxygenase-1 (COX-1) (1), which induces analgesic and anti-inflammatory effects. Aspirin can also produce its antithrombotic effect through irreversible acetylation of a serine in COX-1 of platelets (2), which abolishes production of thromboxane A2 for the life of the platelet. However, in addition to the beneficial effects of aspirin in cardiovascular and cerebrovascular function, its consumption may also result in serious gastrointestinal toxicities such as mucosal lesions. Thus, enteric-coated forms of aspirin have been synthesized to minimize these side effects. This drug formation has a film coating that resists gastric acid and prevents tablet dissolution in the stomach. Despite the use of this form of the drug, it still causes gastrointestinal injuries, which may be due to its general action of inhibiting COX-1 (3). The prevalence of gastroduodenal lesions may not be dependent on the duration of aspirin administration. Most low-dose aspirin users with gastroduodenal injuries are asymptomatic till their progressive patterns appear (4). Therefore, an endoscopic evaluation of this side effect in this population is vital. The current study represents the endoscopic findings in low-dose enteric-coated aspirin users.

MATERIALS AND METHODS

The current study was conducted on 633 consecutive patients with gastrointestinal hemorrhage who admitted to our tertiary referral hospital (Ayatollah Taleghani Hospital) for endoscopy assessment. Patients were excluded if they had an uncontrolled systemic disease, malignancy, previous gastric surgery, unstable angina, myocardial infarction, stroke, or transient ischemic attack within the three months prior to the first endoscopy. Other reasons for exclusion were concomitant treatment with other non-steroidal anti-inflammatory drugs (NSAIDs), histamine receptor antagonists, proton pump inhibitors, corticosteroids, bisphosphonates, anticoagulants, acid suppressants, or prostaglandin analogues. This study was performed in Ayatolloah Taleghani Hospital and Shahid Beheshti Medical University, and was approved by the ethics committee of Ayatollah Taleghani Hospital. Fully informed consent was signed by each patient before participating in the study.

Patients were divided into two groups as low-dose aspirin users (n=168) and non-aspirin users (n=495). Aspirin users included those who were taking 80-100 mg of enteric-coated aspirin per day. Prior to endoscopy, a self-administered questionnaire was filled out describing the patients' demographics, medical history and abdominal symptoms. Endoscopy was performed after three minutes' local anesthesia to the pharynx with lidocaine. Endoscopy findings were assessed as follows: mucosal defect >5 mm as ulcer and mucosal defect <5 mm as flat erosion. Evidences of gastrointestinal malignancies and other abnormal findings were also recorded. *Helicobacter pylori (H. pylori)* status was determined by the presence of serum *H. pylori* immunoglobulin (Ig)G antibodies with an enzyme-linked immunosorbent assay kit using the E plate test. Continuous variables were compared using *t* test or non-parametric Mann-Whitney U test whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the groups. Categorical variables across the two groups were compared using the chi-square test or Fisher's exact test if required. For determining the triggering effects of low-dose aspirin on the appearance of gastric ulcer and also early mortality after the endoscopy procedure, multivariable logistic regression analysis was used, and results of this analysis were presented as odds ratio (OR) and 95% confidence intervals (95% CIs) for OR. We considered two-tailed p values ≤0.05 to be statistically significant. Analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (version 16.0) for Windows.

RESULTS

A total of 633 patients (378 males, 255 women; average age, 56 years) were enrolled. Demographic and clinical characteristics are shown in Table 1.

The male-to-female ratio was similar in the aspirin user and non-user groups (1.5 versus 1.6). Among gastrointestinal manifestations, melena alone was more prevalent in aspirin users, and the

Table 1. Demographic characteristics in patients

Characteristics	Aspirin group (n=168)	Control group (n=495)	*p-value*
Female gender	67 (39.9)	188 (38.0)	0.662
Age (yr)	62.49±17.04	53.86±19.54	<0.001
Hematemesis	83 (49.4)	265 (53.5)	0.354
Melena alone	69 (41.1)	119 (24.0)	<0.001
Rectorrhagia alone	23 (13.7)	119 (24.0)	0.005
History of cirrhosis	2 (1.2)	114 (23.0)	<0.001
History of GI bleeding	21 (12.5)	88 (17.8)	0.111
History of GI cancer	2 (1.2)	29 (5.9)	0.013
Helicobacter pylori detection	95 (56.5)	182 (36.8)	<0.001

Data are presented as mean±SD or number (%).

