Thomas HJ, Tomlinson IP. Multiple colorectal adenomas, classic adenomatous polyposis, and germ-line mutation in MYH. *N Engl J Med* 2003;**348**:791–9.

16. Glocker EO, Kotlarz D, Boztug K, Gertz EM, Schäffer AA, Noyan F, Perro M, Diestelhorst J, Allroth A, Murugan D, Hätscher N, Pfeifer D, Sykora KW, Sauer M, Kreipe H, Lacher M, Nustede R, Woellner C, Baumann U, Salzer U, Koletzko S, Shah N, Segal AW, Sauerbrey A, Buderus S, Snapper SB, Grimbacher B, Klein C. Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. *New Engl J Med* 2009;**361**: 2033–45.
17. Modigliani R, Poitras P, Galian A, Messing B, Guyet-Rousset P, Libeskind M, Piel-Desruisseaux JL, Rambaud JC. Chronic non-specific ulcerative duodenojejunoileitis. Report of four cases. *Gut* 1979;**20**:318–28.
18. Robertson DA, Dixon MF, Scott BB, Simpson FG, Losowsky MS. Small intestinal ulceration. Diagnostic difficulties in relation to coeliac disease. *Gut* 1983;**24**:565–74.
19. Biagi F, Lorenzini P, Corazza GR. Literature review on the clinical relationship between ulcerative jejunoileitis, coeliac disease, and enteropathy associated T-cell lymphoma. *Scand J Gastroenterol* 2000;**35**:785–90.
20. Orholm M, Munkholm P, Langholz E, Nielsen OH, Sørensen TI, Binder V. Familial occurrence of inflammatory bowel disease. *N Engl J Med* 1991;**324**:84–8.
21. Probert CS, Jayanthi V, Hughes AO, Thompson JR, Wicks AC, Mayberry JF. Prevalence and family risk of ulcerative colitis and Crohn's disease. An epidemiological study among Europeans and south Asians in Leicestershire. *Gut* 1993;**34**:1547–51.
22. Yang H, McElree C, Roth MP, Shanahan F, Targan SR, Rotter JI. Familial empirical risks for inflammatory bowel disease. Differences between Jews and non-Jews. *Gut* 1993;**34**:517–24.
23. Bayless TM, Tokayer AZ, Polito JM, Quaskey SA, Mellits ED, Harris ML. Crohn's disease. Concordance for site and clinical type in affected family members. Potential hereditary influences. *Gastroenterology* 1996;**111**:673–9.
24. Peeters M, Nevens H, Baert F, Hiele M, de Meyer AM, Vlietinck R, Rutgeerts P. Familial aggregation in Crohn's disease. Increased age-adjusted risk and concordance in clinical characteristics. *Gastroenterology* 1996;**111**:597–603.
25. Carbonnel F, Macaigne G, Beaugerie L, Gendre JP, Cosnes J. Crohn's disease severity in familial and sporadic cases. *Gut* 1999;**44**:91–5.
26. Freeman HJ. Familial Crohn's disease in single or multiple first-degree relatives. *J Clin Gastroenterol* 2002;**35**:9–13.
27. Sanderson IR, Risdon RA, Walker-Smith JA. Intractable ulcerating enterocolitis of infancy. *Arch Dis Child* 1991;**66**:295–9.
28. Reifen RM, Cutz E, Griffiths AM, Ngan BY, Sherman PM. Tufting enteropathy. A newly recognized clinicopathologic entity associated with refractory diarrhea in infants. *J Pediatr Gastroenterol Nutr* 1994;**18**:379–85.
29. Goulet O, Kedinger M, Brousse N, Cuenod B, Colomb V, Patey N, de Potter S, Mougenot JF, Canioni D, Cerf-Bensussan N. Intractable diarrhea of infancy. A new entity with epithelial and basement membrane abnormalities. *J Pediatr* 1995;**127**: 212–9.
30. Sidbu R, Brunt LK, Morley SR, Sanders DS, McAlindon ME. Undisclosed use of nonsteroidal anti-inflammatory drugs may underlie small-bowel injury observed by capsule endoscopy. *Clin Gastroenterol Hepatol* 2010;**11**:992–5.

Dig Dis Sci (2011) 56:3247–3253
DOI 10.1007/s10620-011-1742-7

ORIGINAL ARTICLE

Double-Contrast Barium Enteroclysis as a Patency Tool for Nonsteroidal Anti-Inflammatory Drug-Induced Enteropathy

Takayuki Matsumoto · Motohiro Esaki · Koichi Kurahara · Fumihito Hirai · Tadahiko Fuchigami · Toshiyuki Matsui · Mitsuo Iida

Received: 30 March 2011 / Accepted: 26 April 2011 / Published online: 13 May 2011

Abstract
Background Evaluating small bowel patency is recommended for capsule endoscopy in patients suspected of nonsteroidal anti-inflammatory drug-induced (NSAID) enteropathy.
Aims The aim of this investigation was to examine whether radiography is a candidate of patency tool in NSAID enteropathy.
Methods We reviewed double-contrast barium enteroclysis in 21 patients with NSAID enteropathy diagnosed either by capsule endoscopy or balloon-assisted endoscopy. The endoscopic findings were classified into circular ulcers, linear ulcers and small mucosal defects. The radiographic signs of the corresponding endoscopic findings were retrieved and the depiction rate was calculated.
Results Of the 21 patients, endoscopy detected circular ulcers, linear ulcers, and small ulcers in 12, 3 and 12 patients, respectively. Small bowel radiography depicted circular narrowing as pseudo-folds in 10 patients (83%) and linear ulcers as eccentric rigidity in 2 patients (67%). However, radiography was able to depict small mucosal defects in only 3 patients (17%). Two of 5 patients with pseudo-folds experienced retention of the capsule.
Conclusion "Pseudo-folds" is a sign corresponding to circular ulcer in NSAID enteropathy, which may be predictive of capsule retention.

Keywords Nonsteroidal anti-inflammatory drug · Small bowel · Capsule endoscopy · Balloon-assisted enteroscopy · Radiography

T. Matsumoto (✉) · M. Esaki · M. Iida
Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Maidashi 3-1-1, Higashi-ku, Fukuoka 812-8582, Japan
e-mail: matane@intmed2.med.kyushu-u.ac.jp

K. Kurahara · T. Fuchigami
Department of Gastroenterology, Matsuyama Red Cross Hospital, Matsuyama, Japan

F. Hirai · T. Matsui
Department of Gastroenterology, Fukuoka University Chikushi Hospital, Chikushino, Japan

Introduction

It has become evident that patients taking nonsteroidal anti-inflammatory drugs (NSAID) are at high risk of small bowel mucosal lesions [1, 2]. In observational studies by means of video-capsule endoscopy (VCE) or balloon-assisted endoscopy (BAE), more than 50% of patients under long-term NSAID use had small bowel ulcers [3–6]. The endoscopic findings of NSAID enteropathy vary widely, from diminutive mucosal defects to sharply demarcated ulcers [3, 4, 7–9]. Amongst various types of mucosal lesions, severe and concentric strictures of the small bowel, referred to as diaphragms, are the most characteristic of NSAID enteropathy [10, 11].

In the early period after the introduction of CE, cases of NSAID enteropathy with the diaphragms were examined by the procedure, and as a consequence, those cases suffered from capsule retention [12, 13]. It has subsequently been reported that NSAID enteropathy is one of the major causes of the retention of the capsule. In a single center analysis, Li et al. [14] reported that 8 of 14 patients who experienced capsule retention had NSAID enteropathy. In an extensive review by Liao et al. [15], NSAID enteropathy has been shown to be the third most frequent cause of capsule retention, accounting for 18.4% of such cases.

In order to avoid capsule retention, a patency capsule system has been developed and become clinically available [16–18]. However, the patency system is time-consuming, requiring 5 days for final decisions at most [18]. Furthermore, it is a historical fact that diaphragms could be diagnosed by small bowel radiography in the 1990s [19–22]. We thus made a retrospective analysis of our patients with endoscopically diagnosed NSAID enteropathy to assess the role of double-contrast barium enteroclysis as a procedure for luminal patency in the disease.

Methods

Patients

We reviewed patients with small bowel ulcers detected by VCE or BAE at our institutions during the period 2003–2011, and identified 53 patients who fulfilled the following criteria for NSAID enteropathy. The criteria included (1) presence of small bowel mucosal lesions, (2) NSAID intake for at least a week just prior to enteroscopy, and (3) ulcer healing after discontinuance of the NSAID without any specific treatment. Among the patients, we recruited 21 who had been examined by double-contrast barium enteroclysis (DCBE) prior to enteroscopy for the present investigation. Written informed consent was obtained from each subject with regards to the purpose and the method of each examination. This retrospective study was undertaken according to the Helsinki Declaration.

There were 7 females and 14 males, and the ages at the time of enteroscopy ranged from 46 to 88 years (mean, 68 years). The indication for enteroscopy was overt obscure gastrointestinal bleeding (OGIB) in 13 patients, abdominal pain in 5, and occult OGIB in 3. Seventeen patients had been taking a single NSAID, while 4 patients were under two species of NSAID. The species of NSAID were loxioprofen (7 patients), diclofenac (6), low-dose aspirin (4), indomethacin (2), meloxicam (2), ibuprofen, naproxen, ampyroxicam and celecoxib (each in 1 patient). The indication for NSAID use was osteoarthropathy in 10 patients, rheumatoid arthritis in 6, other arthralgia in 2, and cardiovascular diseases in 3. Time duration from the start of NSAID until the diagnosis of the enteropathy ranged from 0.2 to 240 months with a mean of 52 months.

Enteroscopy

VCE was performed by either PillCam SB system (Given Imaging, Yoqneam, Israel) or EndoCapsule system (Olympus, Tokyo, Japan), according to the manufacturer's recommendation. After an overnight fast, patients were prepared by simethicone with tap water or 900 ml of magnesium citrate prior to the examination [23]. Patients were then instructed to ingest the capsule and the images for the subsequent 8 h were recorded. The VCE images were reviewed by one of the authors (M.E.), who was informed of the patients' characteristics including NSAID use. Capsule retention was regarded as a case of retained capsule for more than 3 days, which required subsequent endoscopic or surgical procedure for removal.

