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PROSPECTIVE STUDY

Small bowel ulcerative lesions are common in elderly NSAIDs users with peptic ulcer bleeding

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Abstract

AIM: To determine the frequency of small bowel ulcerative lesions in patients with peptic ulcer and define the significance of those lesions.

METHODS: In our prospective study, 60 consecutive elderly patients with upper gastrointestinal bleeding from a peptic ulceration (cases) and 60 matched patients with a non-bleeding peptic ulcer (controls) underwent small bowel capsule endoscopy, after a negative colonoscopy (compulsory in our institution). Controls were evaluated for non-bleeding indications. Known or suspected chronic inflammatory conditions and medication that could harm the gut were excluded. During capsule endoscopy, small bowel ulcerative lesions were counted thoroughly and classified according to Graham classification. Other small bowel lesions were also recorded. Peptic ulcer bleeding was controlled endoscopically, when adequate, proton pump inhibitors were started in both cases and controls, and *Helicobacter pylori* eradicated whenever present. Both cases and controls were followed up for a year. In case of bleeding recurrence upper gastrointestinal endoscopy was repeated and whenever it remained unexplained it was followed by repeat colonoscopy and capsule endoscopy.

RESULTS: Forty (67%) cases and 18 (30%) controls presented small bowel erosions (P = 0.0001), while 22 (37%) cases and 4 (8%) controls presented small bowel ulcers (P < 0.0001). Among non-steroidal anti-inflammatory drug (NSAID) consumers, 39 (95%) cases and 17 (33%) controls presented small bowel erosions (P < 0.0001), while 22 (55%) cases and 4 (10%) controls presented small bowel ulcers (P < 0.0001). Small bowel ulcerative lesions were infrequent among patients not consuming NSAIDs. Mean entry hemoglobin was 9.3 (SD = 1.4) g/dL in cases with small bowel ulcerative lesions and 10.5 (SD = 1.3) g/dL in those without (P = 0.002). Cases with small bowel ulcers necessitate more units of packed red blood cells. During their hospitalization, 6 (27%) cases with small bowel ulcers presented bleeding recurrence most possibly attributed to small bowel ulcers, nevertheless 30-d mortality was zero. Presence of chronic obstructive lung disease and diabetes was related with unexplained recurrence of hemorrhage in logistic regression analysis, while absence of small bowel ulcers was protective (relative risk 0.13, P = 0.05).

CONCLUSION: Among NSAID consumers, more bleeders than non-bleeders with peptic ulcers present small bowel ulcers; lesions related to more severe bleeding and unexplained episodes of bleeding recurrence.

Key words: Non-steroidal anti-inflammatory drugs; Aspirin; Wireless capsule endoscopy; Small bowel ulcerative lesions; Peptic ulcer bleeding

Core tip: Non-steroidal anti-inflammatory drugs (NSAIDs) can frequently cause small bowel ulcerative lesions. In our prospective case control study we found that 95% of elderly patients with peptic ulcer bleeding consuming NSAIDs also presented small bowel erosions and 55% small bowel ulcers. Small bowel ulcerative lesions were 3 times less frequent in patients with a non-bleeding peptic ulcer consuming NSAIDs, and infrequent among patients with a peptic ulcer not receiving NSAIDs. Small bowel ulcers in peptic ulcer bleeders were related with lower entry hemoglobin and increased need for blood transfusion. Moreover, they could be incriminated for unexplained bleeding recurrence despite successful peptic ulcer hemostasis.

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INTRODUCTION

Non-steroidal anti-inflammatory drug (NSAID) therapy reduces inflammation and pain very effectively[1], whilst low-dose aspirin is a common antithrombotic drug[2]. Benefits from NSAID use are offset by potentially life-threatening gastrointestinal complications[3-5]. NSAIDs can cause functional and structural small intestinal abnormalities[4,5]. The later could be accessed by either double-balloon[6] or capsule endoscopy (WCE)[1].

WCE identified small bowel mucosal damage (mucosal breaks, reddened folds, petechiae and denuded mucosa) in 50%-70% of healthy volunteers after a short course of NSAIDs and even more lesions in chronic NSAID consumers[1,7,8]. On the contrary mucosal damage was present only in 10% of subjects not exposed to NSAIDs[1]. Although small bowel mucosal lesions are frequent, they rarely produce small and large bowel complications[9]. Less than 1% of overt or obscure gastrointestinal bleeding cases can be attributed to small bowel ulcerative lesions[10]. Type of NSAID treatment (aspirin, non-aspirin NSAIDs) and patient age can increase the risk for a bleeding episode[11]. The role of a concurrent peptic ulcer is rather unknown.

In a small study, 90% of patients with a non-bleeding gastric ulcer receiving low dose aspirin also presented small bowel mucosal lesions[12]. A small pilot study in our department provided an indication that small bowel ulcerative lesions are even more frequent in peptic ulcer bleeders[13].

Our primary end-point was to determine the frequency of small bowel ulcerative lesions in patients with peptic ulcer bleeding compared to those with non-bleeding ulcers. While our secondary end-points were to determine: (1) whether NSAID use affects the frequency of small bowel lesions and (2) whether presence of small bowel lesions affects the severity of the bleeding episode and its' outcome.

MATERIALS AND METHODS

Patients-data

Our study was a prospective one. 60 consecutive patients older than 18 years, admitted in NIMTS Hospital (Military Insurance Fund Hospital) between the 1/1/2008 and 31/12/2009 with upper gastrointestinal bleeding due to a peptic ulcer entered the study (cases). None had a previous history of iron deficiency anemia. Each case was matched for age, gender, smoking, and alcohol consumption, to a non-bleeding ulcer patient (control) evaluated with WCE, between 1/1/2008 and 31/12/2012 in our department. Controls had WCE performed for chronic diarrhea or unexplained diffuse abdominal pain.

