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CASE CONTROL STUDY

Small-bowel mucosal injuries in low-dose aspirin users with obscure gastrointestinal bleeding

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Abstract

AIM: To investigate the clinical differences between small intestinal injuries in low-dose aspirin (LDA) users and in non-steroidal anti-inflammatory drug (NSAID) users who were examined by capsule endoscopy (CE) for obscure gastrointestinal bleeding (OGIB).

METHODS: A total of 181 patients who underwent CE for OGIB were included in this study. Based on clinical records, laboratory data such as hemoglobin levels, major symptoms, underlying diseases, the types and duration of LDA and NSAID use, and endoscopic characteristics of CE were reviewed.

RESULTS: Out of a total of 45 cases of erosive lesions, 27 cases were taking LDA or NSAIDs (7 were on NSAIDs, 9 were on LDA alone, 9 were on LDA and thienopyridine, and 2 were on LDA and warfarin).The prevalence of ulcers or erosion during chronic use of LDA, LDA and the anti-platelet drug thienopyridine (clopidogrel or ticlopidine), and NSAIDs were 64.3%, 80.0%, and 75.0%, respectively. Erosive lesions were observed predominantly in chronic LDA users, while ulcerative lesions were detected mainly in NSAID users. However, concomitant use of thienopyridine such as clopidogrel with LDA increased the proportion of ulcers. The erosive lesions were located in the whole of the small intestine (jejunum and ileum), whereas ulcerative lesions were mainly observed in the ileum ($P < 0.05$).

CONCLUSION: Our CE findings indicate that chronic LDA users and NSAID users show different types and locations of small-bowel mucosal injuries. The concomitant use of anti-platelet drugs with LDA tends to exacerbate the injuries from LDA-type to NSAID-type injuries.

Key words: Non-steroidal anti-inflammatory drugs; Low-dose aspirin; Small-bowel mucosal injuries; Obscure gastrointestinal bleeding; Capsule endoscopy

Core tip: The aim of this study is that to clarify the clinical feature of ulcerative or erosive lesion of small intestine in the long-term non-steroidal anti-inflammatory drug (NSAID) users who were examined by capsule endoscopy for obscure gastrointestinal bleeding. The ulcerative lesions were predominantly located in both jejunum and ileum or just in ileum while erosive lesions were predominantly found in both jejunum and ileum or just in jejunum significantly. These findings indicate the possibility that distribution of NSAID-induced small intestinal lesion differ according to the types of mucosal injury.

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INTRODUCTION

It has been demonstrated that low-dose aspirin (LDA) and non-steroidal anti-inflammatory drugs (NSAIDs) increase the risk of gastroduodenal mucosal injury[1,2]. Recent reports using new methods of investigating the small intestine, such as double balloon endoscopy (DBE)[3] and capsule endoscopy (CE)[4], have also shown that NSAIDs can cause mucosal damage in the small intestine[5-8]. Obscure gastrointestinal bleeding (OGIB) is defined as bleeding of unknown origin that persists or recurs after a negative initial or primary upper endoscopy and colonoscopy and radiologic evaluation of the small bowel[9,10]. The clinical features of the ulcerative or erosive lesions of the small intestine in long-term NSAID users who were examined subsequently by CE for OGIB have not been sufficiently reported.

In the present study, 181 OGIB cases were examined with CE and were investigated with the following aims: to evaluate the prevalence of ulcerative or erosive lesions in the small intestine in chronic LDA or NSAID users in OGIB cases, to analyze the clinical features including endoscopic findings of these lesions, and to analyze the clinical course of these cases.

MATERIALS AND METHODS

Patients

Between June 2007 and September 2013, 181 patients who underwent CE for OGIB at Tokyo Medical University Ibaraki Medical Center were analyzed in this study.

