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Clinical Study

Is Occult Obscure Gastrointestinal Bleeding a Definite Indication for Capsule Endoscopy? A Retrospective Analysis of Diagnostic Yield in Patients with Occult versus Overt Bleeding

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Background/Aim. Usefulness of capsule endoscopy (CE) for diagnosing small-bowel lesions in patients with obscure gastrointestinal bleeding (OGIB) has been reported. Most reports have addressed the clinical features of overt OGIB, with few addressing occult OGIB. We aimed to clarify whether occult OGIB is a definite indication for CE. *Methods*. We retrospectively compared the cases of 102 patients with occult OGIB and 325 patients with overt OGIB, all having undergone CE. The diagnostic yield of CE and identification of various lesion types were determined in cases of occult OGIB versus overt OGIB. *Results*. There was no significant difference in diagnostic yield between occult and overt OGIB. The small-bowel lesions in cases of occult OGIB were diagnosed as ulcer/erosive lesions ($n = 18$, 18%), vascular lesions ($n = 11$, 11%), and tumors ($n = 4$, 3%), and those in cases of overt OGIB were diagnosed as ulcer/erosive lesions ($n = 51$, 16%), vascular lesions ($n = 31$, 10%), and tumors ($n = 20$, 6%). *Conclusion*. CE detection rates and CE identification of various small-bowel diseases do not differ between patients with occult versus overt OGIB. CE should be actively performed for patients with either occult or overt OGIB.

1. Introduction

Obscure gastrointestinal bleeding (OGIB) accounts for approximately 5% of all cases of GI bleeding and is frequently due to a lesion in the small bowel [1–4]. OGIB is defined as bleeding from the gastrointestinal tract that persists or recurs without an obvious source being discovered by esophagogastroduodenoscopy (EGD), colonoscopy, or radiologic evaluation of the small bowel, that is, small bowel follow-through (SBFT) or enteroclysis [3]. OGIB is classified as either occult or overt, with occult OGIB defined as iron deficiency anemia (IDA), with or without a positive fecal occult blood test [5, 6], and overt OGIB defined as clinically perceptible bleeding that recurs or persists despite negative initial endoscopic (EGD and colonoscopy) and radiologic evaluations (SBFT or enteroclysis).

Usefulness of capsule endoscopy (CE) for diagnosing small-bowel lesions in patients with OGIB has been reported [7–10]. CE is used especially in patients with overt OGIB, with most previous reports addressing mainly the clinical features of overt OGIB. Few reports address the clinical features of occult OGIB. We conducted a comparative retrospective study to clarify whether occult OGIB is a definite indication for CE.

2. Material and Methods

2.1. Patients. From our hospital records, we identified 427 patients who had undergone CE for OGIB between April 2006 and February 2013: 102 with occult OGIB and 325 with overt OGIB. Patients with ongoing overt OGIB were not included in this study.

Occult OGIB was defined as IDA and/or a positive fecal occult blood test, and overt OGIB was defined as clinically perceptible bleeding that recurs or persists despite negative

initial endoscopic (EGD and colonoscopy) and radiologic evaluations (SBFT or enteroclysis).

IDA was diagnosed according to standard criteria, that is, a blood hemoglobin concentration of <13.8 g/dL for men, <11.5 g/dL for postmenopausal women, and <11 g/dL for premenopausal women, with a plasma ferritin level of <30 mg/L and a mean corpuscular volume of <80 fL [11]. Occult blood in the stool was detected by immunochemical fecal occult blood test. Transabdominal ultrasonography (TUS) and/or abdominal computed tomography (CT) were performed to uncover stenosis of the gastrointestinal tract and/or small-bowel disease before CE in all patients [12].

2.2. CE Examinations and Findings. When CE was performed, the CE capsule (PillCam SB1/SB2; Given Imaging Ltd., Yoqneam, Israel) was swallowed with a solution of dimethicone after an overnight fast. Most patients were given 34 g magnesium citrate for bowel preparation on the night before the procedure. Patients were allowed to drink clear liquids 2 hours after swallowing the capsule and to eat a light meal at 4 hours. Images were analyzed with Rapid Reader 4.0/5.0/6.5 software on a RAPID workstation (both from Given Imaging). CE images were reviewed independently by two gastroenterologists. If the gastroenterologists' findings differed, consensus was reached through discussion. Total CE was considered successful when the capsule reached the cecum within the recording time. Capsule retention was defined as a capsule remaining in the digestive tract for a minimum of 2 weeks.

CE findings were categorized as positive when a bleeding source was detected within the small bowel and as negative when no bleeding source was detected within the small bowel. We defined a bleeding source as a lesion with obvious bleeding (active bleeding or blood clot) or a lesion without obvious bleeding but that could be the cause of bleeding. Some detected lesions were considered not to be sources of bleeding, such as small red spots and erosions without active bleeding or blood clot. Small-bowel lesions were subclassified as vascular, ulcer/erosion, tumor, or other types of lesion.

2.3. Data Collection. Patients' clinical records were obtained, and demographic, clinical, procedural, and diagnostic data were extracted for analyses. Information gathered included age, sex, type of gastrointestinal bleeding (occult versus overt), hemoglobin concentration upon CE examination, plasma ferritin level upon CE examination, need for blood transfusion, time from the first OGIB episode, previous endoscopic diagnosis, CE findings, and results of pathologic examination of biopsy specimens obtained by double balloon endoscopy (DBE) or surgery. The total CE rate and the CE complication rate were determined for each of the 2 study groups (occult OGIB and overt OGIB). The diagnostic yield was determined in each group in terms of the detection of small-bowel lesions and identification of the various types of small-bowel lesions. In cases of occult OGIB, patient characteristics were examined in relation to lesion types.