Oral and anal BAEs were performed with Double Balloon Enteroscopy System (Fujifilm, Tokyo, Japan) under fluoroscopy [24]. After an overnight fast, the patients were prepared by 2 l of electrolyte lavage solution in cases of anal BAE. The route for BAE was determined by the endoscopists on the basis of the patients' characteristics. The patients were prepared by continuous intravenous infusion, and examined by enteroscopy under a light sedation by intravenous midazolam. The scope was advanced as far as possible with reciprocal insertion of the scope and the overtube.

The VCE and BAE findings were classified into circular ulcers, linear ulcers, and small mucosal defects [7]. A severe, concentric stenosis with diaphragm was regarded as circular ulcers. Small mucosal defects included red spots and small ulcers.

Double-Contrast Barium Enteroclysis

Small bowel radiography was performed with a double-contrast technique as has previously described [25]. In brief, patients were prepared by an insertion of a naso-jejunal tube under fluoroscopy. The tube was fixed at the ligament of Treitz by a pneumodilatation of the balloon at the tip of the tube. Then, 200–300 ml of 70% v/w barium sulphate was slowly injected through the tube until the terminal ileum was filled with the contrast material. The small intestine was then inflated with 800–1,000 ml of air injected through the tube. When a sufficient inflation was achieved, 40 mg of scopolamine butyl bromide was injected intravenously to inhibit peristalsis and to obtain double-contrast images.

Assessment

We first compared clinical features between patients with and without each endoscopic finding. Radiographic images were then reviewed by two enteroscopists (T.M. and M.E.) with a reference to each enteroscopic finding. The depiction rate of each enteroscopic finding was calculated.

Statistical Analyses

When comparing two groups, Mann–Whitney test, chi-squared test or Fisher's exact probability test were used

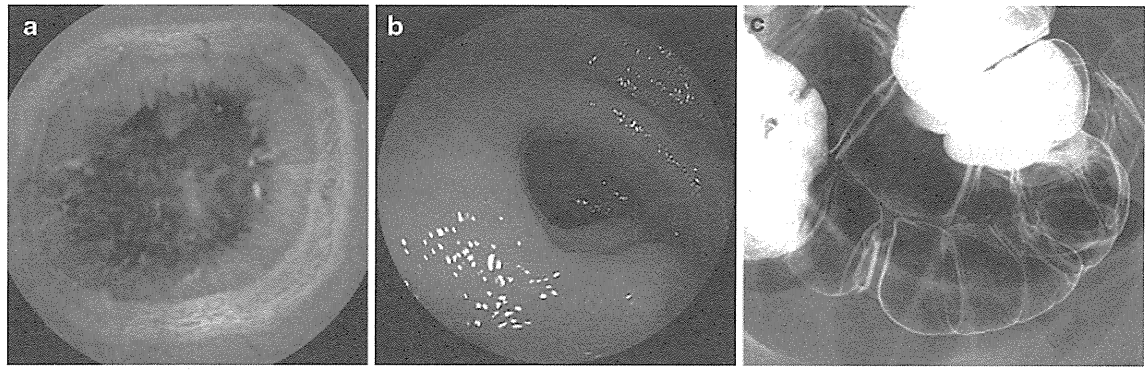

Fig. 1 Enteroscopic and radiographic findings of a case of circular ulcers in the ileum. A 78-year-old female who had been diagnosed as rheumatoid arthritis and had been under celecoxib was examined because of anemia. Under VCE (**a**) and oral BAE (**b**), multiple circular ulcers were found. Double-contrast barium enteroclysis depicted the ulcers as concentric and multiple stenoses in the ileum (**c**). The findings are compatible with "pseudo-folds"

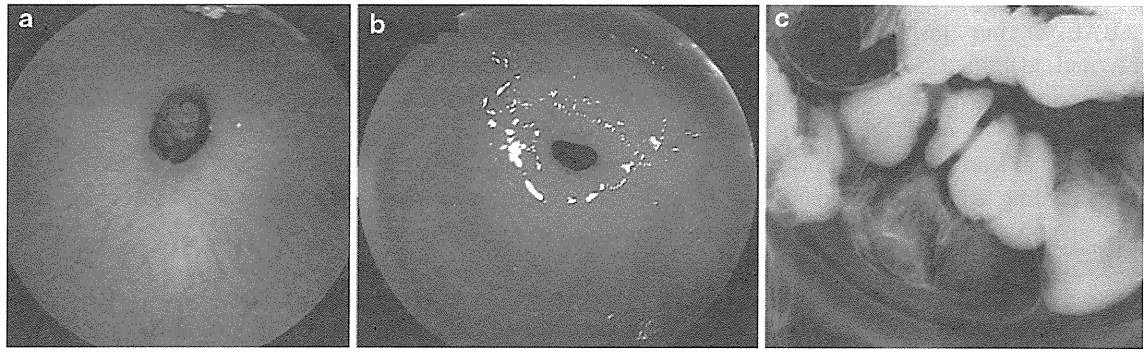

Fig. 2 Enteroscopic and radiographic findings of a case of diaphragms in the ileum. A 72-year-old female had been taking diclofenac for rheumatoid arthritis for 24 months, during which repeated abdominal pain occurred. VCE (**a**) and anal BAE (**b**) detected concentric stenosis in the ileum. Double-contrast barium enteroclysis showed concentric stenosis in the lower part of the ileum (**c**). The findings are compatible with condensed "pseudo-folds." This case experienced capsule retention

where appropriate. Probabilities less than 0.05 were considered to be significant.

Results

Enteroscopic Findings

The subjects were examined by 13 anal BAEs, 8 oral BAEs, and 10 VCEs. Eleven subjects were examined by BAE alone, and 3 patients by VCE alone. The remaining 7 subjects were examined by both BAE and VCE.

Circular ulcers (Fig. 1a, b), linear ulcers and small mucosal defects were found in 12, 3 and 12 patients, respectively. The predominant site of involvement within the small bowel was the jejunum in 3 subjects, the ileum in 6 and both the jejunum and the ileum in 8. Three subjects had both circular ulcer and small mucosal defects. The other 3 subjects had both linear ulcer and small mucosal defects, while 6 subjects had small mucosal defects alone. Six of 12 subjects with circular ulcers had diaphragms (Fig. 2a, b). Among 10 subjects examined by VCE, 2 experienced capsule retention, which was treated by endoscopic balloon dilatation under BAE.

Table 1 compares clinical features between patients with circular ulcers and those without. While neither gender, age at the time of diagnosis of NSAID enteropathy, predominant site of involvement nor duration of NSAID use was different between the two groups, overt OGIB was less frequent in patients with circular ulcers than those without the ulcers (11 vs. 42%, $P = 0.037$). There was also a trend towards less frequent cardiovascular disease in patients with circular ulcer as the indication of NSAID use. Four of 12 patients with circular ulcers had been taking two NSAID species while patients without circular ulcer had been taking a single species of NSAID (33 vs. 0%, $P = 0.08$). Laboratory data including serum protein, hemoglobin and C-reactive protein values were not different between the two groups.

Table 1 Comparison of clinical features between patients with and without circular ulcers

Clinical features	Patients with circular ulcers ($n = 12$)	Patients without circular ulcers ($n = 9$)	Probability
Sex (female/male)	4/8	3/6	1.0
Age (range, median) (years)	46–88, 68.5	47–87, 80	0.26
Indication of NSAID use			
Arthropathy/CVD	12/0	6/3	0.06
Indication for enteroscopy			
Overt OGIB/others	5/7	8/1	0.037
Predominant site			0.81
Jejunum	2	1	
Jejunum and ileum	5	3	
Ileum	5	5	
Laboratory data (range, median)			
Hemoglobin (g/dl)	4.9–13.7, 8.5	5.6–13.5, 8.8	0.36
Serum protein (g/dl)	3.9–7.8, 9.2	4.3–7.9, 8.8	0.52
C-reactive protein (mg/dl)	0.01–11.6, 0.12	0.10–3.88, 0.73	0.10
Use of two NSAIDs species	4	0	0.08
Duration of NSAID use (range, median) (months)	0.2–240, 30	1–192, 12	0.55
NSAID species			
Loxioprofen	4	3	
Diclofenac	4	2	
Aspirin	1	3	
Indomethacin	2	0	
Others	5	1	

OGIB Obscure gastrointestinal bleeding, *CVD* cardiovascular diseases

Table 2 indicates a comparison between subjects with small mucosal defects and those without. As summarized in the table, subjects with small mucosal defects were taking multiple NSAID less frequently than those without (0 vs. 44%, $P = 0.02$). In addition, hemoglobin value was higher in subjects with small mucosal defect than in those without. There was also a trend towards higher serum protein value in the former than in the latter.

Radiography

Review of the radiographic images in 12 subjects with circular ulcers revealed that concentric narrowing with extremely short width was depicted in 10 patients (Figs. 1c and 2c). The narrowing apparently mimicked normal-appearing folds of the jejunum. Such "pseudo-folds" was found in multiplicity. However, the longitudinal alignment of the pseudo-folds was irregular, and the distance inbetween the folds was not uniform. The proximal part of the bowel was not dilated in any subject with circular ulcers. In 2 of 3 subjects with linear ulcers, radiography revealed eccentric rigid area with converging folds.

Radiography failed to depict any significant findings in 10 of 12 subjects with small mucosal defects. In 2 subjects, compression images showed tiny barium flecks in the lower part of the ileum. The depiction rate of NSAID enteropathy was thus 83% for circular ulcers, 67% for linear ulcers and 17% for small mucosal defects.

Among 10 patients examined by VCE, 2 of 5 subjects with pseudo-folds experienced capsule retention. The capsule was not retained in the other 5 subjects without the radiographic signs.

Discussion

Our retrospective investigation revealed that DCBE could depict circular ulcers in NSAID enteropathy, while it failed to depict small mucosal defects. We could also show that patients with circular ulcers complained of overt OGIB less frequently than those without, and they tended to have been under two species of NSAID. These observations suggest that radiography together with clinical manifestations may be a tool for patency in patients suspected of having NSAID enteropathy.

