Small Intestinal Mucosal Injury not Associated with Acute Gastrointestinal bleeding Induced by Aspirin: a retrospective observational study

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Research article

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Abstract

Background

To investigate the characteristics of small intestinal injuries and its association with upper gastrointestinal ulcers and *Helicobacter pylori* infection in aspirin induced acute gastrointestinal bleeding patients.

Methods

Esophagogastroduodenoscopy and capsule endoscopy were used to examine the gastrointestinal injuries. Serum antibody was used to test the history of *Helicobacter pylori* infection. Clinical history, underlying diseases, the duration of aspirin use, and proton pump inhibitors use were recorded.

Results

A total of 72 patients were involved with 58 cases (80.6%) of active upper gastrointestinal peptic ulcers and 9 cases (12.5%) with small intestinal injuries (erosive/ulcerative lesions). Fifty percent of patients (36 cases) was reported *Helicobacter pylori* infection.

Conclusions

It was upper gastrointestinal ulcers that accounting for most of aspirin-induced acute gastrointestinal bleeding instead of the intestinal mucosal injuries.

Introduction

Though steadily decreasing, the prevalence of *H. pylori* infection was high in China, causing peptic ulcer disease still common. Since the western life style becomes popular, cardio-cerebrovascular disease is on the increase. As long as the use of aspirin for prevention or treatment of cardiovascular and cerebrovascular events has been thought as an effective way, the side effects appear to be increasing, including the deadly risks of gastrointestinal(GI) bleeding and cerebral hemorrhage[1, 2]. Acute GI bleeding can present in the form of hematemesis, “coffee-ground” emesis, melena, and hematochezia, which have become the common diseases in emergency department[3]. It could be caused by gastric ulcer and intestinal ulcer.

Proton pump inhibitors (PPIs) are effective in preventing upper GI bleeding, but acid suppression with PPIs has no benefit for small intestinal bleeding and may result in bacterial overgrowth, in turn leading to further small bowel injury[4]. Shiotani *et al.*[5] reported 60% of intestinal ulcers or erosions accounted for in healthy volunteers taking aspirin and Iwamoto *et al.*[6] reported 64.3% using capsule endoscopy (CE).
It suggests that aspirin-induced small intestinal injury may be subclinical and asymptomatic, but whether it plays a role in acute GI bleeding has not been fully studied.

The purpose of this study was to investigate prevalence of the stomach and intestine damage in aspirin-induced acute GI bleeding by Esophagogastroduodenoscopy (EGD) and capsule endoscopy (CE).

Materials And Methods

Study subjects

It was designed as a retrospective observational, single-center study. A total of 72 patients presenting to the emergency department of Renji hospital Shanghai with acute GI bleeding were screened for eligibility during the study period from December 2017 to December 2019.

Inclusion criteria were acute GI bleeding defined as hematemesis, melena and hematochezia. They had been treated on enteric-coated aspirin (100 mg/day) daily at least one month for ischemic heart disease, valvular disease, cerebrovascular disease, venous thrombus, primary thrombocytosis. All subjects underwent blood biochemistry test and EGD within 48 hours. Capsule endoscopy was performed within 7 days of admission after abdominal computed tomography enterography (CTE) scanning.

The subjects who had contraindications for EGD, CTE and CE or had not finished all these three examinations, who had a known stricture or fistula of the small intestine, who were pregnant, younger than 18 years, in instable clinical status, use of other oral anticoagulants drugs (Clopidogrel, dabigatran, rivaroxaban) and nonsteroidal anti-inflammatory drugs (NSAIDs) were excluded. The ethical committee of Renji hospital approved this study.

Serological test of H. pylori

_H. pylori_ infection was detected by anti-__H. pylori__ antibody (MP Biomedicals Asia Pacific Pte. Ltd. Singapore).

Computed Tomography Enterography (CTE)

Computed Tomography Enterography (CTE) (GE-hispeed NX/i2, United States) examination was performed from the diaphragmatic apex to the superior margin of the pubic symphysis. The enhancer was Niopam (Iopamidol, 370mg/mL, Shanghai Bracco Sine Pharmaceutical Corp. Ltd), with a total dose of 60–100 ml, and a high pressure injector was used to inject the drug through the cubital vein with a pellet injection rate of 3.5 ml/s. Double-phase arterial and venous scans were performed at 20–30 s and 65 s after the injection of the booster. The current is set as 150-400mAs, the voltage is 120 kV, the matrix is 512 × 512, colalignment: 0.625 mm × 8 mm, FOV: 35 cm × 35 cm, reconstruction thickness: 1.25 mm, reconstruction interval: 0 mm.