Upper gastrointestinal endoscopy was performed for each case within 24 h from admission and comprised hemostasis for Forrest I a, I b or II a ulcers[14]. For controls upper gastrointestinal endoscopy was performed before WCE study. During entry gastroscopy, *Helicobacter pylori* (*H. pylori*) infection was determined using rapid urease test and histology (haematoxylin-eosin and modified Giemsa). A negative colonoscopy was an inclusion prerequisite for both cases and controls. Colonoscopy was obligatory in our hospital for every case of gastrointestinal bleeding, regarded as alarm symptomatology not with-held by upper-endoscopy findings, because a significant percentage of patients with peptic ulcer might have a colonic pathology as well[15]. No case or control was on proton pump inhibitor or H-2 receptor blocker before the study period. Continuous *iv* infusion of pantoprazole 8 mg/h after a bolus of 40 mg was started after hemostasis for 48 h; switched thereafter to pantoprazole 40 mg *po* o.d. Cases not necessitating hemostasis and controls received pantoprazole 40 mg *po* o.d.

Hemoglobin levels were measured in every case on admission and daily thereafter until discharge. Hemoglobin drop on admission was calculated from a reference level of 14 g/dL.

Exclusion criteria were pregnancy, known or suspected complete or partial stenosis of the small intestine, gastric or intestinal surgery, established delayed gastric emptying or diabetic gastroparesis, history of, or active, malignancy, history of hypersensitivity to proton pump inhibitors and presence of any serious central nervous system, psychiatric, cardiovascular, respiratory, musculoskeletal, or intestinal disease preventing the performance of WCE. We also excluded patients with known or suspected small bowel inflammation, including Crohn's disease, spondyloarthropathy, and seronegative

athritides; patients with celiac disease and patients on medication that influence NSAID enteropathy[16] (biologicals, sulphasalazine, misoprostol, metronidazole and biphosphonates). No case or control had a systemic rheumatic disease or received anticoagulants. Alcohol intake was withheld during the study period.

Actual NSAIDs consumption (including self medication and defaults from prescribed drugs) was accessed before WCE using a life style and medication questionnaire[17]. We validated the questionnaire, applying it to 20 patients before study initiation (k-value = 0.81). Although we intended to record any NSAID consumption, we have considered NSAIDs consumers only those patients who had received even a single dose of NSAIDs the week preceded WCE study. Continuous NSAIDs consumption (both aspirin and non-aspirin) for up to 2 wk was recorded as short term, while longer-term use was considered long-term[1,7,8].

The study protocol has the approval of the Scientific Council of NIMTS Hospital, standing for Ethics Committee of NIMTS Hospital. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008). All patients gave and signed written informed consent, before entering the study.

Capsule endoscopy

Both cases and controls underwent WCE within 4 d after upper gastrointestinal endoscopy and colonoscopy. WCE study (Given SB2 video capsule system; Given Imaging Ltd) was performed according to conventional procedures described elsewhere[10] and it was part of the investigation protocol.

Monitoring period was 9 h. A.Z. has initially gone through all videos and defined the second part of the duodenum. Two independent endoscopists (P. T. and C. K) with vast endoscopic experience separately reviewed all videos, starting video reading from the second part of the duodenum. Both had no information on patient clinical characteristics or presence of any gastric or duodenal bulb lesions. In case of investigator disagreement, a third blinded expert (P. A.) reviewed the findings with the purpose of reaching a consensus. Small bowel mucosal lesions were classified according to Graham *et al*[1]: category 0, normal; category 1, petechiae/red spots; category 2, 1-4 ulcerative lesions up to 5 mm (erosions); category 3, > 4 erosions; and category 4, larger ulcerative lesions. Because agreement between the two investigators was almost perfect (k-value = 0.84) for grade-3 and 4 lesions and fair (k-value = 0.28) for scarce red spots and petechiae and because grade-2 lesions could be found in normal subjects[1], we confined the analysis in grade-3 (erosions) and 4 (larger ulcers) lesions. Other pathologic findings, mainly lymphangiectasia, angiodysplasias and polypoid lesions/tumors were also reported.

Patients with any small bowel pathology undergone repeat capsule endoscopy study a year later. In the meanwhile, NSAID use was prevented; *H. pylori* infection eradicated and polypoid/submucosal lesions received relevant treatment.

To overcome relevant biases, both Head of the Department (G. A.), responsible for treatment decision and ward trainee doctors were unaware of WCE report, unless it was decisive to refer for surgical or endoscopic treatment.

Statistical analysis

Student's *t*-test was used to calculate the difference between the means. The chi-square test or Fisher's exact test was used for nonparametric data as appropriate. A $P < 0.05$ was considered to be statistically significant. We performed logistic regression analysis to access risk factors for unexplained bleeding recurrence. We included known risk factors for ulcer bleeding recurrence (old age, male gender, diabetes mellitus, body mass index and presence of chronic obstructive lung disease) as well as a possible risk factor, presence of small bowel ulcers. The magnitude of each association was expressed in terms of odds ratio and the corresponding 95% confidence interval.