Continuous data are presented as mean ± SD, and categorical data are presented as frequencies (percentages). Between-group differences in age and laboratory values were analyzed by Student's t-test. The proportions of patients with small-bowel lesions and no small-bowel lesions were compared by Fisher's exact test. The proportions of patients with vascular lesions, ulcer or erosion, and tumor were also analyzed by Fisher's exact test. All analyses were performed with JMP-J software. $P < 0.05$ was considered statistically significant.

The study protocol was approved by the ethics committee of Hiroshima University Hospital, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

3. Results

Patient characteristics are shown per study group (occult OGIB and overt OGIB) in Table 1. There was no significant difference between the 2 groups in age, time from the first OGIB episode, or hemoglobin concentration at the time of examination. The plasma ferritin level was significantly lower in the occult OGIB group than in the overt OGIB group ($P = 0.0003$). Moreover, the percentage of patients requiring blood transfusion was significantly lower in the occult OGIB group (16%, $n = 16$) than in the overt OGIB group (34%, $n = 110$) ($P < 0.01$). Indications for CE among patients with occult OGIB were recurrent/persistent IDA ($n = 68$), recurrent/persistent IDA in addition to a positive fecal occult blood test ($n = 29$), and a positive fecal occult blood test ($n = 5$).

Total CE was achieved in 74 of the 102 patients (73%) with occult OGIB and in 234 of the 325 patients (72%) with overt OGIB, with no significant difference in the total CE rate between the 2 groups ($P = 0.91$). Capsule retention was noted in 1 of the 102 patients (1%) with occult OGIB and in 2 of the 325 patients (0.6%) with overt OGIB. The occult OGIB patient was found to have small-bowel strictures resulting from tuberculosis. One of the 2 overt OGIB patients had a strictured small bowel resulting from tuberculosis, and the other had a nonspecific ulcer. Two of these 3 patients underwent DBE and 1 underwent surgery to remove the capsule.

The final diagnoses are shown in Table 2. Among the occult OGIB patients, the final diagnosis was either small-bowel lesion(s) ($n = 33$, 32%) or no lesion in the small-bowel ($n = 69$, 68%). Among the overt OGIB patients also, the final diagnosis was either small-bowel lesion(s) ($n = 106$, 33%) or no lesion in the small bowel ($n = 219$, 67%), with no significant difference in diagnostic yield between the 2 groups. Among patients with occult OGIB, small-bowel lesions were ulcer or erosive lesion(s) ($n = 18$, 18%), vascular lesion(s) ($n = 11$, 11%), and tumor(s) ($n = 4$, 3%), whereas lesions among overt OGIB patients were ulcer or erosive lesion(s) ($n = 51$, 16%), vascular lesions ($n = 31$, 10%), and tumor(s) ($n = 20$, 6%), with no difference in the various small-bowel lesion types between the 2 groups.

Of the 18 ulcer/erosive lesions found in patients with occult OGIB, NSAID ulcer was most common ($n = 10$, 55%), followed by non-specific ulcer/erosion ($n = 3$, 16%), intestinal tuberculosis ($n = 2$, 11%), Crohn's disease ($n = 1$, 6%), chronic nonspecific multiple ulcers of the small intestine

Table 1: Characteristics of patients with OGIB, per study group.

Characteristic	Occult OGIB ($n = 102$)	Overt OGIB ($n = 325$)	P value
Sex ratio (male/female)	50/52	198/127	<0.05
Age (years)	65.2 ± 17.3	65.3 ± 15.8	NS
Mean time from the first OGIB episode (months)	2.8 ± 2.7	1.7 ± 2.7	NS
Mean hemoglobin concentration at time of examination (g/dL)	7.8 ± 2.1	8.2 ± 2.7	NS
Plasma ferritin (mg/L)	10.1 ± 8.9	137.8 ± 210	0.0003
Blood transfusion	16 (16%)	110 (34%)	<0.01

Number of patients or mean ± SD values are shown.
NS: not significant.

Table 2: Final diagnoses per study group.

	Occult OGIB ($n = 102$)	Overt OGIB ($n = 325$)	P value
Small-bowel lesion	33 (32)	106 (33)	NS
Vascular lesion	11 (11)	31 (10)	NS
Ulcer or erosive lesion	18 (18)	51 (16)	NS
Tumor	4 (3)	20 (6)	NS
Other	0	4 (1)	NS
No small-bowel lesion	69 (68)	219 (67)	NS

Number (%) of patients is shown.
NS: not significant.

(CNSU) ($n = 1$, 6%), and radiation enterocolitis ($n = 1$, 6%). Of the 51 ulcer/erosive lesions found in patients with overt OGIB, nonspecific ulcer/erosion was most common ($n = 18$, 35%), followed by NSAID ulcer ($n = 13$, 25%), anastomotic ulcer ($n = 6$, 12%), intestinal tuberculosis ($n = 4$, 8%), Crohn's disease ($n = 3$, 6%), Henoch-Schönlein purpura ($n = 2$, 4%), Behçet's disease ($n = 1$, 2%), radiation enterocolitis ($n = 1$, 2%), CNSU ($n = 1$, 2%), eosinophilic gastroenteritis ($n = 1$, 2%), and amyloidosis ($n = 1$, 2%). There was no celiac disease.

Of the 11 vascular lesions found in patients with occult OGIB, angioectasia was most common ($n = 9$, 82%), followed by hemangioma ($n = 1$, 9%) and blue rubber bleb nevus syndrome ($n = 1$, 9%). Of the 31 vascular lesions found in patients with overt OGIB, angioectasia was most common ($n = 23$, 74%), followed by hemangioma ($n = 4$, 13%), arteriovenous malformation ($n = 3$, 10%), and varices ($n = 1$, 3%).

