Atherosclerosis and acetylsalicylic acid are independent risk factors for hemorrhage in patients with gastric or duodenal ulcer

Ateroskleroz ve asetilsalisilik asit gastrik ve duodenal ülser kanaması için bağımsız risk faktörleridir

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ABSTRACT

Objective: Risk factors for hemorrhage due to gastric and/or duodenal ulcer in patients diagnosed by upper gastrointestinal (GI) endoscopy were investigated in the present study.
Methods: Medical records of 350 patients (226 males, 124 females) diagnosed as duodenal or gastric ulcers by GI endoscopy in the gastroenterology clinic were scanned retrospectively. Upper GI hemorrhage was detected in 92 patients by upper endoscopic examination. The medical history of non-steroidal anti-inflammatory drugs (NSAIDs) or acetylsalicylic acid (ASA) usage and the presence of coronary artery disease (CAD) were investigated in all patients with or without hemorrhage. Results were evaluated by Chi-square test and logistic regression analysis.
Results: The mean age of the patients was 50.4±15.7 years (range: 25 to 82 years). Hemorrhage due to gastric or duodenal ulcer was identified in 92 patients (26%). Mean age was 64.6±11.4 years in patients with hemorrhage and 45.7±13.9 years in patients without hemorrhage. ASA usage was more common than NSAID in patients with ulcer hemorrhage (NSAID usage n=35 (40%); ASA usage n=51 (60%); p=0.035). Hemorrhage was reported in 20% of the females and in 28% of the males who have ulcer (p=0.055). Risk factors for hemorrhage were CAD (OR:24.75, 95% CI=1.6-96.7, p=0.001), ASA usage (OR:9.76, 95% CI=2.1-37.5, p=0.021), NSAID usage (OR: 4.72, 95%CI=1.1-16.5, p=0.032), age (OR: 11.59, 95% CI= 2.7-12.1, p=0.001), and male gender (OR: 2.56, 95% CI= 0.8, 9.6, p=0.052).
Conclusion: Advanced age, atherosclerosis, male gender and NSAID administration (particularly aspirin) are the major risk factors of upper GI hemorrhage in patients with gastric and/or duodenal ulcer. *(Anadolu Kardiyol Derg 2011 1: 53-6)*
Key words: Aspirin, coronary artery disease, upper gastrointestinal hemorrhage, non-steroidal anti-inflammatory drug, logistic regression analysis

ÖZET

Amaç: Üst gastrointestinal (Gİ) endoskopide gastrik ve/veya duodenal ülser saptanan vakalarda ülser kanaması için risk faktörleri araştırıldı.
Yöntemler: Üst Gİ endoskopisinde duodenum ve gastrik ülser saptanan 350 vakanın (226 Erkek, 124 Kadın) dosyalarından retrospektif analiz yapıldı. İncelenen 92 vakada endoskopi sırasında Gİ kanama saptanmıştı. Kanaması olan ve olmayan hastaların tümünde nonsteroidal antienflamatuvar ilaç (NSAID) ve asetil salisilik asit (ASA) kullanımı ile koroner arter hastalığı (KAH) varlığı araştırıldı. Sonuçlar Ki-kare testi ve lojistik regresyon analizi ile değerlendirildi.
Bulgular: Vakaların yaş ortalaması 50.4±15.7 (25- 82) yıl idi. Doksan iki vakada (%26) gastrik veya duodenal ülsere bağlı kanama görüldü. Kanamalı hastalarda yaş ortalaması 64.6±11.4/ yıl, kanama olmayanlarda 45.7±13.9/yıl idi. Ülser kanaması olan vakalarda ASA kullanımı daha fazlaydı (NSAID, n=35 (%40); ASA, n=51 (%60); p=0.035). Ülseri olan kadınların %20'sinde kanama görülürken, erkeklerin %28'inde kanama görüldü (p=0.055). Kanama riski KAH'lı vakalarda (OR:24.75, %95 güven aralığı (GA)=1.6-96.7, p=0.001), ASA (OR:9.76, %95 GA=2.1-37.5, p=0.021), NSAID (OR:4.72, %95 GA=1.1-16.5 p=0.032), yaş (OR:11.59, %95 GA=2.7-12.1, p=0.001), erkek cinsiyet için (OR:2.56, %95 GA=0.8, 9.6, p=0.052) olarak belirlendi.
Sonuç: İleri yaş, ateroskleroz, erkek cinsiyet ve NSAİD (özellikle aspirin) kullanımı gastrik ve/veya duodenal ülserli hastalarda üst Gİ kanaması bakımından majör risk faktörleridir. *(Anadolu Kardiyol Derg 2011 1: 53-6)*
Anahtar kelimeler: Aspirin, koroner arter hastalığı, üst gastrointestinal kanama, nonsteroidal anti-inflamatuvar ilaç, lojistik regresyon analizi