Table 2. Endoscopic findings in patients who were examined by endoscopy

Characteristics	Aspirin group (n=168)	Control group (n=495)	*p-value*
Upper endoscopy			
Duodenal ulcer	32 (19.0)	81 (16.4)	0.439
Gastric ulcer	46 (27.4)	32 (6.5)	<0.001
Erosive gastritis	28 (16.7)	57 (11.5)	0.082
Esophagitis	7 (4.2)	18 (3.6)	0.724
Esophageal varices	4 (2.4)	94 (19.0)	<0.001
Gastric cancer	6 (3.6)	37 (7.5)	0.077
Lower endoscopy			
Colon cancer	1 (0.6)	17 (3.4)	0.053
Colon polyps	5 (3.0)	18 (3.6)	0.713
Diverticulitis	6 (3.6)	8 (1.6)	0.119
Inflammatory bowel disease	0 (0)	27 (5.8)	0.154
Hemorrhoid	3 (1.8)	19 (3.8)	0.209
Angiodysplasia	3 (1.8)	5 (1.0)	0.411

Data are presented as number (%).

control group suffered more from rectorrhagia. Regarding their medical history, a history of gastrointestinal malignancies and cirrhosis was observed more in non-users. There were no significant differences between the two groups in terms of hematemesis and previous gastrointestinal bleeding. *H. pylori* infection was also detected more in the aspirin-user group. Ulcer lesions were found in 78 patients in the aspirin-user group (gastric ulcer in 27.4% and duodenal ulcer in 19.0%) and in 113 patients in the control group (gastric ulcer in 6.5% and duodenal ulcer in 16.4%). Overall prevalence of duodenal ulcer was similar between the two groups; however, gastric ulcer was seen more in the aspirin-user group (Table 2).

There were no significant differences in the appearance of upper gastrointestinal erosions, gastric cancer or lower endoscopy findings between the groups. Multivariable analysis (Table 3) showed that the use of low-dose enteric-coated aspirin could strongly predict gastric ulcers in patients examined by endoscopy (OR: 4.047, 95%CI: 2.369 – 6.915, p<0.001). Hosmer–Lemeshow goodness of fit revealed: χ^2=7.120, p=0.524.

Overall prevalence of peptic ulcer disease in those with confirmed *H. pylori* infection was significantly higher than in the others (54.5% versus 10.4%, p<0.001). Regarding the influence of *H. pylori* on the appearance of peptic ulcer disease, the presence of this infection was strongly associated with peptic ulcer disease in the presence of aspirin use (OR: 9.643, 95%CI: 6.408–14.511, p<0.001).

Early post-procedure mortality (death in 30 days

Table 3. Triggering effects of low-dose aspirin on appearance of gastric ulcer

Item	Multivariable *p-value*	Odds Ratio	95% Confidence Interval
Aspirin use	<0.001	4.047	2.369 – 6.915
Female gender	0.038	1.803	1.034 – 3.142
Advanced age	0.118	1.012	0.997 – 1.028
Positive H. pylori	<0.001	3.256	1.875 – 5.654
History of cirrhosis	0.224	0.505	0.168 – 1.519
History of GI bleeding	0.275	1.456	0.742 – 2.856

Table 4. Triggering effects of low-dose aspirin on early mortality

Item	Multivariable *p-value*	Odds Ratio	95% Confidence Interval
Aspirin use	0.003	3.333	1.512 – 7.348
Female gender	0.519	0.806	0.420 – 1.550
Advanced age	0.004	1.030	1.009 – 1.051
Positive *H. pylori*	0.012	0.361	0.164 – 0.796
History of cirrhosis	0.001	6.126	2.712 – 13.834
History of GI bleeding	0.129	0.494	0.199 – 1.227

Hosmer–Lemeshow goodness of fit: χ^2=9.537, p=0.299

after the first episode of bleeding) was recorded in 10.1% of patients who were treated with low-dose aspirin and in 5.9% of non-users, and this was slightly higher in the aspirin users (p=0.060). Multivariable analysis (Table 4) also demonstrated that the use of aspirin had a main triggering effect on short-term mortality following gastrointestinal endoscopy (OR: 3.333, 95%CI: 1.512–7.348, p=0.003).