Characteristics of the 4 cases of occult OGIB arising from a tumor are given in Table 3. Tumor types were as follows: jejunal carcinoma ($n = 1$, 25%), gastrointestinal stromal tumor (GIST) ($n = 1$, 25%), aberrant pancreas ($n = 1$, 25%), and T-cell lymphoma ($n = 1$, 25%). Of the 20 tumors identified in patients with overt OGIB, GIST was the most common ($n = 9$, 45%), followed by adenoma/hamartomatous polyp(s) ($n = 3$, 15%), lipoma ($n = 2$, 10%), ectopic gastric mucosa ($n = 1$, 5%), carcinoid tumor ($n = 1$, 5%), primary small-bowel cancer ($n = 1$, 5%), aberrant pancreas ($n = 1$, 5%), malignant lymphoma ($n = 1$, 5%), and polyp in a case of familial adenomatous polyposis (FAP) ($n = 1$, 5%).

Diagnostic (final) and treatment modalities are shown per bleeding type in Table 4. Among patients with occult OGIB, vascular lesions were diagnosed endoscopically, that is, on the basis of CE and/or DBE findings ($n = 11$). Ulcer or erosive lesions were diagnosed endoscopically on the basis of CE and/or DBE findings ($n = 14$), response to medical treatment ($n = 3$), or DBE biopsy ($n = 1$). Tumors were diagnosed by surgery ($n = 3$) or DBE biopsy ($n = 1$). Among patients with overt OGIB, vascular lesions were diagnosed endoscopically on the basis of CE and/or DBE findings ($n = 31$). Ulcer/erosive lesions were diagnosed endoscopically on the basis of CE and/or DBE findings ($n = 48$), DBE biopsy ($n = 2$), or response to medical treatment ($n = 1$). Tumors were diagnosed upon surgery ($n = 12$), upon resection under DBE ($n = 4$), endoscopically on the basis of CE findings ($n = 3$), or by DBE biopsy ($n = 1$). Six of the 11 occult OGIB patients (55%) with a vascular lesion underwent endoscopic hemostasis, 7 of the 18 patients (39%) with ulcer/erosive lesion received treatment, and the 4 patients (100%) with tumor underwent surgery or chemotherapy. Of patients with overt OGIB, 27 of the 31 patients (87%) with a vascular lesion underwent endoscopic hemostasis or interventional radiology. Thirty of the 51 patients (59%) with an ulcer or erosive lesion received treatment. Seventeen of the 20 patients (85%) with tumor underwent surgery, endoscopic resection, or chemotherapy.

Clinical characteristics of patients with occult OGIB are shown per positive and negative CE examinations in Table 5. The hemoglobin concentration was significantly high in patients in whom an ulcer or erosive lesion was found in comparison to the concentration in patients in whom no small-bowel lesion was found. The platelet count was significantly high in patients in whom a tumor was found in

Table 3: Cases of occult OGIB due to tumor.

Patient	Final diagnosis	Indication for CE	Treatment
26-year-old woman	Aberrant pancreas	Positive FOBT, IDA	Surgery
40-year-old woman	T-cell lymphoma	Positive FOBT, IDA	Chemotherapy
68-year-old woman	Jejunum carcinoma	Positive FOBT, IDA	Surgery
81-year-old woman	GIST	IDA	Surgery

FOBT: fecal occult blood test; IDA: iron deficiency anemia; GIST: gastrointestinal stromal tumor.

Table 4: Diagnosis (final) and treatment modalities, per bleeding type.

Final diagnosis	Diagnostic modality	Treatment modality
Occult OGIB (n = 33)		
Vascular lesion (11)	DBE (7), CE (4)	Endoscopic hemostasis (6), follow up (no treatment) (5)
Ulcer or erosive lesion (18)	CE (8), DBE (6), CE+ response to medical treatment (3), and biopsy by DBE (1)	Medication (6), withdrawal of NAIDs (1), and follow up (no treatment) (11)
Tumor (4)	Surgery (3), biopsy by DBE (1)	Surgery (3), medication (1)[†]
Overt OGIB (n = 106)		
Vascular lesion (31)	DBE (29), CE (2)	Endoscopic hemostasis (26), IVR (1), and follow up (no treatment) (4)
Ulcer or erosive lesion (51)	DBE (33), CE (15), biopsy by DBE (2), CE+ response to medical treatment (1)	Medication (18)[†], withdrawal of NSAIDs (9), surgery (2), endoscopic hemostasis (1), and follow up (no treatment) (21)
Tumor (20)	Surgery (12), resection by DBE (4), CE (3), and biopsy by DBE (1)	Surgery (12), endoscopic resection (4), medication (1)[†], and follow up (no treatment) (3)
Other (4)	DBE (3), CE (1)	Endoscopic hemostasis (1), follow up (no treatment) (3)

Number of patients is shown.
[†]Anti-tubercular drugs, 5-ASA, steroid, medication for gastritis, or chemotherapy.
CE: capsule endoscopy; DBE: double balloon endoscopy; OGIB: obscure gastrointestinal bleeding; IVR: interventional radiology; NSAIDs: non-steroidal anti inflammatory drugs.

Table 5: Clinical characteristics of patients with occult OGIB, per diagnosis.

Characteristic	Vascular lesion (n = 11)	Ulcer or erosive lesion (n = 18)	Tumor (n = 4)	No lesion (n = 69)
Age (years)	68.8 ± 17.9	70.8 ± 16.1	53.8 ± 25.2	63.4 ± 17.5
Sex ratio (male/female)	9/2[a]	8/10	0/4	33/36
Laboratory values				
WBC (/μL)	5287 ± 1553	6030 ± 2416	5958 ± 1402	5287 ± 2130
Hemoglobin (g/dL)	7.4 ± 2.0	9.3 ± 2.4[b]	8.0 ± 2.4	7.6 ± 2.0
Platelets (/μL)	21.5 ± 5.9	22.5 ± 8.7	33.6 ± 8.8[a]	23.0 ± 9.2
Total protein (g/dL)	6.6 ± 0.9	6.6 ± 0.6	6.1 ± 1.6	6.9 ± 0.6
Albumin (g/dL)	3.8 ± 0.5	3.9 ± 0.5	3.9 ± 0.3	4.0 ± 0.6
CRP (mg/dL)	0.40 ± 0.85	0.68 ± 0.96	0.08 ± 0.39	0.35 ± 0.80
Plasma ferritin (mg/L)	7.5 ± 4.6	13.5 ± 12.1	13.6 ± 11.0	9.3 ± 8.7
Symptom(s)				
Diarrhea	0 (0)	0 (0)	0 (0)	5 (7)
Body weight loss	0 (0)	0 (0)	1 (25)	2 (3)