CE

CE was performed using a PillCam SB (Given Imaging). Patients fasted for 10 h before capsule ingestion. Drinking clear fluids was allowed 2 h and eating a light snack was allowed 4 h after ingestion of the capsule. The data recorder was removed 8 h later, and the patients were subsequently discharged. Data were downloaded and interpreted by experienced endoscopists. The patients were asked to report any adverse events and to confirm excretion of the capsule in their stool.

Data analysis

Based on clinical records, laboratory data such as hemoglobin levels, major symptoms, underlying diseases, the types and duration of NSAIDs, and endoscopic characteristics of CE were reviewed. The morphologies of the lesions were classified into red spots, small erosion, large erosion, or ulcers as previously reported[7]. A red spot was defined as a red spot or crimson area of mucosa with presentation of villous architecture. A small erosion was defined as a circumscribed area of mucosal disruption denuded of villi with or without exudates or red color with a diameter equivalent to that of a valvulae conniventes. Large erosions were defined as circumscribed breaks in the mucosa larger than the equivalent diameter of a valvulae conniventes. In the present study, red spots, small erosion, and large erosion were included in the CE erosion results (Figure 1A). Ulcers were defined as large erosion with a central area with exudates[7] (Figure 1B).

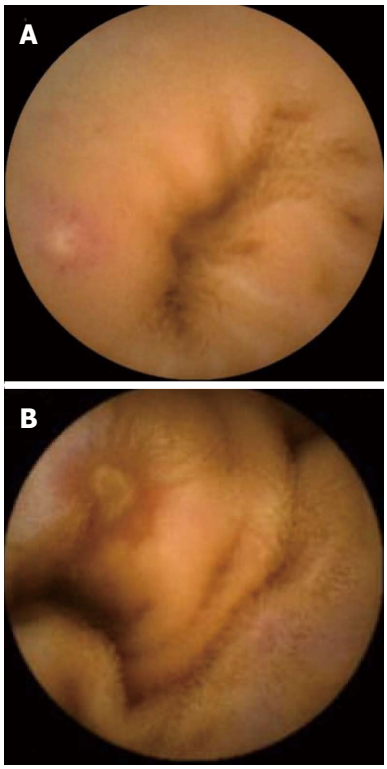

Figure 1 Endoscopy. A: Endoscopic finding of erosion (a small erosion was defined as a circumscribed area of mucosal disruption denuded of villi with or without exudates or red color with a diameter equivalent to a valvulae conniventes); B: Endoscopic finding of ulcer (ulcers were defined as a large erosion with a central area with exudates).

The small bowel was divided into two segments (proximal and distal) equally on the basis of each subject's small bowel transit time.

Statistical analysis

The continuous variables were expressed as mean values ± SD. We compared the categorical variables using the Fisher's exact test and the continuous variables using the Mann-Whitney test. A P value of less than 0.05 was considered statistically significant.

RESULTS

Out of a total of 181 CE cases for OGIB, 13 cases (7.2%) were diagnosed as ulcerative lesions and 45 cases (24.9%) as erosive lesions of the small intestine. Out of a total of 13 cases of ulcerative lesions, 8 cases were taking LDA or NSAIDs (5 were on NSAIDs while 3 were on LDA and the anti-platelet drug, thienopyridine; clopidogrel). Out of a total of 45 cases of erosive lesions, 27 cases

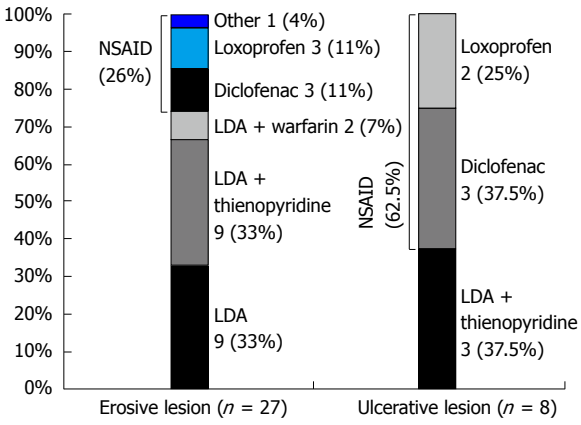

Figure 2 Proportion of types of non-steroidal anti-inflammatory drugs in the ulcerative or erosive lesions of the small intestine in obscure gastrointestinal bleeding cases. NSAID: Non-steroidal anti-inflammatory drug; LDA: Low-dose aspirin.