In the 1980s and 1990s, diaphragms of the small bowel drew much attention as the characteristic lesion of NSAID enteropathy. The diaphragms were histologically characterized by

Table 2 Comparison of clinical features between patients with and without small mucosal defects

Clinical features	Patients with mucosal defects ($n = 12$)	Patients without mucosal defects ($n = 9$)	Probability
Sex (female/male)	5/7	2/7	0.11
Age (range, median) (years)	47–87, 75	46–88, 67	0.30
Indication of NSAID use			
Arthropathy/CVD	9/3	9/0	0.23
Indication for enteroscopy			
Overt OGIB/others	9/3	4/5	0.17
Predominant site			0.48
Jejunum	1	2	
Jejunum and ileum	4	4	
Ileum	7	3	
Laboratory data (range, median)			
Hemoglobin (g/dl)	5.6–13.7, 9.7	4.9–10.1, 8.8	0.036
Serum protein (g/dl)	4.3–7.9, 6.2	3.9–7.2, 5.4	0.051
C-reactive protein (mg/dl)	0.01–3.9, 0.72	0.01–11.6, 0.06	0.12
Use of two NSAID species	0	4	0.02
Duration of NSAID use (range, median) (months)	1–240, 18	0.2–240, 24	0.97
NSAID species			
Loxioprofen	3	4	
Diclofenac	3	3	
Aspirin	3	1	
Indomethacin	0	2	
Others	3	3	

OGIB Obscure gastrointestinal bleeding, *CVD* cardiovascular diseases

marked fibrosis with shallow ulcers at the tip of the Kerckring's folds [10, 11]. While 6 of our 21 subjects actually had diaphragms, we also found circular ulcers in those 6 patients as well as in another 6 patients without apparent diaphragms. It is thus suggested that circular ulcers are the most typical and representative mucosal lesions in NSAID enteropathy. However, it is a fact that there have been cases of diaphragms, which were missed by small bowel radiography and diagnosed by enteroscopy [26–28]. In those reports, small bowel radiography probably failed to depict extremely thin narrowing without dilatation of the proximal bowel.

In the literature, the radiographic features of NSAID-induced diaphragms have been discussed in symptomatic patients who were examined by barium follow-through study [19, 21, 22]. Zalev et al. [22] analyzed four symptomatic cases of diaphragms and found that lifesaver-like stricture and babel-like configuration were depited by small bowel radiography. Although those descriptions were heterogeneous with regards to the width of the narrow septae, they are in concert with respect to concentric and multiple stenoses [19–22]. Our results indicated that the circular ulcers, as well as diaphragms, were depicted as apparently normal folds when the affected small bowel was insufflated with an appropriate amount of air under DCBE. It thus seems likely that the radiologic finding referred to as "pseudo-folds" sign may be applicable and specific to the diagnosis of NSAID enteropathy.

It has been reported that VCE detected small mucosal defects even in healthy subjects after short-term NSAID use [29–31]. However, DCBE failed to depict most of small mucosal defects in our subjects with NSAID enteropathy. With this regard, VCE or BAE is the procedure of choice for the diagnosis of the disease. Even though VCE has advantages as to safety and convenience, it has also been shown that NSAID enteropathy is one of the major conditions associated with capsule retention [14, 15]. A conspicuously high incidence of capsule retention in NSAID enteropathy seems to be a consequence of undiagnosed diaphragms. Small bowel radiography thus seems to have a role as a patency tool for VCE in patients suspected of having NSAID enteropathy. In fact, capsule retention did occur in 2 of our 5 patients with pseudo-folds sign, while none of the subjects without the sign experienced the adverse event.

Despite a worldwide, huge population exposed to NSAID, cases of diaphragm are encountered infrequently. In addition, clinical features predisposed to diaphragms are poorly understood except for long-term NSAID use [10–13, 19–22, 26–28]. Although the difference did not

reach statistical significance, our analyses of the subjects' demographics revealed that the simultaneous use of two NSAID species was associated with the occurrence of circular ulcers. In addition, subjects with circular ulcers experienced overt OGIB less frequently than those without. Conversely, subjects with small mucosal defects had less severe anemia and hypoproteinemia, and they had been taking only a single NSAID. These observations strongly suggest that circular ulcers are the consequence of chronic and repeated exposure to NSAID. Accordingly, the history of NSAID intake and clinical manifestations seem to be predictive of circular ulcers, and presumably, of diaphragms.

Recently, patency capsule system for patients at a high risk of capsule retention has become available [16–18]. Although the system has been shown to be a sensitive procedure [16–18], it requires at least 30 h for the final decision. There are also difficulties in determining the localization of the patency capsule under radiographs or by the scanners [17]. Even though Postgate et al. [17] reported that small bowel radiography was normal or minimally abnormal in patients in whom the patency capsule was retained, they did not include any case of NSAID enteropathy. It thus seems possible that DCBE with a special reference to pseudo-folds sign may be a convenient tool for the determination of luminal patency in patients taking NSAID.

Maglinte et al. [32] proposed double-contrast enteroclysis to be equal or superior to VCE for the evaluation of mucosal details such as aphthous lesions and scarred ulcers in Crohn's disease. Our results showed that this was not the case for NSAID enteropathy, probably due to the difference in the number and the depth of diminutive lesions between Crohn's disease and NSAID enteropathy. In addition, CT- and MR-enterographies have become alternative to and more informative than small bowel radiography for the evaluation of transmural or stenotic lesions in Crohn's disease [33–37]. Since CT- and MR-enterographies are also able to depict mucosal alterations, these procedures may be other candidates as a patency tool for NSAID enteropathy.

In conclusion, an analysis of clinical and radiographic features of 21 patients with NSAID enteropathy revealed DCBE to be applicable as a patency tool prior to VCE for subjects suspected of having the disease. On that occasion, the pseudo-folds sign may be suggestive of circular ulcers and the diaphragms. Given such circumstances, BAE with a preparation of endoscopic balloon dilatation would be practically preferred to VCE [9, 38]. The value of small bowel radiography in comparison with patency capsule should be examined in the area of widespread use of NSAID including aspirin.

References

1. Allison MC, Howatson AG, Torrance CJ, Lee FD, Russell RI. Gastrointestinal damage associated with the use of nonsteroidal antiinflammatory drugs. *N Engl J Med.* 1992;327:749–754.
2. Laine L, Smith R, Min K, Chen C, Dubois RW. Systematic review. The lower gastrointestinal adverse effects of non-steroidal anti-inflammatory drugs. *Aliment Pharmacol Ther.* 2006;24:751–767.
3. Graham DY, Opium AR, Willingham FF, Qureshi WA. Visible small-intestinal mucosal injury in chronic NSAID users. *Clin Gastroenterol Hepatol.* 2005;3:55–59.
4. Maiden L, Thjodleifsson B, Seigal A, et al. Long-term effects of nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 selective agents on the small bowel: a crosssectional capsule enteroscopy study. *Clin Gastroenterol Hepatol.* 2007;5:1040–1045.
5. Matsumoto T, Kudo T, Esaki M, et al. Prevalence of nonsteroidal anti-inflammatory drug-induced enteropathy determined by double-balloon endoscopy. A Japanese multicenter study. *Scand J Gastroenterol.* 2008;43:490–496.
6. Sidhu R, Brunt LK, Morley SR, Sanders DS, McAlindon ME. Undisclosed use of nonsteroidal anti-inflammatory drugs may underlie small-bowel injury observed by capsule endoscopy. *Clin Gastroenterol Hepatol.* 2010;8:992–995.
7. Matsumoto T, Nakamura S, Esaki M, et al. Enteroscopic features of chronic nonspecific multiple ulcers of the small intestine. Comparison with nonsteroidal anti-inflammatory drug-induced enteropathy. *Dig Dis Sci.* 2006;51:1357–1363.
8. Hayashi Y, Yamamoto H, Kita H, et al. Non-steroidal anti-inflammatory drug-induced small bowel injuries identified by double-balloon endoscopy. *World J Gastroenterol.* 2005;21:4861–4864.
9. Hayashi Y, Yamamoto H, Taguchi H, et al. Nonsteroidal anti-inflammatory drug-induced small-bowel lesions identified by double-balloon endoscopy. Endoscopic features of the lesions and endoscopic treatments for diaphragm disease. *J Gastroenterol.* 2009;44:57–63.
10. Lang J, Price AB, Levi AJ, Burke M, Gumpel JM, Bjarnason I. Diaphragm disease. Pathology of disease of the small intestine induced by nonsteroidal anti-inflammatory drugs. *J Clin Pathol.* 1988;41:516–526.
11. Bjarnason I, Hayllar J, MacPherson AJ, Russell AS. Side effects of nonsteroidal anti-inflammatory drugs on the small and large intestine. *Gastroenterology.* 1993;104:1832–1847.
12. Yousfi MM, de Petris G, Leighton JA, et al. Diaphragm disease after use of nonsteroidal anti-inflammatory agents. First report of diagnosis with capsule endoscopy. *J Clin Gastroenterol.* 2004;38:686–691.
13. Manetas M, O'Loughlin C, Kelemen K, Barkin JS. Multiple small-bowel diaphragms. A cause of obscure GI bleeding diagnosed by capsule endoscopy. *Gastrointest Endosc.* 2004;60:848–851.
14. Li F, Gurudu SR, De Petris G, et al. Retention of the capsule endoscope. A single-center experience of 1000 capsule endoscopy procedures. *Gastrointest Endosc.* 2008;68:174–180.
15. Liao Z, Gao R, Xu C, Li ZS. Indications and detection, completion, and retention rates of small-bowel capsule endoscopy. A systematic review. *Gastrointest Endosc.* 2010;71:280–286.
16. Spada C, Shah SK, Riccioni ME, et al. Video capsule endoscopy in patients with known and suspected small bowel stricture previously tested with the dissolving patency capsule. *J Clin Gastroenterol.* 2007;41:576–582.
17. Postgate AJ, Burling D, Gupta A, Fitzpatrick A, Fraser C. Safety, reliability, and limitations of the given patency capsule in patients at risk of capsule retention. A 3-year technical review. *Dig Dis Sci.* 2008;53:2732–2738.