Number (%) of patients or mean ± SD values is shown.
[a]$P < 0.05$, [b]$P < 0.01$, compared with no lesion.
WBC: white blood cell count; CRP: C-reactive protein.

comparison to that in patients in whom no small-bowel lesion was found. The white blood cell count, hemoglobin concentration, platelet count, and total protein, serum albumin, CRP, and plasma ferritin levels did not differ between patients in whom a vascular lesion was found and those in whom no small-bowel lesion was found.

4. Discussion

The reported overall diagnostic yield of CE [13] and/or balloon endoscopy [14, 15] in patients with OGIB is 46–81% [8, 9, 16–30]. In cases of occult OGIB, specifically, the diagnostic yield of DBE is 42.1–76.5% [16, 24] and CE is 39–64.1% [9, 25–29]. In cases of overt OGIB, specifically, the diagnostic yield of CE or DBE is 53–87% [9, 17, 24, 25, 27–30]. Although DBE allows for tissue biopsy, small-bowel lesions are detected at the same rate by CE and DBE [31–33]. A diagnostic yield of 32% was achieved among our patients with occult OGIB due to small-bowel lesions, and this yield was similar to yields previously reported [9, 16, 24–29]. Sun et al. [24] reported an even higher diagnostic yield of 76.5% with DBE in patients with occult OGIB. We believe the difference in yield between their study and ours was due to the fact that their count included lesions outside the small intestine.

IDA is one of the major symptoms in patients with occult OGIB. Yamada et al. [34] performed CE in patients with IDA but without abnormalities found upon upper and lower endoscopy and reported that clinically significant lesions were statistically more prevalent in patients with IDA than in healthy volunteers (46% versus 15%).

Apostolopoulos et al. [35] performed CE in patients with IDA but without upper and lower endoscopic abnormalities and reported discovery of small-bowel lesions in 57% of cases. These data, together with the results of our study, lead us to believe that small-bowel examination is necessary in patients with IDA.

The diagnostic yield in our patients with overt OGIB was low compared to yields previously reported [9, 17, 24, 25, 28–30]. Patients with ongoing OGIB were included in these reported studies. The previously reported diagnostic yield among patients with ongoing OGIB is 76–92% [36–39], suggesting that features of ongoing overt OGIB differ from those of previous overt OGIB. We think that the discrepancy between previously reported diagnostic yields and our diagnostic yield may be due to our exclusion of ongoing OGIB. Investigation regarding any relation between the time to examination (time between presentation and examination) and the diagnostic yield is difficult in cases of occult OGIB; however, we believe that the diagnostic yield may differ according to the time between detection of fecal occult blood and/or diagnosis of chronic anemia and the time of small-bowel endoscopy. Future analysis of this issue is needed.

Ulcer or erosive lesion was the most common small-bowel lesion in our patients, whether those with occult OGIB or those with overt OGIB. In a fairly recent study, tumor was the most frequent source of bleeding in patients with either type of OGIB [24]. In a second fairly recent study, vascular lesions were the most frequent source of bleeding regardless of the type of OGIB [28], and in another study, ulcer/erosion was the most frequent source of bleeding [25]. The differences in the most common bleeding source could be due to differences in patient/clinical characteristics. The average age of patients among whom tumors were the most common [24] was low at 48.2 years, and DBE alone was used in that reported series. Vascular lesions were found at a fairly low rate in our series, but this could be because nonspecific red spots were considered unlikely sources of bleeding and were excluded from among the vascular lesions identified in our patients. A small angioectasia can be a source of bleeding that is easily overlooked during CE. In recent years, flexible spectral imaging color enhancement (FICE) has been added to RAPID6.5 as an image enhancement mode [40], and we have reported the usefulness of CE with FICE for visualizing small-bowel lesions such as angioectasia, erosion/ulceration, and various tumors [41]; FICE improves detection of angioectasia [42]. We anticipate future refinement of FICE-based diagnostic strategies for minute angioectasia.

Not all factors associated with positive CE findings in cases of occult OGIB are clear. However, in this study, it was shown that small-bowel lesions should be suspected in patients with occult OGIB and a high platelet count. If analyses of larger patient groups can establish predictor variables for various small-bowel lesions such as ulcers, vascular lesions, tumors, and other types of lesions, a standard diagnostic strategy that includes small-bowel testing can also be established.

5. Conclusion

With respect to detection of small-bowel lesions and identification of the various types of lesions, we found no difference in the diagnostic yield of CE between overt and occult OGIB cases. We recommend that CE be performed as actively for patients with occult OGIB as for those with overt OGIB.

Conflict of Interests

The authors have no conflict of interests to declare.

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RESEARCH ARTICLE Open Access

Effectiveness of polaprezinc for low-dose aspirin-induced small-bowel mucosal injuries as evaluated by capsule endoscopy: a pilot randomized controlled study

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Abstract

Background: Treatment of low-dose aspirin (LDA)-induced small-bowel injury has not been established. Polaprezinc, a chelate of zinc and L-carnosine, may be efficacious for such injury. We conducted a pilot randomized controlled study to investigate whether polaprezinc is effective against LDA-induced small-bowel injuries.

Methods: Consecutive patients under long-term (>3 months) LDA treatment and who agreed to participate in our study underwent initial capsule endoscopy (CE). Patients with LDA-induced small-bowel injury apparent upon initial CE (n = 20) were randomized into a polaprezinc (150 mg/day for 4 weeks) group and a control (no polaprezinc treatment) group. All underwent follow-up CE after 4 weeks. Changes in the number and characteristics of small-bowel mucosal injuries were compared within and between the two groups.