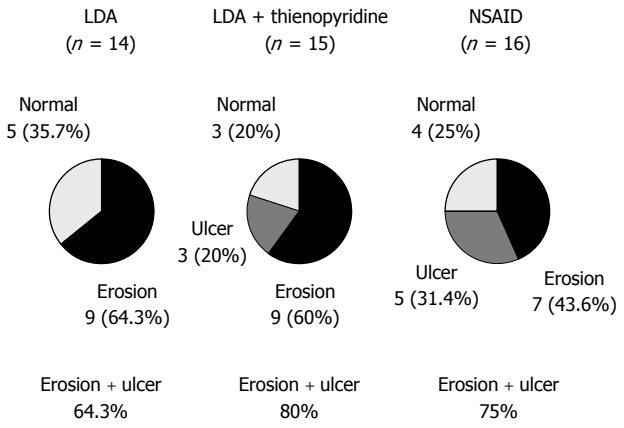

Figure 3 Prevalence of ulcerative or erosive lesions in chronic non-steroidal anti-inflammatory drug and low-dose aspirin users. NSAID: Non-steroidal anti-inflammatory drug; LDA: Low-dose aspirin.

were taking LDA or NSAIDs (7 were on NSAIDs, 9 were on LDA alone, 9 were on LDA and thienopyridine, and 2 were on LDA and warfarin). Erosive lesions were observed predominantly in chronic LDA users, whereas ulcerative lesions were detected mainly in NSAID users (Figure 2).

The prevalence of ulcers or erosion during chronic use of LDA, LDA and thienopyridine, and NSAIDs was 64.3%, 80.0%, and 75.0%, respectively (Figure 3). The concomitant use of thienopyridine (clopidogrel) with LDA increased the proportion of ulcers from 0% to 20%.

The locations of erosive and ulcerative lesions are shown in Figure 4. The erosive lesions were located in the entire small intestine (jejunum and ileum), whereas ulcerative lesions were observed mainly in the ileum ($P < 0.05$).

Details of the characteristics of ulcerative lesions of chronic LDA or NSAID users are summarized in Table 1. In 4 of the 8 ulceration cases, LDA or NSAID was withdrawn. In 4 patients who had continued the LDA

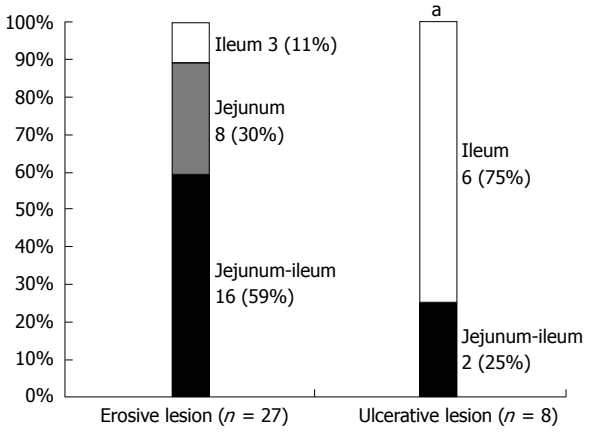

Figure 4 Location of ulcerative or erosive lesions of the small intestine in obscure gastrointestinal bleeding cases. [a]$P < 0.05$ *vs* erosive lesions.

(*n* = 3) or NSAID (*n* = 1), 3 cases used prostaglandin and one case used rebamipide. Eventually, significant improvement of the ulcerative lesions was confirmed in all 4 cases with clinical course or CE finding.