18. Herrerias JM, Leighton JA, Costamagna G, et al. Agile patency system eliminates risk of capsule retention in patients with known intestinal strictures who undergo capsule endoscopy. *Gastrointest Endosc*. 2008;67:902–909.
19. Levi S, de Lacey G, Price AB, Gumpel MJ, Levi AJ, Bjarnason I. "Diaphragm-like" strictures of the small bowel in patients treated with non-steroidal anti-inflammatory drugs. *Br J Radiol*. 1990; 63:186–189.
20. Matsuhashi N, Yamada A, Hiraishi A, et al. Multiple strictures of the small intestine after long-term nonsteroidal anti-inflammatory drug therapy. *Am J Gastroenterol*. 1992;87:1183–1186.
21. Scholz FJ, Heiss FW, Roberts PL, Thomas C. Diaphragm-like strictures of the small bowel associated with use of nonsteroidal anti-inflammatory drugs. *Am J Roentgenol*. 1994;162:49–50.
22. Zalev AH, Gardiner GW, Warren RE. NSAID injury to the small intestine. *Abdom Imaging*. 1998;23:40–44.
23. Esaki M, Matsumoto T, Kudo T, Yanaru-Fujisawa R, Nakamura S, Iida M. Bowel preparations for capsule endoscopy. A comparison between simethicone and magnesium citrate. *Gastrointest Endosc*. 2009;69:94–101.
24. Matsumoto T, Moriyama T, Esaki M, Nakamura S, Iida M. Performance of antegrade double-balloon enteroscopy. Comparison with push-enteroscopy. *Gastrointest Endosc*. 2005;62:392–398.
25. Matsumoto T, Esaki M, Yada S, Jo Y, Moriyama T, Iida M. Is small-bowel radiography necessary before double-balloon endoscopy? *Am J Roentgenol*. 2008;191:175–181.
26. Shumaker DA, Bladen K, Katon RM. NSAID-induced small bowel diaphragms and strictures diagnosed with intraoperative enteroscopy. *Can J Gastroenterol*. 2001;15:619–623.
27. Achanta KK, Petros JG, Cave DR, Zinny M. Use of intraoperateive enteroscopy to diagnose nonsteroidal anti-inflammatory drug injury to the small intestine. *Gastrointest Endosc*. 1999;49: 544–546.
28. Nosho K, Endo T, Yoda Y, et al. Diaphragm disease of small intestine diagnosed by double-balloon enteroscopy. *Gastrointest Endosc*. 2005;62:187–189.
29. 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.
30. Goldstein JL, Eisen GM, Lewis B, et al. Video capsule endoscopy to prospectively assess small bowel injury with celecoxib, naproxen plus omeprazole, and placebo. *Clin Gastroenterol Hepatol*. 2005;3:133–141.
31. Goldstein JL, Eisen GM, Lewis B, Gralnek IM, Zlotnick S, Fort JG. 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.
32. Maglinte DDT, Sandrasegaran K, Chiorean M, Dewitt J, Lappas JC. Radiographic investigations complement and add diagnostic information to capsule endoscopy of small bowel diseases. *Am J Roentgenol*. 2007;189:306–312.
33. Vogel J, Moreira AL, Baker M, et al. CT enterography for Crohn's disease. Accurate preoperative diagnostic imaging. *Dis Colon Rectum*. 2007;50:1761–1769.
34. Wiarda BM, Kuipers EJ, Heitbrink MA, van Oijen J. MR enteroclysis of inflammatory small-bowel diseases. *AJR*. 2006;187: 522–531.
35. Paulsen SR, Huprich JE, Fletcher JG, et al. CT enterography as a diagnostic tool in evaluating small bowel disorders. Review of clinical experience with over 700 cases. *Radiographics*. 2006;26: 641–657.
36. Liu YB, Liang CH, Zhang ZL, et al. Crohn's disease of the small bowel. Multidetector row CT with CT enteroclysis, dynamic contrast enhancement, CT angiography, and 3D imaging. *Abdom Imaging*. 2006;31:668–674.
37. Masselli G, Casciani E, Polettini E, Lanciotti S, Bertini L, Gualdi G. Assessment of Crohn's disease in the small bowel. Prospective comparison of magnetic resonance enteroclysis with conventional enteroclysis. *Eur Radiol*. 2006;16:2817–2827.
38. Kamata Y, Iwamoto M, Nara H, et al. A case of rheumatoid arthritis with protein losing enteropathy induced by multiple diaphragmatic strictures of the small intestine. Successful treatment by bougieing under double-balloon enteroscopy. *Gut*. 2006; 55:1372.

Original Paper

Incidence of Small Intestinal Lesions in Patients with Iron Deficiency Anemia

Atsuo Yamada, Hirotsugu Watabe, Yutaka Yamaji, Haruhiko Yoshida, Masao Omata and Kazuhiko Koike
Department of Gastroenterology, Graduate School of Medicine, the University of Tokyo, Hongo, Bunkyo-ku, Tokyo, Japan
Corresponding author: Hirotsugu Watabe, Department of Gastroenterology, Graduate School of Medicine, University of Tokyo, Hongou, Bunkyo-ku, Tokyo, 113-8655, Japan
Tel: +81338155411, Fax: +81338140021, E-mail: hwatabe-gi@umin.net

KEY WORDS: Iron deficiency anemia; Capsule endoscopy; Small intestinal lesion

ABBREVIATIONS: Body Mass Index (BMI); Capsule Endoscopy (CE); Fecal Occult Blood (FOB); Fecal Occult Blood Test (FOBT); Hemoglobin Concentration (Hb); Iron Deficiency Anemia (IDA); Mean Corpuscular Hemoglobin Concentration (MCHC); Mean Corpuscular Volume (MCV); Non-Aspirin Non-Steroidal Anti-Inflammatory Drugs (NANSAIDs); Obscure Gastrointestinal Bleeding (OGIB); Odds Ratio (OR); Serum Ferritin (sFR)

ABSTRACT

Background/Aims: A major etiology of iron deficiency anemia (IDA) is chronic blood loss from the gastrointestinal tract or gynecological organs. The impact of small intestinal lesions on IDA is as yet unclear. The aim of the present study was to estimate the incidence of small intestinal lesions in patients with IDA and elucidate the pathogenic nature of small intestinal mucosal abnormalities for IDA.
Methodology: Between January 2007 and October 2008, a total of 30 IDA patients (hemoglobin (Hb) <13.5g/dL for all men and post-menopausal women, Hb <11.0g/dL for pre-menopausal women) without any bleeding sources detected by upper and lower endoscopy were enrolled. All patients underwent CE. The Given Imaging Ltd. database containing 61 healthy volunteers was used as a control. The prevalence of small intestinal lesions was compared.
Results: The prevalence of significant lesions including angioectasias, tumors and erosions was higher in patients with IDA than controls (47% *vs.* 15%, $p<0.01$). Multivariate analysis showed that IDA was related to significant lesions in the small intestine (OR: 4.7, 95%CI: 1.1–21.3, $p=0.04$).
Conclusions: Subjects with iron deficiency anemia after negative work-up on the bleeding source by conventional upper and lower endoscopies should undergo capsule endoscopy.

INTRODUCTION

Iron deficiency anemia (IDA) is one of the most common diseases among the general population. The prevalence of IDA in developed countries is estimated to be 2-5% of adult men and post-menopausal women (1-3). A major etiology of IDA is chronic blood loss from the gastrointestinal tract or gynecological organ (3-5). One cross sectional study investigating the gastrointestinal tract by gastroscopy and colonoscopy revealed that the incidence of bleeding sources in the gastrointestinal tract in patients with IDA was approximately 70% (4). In addition, the American Gastroenterological Association (AGA) Institute states that IDA is one of the manifestations of obscure gastrointestinal bleeding (OGIB) (6). AGA Institute also states that patients with occult gastrointestinal blood loss and IDA with negative work-up on gastroscopy and colonoscopy need comprehensive evaluation, including capsule endoscopy (CE) (6). However, the prevalence of small intestinal abnormalities in patients with IDA without fecal occult blood (FOB) is unclear.

CE has revolutionized the diagnostic workup for the small intestine (7-9). CE is the least invasive procedure to investigate the small intestine. Indeed, CE discovered many lesions including angioectasia, ulcer and tumor in the small intestine in patients with OGIB (8-10). In the present study we aimed to estimate the incidence of small intestinal lesions in patients with IDA with or without FOB and elucidate the pathogenic nature of small intestinal mucosal abnormalities for IDA.

METHODOLOGY

This study was conducted as a single-center consecutive series of the patients with IDA. The study was approved by the ethical committee of our institute. Written informed consent was obtained from each study patient.

Diagnostic criteria of IDA

We used two different diagnostic criteria of IDA according to menopausal status. Namely, for all men and post-menopausal women, IDA was diagnosed when all of the following criteria were met: hemoglobin concentration (Hb) <13.5g/dL, serum ferritin (sFR) <65ng/dL, mean corpuscular volume (MCV) <80fl and mean corpuscular hemoglobin concentration (MCHC) <28pg. For pre-menopausal women, IDA was diagnosed as follows; Hb <11.0g/dL, sFR <15ng/dL, MCV <80fl and MCHC <28pg.

Study enrolment

All IDA patients were diagnosed by non-GI doctors. The patients were encouraged to receive both upper and lower endoscopy for evaluation of bleeding sources. In addition, female patients underwent

Hepato-Gastroenterology 2011; 58:1240-1243

gynecological screening to detect bleeding sources in the gynecological organ. Subjects without any bleeding source in the upper and lower gastrointestinal tract and gynecological organ were referred to our small intestinal endoscopy unit. Between January 2007 and October 2008, all patients referred to our unit were candidates for the study. Exclusion criteria were the following: installation of a cardiac pacemaker (n=1), past history of bowel obstruction (n=2), and refusal to provide written informed consent (n=2). Finally, a total of 30 IDA patients were enrolled in the present study.

Capsule endoscopy procedures

Capsule endoscopy was performed using Pillcam® SB (Given Imaging, Yoqneam, Israel). Patients fasted for 12h and took 40mg of simethicone orally before CE to prevent bubble formation in the intestine. No other bowel preparation was undertaken. Patients were allowed to drink 2h after capsule ingestion and to eat 4h after capsule ingestion. At 8h after capsule ingestion, or when the battery would run out, the sensor array and recording device were removed. Two experienced gastroenterologists independently reviewed the CE images at 12-20 frames per second without any information on clinical background. After the independent review, the reviewers discussed all CE findings and reached a consensus.