CTE images were interpreted by experienced consultants of GI tract radiology who were blinded to patients’ clinical and endoscopic evaluations.
Esophagogastroduodenoscopy (EGD)

Esophagogastroduodenoscopy (EGD) examinations were performed with a gastroscope (GIF-H290, Olympus Medical Systems, Tokyo, Japan) by two endoscopists with more experience, who were not informed of the treatment assignments. The esophagus, stomach and first and second parts of the duodenum were comprehensively observed, with size of each lesion estimated by comparison with the opening diameter of biopsy forceps (5.5 mm). Peptic ulcer was defined as a > 5 mm in diameter mucosal break with depth in the stomach and/or duodenum.

Capsule Endoscopy (CE)

For CE of the small intestine, a PillcamSB3 video capsule endoscopic device (Given Imaging Ltd, GA USA) was employed. The system includes PillCam™ SB3 capsule, Sensor Array, a data recorder, and a computer workstation.

After the examination, the images were transmitted from the recorder to the computer workstation. The CE findings were blind evaluated by one independent gastroenterologist who had interpreted more than 100 CE studies. All patients were asked to ingest of polyethylene glycol electrolyte solution (Wanhe Pharmaceutical Co. Ltd; china) 12 h before the procedure and took 8 ml of simethicone emulsion (Berlin-Chemie, Germany), 30 min before swallowing the capsule. The patients were observed for adverse events until the capsule had been excreted.

Small intestinal mucosal injury was assessed based on the number of findings with respect to five types of injury: normal, erythema, small erosion, big erosion and ulcer. Erythema was defined as a red region with a border extending from the peripheral normal mucosa, erosion was defined as a defect of the normal lustrous mucosa and ulcer was defined as mucosal defects covered with white moss based on the classification reported by Graham.[7]

Statistical Analysis

Categorical variables are represented by mean values ± standard deviation (SD) and frequency or percentage. The statistical analysis was carried out using SPSS for Windows (version 16.0).

Results

Patient Background

Seventy-two patients (9 female, 63 male) were available for analysis. Mean age was 64.2±8.3 years (range 39–81 years). Most of the patients took aspirin for cardiovascular (30/72, 41.7%) and cerebrovascular (21/72, 29.2%) diseases, the sum was 73.6%. The duration of aspirin use was from one month to 240 months, with an average of 54.2±57.3 months. Six patients (6/72, 8.3%) took PPIs at the same time. Eight patients (8/72,11.1%) had a history of peptic ulcer disease (Table 1).
Table 1
Demographics and medical information of Patients at baseline

| Item                                      | n = 72                      |
|-------------------------------------------|----------------------------|
| Age, years, mean±SD                      | 64.2±8.3                   |
| Gender, Male, n (%)                       | 62(86.1%)                  |
| Body weight, kg, mean±SD                 | 68.9±10.1                  |
| Smoking, n (%)                            | 31(43.1%)                  |
| Alcohol use, n (%)                        | 19(26.4%)                  |
| Medical history, n (%)                    |                            |
| Cardiovascular                            | 32(44.4%)                  |
| Cerebrovascular                           | 21(29.2%)                  |
| Hypertension                              | 8(11.1%)                   |
| Carotid stenosis                          | 4(5.6%)                    |
| Artery dissection post-stenting           | 3(4.2%)                    |
| Primary thrombocytosis                    | 1(1.4%)                    |
| Venous embolism                           | 1(1.4%)                    |
| Precautionary measure                     | 2(2.8%)                    |
| Peptic ulcer history, n (%)               | 8(11.1%)                   |
| H. pylori treatment history, n (%)        | 2(2.8%)                    |
| PPI users, n (%)                          | 6(8.3%)                    |
| Aspirin duration, month, mean±SD          |                            |
| Median(range)(IQR)                        | 54.2 ± 57.3,36(1-240) (48) |

Esophagogastroduodenoscopy Findings

Forty-eight (58/72, 80.6%) patients had active upper peptic ulcers, including 24 gastric ulcer, 21 duodenal ulcer, and 13 concurrent gastric and duodenal complex ulcers. These ulcers were I (2 cases), IIa (7 cases), IIb (18 cases), IIC (13 cases) and III (18 cases) in Forrest classification.

Three cases of cardiac mucosal laceration (Mallory-Weiss syndrome), four cases of tumors (three gastric cancer and one mucosa associated lymphadenoma) and one case of large polypus in duodenum found in the rest of fourteen (14/72, 19.4%) patients had not been found active peptic ulcer by EGD that may contribute to active bleeding.
H. pylori infection

Thirty-six patients (36/72, 50%) were positive for serological test. Two patients had H. pylori infection treatment history, but they did not confirm the eradication. For those with active upper peptic ulcer, thirty-three patients (33/58, 45.8%) were positive.