DISCUSSION

The damage to the gastric and duodenal mucosa caused by NSAIDs is well established, and there has been increasing recognition of the damage caused to the mucosa of the small intestine by NSAID treatment[1,2,5-8]. The pathogenesis of NSAID-induced small intestinal damage has been investigated, and a number of mechanisms have been implicated, including the toll-like receptor 4/MyD88-dependent pathway[11], dual inhibition of COX enzymes[12], enterohepatic circulation of NSAIDs[13], mitochondrial damage[14], and ischemia-reperfusion injury[15].

The prevalence of NSAID-induced small bowel lesions in the cases who had undergone CE or BDE for OGIB has also been investigated. A previous report has shown that among the 108 cases that underwent DBE for OGIB, 5 cases (4.6%) were diagnosed with NSAID–associated ulcers of the small intestine (5). A multicenter study has shown that 31 cases (4.7%) were diagnosed with NSAID-induced ulcerative lesions among 661 cases who underwent DBE for OGIB (6). In our present study, 4.4% and 14.9% of the cases were diagnosed with ulcerative lesion and erosive lesions for chronic LDA or NSAID users in OGIB cases by CE, respectively. Collectively, 19.3% of the cases were diagnosed with mucosal lesions with long-term LDA or NSAID treatment in OGIB cases by CE. The prevalence of NSAID-induced mucosal injury among chronic NSAID users has been reported in several studies[7,16,17]. Small intestinal ulceration was found in 21 patients (8.4%) among 249 long-term NSAID users and just 3 patients (0.6%) among 464 non-users in a previous investigation where the stomach, duodenum, and small intestine of 713 post-mortem patients were examined (16). Another recent study using video capsule endoscopy has demonstrated occurrence of small bowel injury in 71% of NSAID users compared with

Table 1 Details of the characteristics of ulcerative lesions in chronic non-steroidal anti-inflammatory drug users

Age	Gender	UD	Species (duration)	Symptom	Hemoglobin (g/dL)	Location	Number	Treatment	Clinical course
67	F	Headache	Loxoprofen (6M)	Tarry stool/anemia	9.5	Ileum	Multiple	Withdrawal of NSAID	Improved
83	M	OD	Diclofenac (6M)	FOBT (+) anemia	11.5	Jejunu Ileum	Multiple	Withdrawal of NSAID	Improved
59	M	ID	LDA + clopidogrel (6M)	Tarry stool/anemia	10.3	Ileum	Multiple	Continuation of LDA PG	Improved
70	M	CD	LDA + clopidogrel (2Y)	Tarry stool/anemia	9.3	Jejunum Ileum	Multiple	Continuation of LDA PG	Improved
79	F	RA	Diclofenac (4Y)	Tarry stool/anemia	8.3	Ileum	Multiple	Continuation of NSAID rebamipide	Improved
74	F	ID	LDA + clopidogrel (1Y)	Anemia/abdominal pain	9.3	Ileum	Multiple	Continuation of LDA PG	Improved
63	M	OD	Loxoprofen (6Y)	Tarry stool/anemia	11.2	Ileum	Multiple	Withdrawal of NSAID	Improved
73	F	OD	Diclofenac (5Y)	Tarry stool/anemia	10.4	Ileum	Multiple	Withdrawal of NSAID	Improved
					10.0 ± 1.0				

UD: Underlying diseases; OD: Orthopedic diseases; ID: Ischemic heart diseases; CD: Cerebrovascular diseases; RA: Rheumatoid arthritis; LDA: Low-dose aspirin; NSAID: Non-steroidal anti-inflammatory drug.

10% of the controls, indicating that NSAID damage is more frequent and extensive than suggested by ileoscopy performed at the time of colonoscopy[7].