Assuming that: (1) two thirds of patients with peptic ulcer consumed NSAIDs; (2) 30% of patients with no bleeding peptic ulcer consuming NSAIDs and 10% of those not consuming NSAIDs had > 4 erosions[9]; and (3) 90% of peptic ulcer bleeders, consuming NSAIDs and 10% of those not consuming NSAIDs had > 4 erosions[13]: we estimated that a sample size of 30 patients in each patient group was adequate to reach a study power of 90%. We doubled sample size to secure adequate subgroup analysis (aspirin, non-aspirin NSAIDs).

RESULTS

Patients

A duodenal ulcer was found in 38 (63%) cases and as many controls and a gastric ulcer in 32 (53%) cases and an equal number of controls. Both gastric and duodenal ulcers were present in 10 (17%) cases and 10 (17%) controls. 6 (10%) cases had bled from the gastric and 4 (7%) from the duodenal ulcer. Hemostasis was performed in 12 (20%) cases; 8 (13%) with a duodenal and 4 (7%) with a gastric ulcer. Thirty-two (53%) cases and as many controls were receiving NSAIDs short-term ($P = 1.00$), while 8 (13%) cases and as many controls were on NSAIDs long-term ($P = 1.00$). There was no difference between cases and controls in any demographic or disease related characteristic, apart from diffuse abdominal pain that was more frequent among controls (Table 1). No case or control had chronic renal failure, liver failure or cirrhosis and none was receiving anticoagulants.

Findings in capsule endoscopy

Small bowel ulcerative lesions were found in 40 (67%)

Table 1 Demographic and disease related characteristics of bleeders and controls

Characteristic	Patients (n = 60)	Controls (n = 60)	P
Mean age (yr)	75 (SD = 8)	74 (SD = 9)	0.26
Male gender	44 (73%)	44 (73%)	1.00
Active smoking	18 (30%)	18 (30%)	1.00
Alcohol abuse	12 (20%)	12 (20%)	1.00
BMI > 25	36 (60%)	36 (60%)	1.00
NSAIDs consumption	40 (67%)	40 (67%)	1.00
Ischaemic heart disease	20 (33%)	20 (33%)	1.00
Chronic pain	6 (10%)	22 (37%)	0.006
Diabetes melitus	11 (18%)	12 (20%)	0.82
COPD	4 (7%)	4 (7%)	1.00
Low dose aspirin use[1]	22 (37%)	22 (37%)	1.00
Non aspirin NSAIDs use[1]	24 (40%)	24 (40%)	1.00
COX-2 selective use	6 (10%)	6 (10%)	1.00
Non selective NSAIDs use	18 (30%)	18 (30%)	1.00
Clopidogrel co-administration	12 (20%)	12 (20%)	1.00
Gastric passing time (min)	41 (SD = 49)	42 (SD = 57)	0.46
Small bowel passing time (min)	221 (SD = 117)	271 (SD = 117)	0.01
H. pylori positive	37 (60%)	37 (62%)	1.00

[1]Three bleeders and 6 controls received both low-dose aspirin and non-aspirin NSAIDs. SD: Standard deviation; NSAIDs: Non-steroidal anti-inflammatory drugs; BMI: Body mass index; COPD: Chronic obstructive lung disease; COX-2 selective use: Cyclooxygenase-2 selective inhibitors.

cases and 18 (30%) controls (P = 0.0001). All of them had erosions (grade-3 lesions), while small bowel ulcers (grade-4 lesions) were found 22 cases (37%) and 4 (8%) controls (P = 0.0001). Small bowel erosions were found in 27 (71%) cases with a duodenal and 20 (62%) with a gastric ulcer (P = 0.45), while small bowel ulcers were found in 16 (42%) cases with a duodenal and 10 (31%) with a gastric ulcer (P = 0.35). Moreover erosions were found in 14 (37%) controls with a duodenal and 9 (28%) with a gastric ulcer (P = 0.44), while small bowel ulcers were found in 3 (8%) controls with a duodenal and 2 (6%) with a gastric ulcer (P = 0.79).

Among NSAID consumers, 39 (98%) cases and 17 (43%) controls presented small bowel ulcerative lesions (P < 0.0001). All of them had small bowel erosions, while small bowel ulcers were present in 22 (55%) cases and 4 (10%) controls (P < 0.0001). Small bowel erosions were found in 26 (96%) cases with a duodenal and 20 (100%) with a gastric ulcer (P = 0.38), while larger ulcerative lesions were found in 16 (100%) cases with a duodenal and 10 (100%) with a gastric ulcer (P = 1.00). Moreover erosions were found in 13 (48%) controls with a duodenal and 9 (45%) with a gastric ulcer (P = 0.83), while larger ulcerative lesions were found in 3 (11%) controls with a duodenal and 2 (10%) with a gastric ulcer (P = 0.90).

There was no difference in small bowel mucosal lesions between cases and controls consuming no NSAIDs (Table 2). All cases and controls with small bowel erosions reporting no NSAID consumption admitted that they had received at least a single NSAID dose more than a week before WCE.

Among NSAID consumers, cases presented more small bowel erosions than controls both in the jejunum and the in the ileum (Table 3).