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Introduction

Frequency of non-steroidal anti-inflammatory drug (NSAID) administrations including acetylsalicylic acid (ASA), increases in patients with advanced ages, due to the different diseases such as joint and muscular diseases, ischemic heart disease, peripheral artery disease and stroke. Gastrointestinal (GI) toxicities associated with NSAIDs, such as primarily ulcer and bleeding, increase depending on this reasons (1, 2). Endoscopic studies reveal ulcers in 10-25% of patients who used NSAIDs while the frequencies of ulcer complications such as hemorrhage, perforation and pyloric obstruction, vary between 1.3-5% (3-5). Although dyspeptic complaints are common in NSAID used patients, it is not possible to anticipate whether it may lead ulcer or not. Gastrointestinal complications in long-term NSAID usage were found to be associated with history of previous peptic ulcer and the upper GI hemorrhage, presence of a cardiovascular disease and advanced age (6, 7). Other risk factors are concomitant corticosteroid and/or oral anticoagulant usage, diabetes mellitus, cerebrovascular disease and heart failure (8-10). Atherosclerosis, however, may be an independent risk factor. NSAID usage in patients with atherosclerosis also may increase the risk of hemorrhage. The risk of hemorrhage is not known in elderly patients especially using aspirin for atherosclerotic heart disease. There are two important questions too; what is the re-bleeding risk of these patients and, is it safe for them to continue aspirin usage?

We aimed to investigate GI toxicity associated with NSAID administration in atherosclerotic patients. Thus, the patients who diagnosed as gastric and/or duodenal ulcer by upper gastrointestinal endoscopy were investigated retrospectively for atherosclerosis and other risk factors for ulcer hemorrhage.

Methods

The files of patients who examined by upper GI endoscopy were investigated retrospectively. Three hundred fifty patients (226 male, 124 female) were diagnosed with duodenal or gastric ulcer by upper endoscopic examination in our clinic between 2004 and 2006. The mean age of the patients was 50.4±15.7 years (25-82 years). Upper GI hemorrhages were detected in 92 of them. Endoscopically, there were no signs of hemorrhage in 258 patients. The medical history of NSAIDs or ASA usage and the presence of coronary artery disease (CAD) were investigated in all patients with or without hemorrhage. According to the patients' records; sixty-one patients had established diagnosis of CAD and, sixty-nine patients had used ASA with the doses of 100-300 mg/day and 57 had used NSAIDs (indomethacin, naproxen sodium, diclofenac sodium). All of the cases with CAD had used ASA. Since there is no difference between these dosages to develop gastric or duodenal ulcer, the patients were not divided to subgroups as reported in the literature (11). The patients were assessed for hemorrhage risk of ASA and NSAIDs usage, age, presence of atherosclerosis and gender effect.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 10.0 (IBM, Chicago, IL, USA). The t-test for independent samples was used to investigate the age distribution between groups. Pearson's Chi-square test was used to determine relationships between non-continuous variables. Logistic regression analysis was used to analyze the risk factors for GI hemorrhage with following variables included in the model: dependent variable (GI hemorrhage) and independent variables (ASA and, NSAID usage, presence of CAD and male gender). Differences were considered as statistically significant at $p<0.05$.