Fecal occult blood test

All study patients underwent fecal occult blood test (FOBT). FOBT was performed within 4 weeks before or after CE. Fecal occult blood concentration was measured by the immunochemical test using OC-Hemodia® Auto III (Eiken Chemical Co., Tokyo, Japan). FOBT was judged as positive when fecal hemoglobin concentration was 100ng/ml or higher.

The database on healthy volunteers

The Given Imaging Ltd. database contains data on 67 clinical studies that used CE. The database includes 87 healthy volunteers. Among them, 61 healthy volunteers received CE using Pillcam SB®. Their CE findings were used as control data in the case control study.

Statistical analyses

The prevalence of lesions in the small intestine was compared between patients with IDA and control subjects. In the analysis, the following lesions were designated as significant lesions: angioectasia, erosion and tumor. Any other lesions were designated as insignificant lesions. Furthermore, we conducted a case-control study to estimate the risk factors for IDA and significant lesions in the small intestine.

All statistical analyses were performed with SAS version 9.12 for Windows software (SAS Institute Inc., North Carolina, USA). In all analyses, means were compared with unpaired Student's *t*-test and frequency distributions with Fisher's exact probability test or chi-squared test. Parametric data was expressed as mean ± SD. Odds ratio (OR) was calculated with multivariate unconditional logistic regression. A *p*-value <0.05 was considered statistically significant.

TABLE 1 Baseline Characteristics of Patients with Iron Deficiency Anemia and Healthy Volunteers

	IDA† patients	Healthy volunteers	*p*-value
N	30	61	
Age (mean±SD)	60.0±14.3	37.5±13.0	<0.01*
Gender (Male / Female)	16 (53%) / 14(47%)	30 (49%) /31(51%)	0.82**
Body mass index	21.8±3.3	23.9±3.8	<0.01*
Hemoglobin (g/dL)	7.8±2.1	n/a‡	
Ferritin (μg/dL)	8.5±9.0	n/a‡	
FOBT§ (+/-)	10 (33%)	n/a‡	
Duration of IDA† (mean ± SD)	2.4±2.9 years	n/a‡	
Co-morbidities			
Liver cirrhosis	7 (23%)	0 (0%)	
Ischemic heart disease	4 (13%)	0 (0%)	
Renal failure	1 (3%)	0 (0%)	
Medication			
NANSAIDs¶	1 (3%)	0 (0%)	
Aspirin	7 (23%)	0 (0%)	

*Unpaired student's *t*-test
**Chi-square test
†Iron deficiency anemia
‡No available data
§Fecal occult blood test
¶Non-aspirin non-steroidal anti-inflammatory drugs

TABLE 2 The Prevalence of Mucosal Abnormalities in the Small Intestine in Patients with Iron Deficiency Anemia and Healthy Volunteers

Findings	IDA† patients (n=30)	Healthy volunteers (n=61)	*p*-value*
Blood	5 (17%)	0 (0%)	<0.01
Significant lesions‡	14 (47%)	9 (15%)	<0.01
Angioectasia	6 (20%)	5 (8%)	0.10
Erosion	7 (23%)	5 (8%)	0.045
Tumor	2 (7%)	0 (0%)	0.04
Insignificant lesions	28 (93%)	56 (92%)	>0.9
Red spot	20 (67%)	45 (74%)	0.48
Lymphangiectasia	15 (50%)	38 (62%)	0.26
Venous ectasia	3 (10%)	3 (5%)	0.36
Diverticulum	0 (0%)	2 (3%)	>0.9
Red mucosa	19 (63%)	19 (31%)	<0.01
No lesion§	2 (7%)	5 (8%)	>0.9

*Fisher's exact test
†IDA: iron deficient anemia
‡Significant lesions include erosion, angioectasia and tumor
§Subjects without any lesions

TABLE 3 The Prevalence of Small Intestinal Mucosal Findings in Patients with Iron Deficiency Anemia with and without Fecal Occult Blood

Findings	FOBT† (+) (n=10)	FOBT† (-) (n=20)	*p*-value*
Angioectasia	2 (20%)	4 (20%)	>0.9
Erosion	4 (40%)	3 (15%)	0.18
Tumor	2 (20%)	0 (0%)	0.10
Blood	3 (30%)	2(10%)	0.3
Red spot	8 (80%)	12 (60%)	0.42
Lymphangiectasia	6 (60%)	9 (45%)	0.70
Venous ectasia	1(10%)	2 (10%)	>0.9
Diverticulum	0 (0%)	0 (0%)	>0.9
Red mucosa	6 (60%)	13 (65%)	>0.9

*Fisher's exact test
†Fecal occult blood test

RESULTS

Baseline characteristics of the study subjects

Baseline clinical characteristics of the study subjects are summarized in **Table 1**. Of the 30 patients with IDA, the mean hemoglobin level was 7.8±2.1g/dL. The median duration of IDA was 1.1 (0.1-10) years. Ten patients (33%) had positive FOBT at enrolment. Twelve patients (40%) had comorbidities including liver cirrhosis (n=7), ischemic heart disease (n=4), and chronic renal failure (n=1). Seven patients were administered aspirin and 1 patient was administered non-aspirin non-steroidal anti-inflammatory drugs (NANSAIDs).

Compared with control subjects, the mean age was higher in patients with IDA (60.0±14.3 *vs.* 37.5±13.0, $p<0.01$). Body mass index was lower in patients with IDA (21.8±3.3 *vs.* 23.9±3.8, $p<0.01$).

Small intestinal findings detected by capsule endoscopy

Findings in the small intestine detected by CE are summarized in **Table 2**. Of these 30 IDA patients, 14 patients had significant lesions (47%). These findings included erosions in 7 patients (23%), angioectasias in 6 patients (20%), tumors in 2 patients (7%). On the other hand, control subjects had fewer significant lesions (15%, $p<0.01$). The difference between cases and controls was more evident in erosion (23% *vs.* 8%, $p<0.05$) and tumor (7% *vs.* 0%, $p<0.05$), than angioectasia (20% *vs.* 8%, $p=0.1$).

The overall prevalence of insignificant lesions did not differ between patients with IDA and control subjects (93% *vs.* 92%, $p>0.9$). However, red mucosa was more frequently detected in patients with IDA versus control subjects (63% *vs.* 31%, $p<0.01$).

Influence of fecal occult blood on the prevalence of small intestinal lesions in patients with IDA

The prevalence of mucosal lesions in the small intestine in patients with IDA with and without fecal occult blood is summarized in **Table 3**. There was no difference in the prevalence of mucosal lesions in the small intestine between patients with and without fecal occult blood.

Case control analysis for risk factors of IDA and small intestinal lesions

Multivariate analysis showed that age and body mass index (BMI) are related to IDA (**Table 4**). OR for each 10 year increment of age was 3.1 (95% confidence interval: 1.8–5.2, $p<0.001$). OR for 1 increment of BMI was 0.7 (95%CI: 0.6–0.9, $p=0.003$).

Multivariate analysis also showed that female gender and IDA were related to significant lesions in the small intestine (**Table 5**). OR of females was 6.8 (95% CI: 2.0–23.8, $p=0.003$). OR of IDA was 4.7 (95%CI: 1.1–21.3, $p=0.04$).

DISCUSSION

The present study revealed that the prevalence of small intestinal significant lesions including angioectasia, ulcers, and tumors in Japanese patients with IDA was approximately 50%. Our result was comparable to other studies. One European prospective study reported that 57% of IDA patients had small intestinal lesions (11). Muhammad *et al.* retrospectively investigated IDA patients in the United States and reported that the incidence of small intestinal lesions was 50-69% (12). The current data suggests that the incidence of small intestinal lesions in IDA is globally similar. In addition, capsule endoscopy detected 2 patients with small intestinal malignant tumor in the present study, suggesting that patients with IDA and negative upper and lower endoscopies should undergo CE.

We compared the prevalence of significant lesions between IDA patients with and without posi-

TABLE 4 Odds Ratios of Iron Deficiency Anemia According to Clinical Characteristics and Capsule Endoscopy Findings Calculated by Logistic Regression Analysis

Variables	Odds ratio	95%CI†	*p*-value
Age (for each 10 year increment)	3.1	1.8-5.2	<0.001
Female (*vs.* Male)	0.3	0.07-1.3	0.11
Body mass index (kg/m^2)	0.7	0.6-0.9	0.003
Significant lesions‡	3.7	0.7-19.3	0.13

†95% confidence interval
‡Significant lesions include erosion, angioectasia and tumor

TABLE 5 Odds Ratios of Significant Lesions in the Small Intestine Calculated by Logistic Regression Analysis†

Variables	Odds ratio	95% CI‡	*p*-value
Age (for each 10 year increment)	1.5	0.9-2.2	0.12
Female (*vs.* Male)	6.8	2.0-23.8	0.003
Body mass index (kg/m^2)	1.1	0.96-1.3	0.2
Iron deficiency anemia	4.7	1.1-21.3	0.04

†Significant lesions include erosion, angioectasia and tumor
‡95% confidence interval

tive fecal occult blood test. Although study sample size was not large enough to obtain a statistically powerful result, there was no significant association between small intestinal significant lesions and fecal occult blood. Muhammad *et al.* reported that the diagnostic yield of CE in patients with IDA with and without OGIB were 59% and 55%, respectively (12). The present study indicates that even patients with IDA with negative FOBT should receive CE.

The case control analysis showed that age and low BMI were related to IDA. It is reasonable that aging is a risk factor for IDA, because CE revealed tumors and ulcers in the small intestine in the present study. Aging is a well known risk factor for tumors as well as ulcers (12-14). In terms of BMI, the mechanism of the association is unclear. Malnutrition combined with a low iron diet may induce IDA (15). Although it did not reach statistical significance, significant lesions in the small intestine also seemed to be a risk factor for IDA, implying that the significant lesions may potentially be an etiology of IDA.