Small bowel erosions were present in 31 (97%) cases receiving NSAIDs long-term and 8 (100%) short-term

Table 2 Small bowel mucosal lesions found during video capsule endoscopy in both bleeders and controls

Patient group	Cases	Controls	P
All patients	n = 60	n = 60	
Grade 4 lesions	22 (37%)	4 (8%)	0.0001
Grade 3 lesions	40 (67%)	18 (30%)	0.0001
Grade 2 lesions	41 (68%)	21 (35%)	0.0003
Grade 1 lesions	42 (70%)	28 (47%)	0.0100
NSAID consumers	n = 40	n = 40	
Grade 4 lesions	22 (55%)	4 (10%)	< 0.0001
Grade 3 lesions	39 (95%)	17 (33%)	< 0.0001
Grade 2 lesions	40 (100%)	20 (50%)	< 0.0001
Grade 1 lesions	40 (100%)	26 (65%)	< 0.0001
No-NSAID consumers	n = 20	n = 20	
Grade 4 lesions	0	0	
Grade 3 lesions	1 (5%)	1 (5%)	1.00
Grade 2 lesions	1 (5%)	1 (5%)	1.00
Grade 1 lesions	2 (10%)	2 (10%)	1.00

NSAIDs: Non-steroidal anti-inflammatory drugs.

Table 3 Number of mucosal lesions found during video capsule endoscopy in both bleeders and controls consuming non-steroidal anti-inflammatory drugs, after stratification according to the type of non-steroidal anti-inflammatory drug consumed

Patient group	Patients	Controls	P
All patients	n = 40	n = 40	
Jejunum			
Grade 4 lesions	1 (SD = 2)	0.3 (SD = 0.7)	0.02
Grade 3 lesions	10.8 (SD = 4.3)	1 (SD = 0.6)	< 0.0001
Ileum			
Grade 4 lesions	1.1 (SD = 1.9)	0.2 (SD = 0.3)	0.002
Grade 3 lesions	8.1 (SD = 4.8)	1.2 (SD = 2.2)	< 0.0001
Low dose aspirin users	n = 22	n = 22	
Jejunum			
Grade 4 lesions	0.8 (SD = 1.3)	0.2 (SD = 0.4)	0.02
Grade 3 lesions	9.9 (SD = 4.7)	0.8 (SD = 0.5)	< 0.0001
Ileum			
Grade 4 lesions	0.9 (SD = 1.4)	0.1 (SD = 0.3)	0.006
Grade 3 lesions	10.3 (SD = 4.6)	1 (SD = 1.6)	< 0.0001
Non-aspirin NSAID consumers	n = 24	n = 24	
Jejunum			
Grade 4 lesions	1.4 (SD = 2.6)	0.4 (SD = 0.9)	0.04
Grade 3 lesions	11.9 (SD = 3.8)	1.2 (SD = 0.7)	< 0.0001
Ileum			
Grade 4 lesions	1.6 (SD = 2.4)	0.3 (SD = 0.3)	0.02
Grade 3 lesions	7.7 (SD = 4.8)	1.4 (SD = 2.3)	< 0.0001
COX-2 NSAID consumers	n = 6	n = 6	
Jejunum			
Grade 4 lesions	0.3 (SD = 0.6)	0	0.27
Grade 3 lesions	5.7 (SD = 6.7)	0.4 (SD = 1.4)	0.04
Ileum			
Grade 4 lesions	0.7 (SD = 1.2)	0	0.15
Grade 3 lesions	6.7 (SD = 5.7)	0.5 (SD = 0.7)	0.01

NSAIDs: Non-steroidal anti-inflammatory drugs; SD: Standard deviation; COX-2: Cyclooxygenase-2 selective inhibitors.

Table 4 Logistic regression analysis of demographic characteristics and co-morbidities related to a hemorrhage recurrence possibly related to the small bowel

Characteristic	Relative risk	Confidence intervals	*P*
Age	1.03	0.96-1.10	0.40
Male gender	3.63	0.61-21.46	0.15
Body mass index	1.22	0.90-1.63	0.19
Diabetes	2.14	1.35-3.40	0.001
Chronic obstructive lung disease	6.67	1.01-46.3	0.05
Absence of small bowel ulcers	0.13	0.01-0.99	0.05

(P = 0.61), while larger ulcerative lesions were found in 19 (59%) cases consuming NSAIDs long-term and 3 (38%) consuming them short-term (P = 0.27). On the other hand, small bowel erosions were found in 15 (47%) controls consuming NSAIDs long-term and 3 short-term (38%, P = 0.63); while small bowel ulcers were found in 3 (9%) controls consuming NSAIDs long-term and 1 long-term (13%, P = 0.79).

Twenty-four (67%) H. *pylori* positive and 15 (63%) negative cases (P = 0.74), as well as 11 (31%) H. *pylori* positive and 7 (29%) negative controls (P = 0.91) presented small bowel ulcerative lesions.

Small bowel ulcerative lesions were present in all cases (n = 16) and 1 (5%) control consuming low-dose aspirin only (P < 0.0001); 14 (78%) cases and 2 (9%) controls receiving non-aspirin NSAIDs only (P = 0.0001); 5 cases (83%) and 2 (33%) controls receiving both types of NSAIDs (P = 0.08). 4 (67%) cases receiving cyclooxygenase-2 selective inhibitors and one (16%) control presented small bowel erosions (P = 0.08), while larger lesions presented only in 2 (33%) cases (P = 0.12).

There was no difference between the two groups concerning presence of angiodysplasias [24 (40%) cases *vs* 25 (42%) controls, P = 0.85] and polypoid/submucosal lesions [2 (3%) cases *vs* 2 (3%) controls, P = 1.00].

Clinical course of peptic ulcer hemorrhage

Mean entry hemoglobin was 9.3 (SD = 1.4) g/dL in cases with grade-3 or 4 lesions and 10.5 (SD = 1.3) g/dL in those without (P = 0.002). It was 9.9 (SD = 1.5) g/dL in cases with small bowel erosions and 8.6 g/dL (SD = 1.2) in those with larger ulcerative lesions (P = 0.002). Thus calculated hemoglobin drop due to the bleeding episode was 4.7 g/dL in cases with grade 3 or 4 lesions and 3.5 g/dL in cases without ulcerative lesions (P = 0.001).