Results

Clinical characteristics of patients

Of the 350 patients studied, 124 were female (35%) and 226 (65%) were male. Hemorrhages associated with gastric or duodenal ulcer were reported in 92 of 350 patients (26%), (Table 1). Mean age of the patients with hemorrhage was 64.6±11.4 years while mean age of those without hemorrhage was 45.7±13.9 years. Hemorrhage was more common in patients over 60 years ($p<0.001$, Table 1).

Endoscopy results

The distribution of ulcers in all patients showed in Table 2. Although duodenal ulcers were more common than gastric ulcers (duodenal ulcer 51.7%, gastric ulcer 48.3%), hemorrhage was more frequent in corpus ulcers ($p=0.025$, Table 2). There were no differences between NSAIDs (n=22) and ASA (n=18) usage in patients with ulcer without hemorrhage, whereas ASA usage was more common in patients with bleeding ulcer. Hemorrhage was observed in 35 of 57 patients using NSAIDs (61.5%) and in 51 of 69 patients using ASA (74%), (Table 3). Hemorrhage occurred in 20% of female patients and 28% of male patients with ulcer. Although the frequency of hemorrhage was higher in males, the difference was not statistically significant ($p=0.052$, Table 1).

Hemorrhage was detected in 83.6% of patients with ulcer and CAD, whereas only 20% of patients without CAD had hemorrhage ($p=0.001$, Table 3).

Predictors of GI hemorrhage

The logistic regression analysis carried out to investigate the risk factors contributing to hemorrhage showed that presence of

Table 1. Distribution of gender, age and non-bleeding and bleeding rates of patients enrolled in the study

Variables	Total	Hemorrhage	No hemorrhage	p*
Female, n (%)	124 (35)	25 (20)	99 (80)	0.052
Male, n (%)	226 (65)	67 (28)	159 (72)	
Total, n (%)	350 (100)	92 (26)	258 (74)	
Mean age, years	50.4±15.7	64.6±11.4	45.7±13.9	0.001

Data are expressed as frequency distribution, percentages and mean±standard deviation
*Pearson's Chi-square test and t-test for independent samples

CAD (OR: 24.75, 95% CI=1.6-96.7, p=0.001) was associated with a marked increase in the hemorrhage risk. Other significant risk factors for hemorrhage were ASA (OR: 9.76, 95% CI=2.1-37.5, p=0.021) and NSAID usage (OR: 4.72, 95% GA=1.1-16.5, p=0.032), older age (OR: 11.59, 95% CI= 2.7-12.1, p=0.001), and male gender (OR: 2.56, 95% CI= 0.8- 9.6, p=0.052) (Table 4).

Discussion

In this study, it was found that CAD alone, much more increases the risk of hemorrhage of gastric or duodenal ulcers than other risk factors such as ASA or NSAIDs usage and age.

In western countries, gastric ulcer is primarily associated with NSAID and ASA administration whereas duodenal ulcer is more associated with *Helicobacter pylori*. In both cases, imbalance between protective and damaging factors can lead to ulcer (12-14). Physiological prostaglandins (PGE) are extremely critical in protecting gastric mucosa. Non-steroidal anti-inflammatory drugs disturb mucosal barrier by inhibiting the synthesis of physiological PGs through inhibition of the COX-2 enzyme. In advanced ages, as another risk factor for ulcer development, mucus production decreases due to atrophy in gastric goblet cells (15-18). Mucus is one of the major barriers in protecting the gastric mucosa against acid. When this defense system fails, mucosal damage occurs as a result of exposure to acids and pepsins. It has been shown that coronary atherosclerosis accompanies with systemic atherosclerosis (19). Thus, in cases with coronary atherosclerosis, mucosal perfusion may change depending on severity of atherosclerosis. Predisposition to mucosal damage is increased in patients with CAD due to both advanced ages and impairment of mucosal perfusion. It also can lead to decreased regenerative ability of the damaged tissue. Therefore, advanced age, CAD, ASA and NSAID administration have a synergistic effect in ulcer development by reducing mucus production and regeneration potential. As a consequence, risk for ulcer development and hemorrhage increases (20).