Results: The median number of reddened lesions and erosions/ulcers upon follow-up CE in the polaprezinc group significantly decreased ($P < 0.05$). However, there was no significant difference in the median number of reddened lesions and erosions/ulcers upon follow-up CE in the control group.

Conclusions: Co-administration of polaprezinc may be effective against small-bowel mucosal injury associated with long-term LDA therapy.

Trial registration: UMIN Clinical Trials Registry UMIN000003687.

Keywords: Small-bowel mucosal injury, Low-dose aspirin, Polaprezinc, Capsule endoscopy

Background

Aspirin, a nonsteroidal anti-inflammatory drug (NSAID), is one of the most-prescribed medications worldwide, and low-dose aspirin (LDA), usually defined as 75-325 mg daily, is commonly used for primary and secondary prevention of cardiovascular events and stroke [1-3]. However, the use of NSAIDs, including aspirin, is associated with risk of upper gastrointestinal mucosal damage, manifesting as peptic ulcer and/or bleeding [4-7]. NSAIDs, including aspirin, can also induce small-bowel injury and, now that small-bowel endoscopy is available for detection of small-bowel lesions, have become a matter of interest to gastroenterologists [8-10].

Neither protection against nor treatment of LDA-induced small-bowel mucosal injuries has been established. In Japan, polaprezinc is commonly used for the treatment of gastric ulcer. Polaprezinc is a chelate compound consisting of zinc and L-carnosine that is thought to function in protecting intercellular tight junctions [11,12], as an anti-oxidant [13], in preventing apoptosis [14-16], and in reducing inflammation [17]. Omatsu et al. [14] speculated that polaprezinc protects rat intestinal epithelial (RIE-1) cells from indomethacin-induced apoptosis via its reactive oxygen species (ROS)-quenching effect. Mahmood et al. [18] reported that zinc carnosine prevented the rise in gut permeability caused by indomethacin in healthy volunteers,

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strongly suggesting a small-bowel protective effect. Polaprezinc may have potential to protect against or treat NSAID-induced small-bowel injury. Therefore, we conducted a pilot randomized controlled study to assess the effectiveness of polaprezinc for treatment of LDA-induced small-bowel injuries.

Methods

Patients

Consecutive patients undergoing upper gastrointestinal endoscopy or colonoscopy at Hiroshima University Hospital and taking LDA between May 2010 and September 2011 were screened for inclusion in the study. These patients were visiting our hospital for endoscopic treatment of gastrointestinal tumor, follow-up endoscopic examination after endoscopic treatment, treatment of gastrointestinal bleeding outside the small intestine, or examination for obscure gastrointestinal bleeding (OGIB). Inclusion criteria were as follows: use of low-dose enteric-coated aspirin at 100 mg once daily for more than 3 months; no current use of antibiotics; age ≥ 21years; an initial CE examination. Exclusion criteria were as follows: use of NSAIDs other than LDA; inflammatory bowel disease; digestion-absorption disorder; polaprezinc treatment; use of other medicines for gastritis, e.g., misoprostol or rebamipide, within the prior 6 months; use of antibiotics or thyroxine sodium; stenosis of the gastrointestinal tract or severe adhesion; pregnancy or nursing; severe ulcerative lesion(s) observed upon initial CE, absence of small-bowel injury upon initial CE, and failure of the CE capsule to reach the cecum. Twenty patients in whom LDA-induced small-bowel injury was identified upon initial CE, as described below, comprised the final study group.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of Hiroshima University Hospital. All patients screened for inclusion in the study were provided written informed consent for participation. The trial is registered with the UMIN Clinical Trials Registry as number UMIN000003687.

Study protocol

The 20 patients in whom LDA-induced small-bowel injury was identified during the screening process were randomized into two groups: a polaprezinc group (n = 10) and a control group (n = 10). For allocation of patients to the study groups, we followed a block randomization scheme. Patients were given their assignments in sealed envelopes that had been shuffled previously. Patients in the polaprezinc group were given polaprezinc at 150 mg daily for 4 weeks, whereas patients in the control group were not given polaprezinc during the 4-week period. All patients continued LDA at 100 mg daily. Initial CE was defined as CE performed at the time patients were first examined in our department; follow-up CE was performed after 4 weeks in both groups.

CE procedure and evaluation

The CE capsule (PillCam SB2; Given Imaging Ltd, Yoqneam, Israel) was swallowed with a solution of dimethicone after an overnight fast, without any other preparation. Images were analyzed with Rapid Reader 6.5 software on a RAPID 6.0 workstation (both from Given Imaging). CE images were reviewed independently by two of four experienced gastroenterologists (I.W., T.A., H.I., T.S.) who were not provided any clinical information. If the gastroenterologists' findings differed, consensus was reached through discussion.

NSAID-induced small-bowel injury is characterized by multiple petechiae/red spots, denuded area, scars, mucosal erosions, and ulcers with a round, irregular, or punched-out appearance, or circumferential ulcers with stricture [19]. Such LDA-induced small-bowel injury was diagnosed at the time of initial CE.