Cases with small bowel ulcerative lesions necessitated transfusion of 2.8 (SD = 1.2) units of packed red blood cells units while those without 1.1 (SD = 0.6, P < 0.0001). In addition, cases with small bowel ulcers necessitated transfusion of 3.9 (SD = 1.3) packed red blood cells units, while those with small bowel erosions 1.7 (SD = 0.9, P < 0.0001).

After admission and despite successful hemostasis, 7 (32%) cases with small bowel ulcers and none without presented a drop of hemoglobin > 2 g/dL (P = 0.05). Repeat upper gastrointestinal endoscopy revealed peptic ulcer rebleeding in one of them followed by repeat hemostasis, while repeat colonoscopy was negative. In repeat WCE study (because balloon enteroscopy was not available in the country), the remaining patients had at least one small bowel ulcer with a visible vessel on ulcer base with (n = 2) or without active bleeding (n = 4). Five (83%) bleeding recurrences that could possibly attributed to small bowel lesions were mild and self-limited. Nevertheless, one case necessitated operative small bowel endoscopy and hemostasis.

Logistic regression analysis, revealed that presence of diabetes mellitus and chronic obstructive lung disease were independent risk factors for bleeding recurrence possibly attributed to the small bowel, while absence of small bowel ulcers were protective (Table 4).

Thirty-day mortality was zero for both cases and controls and none reported any adverse event related to medical treatment or WCE.

Repeat capsule endoscopy a year later, revealed no ulcerative lesion in patients with small bowel ulcerative lesions in the entry endoscopy, providing that they had stopped NSAIDs during follow-up.

DISCUSSION

In our prospective case control study we found that 95% of elderly patients with peptic ulcer bleeding consuming NSAIDs presented small bowel erosions and 55% small bowel ulcers. Moreover, 30% of patients with a non-bleeding peptic ulcer consuming NSAIDs had small bowel erosions and 10% small bowel ulcers. Absence of small bowel ulcerative lesions was recorded in patients with peptic ulcer not receiving any NSAIDs. Small bowel ulcerative lesions in peptic ulcer bleeders were related with lower entry hemoglobin and increased need for blood transfusion. Finally, one out of four small bowel ulcers could bleed during the convalescence period of peptic ulcer bleeding leading to unexplained hemoglobin drop or even melena.

Our study has a number of limitations. It was conducted in a relatively limited number of rather old subjects; the vast majority of whom consumed NSAIDs chronically, while rheumatic disease was excluded. Thus although we included one of the main target groups of NSAID treatment, the elderly, we excluded the other, patients with rheumatic diseases[1]. Our study population old age was a result of reference bias, because our hospital is mainly a Veterans Hospital and referrals from secondary Hospitals usually exclude very young patients. More bowel ulcerative lesions are expected in the elderly because their large[18] and small bowel[19] is more vulnerable to NSAIDs. Patients with rheumatic diseases were excluded because rheumatoid artritis can cause small bowel ulcerative lesions in the absence of NSAID consumption[20]. Rheumatoid arthritis has been related to an increased frequency of iron deficiency anemia[21] and small bowel ulcerative lesions[20], among NSAIDs consumers, but no overt bleeding episodes[21]. Sample size although marginally adequate to explore the role of

aspirin and non-selective NSAIDs, it was insufficient to study the effect of cyclooxygenase-2 selective inhibitors. Proton pump inhibitors were given to all study subjects, a common practice when the study was conducted. Nevertheless recent reports suggest that proton pump inhibitors could exacerbate small bowel ulcerative lesions[22].

Small bowel ulcerative lesions are more frequent in reports including chronic NSAID consumers[1,23] than those including healthy volunteers who received NSAIDs short-term[8,23-26]. A head to head comparison in our study revealed no difference between short and long-term NSAID consumers with concurrent peptic ulcer. Thus, some kind of mucosal adaptation, such as heme oxygenase-1 up regulation[27], could have balanced NSAIDs deleterious effect over time[1].

Small bowel injury and clinically relevant complications associated with the use of NSAIDs, even small dose aspirin, are well recognized[23,25-27]. Nevertheless data on peptic ulcer patients are limited[12]. In our study, prevalence of small bowel ulcerative lesions in NSAID users with non-bleeding peptic ulcer equals the mean of medical literature for non-ulcer NSAIDs consumers[1,23,25-27], even that reported by our group for NSAID consumers with iron deficiency anemia[13]. On the contrary, prevalence of small bowel ulcerative lesions was much higher among NSAID consumers with peptic ulcer bleeding. High prevalence of small bowel mucosal lesions in peptic ulcer bleeders receiving NSAIDs could attributed either to a genetically determined susceptibility for mucosal damage[12] or to an alternated NSAID metabolism due to different CYP2C9 polymorphism[28]. Small bowel ulcerative lesions were 15% more frequent in our study than in Watanabe *et al*[12] report, a small study on 11 non-bleeding gastric ulcer patients receiving low-dose aspirin and proton pump inhibitors. The difference could be attributed to the younger age of Watanabe *et al*[19] patients and the use of low dose aspirin, a less toxic NSAID[11,27]. Inclusion of patients with duodenal ulcer, in our study, could not influence the final outcome, as we found no difference between gastric and duodenal ulcer patients.