Furthermore, the present study revealed that patients with IDA had a higher prevalence of significant lesions in the small intestine than healthy control subjects. Odds ratio of IDA for significant lesions in the small intestine was 4.7. This finding also indicates that these small intestinal significant lesions are related to IDA.

In conclusion, subjects with iron deficiency anemia after negative work-up on bleeding sources by conventional upper and lower endoscopies and gynecological examination should undergo further investigation of the small intestine, irrespective of their fecal occult blood status. Capsule endoscopy is able to detect bleeding sources including tumors, ulcers and angioectasias in the small intestine.

ACKNOWLEDGEMENTS

This study was supported by Given Imaging Ltd., Yoqneam, Israel.

REFERENCES

1. **Goddard A, McIntyre A, Scott B:** Guidelines for the management of iron deficiency anaemia. British Society of Gastroenterology. Gut 2000; 46 Suppl 3-4:IV1-IV5.
2. **Sayer J, Long R:** A perspective on iron deficiency anaemia. Gut 1993; 34:1297-9.
3. **McIntyre A, Long R:** Prospective survey of investigations in outpatients referred with iron deficiency anaemia. Gut 1993; 34:1102-7.
4. **Rockey D, Cello J:** Evaluation of the gastrointestinal tract in patients with iron-deficiency anemia. N Engl J Med 1993; 329:1691-5.
5. **Kepczyk T, Kadakia S:** Prospective evaluation of gastrointestinal tract in patients with iron-deficiency anemia. Dig Dis Sci 1995; 40:1283-9.
6. **Raju G, Gerson L, Das A, Lewis B:** American Gastroenterological Association (AGA) Institute medical position statement on obscure gastrointestinal bleeding. Gastroenterology 2007; 133:1694-6.
7. **Triester S, Leighton J, Leontiadis G, et al.:** A meta-analysis of the yield of capsule endoscopy compared to other diagnostic modalities in patients with non-stricturing small bowel Crohn's disease. Am J Gastroenterol 2006; 101:954-64.
8. **Lewis B, Swain P:** Capsule endoscopy in the evaluation of patients with suspected small intestinal bleeding: Results of a pilot study. Gastrointest Endosc 2002; 56:349-53.
9. **Ell C, Remke S, May A, Helou L, Henrich R, Mayer G:** The first prospective controlled trial comparing wireless capsule endoscopy with push enteroscopy in chronic gastrointestinal bleeding. Endoscopy 2002; 34:685-9.
10. **Pennazio M, Santucci R, Rondonotti E, et al.:** Outcome of patients with obscure gastrointestinal bleeding after capsule endoscopy: Report of 100 consecutive cases. Gastroenterology 2004; 126:643-53.
11. **Apostolopoulos P, Liatsos C, Gralnek IM, et al.:** The role of wireless capsule endoscopy in investigating unexplained iron deficiency anemia after negative endoscopic evaluation of the upper and lower gastrointestinal tract. Endoscopy 2006; 38:1127-32.
12. **Muhammad A, Pitchumoni CS:** Evaluation of iron deficiency anemia in older adults: The role of wireless capsule endoscopy. Journal of Clinical Gastroenterology 2009; 43:627-31.
13. **Haselkorn T, Whittemore A, Lilienfeld D:** Incidence of small bowel cancer in the United States and worldwide: geographic, temporal, and racial differences. Cancer Causes Control 2005; 16:781-7.
14. **Neugut A, Jacobson J, Suh S, Mukherjee R, Arber N:** The epidemiology of cancer of the small bowel. Cancer Epidemiol Biomarkers Prev 1998; 7:243-51.
15. **Alleyne M, Horne M, Miller J:** Individualized treatment for iron-deficiency anemia in adults. Am J Med 2008; 121:943-8.

Digestive Endoscopy
Journal for Gastroenterologists and Endoscopic Surgeons

Digestive Endoscopy (2011) **23**, 124–129 doi:10.1111/j.1443-1661.2010.01050.x

ORIGINAL ARTICLE

SURVEILLANCE OF SMALL INTESTINAL ABNORMALITIES IN PATIENTS WITH HEPATOCELLULAR CARCINOMA: A PROSPECTIVE CAPSULE ENDOSCOPY STUDY

Atsuo Yamada,[1] Hirotsugu Watabe,[1] Shuntaro Obi,[2] Takafumi Sugimoto,[1] Shintaro Kondo,[1] Miki Ohta,[1] Goichi Togo,[1] Keiji Ogura,[1] Yutaka Yamaji,[1] Makoto Okamoto,[1] Haruhiko Yoshida,[1] Takao Kawabe,[1] Kazuhiko Koike[1] and Masao Omata[1]

[1]*Department of Gastroenterology, Graduate School of Medicine, the University of Tokyo, and* [2]*Department of Hepatology, Sasaki Institute, Kyoundo Hospital, Tokyo, Japan*

Background: Patients with hepatocellular carcinoma (HCC) sometimes suffer from obscure gastrointestinal bleeding. Portal hypertension (PH), common in cirrhosis, induces esophagogastric varices. Because of the location, PH also may influence mucosal abnormalities in the small intestine. The objective of this study is to estimate the prevalence of small intestinal mucosal abnormalities in HCC patients using capsule endoscopy (CE).

Patients and Methods: We prospectively conducted CE in HCC patients, and analyzed the findings in relation to hepatic function, the number and size of HCC tumor and findings obtained by conventional endoscopy.

Results: Thirty-six patients (aged 66.7 ± 7.5 years, 29 men) underwent CE. Abnormal findings in the small bowel were found in 16 patients (44%), angioectasias in eight patients (22%), erosions in five (14%), varices in four (11%), polyps in four (11%), and submucosal tumor in one (3%). The patients with angioectasia had a larger spleen index than the no abnormal lesions group (85.4 ± 15.8 *vs* 59.0 ± 24.4, $P = 0.02$). The former group had been more frequently treated for esophageal varices endoscopically (62% *vs* 15%, $P = 0.02$). Large HCC nodules seemed more common in the patients with angioectasia than subjects without abnormal lesions (38% *vs* 5%, $P = 0.06$). Small intestinal varices also seemed to have a positive association with large HCC. During the follow up after CE, one patient with small intestinal polyps suffered from obscure gastrointestinal bleeding.

Conclusions: CE revealed that HCC patients frequently have small intestinal mucosal lesions. In particular, small intestinal angioectasia, which may cause obscure gastrointestinal bleeding, seems to be associated with portal hypertension.

Key words: angioectasia, capsule endoscopy, hepatocellular carcinoma, portal hypertension, small intestine.

INTRODUCTION

Hepatocellular carcinoma (HCC) develops in patients with chronic liver diseases, especially liver cirrhosis. HCC patients often die of liver failure, even if their HCC is still small in size.[1] One of the most lethal complications for HCC patients is gastrointestinal bleeding from various gastrointestinal lesions, such as esophagogastric varices, portal hypertensive gastropathy (PHG), and portal hypertensive colopathy (PHC).[2–4] These lesions are induced by portal hypertension. Accompanying HCC may aggravate portal hypertension by arterial–portal venous shunt and portal venous tumor invasion.[5]

The main source of bleeding in patients with liver cirrhosis is esophageal and gastric varices, followed by peptic ulcers.[6] Even after conducting both upper and lower endoscopies, in 18% of patients, no bleeding source was found, which is categorized as obscure gastrointestinal bleeding (OGIB).[6] However, little is known about the cause of OGIB.

The advent of capsule endoscopy (CE) allowed us to investigate the small intestine.[7] CE is a non-invasive procedure and easy to apply to OGIB patients.[8] A recent study showed that the prevalence of small intestinal mucosal abnormalities in patients with portal hypertension who were either anemic or tested positive in a fecal occult blood test was 67.5%.[9] However, because the subjects of that study were selected on the basis of suspected intestinal bleeding, the prevalence of small bowel abnormalities may have been overestimated. The aim of the present study was to estimate the unbiased prevalence of small intestinal mucosal abnormalities in patients with HCC using CE. We also aimed to elucidate the impact of small intestinal mucosal lesions on their clinical outcomes.

METHODS

This study was conducted as a single-center consecutive series of screenings of the small intestine with CE on patients with HCC. The study design was approved by the ethics committee of Sasaki Institute, Kyoundo Hospital.

Correspondence: Atsuo Yamada, Department of Gastroenterology, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. Email: yamada-a@umin.ac.jp

Conflict of interest: This study was supported by Given Imaging K.K. (Tokyo, Japan).

Received 2 March 2010; accepted 10 May 2010.

Patients

Patients with HCC who received treatments at Kyoundo Hospital, on either an inpatient or outpatient basis, during the study period were candidates for entry into the study. HCC was diagnosed by dynamic computed tomography (CT), considering hyperattenuation in the arterial phase with washout in the late phase as the definite sign of HCC. Ultrasound-guided tumor biopsy was performed when necessary. Exclusion criteria for CE were: severe hepatic dysfunction (Child–Pugh class C), overt gastrointestinal bleeding within 1 month prior to the study enrollment, regular use of non-steroidal anti-inflammatory drugs (NSAIDs), portal vein tumor invasion (Vp3 or Vp4), and installation of a cardiac pacemaker or other electromedical devices. Patients had to be older than 20 years of age. Patients who provided written informed consent were consecutively enrolled.