Small-bowel mucosal injuries were classified as either erosion/ulcer or reddened lesion [20,21] as follows: erosion, a white spot surrounded by a red halo; ulcer, depression with a white coating; reddened lesion, reddish mucosal change such as reddened folds, denuded area, and/or petechiae (Figure 1); red spots were ignored in this study. LDA-induced small-bowel injuries were defined as follows;

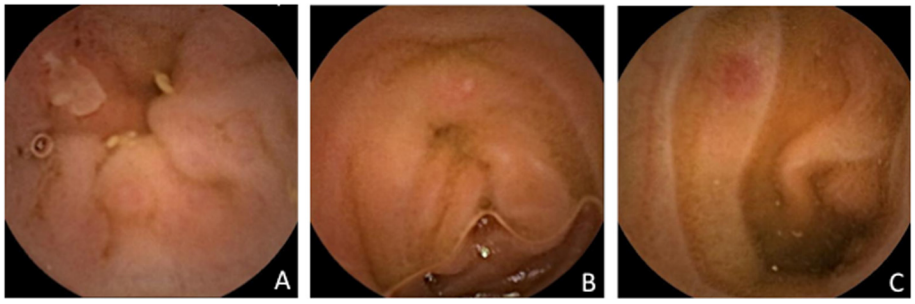

Figure 1 Capsule endoscopy images of small-bowel mucosal injuries induced by low-dose enteric-coated aspirin therapy. (**A**) Ulcer (depression with a white coating), (**B**) erosion (white spot surrounded by a red halo), (**C**) reddened lesion (reddish mucosal change).

(1) ulcer, erosion or reddened lesion detected by capsule endoscopy, (2) use of LDA for more than 3 months, and (3) exclusion of Crohn's disease, intestinal tuberculosis and any other small bowel disease.

We assessed the anatomic distribution of LDA-induced small-bowel mucosal injuries upon initial CE according to the following numerical formula based on capsule transit time through the small intestine [22]: Lesion location, i.e., first, second, or third portion of the small bowel corresponding to the percentage of total transit time, = (CE time when lesion is found – CE time of first duodenal image)/ small bowel transit time.

To evaluate the effectiveness of polaprezinc, the number of small-bowel injuries and CE score [23] were calculated for each patient upon initial CE and upon follow-up CE. Changes in the number of small-bowel injuries and the difference in CE scores between initial CE and follow-up CE were compared between the polaprezinc group and the control group.

The CE score [23] was determined for small-bowel mucosal inflammatory changes. The score was based on three capsule endoscopy variables: villous appearance, ulceration, and stenosis. Severity of the mucosal inflammatory changes was assessed in tertiles by dividing small-bowel capsule transit time into three equal allotments. The total CE score was taken as the highest tertile score plus the stenosis score. The results were classified into three categories based on the final numerical score: normal or clinically insignificant change (total score <135), mild change (total score ≥135 but <789), and moderate to severe change (total score ≥790). This scoring system has been shown to be useful for evaluating aspirin-associated small-bowel mucosal disease activity and for objectively scoring the small-bowel inflammatory disease state [24].

Statistical analysis

Quantitative data are presented as median (range), and categorical data are presented as the number per group. Between-group differences in sex ratio, anti-ulcer drug use, indications for LDA therapy, and tertile CE scores were analyzed by Fisher's exact test. Within-group differences between initial CE and follow-up CE in the number of ulcers/erosions and reddened lesions and in CE scores were analyzed by Wilcoxon signed-rank test. $P < 0.05$ was considered statistically significant. All analyses were performed with JMP-J software.

Table 1 Characteristics of patients with small-bowel mucosal injuries per study group (polaprezinc treatment and no polaprezinc treatment, i.e., control)

Characteristic	Polaprezinc (n = 10)	Control (n = 10)	*P* value
Sex ratio (male/female)	9/1	7/3	N.S.*
Age (years); median (range)	78.5 (64-82)	75.5 (62-86)	N.S.**
Hemoglobin concentration (g/dL); median (range)	13.6 (10.2-15.3)	13.7 (8-15)	N.S.**
Indication for low-dose aspirin therapy			
Valvular heart disease	3	2	
Stroke	3	7	N.S.*
Other	4	1	
Duration of low-dose aspirin (months); median (range)	64.5 (24-120)	48 (36-120)	N.S.**
Anti-ulcer drug			
H2 blocker	1	2	N.S.*
PPI	3	1	
None	6	7	
Initial CE findings			
Median number of erosions/ulcers (range)	2 (0-6)	2 (0-10)	N.S.**
Median number of reddened lesions (range)	3 (0-7)	2 (0-7)	N.S.**
CE score			
Median score (range)	180 (0-450)	225 (0-225)	N.S.**
CE score by category			
Normal or clinically insignificant change (<135)	3	4	
Mild change (≥135 and <790)	7	6	N.S.*
Moderate or severe change (≥790)	0	0	

Number of patients are shown unless otherwise indicated.
*by Fisher's exact test **by Wilcoxon test.
Abbreviations: *CE*, Capsule endoscopy; *PPI*, Proton pump inhibitor; N.S., Not significant.

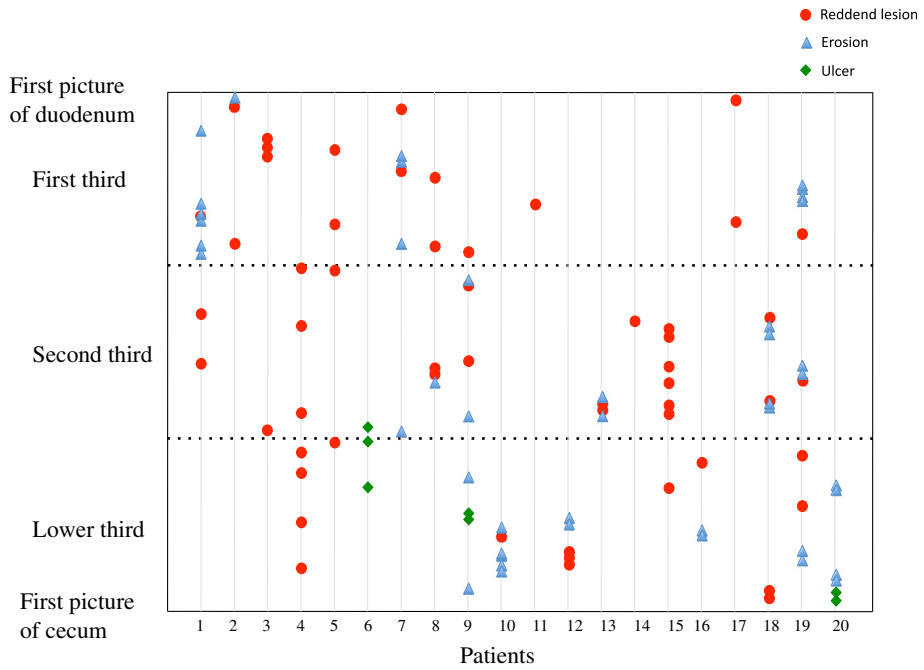

Figure 2 Anatomic distribution of small-bowel mucosal injuries observed by initial CE. Injuries are shown as one of three types for all subjects. Location (first, second, or third portion of the small intestine) of each injury was determined according to time the injury was observed in relation to total capsule transit time through the small intestine.