Although small bowel mucosal lesions are frequent, small and large bowel complications are infrequent[29], but increase with the exposure to NSAIDs use[9]. Presence of small bowel ulcerative lesions in our non-bleeding ulcer patients was rather indolent, while small bowel ulcers could possibly related to obscure bleeding recurrence in peptic ulcer bleeders. Small bowel ulcers were rather infrequent found in 5%-25% of NSAID consumers[1,23,25-27], but 55% of peptic ulcer bleeders. The probability of small bowel lesions responsible for gastrointestinal bleeding beyond gastric/duodenal ulcers states that we should consider WCE in patients with persistent hemorrhage or bleeding recurrence and negative or inconclusive gastroscopy.

Balloon enteroscopy would have been a preferable option for unexplained bleeding recurrence episodes since it also holds therapeutic capabilities[30]. Nevertheless it was not available in our country during most of the study period.

Gastrointestinal bleeding episodes in NSAID consumers characterized by more severe blood loss and need for more transfusions[31,32], due to co-existence of various co-morbidities and bleeding time prolongation as a result of the antiplatelet effect of NSAIDs[32]. Our study pointed out that small bowel ulcerative lesions could be also important. Old age[33,34], obesity[33,35], presence of diabetes mellitus[35] and chronic obstructive lung disease[33,36] are risk factors for peptic ulcer rebleeding after successful hemostasis because they favor microcirculatory disturbances. Although numbers are too small to draw safe conclusions, our study speculated that presence of diabetes mellitus and chronic obstructive lung disease are important for bleeding recurrence due to small bowel lesions.

In conclusion, more than half patients with peptic ulcer bleeding who consume NSAIDs presented small bowel ulcers. Those lesions were related to lower entry hemoglobin, increased need for blood transfusion and possibly unexplained episodes of bleeding recurrence. Despite study limitations, the results provide a compelling argument for the design of further large-scale studies to define the extent of this potential problem, unravel the mechanisms determining a worse prognosis of patients with peptic ulcer bleeding due to NSAID use and develop strategies to treat small bowel lesions in addition to peptic ulceration.

COMMENTS

Background

Non-steroidal anti-inflammatory drugs are very effectively painkillers, while low-dose aspirin is a common antithrombotic drug. Nevertheless they have been incriminated for causing gastric and duodenal ulcers and their complications, the most common of which is bleeding. Non-steroidal anti-inflammatory drugs can also harm the small bowel. Although small bowel lesions are very common their significance is poorly defined.

Research frontiers

There are very few data pointing out that small bowel ulcers might be very common in patients with gastric ulcers receiving non-steroidal anti-inflammatory drugs. Also it seems that patients receiving non-steroidal anti-inflammatory drugs lose more blood and do worse when they bleed. The explanation given today is that their blood is thinner or that they suffer more co-morbidities, such as heart disease, stroke, lung or kidney diseases.

Innovations and breakthroughs

The authors have found that small bowel ulcers are more common in patients with a gastric or a duodenal ulcer receiving non-steroidal anti-inflammatory drugs and presenting with bleeding than those without bleeding. The authors have also found no small bowel ulcers in patients not receiving non-steroidal anti-inflammatory drugs. The ulcer bug does not affect the possibility to develop small bowel lesions. The authors have shown that small bowel ulcers in patients with bleeding that receive non-steroidal anti-inflammatory drugs mean greater blood loss and need for more transfusions. Final the authors found that in patients with a bleeding from a gastric or a duodenal ulcer that receive non-steroidal anti-inflammatory drugs can relapse not only from their gastric or duodenal ulcer but also from a small bowel ulcer.

Applications

The probability of small bowel lesions responsible for bleeding beyond gastric/duodenal ulcers states that the authors should consider pill camera gut investigation in patients with persistent bleeding or bleeding recurrence and

negative or inconclusive gastroscopy.

Terminology

A gastric or a duodenal ulcer represents a wound in the lining of the stomach or the beginning of the small bowel. The most common causes are the ulcer bug and non-steroidal anti-inflammatory drugs.

Peer review

It is an interesting work.

REFERENCES

1 **Graham DY**, Opekun AR, Willingham FF, Qureshi WA. Visible small-intestinal mucosal injury in chronic NSAID users. *Clin Gastroenterol Hepatol* 2005; **3**: 55-59 [PMID: 15645405]

2 **Antithrombotic Trialists' Collaboration**. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; **324**: 71-86 [PMID: 11786451]

3 **Lewis JD**, Bilker WB, Brensinger C, Farrar JT, Strom BL. Hospitalization and mortality rates from peptic ulcer disease and GI bleeding in the 1990s: relationship to sales of nonsteroidal anti-inflammatory drugs and acid suppression medications. *Am J Gastroenterol* 2002; **97**: 2540-2549 [PMID: 12385436]

4 **Bjarnason I**, Hayllar J, MacPherson AJ, Russell AS. Side effects of nonsteroidal anti-inflammatory drugs on the small and large intestine in humans. *Gastroenterology* 1993; **104**: 1832-1847 [PMID: 8500743]

5 **Davies NM**, Saleh JY, Skjodt NM. Detection and prevention of NSAID-induced enteropathy. *J Pharm Pharm Sci* 2000; **3**: 137-155 [PMID: 10954683]

6 **Hayashi Y**, Yamamoto H, Kita H, Sunada K, Sato H, Yano T, Iwamoto M, Sekine Y, Miyata T, Kuno A, Iwaki T, Kawamura Y, Ajibe H, Ido K, Sugano K. Non-steroidal anti-inflammatory drug-induced small bowel injuries identified by double-balloon endoscopy. *World J Gastroenterol* 2005; **11**: 4861-4864 [PMID: 16097059]