DISCUSSION

The mechanism of aspirin-induced gastrointestinal effects has been known as a local stimulus action that is generally caused by direct contact of acetylsalicylic acid with the gastrointestinal mucus and the general action that is a product of circulation after the absorption of acetylsalicylic acid from the gastrointestinal region into the portal veins (4). An inflammatory process that can mediate aspirin-related gastrointestinal lesion has been demonstrated as well, in which antral prostaglandin-E2 basal levels appear to be critical for development of aspirin-induced gastric damage, even in subjects without *H. pylori* infection (5). Some known factors predicting high susceptibility to gastrointestinal complications with low-dose aspirin are advanced age, history of gastric hemorrhage or peptic ulcer disease, use of corticosteroids, and total dose of aspirin (6-8). However, gender, cigarette smoking, alcohol consumption, body mass index, and endoscopic findings of gastric atrophy are not significantly associated with ulcer lesions in low-dose aspirin users (9).

The current study aimed to estimate the incidence rate of gastrointestinal ulcer lesions in patients who underwent diagnostic endoscopy and used pre-procedure regular low-dose enteric-coated aspirin and also to determine the role of aspirin in inducing these lesions in the presence of *H. pylori* infection as a known determinant factor. In our study, the incidence of gastric ulcer lesions was higher in aspirin users than in the non-users (27.4% versus 19.0%), whereas there was no significant difference in the incidence of duodenal ulcer between the two study groups. Some previous studies found a higher incidence of peptic lesions following low-dose aspirin use. In Nema et al.'s (4) report, mucosal injuries were found in 61.4% of low-dose aspirin users and in 10% of non-users. In another study, they also revealed mucosal defects in 48.4% of aspirin users and in 13.0% of non-users (10). Some authors believe that the risk of peptic ulcer complications has been raised in association with aspirin use, and they estimate the OR of these complications in the range of 1.3–3.2 (11-14). However, in some other studies, aspirin in dosages commonly used for cardiovascular prophylaxis did not generally cause significant gastric or duodenal mucosal endoscopic lesions (15). In view of the fact that patients with chronic intake of en-

teric-coated aspirin might have a high frequency of asymptomatic gastroduodenal lesions (16), regular monitoring of these patients regarding the appearance of lesions seems to be necessary. According to our study findings, with regard to poor outcome in low-dose aspirin users with gastrointestinal lesions, this monitoring can even lead to a decrease in the mortality rate in these patients.

We found a strong association between *H. pylori* infection and the presence of peptic ulcer in cases taking low-dose aspirin. An Italian study of symptomatic elderly chronic users of low-dose aspirin found that the prevalence of peptic ulcers was significantly higher (36.6% versus 15.8%) among *H. pylori*-positive subjects than the *H. pylori*-negative subjects (17). However, in another study in Japan, the prevalence of *(H. pylori)* infection was found to be significantly lower in patients considered to have NSAID-associated gastric ulcer than in age-matched non-NSAID-associated gastric ulcer patients (48% versus 96%) (18). Our findings possibly reflect the differences in the prevalence or severity of *H. pylori* gastritis between different countries. The interaction between *H. pylori* and aspirin may also differ according to the topography and severity of the gastritis (19). Infection with *H. pylori* is a clear risk factor for non-NSAID-induced ulcers, and there is evidence of an additive effect of NSAIDs and *H. pylori* for causing duodenal ulcers (20). Therefore, *H. pylori* and aspirin seem to be independent risk factors for peptic ulcer and bleeding, and the additive effect of *(H. pylori)* may be greater among patients taking low-dose aspirin than others.

Another interesting finding of the present study is that advanced age is not a main predictor for gastric erosions, in contrast to the known increased risk for aspirin-induced gastric ulcers. It seems that advancing age can increase the risk of frank ulcers not because of susceptible mucosa, but because of low healing ability (21). Such a conclusion is consistent with the known impairment in healing that occurs with age in other tissues in which it has been studied (22,23).

In conclusion, low-dose enteric-coated aspirin causes significant gastric endoscopic lesions and even predicts short-term mortality due to progression of gastrointestinal disorders. The adverse effect of low-dose enteric-coated aspirin on gastric mucosa is more severe in *H. pylori* infection.