Table 2 Number of small-bowel mucosal injuries and CE scores upon initial and follow-up CE in the polaprezinc treatment group and non-polaprezinc (control) group

	Initial CE	Follow-up CE	*P* value
Polaprezinc group (n = 10)			
Median number of erosions/ulcers (range)	2 (0-6)	0 (0-4)	0.039*
Median number of reddened lesions (range)	3 (0-7)	1 (0-1)	0.003*
Median CE score (range)	180 (0-450)	0 (0-225)	N.S.*
CE score by category			
Normal or clinical insignificant change (<135)	3	6	
Mild change (≥135 and <790)	7	4	N.S.**
Moderate or severe change (≥790)	0	0	
Control group (n = 10)			
Median number of erosions/ulcers (range)	2 (0-10)	0 (0-9)	N.S.*
Median number of reddened lesions (range)	2 (0-7)	2 (0-7)	N.S.*
Median CE score (range)	225 (0-225)	0 (0-450)	N.S.*
CE score by category			
Normal or clinically insignificant change (<135)	4	6	
Mild change (≥135 and <790)	6	4	N.S.**
Moderate or severe change ((≥790)	0	0	

Abbreviations: *CE*, Capsule endoscopy; *N.S.*, Not significant.
*by Wilcoxon signed-rank test **by Fisher's exact test.

Results

Characteristics of the 20 patients randomized to the polaprezinc group or control group are shown per group in Table 1. There was no significant difference between the two groups with regard to sex ratio, age, hemoglobin concentration, indications for LDA, duration of LDA, or anti-ulcer drug use. Neither was there a significant difference between the two groups upon initial CE in the number of erosions/ulcers and reddened lesions, total CE score, or tertile CE scores.

The types and anatomic locations of the small-bowel mucosal injuries observed upon initial CE are shown in Figure 2. Reddened lesions and erosions were evenly distributed throughout the small bowel, but ulcers tended to be located in the third section of the small bowel.

The median number of erosions/ulcers identified upon initial CE in the polaprezinc group was 2 (range 0-6), and the median number of reddened lesions was 3 (range 0-7). The median numbers in the control group were 2 (range 0-10) and 2 (range 0-7), respectively. As shown in Table 2, the median number of erosions/ulcers depicted upon follow-up CE in the polaprezinc group decreased significantly to 0 (range 0-4) ($P = 0.039$). In the control group, there was no significant difference in the median number of erosions/ulcers upon follow-up CE. The median number of reddened lesions in the polaprezinc group decreased significantly to 1 (range 0-1) upon follow-up CE ($P = 0.003$), but in the control group, there was no significant difference in the median number of reddened lesions observed upon follow-up CE. Change in the numbers of small-bowel mucosal injuries from initial CE to follow-up CE in both groups is diagrammed in Figure 3. In addition to the median numbers of reddened lesions, erosions/ulcers, the median number of total lesions (reddened lesions/erosions/ulcers) decreased significantly in the polaprezinc group. The changes in median CE score between initial CE and follow-up CE did not differ between the two groups.

Discussion

NSAIDs, including aspirin, cause small-bowel injury through cyclooxygenase (COX)-dependent and COX-independent pathways [25]. NSAIDs inhibit mucosal prostaglandin (PG) synthesis by inhibiting COX activity. NSAIDs decrease mucosal endogenous PG, resulting in reduction of intestinal mucus, microcirculatory disturbances accompanying abnormally increased intestinal