The clinical features of NSAID-induced small bowel lesions have been documented. Hayashi *et al*[18] analyzed 7 patients with small bowel lesions while taking NSAIDs out of 61 patients who had undergone BDE for OGIB. The results have shown that ulcers or erosions were observed in the ileum in six patients (86%) and in the jejunum in one patient (14%). Another previous report has shown that 12 (57.1%) out of 21 small bowel lesions in chronic NSAID users were found in the ileum[16]. On the other hand, investigating the distribution of CE-detected small bowel lesions revealed that the lesions were found in the proximal, middle, and distal small bowel, suggesting that there were no significant tendencies in the distribution of small bowel lesions[8]. The distribution and types of small intestinal injury due to NSAIDs have been studied, and it has been shown that in the majority of denuded areas located in the proximal part, erosions were found throughout the small intestine, and all of the ulcers were in the distal part, suggesting that the distribution differed according to the type of mucosal injury during short-term NSAID medication[19]. Our results demonstrate differences in the distribution between ulcers and erosion in patients taking long-term LDA or NSAIDs, indicating that ulcers are located mainly in the ileum, whereas erosion was located throughout the small intestine.

LDA is used as a preventive treatment for ischemic heart disease and ischemic cerebrovascular disease[20]. Recent reports have indicated that low-dose aspirin causes not only gastroduodenal mucosal injury but also small bowel injury with high frequency[21,22]. Hayashi *et al*[22] have reported that 8 (44%) of 18 patients diagnosed with NSAID-induced small bowel injury by DBE were taking low-dose aspirin. Watanabe *et al*[23] have investigated small bowel injury with CE in 11 patients who developed gastric ulcers while undergoing low-dose aspirin. The study showed that red spots were found in 100% of the patients and mucosal breaks were found in 90.9% of the patients, indicating that very high incidences of small bowel injury were found in the patients who developed gastric ulcers while undergoing low-dose aspirin treatment. In our results, there were more patients taking LDA in the erosion cases than in the ulcer cases, suggesting the possibility that the characteristic endoscopic features of LDA-induced mucosal injury in the small intestine were smaller in size than in the case of NSAID-induced mucosal injury.

It has been demonstrated that co-administration of prostaglandin and rebamipide reduced the incidence of NSAID-induced small intestinal lesions[24,25]. In our study, NSAIDs were withdrawn if possible. However, in some cases, especially in the case of LDA and the anti-platelet drug, thienopyridine, it was not possible to withdraw the LDA. In these cases, the prostaglandin or rebamipide was used concomitantly and has shown improved clinical course or CE findings after the treatment. These findings suggest that prostaglandin or rebamipide is effective for treating LDA or NSAID-induced mucosal injury of the small intestine.

In conclusion, our CE study demonstrated that erosive lesions were located in the entire small intestine (jejunum and ileum), and such lesions were observed predominantly in chronic LDA users. In contrast, ulcerative lesions were located mainly in the ileum and were found in NSAID users. However, concomitant use of thienopyridine such as clopidogrel with LDA appeared to increase ulcerative lesions in patients without using

NSAIDs, which suggests that small-bowel mucosal injuries can be changed from LDA type to NSAID type by the additional use of anti-platelet drugs.

COMMENTS

Background

It has been demonstrated that low-dose aspirin (LDA) and non-steroidal anti-inflammatory drugs (NSAIDs) increase the risk of gastroduodenal mucosal injury.

Research frontiers

Recent reports have indicated that low-dose aspirin causes not only gastroduodenal mucosal injury but also small bowel injury with high frequency.

Innovations and breakthroughs

It has been demonstrated that co-administration of prostaglandin and rebamipide reduced the incidence of NSAID-induced small intestinal lesions[24,25]. In this study, NSAIDs were withdrawn if possible.

Applications

The concomitant use of anti-platelet drugs with LDA tends to exacerbate the injuries from LDA-type to NSAID-type injuries.

Peer review

This retrospective study analyzed the clinical feature of small intestinal mucosal lesion of the chronic NSAID users in the cases of obscure gastrointestinal bleeding.

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