Capsule endoscopy Finding

Only eighteen patients (18/72, 25%) were showed positive result detected by CE, including six cases of small intestinal mucosal erosion, three cases of small intestinal mucosal ulcer, two cases of small intestinal polyp, seven cases of small intestinal enterovascular malformation. Multiple mucosal lesions (erosion and ulcer) were shown in six patients. Except one case of erosion and another case of small polyp, sixteen lesions would be detected in patients with active upper peptic ulcers. There were no significant differences in clinical characteristics including EGD findings and H. pylori infection between the patients with and without intestinal mucosal injuries.

Discussion

Our study showed that it was peptic ulcers other than small intestinal mucosal injuries caused most of the acute GI bleeding when they used aspirin.

More than 70% of patients in our study took aspirin to prevent cardiovascular and cerebrovascular diseases. H. pylori and aspirin or NSAIDS have synergistic effect to cause GI lesions. While around 50% patients involved had H pylori infection, it was consistent with the report from investigation of our population. But 45.8% of H. pylori infection in active peptic ulcer diseases indicated that other factors other than H. pylori may involve in the pathogenesis. H. pylori treatment and PPI were the main measures to prevent and treat aspirin–induced upper GI diseases. Only two patients tried to treat H. pylori infection and also only six patients took PPI.

The results of this study showed that there was no significant correlation between intestinal mucosal injury and acute GI bleeding, which was contrast to previous report that aspirin could cause up to 50% or more intestinal mucosal injuries as the main cause of bleeding in obscure GI bleeding patients [5, 6]. A cohort study with nested case-control analysis using primary care electronic health records from the United Kingdom reported that aspirin was associated with increased risks of non-fatal GI bleeding but not fatal GI bleeding[8], which supported our viewpoint We also found that there was no significant difference in gastro-duodenal injuries between the small intestinal mucosa injuries group and the non-injuries group. It was as same as the results obtained from a study of macroscopic small bowel mucosal injury assessed by CE. It indicated that upper GI mucosal injuries could not predict the severity of intestinal disease [9].

The true location and extent of aspirin enteropathy are still unclear .Our study found the distribution and type of small intestinal injuries induced by aspirin was in jejunum or ileum which was consistent with the
site of mucosal injuries induced by aspirin in obscure GI bleeding [6, 10]. Shiotani et al. [5] found seven days administration of 100 mg aspirin per day could cause visible small bowel damage and mucosal injuries were most frequently found in the latter half of the proximal small bowel. In our study, multiple small intestinal mucosa erosions or ulcers were detected in those patients and no association was found between the duration of aspirin administration and the distribution of intestinal mucosal injuries.

Aspirin and *H. pylori* infection are considered to be the two important independent risk factors for peptic ulcer and peptic ulcer complications. But their interaction in peptic ulcer disease is controversial with respect to the benefits and risks of radical treatment of *H. pylori* before aspirin use, the totality of evidence remains incomplete. Most current studies supported that *H. pylori* infection combined with aspirin increased the risk of upper GI ulcer disease [11–14]. A few studies had linked *H. pylori* to an increased risk of aspirin-induced intestinal lesions. The results of our study showed that there was no significant difference of *H. pylori* infection between the small intestinal mucosal injuries group and the non-injuries group. It seems that *H. pylori* infection did not lead to an increase or decrease in the risk of small intestinal mucosal injury.

**Conclusion**

In summary, acute GI bleeding induced by aspirin is mainly due to upper GI peptic ulcers instead of intestinal bleeding, partly aggravated by *H. pylori* infection.

**Abbreviations**

| Acronym | Definition |
|---------|------------|
| GI      | Gastrointestinal |
| PPIs    | Proton pump inhibitors |
| EGD     | Esophagogastrroduodenoscopy |
| CE      | Capsule Endoscopy |
| CTE     | Computed Tomography Enterography |
| NSAIDs  | Nonsteroidal anti-inflammatory drugs |

**Declarations**

*Ethics approval and consent to participate:* The ethical committee of Renji hospital approved this study.
Consent for publication: This paper has not been submitted elsewhere for consideration of publication. All authors have read and approved to submit it to your journal.

Competing interests: Hong Lu is a consultant for Takeda and Astrazeneka for proton pump inhibitors in relation to H. pylori infection treatment. Other authors declare no competing interests.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors’ contributions: QG analyzed and interpreted the patient data and was a major contributor in writing the manuscript. HL guided the design and revised of this manuscript. XL and HX assisted data collection and gastroenteroscopy pathological interpretation. ZG and QZ performed Esophagogastroduodenoscopy and Capsule Endoscopy for the patients without informed of the treatment assignments. All authors read and approved the final manuscript.

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