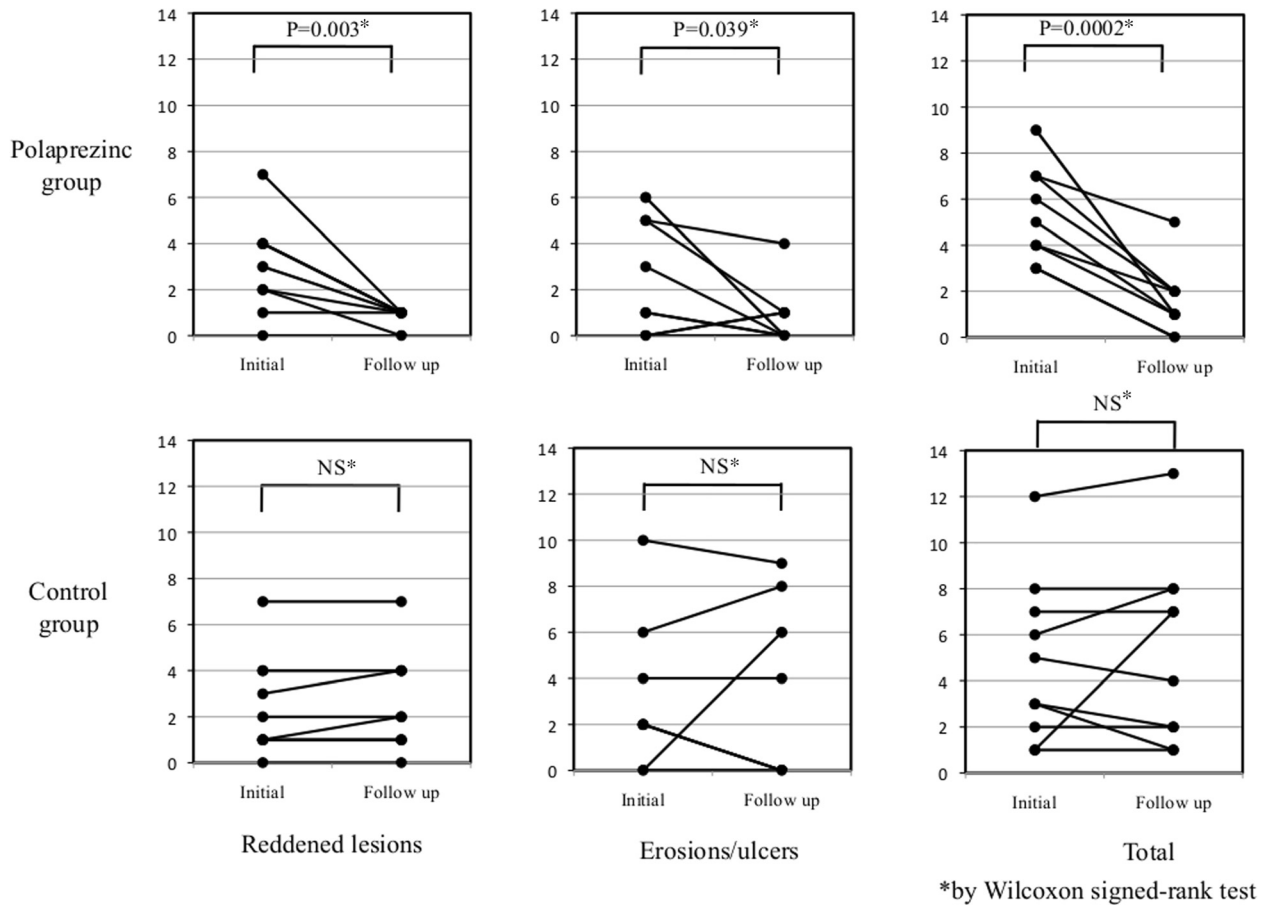

Figure 3 Changes in the numbers of small-bowel mucosal injuries (from initial to follow-up capsule endoscopy).

motility, disruption of intercellular junctions, and increased mucosal permeability. Bjarnason et al. [26] proposed a "three hit" hypothesis independent of the COX-pathway. NSAIDs solubilize phospholipids on the mucosal surface, directly damaging epithelial mitochondria. The mitochondrial damage leads to calcium efflux and to induction of free radicals; disruption of intercellular junctions occurs, and mucosal permeability increases in the small intestine [27]. Mucosal injuries can be caused by the penetration of bile acid, proteolytic enzymes, intestinal bacteria, and/or toxins.

The reported incidence of LDA-induced small-bowel injury is 20-61.5% among healthy volunteers using short-term LDA [24,28-30], and the reported prevalence of LDA-induced small-bowel injury is 42.1-100% specifically among patients with OGIB using long-term LDA [19,24,31,32]. The actual overall clinical prevalence of adverse effects of long-term aspirin on the small bowel in asymptomatic patients remains undocumented.

Endo et al. reported that aspirin-associated small bowel ulcers tended to be located in the distal part of the small bowel [19]. In our patients, although there was no specific anatomic distribution of reddened lesions and erosion, ulcers were specifically found in the ileum upon initial CE, albeit there were only three such cases.

The recommended treatment for small-bowel injury in patients undergoing LDA therapy is withdrawal of the aspirin. However, in the majority of patients, LDA is used as an antiplatelet agent, and it cannot be discontinued due to the increased risk of cardiovascular or cerebrovascular morbidity and mortality. Prevention and healing regimens for LDA-induced small-bowel injuries are needed. To date, several investigations regarding prevention and healing regimens for aspirin-induced small-bowel injury have been reported. Watanabe et al. [32] reported that among patients suffering from cerebral and cardiovascular disorders, misoprostol was administered to those taking LDA for 3 months or more, and, after 8 weeks, CE revealed that red spots as well as mucosal breaks were completely eliminated in 57% of the patients. Unfortunately, there was a high incidence of side effects, e.g., diarrhea, hepatic dysfunction, and albuminuria, and misoprostol is generally contraindicated for women who could be pregnant.

Endo et al. [31] randomized patients taking LDA for 3 months or more into two groups: one given 3-month probiotic treatment (oral *Lactobacillus casei*) and the other not given the 3-month probiotic treatment. CE at 3 months showed that the number of reddened lesions and/or mucosal breaks had decreased in the group given *L. casei.*

The study reported herein is the first randomized controlled study of the effectiveness of polaorezinc on small bowel injury identified by CE in chronic LDA users. Although our study was small (20 patients), limited to a single center, and without a placebo control group, the median number of reddened lesions and erosions/ulcers in those treated with polaprezinc decreased significantly, suggesting that polaprezinc may be clinically effective in treating LDA-induced small-bowel injuries. No polaprezinc-based improvement in CE score was observed in our patients, but this might be due to the small number of ulcers among our study patients, to the fact that the lesions were fairly small, with most being less than one-quarter of the circumference of the small bowel, and to the absence of stenosis.

Generally, small-bowel endoscopy, including CE and DBE, is not performed except in OGIB cases or symptomatic cases. We are convinced that further studies are warranted to determine which patients undergoing LDA therapy should undergo endoscopic examination for small-bowel lesions, which drugs are effective for such lesions, and whether the same drugs can be used even to prevent such lesions.

Conclusions

Co-administration of polaprezinc may be effective for LDA-induced small-bowel injuries.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

IW analyzed the capsule endoscopies, collected the clinical data and wrote the manuscript, with contributions from SO, ST and KC. SO was responsible for the design of the study and collected the clinical data. SY performed the statistical analyses. TA, HI and TS analyzed the capsule endoscopies. All authors read and approved the final manuscript.

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