7 **Maiden L**, Thjodleifsson B, Theodors A, Gonzalez J, Bjarnason I. A quantitative analysis of NSAID-induced small bowel pathology by capsule enteroscopy. *Gastroenterology* 2005; **128**: 1172-1178 [PMID: 15887101]

8 **Smecuol E**, Pinto Sanchez MI, Suarez A, Argonz JE, Sugai E, Vazquez H, Litwin N, Piazuelo E, Meddings JB, Bai JC, Lanas A. Low-dose aspirin affects the small bowel mucosa: results of a pilot study with a multidimensional assessment. *Clin Gastroenterol Hepatol* 2009; **7**: 524-529 [PMID: 19249402 DOI: 10.1016/j.cgh.2008.12.019]

9 **Goldstein JL**, Chan FK, Lanas A, Wilcox CM, Peura D, Sands GH, Berger MF, Nguyen H, Scheiman JM. Haemoglobin decreases in NSAID users over time: an analysis of two large outcome trials. *Aliment Pharmacol Ther* 2011; **34**: 808-816 [PMID: 21810115 DOI: 10.1111/j.1365-2036.2011.04790.x]

10 **Apostolopoulos P**, Liatsos C, Gralnek IM, Kalantzis C, Giannakoulopoulou E, Alexandrakis G, Tsibouris P, Kalafatis E, Kalantzis N. Evaluation of capsule endoscopy in active, mild-to-moderate, overt, obscure GI bleeding. *Gastrointest Endosc* 2007; **66**: 1174-1181 [PMID: 18061718]

11 **Watari I**, Oka S, Tanaka S, Igawa A, Nakano M, Aoyama T, Yoshida S, Chayama K. Comparison of small-bowel mucosal injury between low-dose aspirin and non-aspirin non-steroidal anti-inflammatory drugs: a capsule endoscopy study. *Digestion* 2014; **89**: 225-231 [PMID: 24861046]

12 **Watanabe T**, Sugimori S, Kameda N, Machida H, Okazaki H, Tanigawa T, Watanabe K, Tominaga K, Fujiwara Y, Oshitani N, Higuchi K, Arakawa T. Small bowel injury by low-dose enteric-coated aspirin and treatment with misoprostol: a pilot study. *Clin Gastroenterol Hepatol* 2008; **6**: 1279-1282 [PMID: 18995219 DOI: 10.1016/j.cgh.2008.06.021]

13 **Tsibouris P**, Apostolopoulos P, Kalantzis C, Zalonis A, Karamountzos A, Djabieva I, Alexandrakis G. Small bowel ulcerative lesions are more frequent in NSAIDs consumers with recent overt bleeding than those with iron deficiency anaemia. *Gut* 2010; **59**: A367 [Abstract]

14 **Forrest JA**, Finlayson ND, Shearman DJ. Endoscopy in gastrointestinal bleeding. *Lancet* 1974; **2**: 394-397 [PMID: 4136718]

15 **Pongprasobchai S**, Sriprayoon T, Manatsathit S. Prospective evaluation of gastrointestinal lesions by bidirectional endoscopy in patients with iron deficiency anemia. *J Med Assoc Thai* 2011; **94**: 1321-1326 [PMID: 22256471]

16 **Bjarnason I**, Takeuchi K, Bjarnason A, Adler SN, Teahon K. The G.U.T. of gut. *Scand J Gastroenterol* 2004; **39**: 807-815 [PMID: 15513377]

17 **Tsibouris P**, Hendrickse MT, Isaacs PE. Daily use of non-steroidal anti-inflammatory drugs is less frequent in patients with Barrett's oesophagus who develop an oesophageal adenocarcinoma. *Aliment Pharmacol Ther* 2004; **20**: 645-655 [PMID: 15352913]

18 **Laine L**, Curtis SP, Langman M, Jensen DM, Cryer B, Kaur A, Cannon CP. Lower gastrointestinal events in a double-blind trial of the cyclo-oxygenase-2 selective inhibitor etoricoxib and the traditional nonsteroidal anti-inflammatory drug diclofenac. *Gastroenterology* 2008; **135**: 1517-1525 [PMID: 18823986 DOI: 10.1053/j.gastro.2008.07.067]

19 **Watanabe T**, Tanigawa T, Nadatani Y, Nagami Y, Sugimori S, Okazaki H, Yamagami H, Watanabe K, Tominaga K, Fujiwara Y, Koike T, Arakawa T. Risk factors for severe nonsteroidal anti-inflammatory drug-induced small intestinal damage. *Dig Liver Dis* 2013; **45**: 390-395 [PMID: 23333664 DOI: 10.1016/j.dld.2012.12.005]

20 **Sugimori S**, Watanabe T, Tabuchi M, Kameda N, Machida H, Okazaki H, Tanigawa T, Yamagami H, Shiba M, Watanabe K, Tominaga K, Fujiwara Y, Oshitani N, Koike T, Higuchi K, Arakawa T. Evaluation of small bowel injury in patients with rheumatoid arthritis by capsule endoscopy: effects of anti-rheumatoid arthritis drugs. *Digestion* 2008; **78**: 208-213 [PMID: 19142000 DOI: 10.1159/000190403]

21 **Thiéfin G**, Beaugerie L. Toxic effects of nonsteroidal antiinflammatory drugs on the small bowel, colon, and rectum. *Joint Bone Spine* 2005; **72**: 286-294 [PMID: 16038840]