Capsule endoscopy procedures

The CE device Pillcam SB (Given Imaging, Yoqneam, Israel) was used for small intestinal examination. Patients were required to fast for 12 h, and took 40 mg of simethicone orally before CE to prevent gas bubble formation.[10,11] No other bowel preparation was undertaken. Patients were allowed to drink 2 h and to eat 4 h after ingesting the capsule. After 8 h, when the battery would run out, the sensor array and recording device were removed. Two experienced gastroenterologists independently reviewed the CE images without any clinical background information. After the independent review, the reviewers discussed all CE findings and reached a consensus. Concordance of CE findings between the two reviewers was high; kappa index was 0.833. Small intestinal mucosal abnormalities were categorized as follows:[9,12,13] angioectasia, defined as a circumscribed patchy, flat, sharply demarcated area of redness; small intestinal varices, defined as distended, tortuous or saccular veins; erosion, defined as a discrete lesion with central pallor and surrounding hyperemia, and loss of villi; and red spots, defined as a small area of redness. The small bowel visualized on CE during <50% of the small bowel transit time (SBTT) was presumed to be jejunum and >50% of SBTT was designated ileum. In terms of visualization, we classified the images into four groups according to the degree of residues in each quartile point in the small intestine: excellent, good, fair, and poor.[14]

Measurement and evaluation

The data collected on each patient included age, sex, cause of hepatitis, hepatic function, the number and size of HCC tumors, the size of the spleen measured by abdominal CT, and the findings on the upper gastrointestinal endoscopy and colonoscopy. Spleen size was estimated by spleen index, which was calculated as follows: the greatest longitudinal diameter times the greatest transverse diameter. All study patients underwent gastroscopy and all but four patients underwent colonoscopy. Portal hypertensive gastropathy (PHG) was defined as follows: edematous gastric mucosa with mosaic-like surface and red markings.[15,16] Portal hypertensive colopathy (PHC) was defined as follows: edematous colorectal mucosa with spider angiomas and/or inflammatory changes.[17] All examinations, including blood exams, endoscopies and abdominal CT, were performed within one month of CE.

The primary measurement was that of the prevalence of small bowel abnormalities. In order to assess the risk factor of abnormal findings in the small intestine, correlation between small bowel abnormalities and other clinical findings was evaluated. The clinical outcome after CE was also analyzed.

Statistical analyses

All statistical analyses were performed with SAS version 9.12 for Windows (SAS Institute, Cary, NC, USA). Continuous variables were compared with an unpaired *t*-test, or ANOVA with Fisher's protected least significant difference test, where appropriate, and frequency distributions, with Fisher's exact probability test. A P-value < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the study subjects

During the study period, CE was performed on 36 patients with HCC, 29 men and seven women, with a mean age of 66.7 ± 7.5 years. Their demographic characteristics are shown in Table 1. The most common cause of HCC was HCV infection. The majority of patients, 69%, had Child–Pugh Class A liver function. Six patients (17%) had a history of acute gastrointestinal bleeding, which occurred more than 1 month before the study enrollment. All patients underwent upper gastrointestinal endoscopy within 1 month before CE. Seventeen patients (47%) presented esophageal or gastric varices, nine (25%) received band ligation or sclerotherapy for esophageal or gastric varices, and nine (25%) had PHG. Colonoscopy was performed on 26 patients and PHC was diagnosed in four patients (15%).

Among the study patients, the following treatments were performed before enrolment; hepatectomy in six patients (16%), percutaneous tumor ablation in 22 patients (61%), and transcatheter arterial chemoembolization or transcatheter arterial infusion in 25 patients (69%).

By the end of the recording time of 8 h, the capsule had reached the colon in 26 patients (72%) and remained in the small intestine in 10 patients. No capsule retention was experienced.

Small intestinal findings detected by capsule endoscopy

Of these 36 HCC patients, we detected small intestinal findings in 25 patients (69%). Although 25% of the study subjects had poor visualization in the most distal end of the small intestine, bowel preparation was acceptable (excellent or good or fair) up to the upper 75% of the small intestine. There was no difference in the prevalence of small intestinal findings, including tumor, ulcer/erosion, angioectasia, varix, and red mucosa and spot between patients whose CE reached the cecum and those whose did not (17/26 *vs* 8/10, $P = 0.7$). These findings included angioectasia in eight patients (22%), varices in four patients (11%), erosions in five patients (14%), polyps in four patients (11%), a submucosal tumor in one patient (3%), and red mucosa or spots in

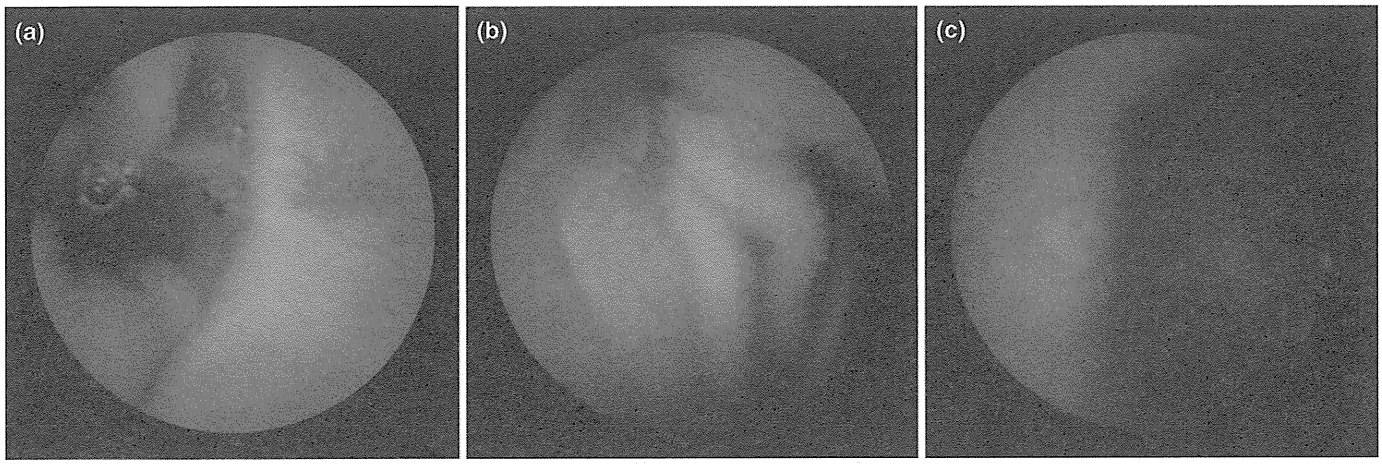

Fig. 1. Typical endoscopic views of the lesions. (a) Angiodysplasia. (b) Varix. (c) Erosion.

Table 1. Demographic characteristics of the study patients

Total number of patients	36
Age, mean (range)	66.7 ± 7.5
Sex	
Male; Female	29 (81%); 7 (19%)
Cause of hepatitis	
HBV; HCV; Alcohol	3 (8%); 29 (81%); 4 (11%)
Laboratory data	
Hemoglobin level, g/dL	12.4 ± 1.7
Platelet count, $\times 10^4/\mu L$	12.1 ± 6.8
Serum albumin level, g/dL	3.6 ± 0.6
Total bilirubin level, mg/dL	1.1 ± 1.2
Upper and lower endoscopic findings	n. (%)
Esophageal or gastric varices	17 (47%)
Prior band ligation/sclerotherapy	9 (25%)
Portal hypertensive gastropathy	9 (25%)
Portal hypertensive colopathy	4 (11%)
Child–Pugh classification	
Class A; Class B	25 (69%); 11 (31%)
Characteristics of hepatocellular carcinoma	
Tumor number >3	19 (53%)
Maximum tumor size >3 cm	7 (19%)
Presence of portal vein tumor thrombosis	6 (16%)
History of hepatectomy	6 (16%)
History of PTA	22 (61%)
History of TACE or TAI	25 (69%)
Current administrative drugs	
Proton pump inhibitor	10 (28%)
H2-Receptor antagonist	7 (19%)
Cytoprotective drugs	10 (28%)

HBV, hepatitis B virus; HCV, hepatitis C virus; PTA, percutaneous tumor ablation; TACE, transcatheter arterial chemoembolization; TAI, transcatheter arterial infusion.

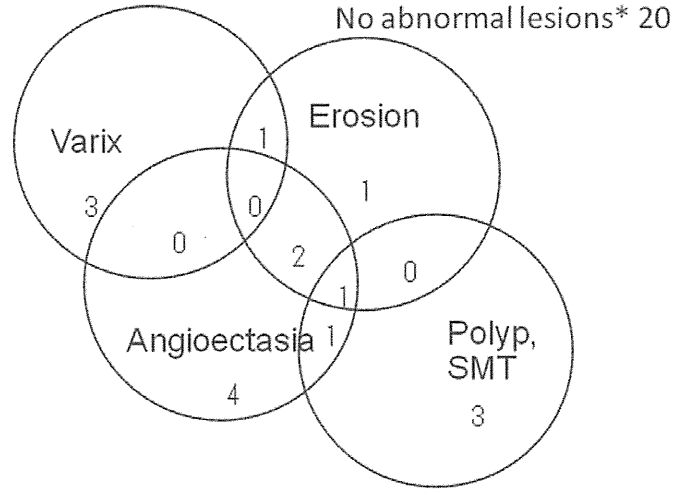

Fig. 2. Small intestinal findings detected by capsule endoscopy. *Nine patients had red spots in the small intestine. SMT, submucosal tumor.

Table 2. Location of mucosal abnormalities in the small intestine in patients with hepatocellular carcinoma

Findings in the small intestine	Number of patients		
	SBTT < 50%	SBTT > 50%	Both
Angioectasia	5	2	1
Varix	2	2	0
Erosion	3	1	1
Polyp	3	1	0
Submucosal tumor	1	0	0

SBTT, small bowel transit time.

20 patients (56%) (Fig. 1). When we regarded red mucosa or spots as insignificant findings, 20 patients were diagnosed with no abnormal lesions. The findings detected with CE are summarized in Fig. 2. Abnormal findings were more likely to be detected in the jejunum (Table 2).