REFERENCES

1. Bochner F, Siebert DM, Rodgers SE, et al. Measurement of aspirin concentrations in portal and systemic blood in pigs: effect on platelet aggregation, thromboxane and prostacyclin production. Thromb Haemost 1989; 61: 211-6.
2. Awtry EH, Loscalzo J. Aspirin. Circulation 2000; 101: 1206-18.
3. Kelly JP, Kaufman DW, Jurgelon JM, et al. Risk of aspirin-associated major upper-gastrointestinal bleeding with enteric-coated or buffered product. Lancet 1996; 348: 1413-6.
4. Nema H, Kato M, Katsurada T, et al. Endoscopic survey of low-dose aspirin-induced gastroduodenal mucosal injuries in patients with ischemic heart disease. J Gastroenterol Hepatol 2008; 23 (Suppl 2): S234-6.
5. Venerito M, Treiber G, Wex T, et al. Effects of low-dose aspirin on gastric erosions, cyclooxygenase expression and mucosal prostaglandin-E2 do not depend on *Helicobacter pylori* infection. Aliment Pharmacol Ther 2006; 23: 1225-33.
6. Rodriguez LAG, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. Lancet 1994; 343: 769–72.
7. Serrano P, Lanas A, Arroyo MT, Ferreira IJ. Risk of upper gastrointestinal bleeding in patients taking low-dose aspirin for the prevention of cardiovascular diseases. Aliment Pharmacol Ther 2002; 16: 1945-53.
8. Rostom A, Moayyedi P, Hunt R. Canadian consensus guidelines on long-term nonsteroidal anti-inflammatory drug therapy and the need for gastroprotection: benefits versus risks. Aliment Pharmacol Ther 2009; 29: 481-96.
9. Shiotani A, Sakakibara T, Yamanaka Y, et al. Upper gastrointestinal ulcer in Japanese patients taking low-dose aspirin. J Gastroenterol 2009; 44: 126-31.
10. Nema H, Kato M, Katsurada T, et al. Investigation of gastric and duodenal mucosal defects caused by low-dose aspirin in patients with ischemic heart disease. J Clin Gastroenterol 2009; 43: 130-2.
11. Kelly JP, Kaufman DW, Jurgelon JM, et al. Risk of aspirin-associated major upper-gastrointestinal bleeding with enteric-coated or buffered product. Lancet 1996; 348: 1413-6.
12. Lanas A, Bajador E, Serrano P, 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.
13. Capet C, Czernichow P, Dupas J, et al. Upper gastrointestinal bleeding in patients treated by low-dose aspirin. Gastroenterol Clin Biol 2001; 25: 233-8.
14. Laine L. Review article: gastrointestinal bleeding with low-dose aspirin-what's the risk? Aliment Pharmacol Ther 2006; 24: 897-908.
15. Greenberg PD, Cello JP, Rockey DC. Relationship of low-dose aspirin to GI injury and occult bleeding: a pilot study. Gastrointest Endosc 1999; 50(5): 618-22.
16. Jaszewski R. Frequency of gastroduodenal lesions in asymptomatic patients on chronic aspirin or nonsteroidal antiinflammatory drug therapy. J Clin Gastroenterol 1990; 12: 10-3.
17. Pilotto A, Franceschi M, Longoa MG, et al. *Helicobacter pylori* infection and the prevention of peptic ulcer with proton pump inhibitors in elderly subjects taking low-dose aspirin. Dig Liver Dis 2004; 36: 666-70.

18. Kamada T, Hata J, Kusunoki H, et al. Endoscopic characteristics and *Helicobacter pylori* infection in NSAID-associated gastric ulcer. J Gastroenterol Hepatol 2006; 21: 98-102.
19. Shiotani A, Graham DY. Pathogenesis and therapy of gastric and duodenal ulcer disease. Med Clin North Am 2002; 86: 1447-66.
20. Hawkey CJ, Wilson I, Naesdal J, et al. Influence of sex and Helicobacter pylori on development and healing of gastroduodenal lesions in non-steroidal anti-inflammatory drug users. Gut 2002; 51: 344-50.
21. Griffin MR. Epidemiology of non-steroidal anti-inflammatory drug-associated gastrointestinal injury. Am J Med 1998; 104: 23-9.
22. Holt DR, Kirk SJ, Regan MC, et al. Effect of age on wound healing in healthy human beings. Surgery 1992; 112: 293-7.
23. Engeland CG, Bosch JA, Cacioppo JT, Marucha PT. Mucosal wound healing: the roles of age and sex. Arch Surg 2006; 141: 1193-7.