22 **Satoh H**, Amagase K, Takeuchi K. Mucosal protective agents prevent exacerbation of NSAID-induced small intestinal lesions caused by antisecretory drugs in rats. *J Pharmacol Exp Ther* 2014; **348**: 227-235 [PMID: 24254524 DOI: 10.1124/jpet.113.208991]

23 **Caunedo-Alvarez A**, Gómez-Rodríguez BJ, Romero-Vázquez J, Argüelles-Arias F, Romero-Castro R, García-Montes JM, Pellicer-Bautista FJ, Herrerías-Gutiérrez JM. Macroscopic small bowel mucosal injury caused by chronic nonsteroidal anti-inflammatory drugs (NSAID) use as assessed by capsule endoscopy. *Rev Esp Enferm Dig* 2010; **102**: 80-85 [PMID: 20361843]

24 **Goldstein JL**, Eisen GM, Lewis B, Gralnek IM, Zlotnick S, Fort JG. Video capsule endoscopy to prospectively assess small bowel injury with celecoxib, naproxen plus omeprazole, and placebo. *Clin Gastroenterol Hepatol* 2005; **3**: 133-141 [PMID: 15704047]

25 **Goldstein JL**, Eisen GM, Lewis B, Gralnek IM, Aisenberg J, Bhadra P, Berger MF. Small bowel mucosal injury is reduced in healthy subjects treated with celecoxib compared with ibuprofen plus omeprazole, as assessed by video capsule endoscopy. *Aliment Pharmacol Ther* 2007; **25**: 1211-1222 [PMID: 17451567]

26 **Shiotani A**, Haruma K, Nishi R, Fujita M, Kamada T, Honda K, Kusunoki H, Hata J, Graham DY. Randomized, double-blind, pilot study of geranylgeranylacetone versus placebo in patients taking low-dose enteric-coated aspirin. Low-dose aspirin-induced small bowel damage. *Scand J Gastroenterol* 2010; **45**: 292-298 [PMID: 19968611 DOI: 10.3109/0036552090

3453182]
27 **Yoda Y**, Amagase K, Kato S, Tokioka S, Murano M, Kakimoto K, Nishio H, Umegaki E, Takeuchi K, Higuchi K. Prevention by lansoprazole, a proton pump inhibitor, of indomethacin -induced small intestinal ulceration in rats through induction of heme oxygenase-1. *J Physiol Pharmacol* 2010; **61**: 287-294 [PMID: 20610858]
28 **Pilotto A**, Seripa D, Franceschi M, Scarcelli C, Colaizzo D, Grandone E, Niro V, Andriulli A, Leandro G, Di Mario F, Dallapiccola B. Genetic susceptibility to nonsteroidal anti-inflammatory drug-related gastroduodenal bleeding: role of cytochrome P450 2C9 polymorphisms. *Gastroenterology* 2007; **133**: 465-471 [PMID: 17681167]
29 **Chan FK**, Lanas A, Scheiman J, Berger MF, Nguyen H, Goldstein JL. Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): a randomised trial. *Lancet* 2010; **376**: 173-179 [PMID: 20638563 DOI: 10.1016/S0140-6736(10)60673-3]
30 **Sánchez-Capilla AD**, De La Torre-Rubio P, Redondo-Cerezo E. New insights to occult gastrointestinal bleeding: From pathophysiology to therapeutics. *World J Gastrointest Pathophysiol* 2014; **5**: 271-283 [PMID: 25133028 DOI: 10.4291/wjgp.v5.i3.271]
31 **Taha AS**, Angerson WJ, Knill-Jones RP, Blatchford O. Clinical outcome in upper gastrointestinal bleeding complicating low-dose aspirin and antithrombotic drugs. *Aliment Pharmacol Ther* 2006; **24**: 633-636 [PMID: 16907895]
32 **Yong D**, Grieve P, Keating J. Do nonsteroidal anti-inflammatory drugs affect the outcome of patients admitted to hospital with lower gastrointestinal bleeding? *N Z Med J* 2003; **116**: U517 [PMID: 12897885]
33 **Lanas A**, Goldstein JL, Chan FK, Wilcox CM, Peura DA, Li C, Sands GH, Scheiman JM. Risk factors associated with a decrease ≥2 g/dL in haemoglobin and/or ≥10% haematocrit in osteoarthritis patients taking celecoxib or a nonselective NSAID plus a PPI in a large randomised controlled trial (CONDOR). *Aliment Pharmacol Ther* 2012; **36**: 485-492 [PMID: 22804104 DOI: 10.1111/j.1365-2036.2012.05213.x]
34 **Hu ML**, Wu KL, Chiu KW, Chiu YC, Chou YP, Tai WC, Hu TH, Chiou SS, Chuah SK. Predictors of rebleeding after initial hemostasis with epinephrine injection in high-risk ulcers. *World J Gastroenterol* 2010; **16**: 5490-5495 [PMID: 21086569]
35 **Park KG**, Steele RJ, Mollison J, Crofts TJ. Prediction of recurrent bleeding after endoscopic haemostasis in non-variceal upper gastrointestinal haemorrhage. *Br J Surg* 1994; **81**: 1465-1468 [PMID: 7820473]
36 **Cheng HC**, Chuang SA, Kao YH, Kao AW, Chuang CH, Sheu BS. Increased risk of rebleeding of peptic ulcer bleeding in patients with comorbid illness receiving omeprazole infusion. *Hepatogastroenterology* 2003; **50**: 2270-2273 [PMID: 14696515]

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