Acetylsalicylic acid and other NSAIDs, advanced age, heart failure, diabetes mellitus, previous ulcer history, smoking and alcohol consumption are important risk factors for ulcer development and hemorrhage (21). Especially in the last decades, ASA administration is gradually increased due to its proven antiaggregant therapeutic effect to prevent thromboembolic events in atherosclerotic heart and cerebrovascular disease. Therefore, ulcer and its complications started to increase gradually (22). Low dose acetylsalicylic acid administrations to prevent thrombotic stroke or myocardial infarction, also can cause gastrointestinal damage and GI complications. It is reported that, ulcers and erosions have been detected endoscopically in 47.8% of patients who received low dose ASA for more than three months (23-26). The short-term administration of ASA has been reported to bring out a higher risk compared to long-term administration (27, 28). The subjects enrolled in the present study were taking a NSAID or ASA for more than 6 months. Our results demonstrated that risk of hemorrhage is higher in ASA using patients than NSAIDS using patients. Faulkner et al. (29) reported a 3-fold increased rate of hospitalization for ulcer complications in patients using ASA compared to with those taking NSAIDs.

Based on the results of the present study, atherosclerosis increases the risk of ulcer complications independently from other risk factors. Therefore, routine administration of proton pump inhibitors or PG agonists (misoprostol) in combination with ASA may be useful in patients with CAD or advanced age.

Table 2. Anatomic distribution of ulcers detected in endoscopic examination

Ulcer location	No hemorrhage		Hemorrhage		p*
	n	%	n	%	
Corpus ulcer	40	15.5 58.8	28	30.4 41.2	0.025
Antrum ulcer	82	31.7 80.3	20	21.7 18.7	NS
Duodenal ulcer	136	52.7 75.5	44	47.8 24.5	NS
Total	258		92		

Data are expressed as number, percentages
Pearson's Chi-square test
In the % column, upper values indicate the ratio among patients with and without hemorrhage, while the values below indicate ratios of cases by ulcer localization. According to these values, gastric ulcer is the condition with the highest rate of hemorrhage

Table 3. The distribution of NSAID and ASA use and coronary artery disease in patients with ulcer hemorrhage and no hemorrhage

Variables	No hemorrhage (n=258)	Hemorrhage (n=92)	p
NSAID, (+) n (%)	22 (38.5)	35 (61.5)	0.012
NSAID, (-) n (%)	239 (80.7)	57 (19.3)	
ASA, (+) n (%)	18 (26)	51 (74)	0.001
ASA, (-) n (%)	237 (82.8)	40 (17.2)	
CAD, (+) n (%)	51(83.6)	10 (16.4)	0.001
CAD, (-) n (%)	7 (20)	29(80)	

Data are expressed as number, percentages
*Pearson's Chi-square test
ASA - acetylsalicylic acid, CAD - coronary artery disease, NSAID - non-steroidal anti-inflammatory drugs

Table 4. Risk factors for hemorrhage according to the logistic regression analysis

Risk factors for ulcer bleeding*	n	Odds ratio (95% confidence interval)	p
CAD	61	24.75 (1.6-96.7)	0.001
ASA	69	9.76 (2.1-37.5)	0.021
NSAIDs	57	4.72 (1.1-16.5)	0.032
Age	350	11.59 (2.7-12.1)	0.001
Male gender	226	2.56 (0.8-9.6)	0.052

Data are expressed as odds ratio and confidence interval
* The logistic regression analysis

Study limitations

Our study is a retrospective analysis study, but prospective studies are most important. Therefore, this is the major limitation of our study. Duration and severity of CAD, and previous bleeding history and other features of patients were not investigated. Aspirin doses and usage duration also were not investigated due to retrospective analysis. Those are limitations of our study.

Conclusion

Advanced age, atherosclerosis, male gender and NSAID-ASA treatments are risk factors for upper GI hemorrhage in patients with gastric and/or duodenal ulcers. Acetylsalicylic acid, however, may increase hemorrhage risk significantly, compared to the other NSAIDs. Acetylsalicylic acid administration, particularly in patients with CAD and aged above 60, is associated with higher risk of hemorrhage.

Conflict of interest: None declared.

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