We compared the clinical difference between subjects in the group with small intestinal abnormal findings and the no abnormal lesions group (Table 3). The patients with angioectasia had a larger spleen index than the no abnormal lesions group (85.4 ± 15.8 *vs* 59.0 ± 24.4, $P = 0.02$). The former group had been more frequently treated for esophageal varices endoscopically (62% *vs* 15%, $P = 0.02$). Large

Table 3. Univariate analysis for abnormal findings in the small intestine

	No abnormal lesions (20)	Angioectasia (8)	*P*-value (*vs* normal)	Varix (4)	*P*-value (*vs* normal)	Erosion (5)	*P*-value (*vs* normal)
Age, years	69.1 ± 7.1	60.3 ± 7.4	0.005*	67.3 ± 4.1	0.59*	61.0 ± 11.0	0.11*
Male/Female (Male%)	15/5 (75%)	7/1 (87%)	0.64†	3/1 (75%)	1†	4/1 (80%)	1†
Hemoglobin level, g/dL	12.4 ± 1.8	12.4 ± 1.1	0.78*	12.3 ± 2.5	0.61*	12.0 ± 1.4	0.97*
Platelet count, $\times 10^4/\mu L$	12.6 ± 6.8	9.4 ± 6.2	0.23*	15.7 ± 11.2	0.64*	12.1 ± 5.9	1*
Serum albumin level, g/dL	3.6 ± 0.7	3.3 ± 0.5	0.13*	3.5 ± 0.5	0.51*	3.5 ± 0.5	0.56*
Prothrombin time activity	79.7 ± 17.0	71.3 ± 15.8	0.21*	89.8 ± 9.8	0.19*	83 ± 17.1	0.67*
Total bilirubin level, mg/dL	1.2 ± 1.5	1.3 ± 0.6	0.15*	0.7 ± 0.3	0.67*	1.0 ± 0.5	0.59*
Child–Pugh A/B (Child B %)	14/6 (30%)	4/4 (50%)	0.4†	3/1 (25%)	1†	5/0 (0%)	0.29†
Esophageal or gastric varices	8 (40%)	6 (75%)	0.21†	1 (25%)	1†	2 (40%)	1†
Esophageal varices size >F2	6 (30%)	2 (25%)	1†	1 (25%)	1†	1 (20%)	1†
Prior band ligation/sclerotherapy	3 (15%)	5 (62%)	0.022†	0 (0%)	1†	1 (20%)	1†
Portal hypertensive gastropathy	6 (30%)	3 (38%)	1†	0 (0%)	0.54†	0 (0%)	0.27†
Portal hypertensive colonopathy	1 (5%)	2 (25%)	0.19†	0 (0%)	1†	0 (0%)	1
Portal vein tumor thrombosis	6 (30%)	0 (0%)	0.14†	0 (0%)	0.54†	0 (0%)	0.29†
Tumor number >3	8 (40%)	4 (50%)	0.69†	3 (75%)	0.3†	3 (60%)	0.62†
Maximum tumor size >3 cm	1 (5%)	3 (38%)	0.06†	2 (50%)	0.06†	2 (40%)	0.09†
History of hepatectomy	3 (15%)	0 (0%)	0.53†	1 (25%)	0.54†	0 (0%)	1†
History of PTA	9 (45%)	5 (63%)	0.67†	4 (100%)	0.10†	3 (60%)	0.64†
History of TACE or TAI	11 (55%)	6 (75%)	0.41†	4 (100%)	0.25†	4 (80%)	0.61†
Spleen Index‡	59.0 ± 24.4	85.4 ± 15.8	0.016*	59.1 ± 14.2	0.81*	60.6 ± 27.6	0.89*

*Kruskal–Wallis test.
†Fisher's exact probability test.
‡Calculated as the greatest longitudinal diameter times the greatest transverse diameter.
PTA, percutaneous tumor ablation; TACE, transcatheter arterial chemoembolization; TAI, transcatheter arterial infusion.

HCC nodules were more common in the patients with angioectasia than in subjects without abnormal findings, although this did not reach statistical significance (38% *vs* 5%, $P = 0.06$). Large HCC nodules seemed to be related to not only angioectasia, but also to small intestinal varices (50% *vs* 5%, $P = 0.06$). No significant difference in clinical characteristics was observed between the erosion group and the no abnormal lesions CE group. In terms of effect of therapy on small intestinal findings, no relationship was found between small bowel findings and prior HCC treatment.

Clinical outcome of the study patients

We followed up all the study patients for 14.4 ± 8.8 months. During the follow up, 10 patients had gastrointestinal bleeding. Among them, four patients had variceal bleeding and four patients had gastroduodenal ulcer bleeding. The remaining two bleeding patients were considered to have obscure gastrointestinal bleeding. One OGIB patient bled from the bile duct due to tumor invasion. Another was treated by blood transfusion and finally died of hepatic failure due to tumor progression. Only one variceal rupture patient died of bleeding. No association was found between gastrointestinal bleeding and small intestinal lesions detected with CE.

DISCUSSION

In the current study we prospectively surveyed small intestinal mucosal abnormalities in patients with HCC without overt ongoing gastrointestinal bleeding. The results showed that mucosal abnormalities were common in those patients, found in 16/36 (44%) patients. Angioectasia showed the highest prevalence (22%), followed by erosion (14%) and varices (11%). De Palma and colleagues reported that 25/37 (67.5%) patients with cirrhosis with anemia and/or positive results for stool occult blood testing without HCC had mucosal inflammatory-like abnormalities or vascular lesions, including cherry-red spots, telangiectasia, angiodysplasia, and varices. They also reported that none of the 34 healthy controls had such mucosal abnormalities and the authors proposed a clinical entity, portal hypertensive enteropathy (PHE).[9] As a matter of fact, the prevalence of mucosal abnormalities in the small intestine was lower in the present study than the study by De Palma *et al.* The reason for this discrepancy is the difference in diagnostic criteria of small intestinal mucosal change. We regarded minimal red mucosa and red spots as insignificant findings. If we defined these changes as inflammatory changes, the prevalence of mucosal abnormalities in the small intestine would be 69%, which is concordant with their results. Patient selection also influences the prevalence of mucosal abnormalities. All of our study patients had HCC and about 72% of our study patients did not have anemia. Our study revealed the high prevalence of small intestinal abnormalities not only in cirrhotic patients with anemia, but also in patients with HCC even without anemia.

The present study revealed that patients with angioectasia had a larger spleen index and a more frequent history of band ligation or sclerotherapy for esophageal varices. Although it did not reach a statistically significant difference, patients with angioectasia had a larger size of HCC than those without angioectasia. Akanuma *et al.* reported that large HCC was a risk factor for esophageal variceal rupture, suggesting an increased portal blood pressure.[5] The mechanism of the development of angioectasia in the small intestine is still unclear. However, our findings suggest that angioectasia may be related to portal hypertension.

The association between mucosal change in the digestive tract and liver dysfunction is controversial. In terms of PHE, De Palma *et al.* reported that PHE was more frequently found in Child C patients,[9] whereas other studies found no association between the prevalence of PHE and Child–Pugh liver function classes.[18,19] On the other side, PHG often appeared after band ligation of esophagogastric varices, suggesting the positive association between PHG and portal hypertension.[20–24] Our present data suggest that the strength of association may depend on the type of PHE. The present study shows a positive correlation between angioectasia and portal hypertension, but any variables were not associated with erosion in the small intestine.

The prevalence of small intestinal varices in the current study was 11%, which was similar to the prevalence of 8.1% reported by De Palma *et al.*[9] but substantially smaller than the 25.7% reported by Goulas *et al.*[18] The latter study indicated that the prevalence of small intestinal varices was associated with the degree of esophageal varices and PHG, or the presence of colonic varices. The difference in the prevalence may be due to the fact that the subjects of the current study were limited to patients with relatively conserved liver function, Child–Pugh class A or B.

Our study suggests that the impact of small intestinal lesions on clinical outcomes in patients with HCC seems insignificant. Apart from one hemobilia patient, we found only one OGIB patient. The patient had one small polyp and one red spot in the small intestine, which may have been a bleeding source.

There are several limitations to the present study. First, patients with Child–Pugh class C were excluded from the study. As patients with severe liver dysfunction are not able to undergo surgical removal of the CE in case of capsule retention, we excluded them. The present study showed that even patients with relatively conserved liver function had mucosal abnormalities in the small intestine. Second, we did not conduct any specific bowel preparation. Poor visualization may reduce the diagnostic yield of CE, especially in the furthest quartile of the small bowel. Admittedly, we may have underestimated the prevalence of mucosal abnormalities in the small intestine. Third, our study sample was not enough to obtain conclusive clinical outcomes of small intestinal lesions in patients with HCC. A larger and longer prospective study is needed.

In conclusion, this capsule endoscopy study revealed that HCC patients have a tendency to small intestinal mucosal lesions. In particular, small intestinal angioectasia seems to be associated with portal hypertension, while the risk of bleeding remains to be evaluated in prospective studies.

ACKNOWLEDGMENTS

A part of the present study was presented at the 74th annual meeting of the Japan Gastroenterological Endoscopy Society (October 2007, Kobe).

REFERENCES

1. Kaibori M, Ishizaki M, Saito T, Matsui K, Kwon AH, Kamiyama Y. Risk factors and outcome of early recurrence after resection of small hepatocellular carcinomas. *Am. J. Surg.* 2009; **198**: 39–45.
2. Arendt T, Barten M, Lakner V, Arendt R. Diffuse gastric antral vascular ectasia: Cause of chronic gastrointestinal blood loss. *Endoscopy* 1987; **19**: 218–20.
3. Gostout CJ, Viggiano TR, Balm RK. Acute gastrointestinal bleeding from portal hypertensive gastropathy: Prevalence and clinical features. *Am. J. Gastroenterol.* 1993; **88**: 2030–3.
4. Viggiano TR, Gostout CJ. Portal hypertensive intestinal vasculopathy: A review of the clinical, endoscopic, and histopathologic features. *Am. J. Gastroenterol.* 1992; **87**: 944–54.
5. Akanuma M, Yoshida H, Okamoto M *et al.* Risk factors for esophageal variceal bleeding in patients with hepatocellular carcinoma. *Hepatogastroenterology* 2002; **49**: 1039–44.
6. Christensen E, Fauerholdt L, Schlichting P, Juhl E, Poulsen H, Tygstrup N. Aspects of the natural history of gastrointestinal bleeding in cirrhosis and the effect of prednisone. *Gastroenterology* 1981; **81**: 944–52.
7. Yu M. M2A capsule endoscopy. A breakthrough diagnostic tool for small intestine imaging. *Gastroenterol. Nurs.* 2002; **25**: 24–7.
8. Pennazio M, Santucci R, Rondonotti E *et al.* Outcome of patients with obscure gastrointestinal bleeding after capsule endoscopy: Report of 100 consecutive cases. *Gastroenterology* 2004; **126**: 643–53.
9. De Palma GD, Rega M, Masone S *et al.* Mucosal abnormalities of the small bowel in patients with cirrhosis and portal hypertension: A capsule endoscopy study. *Gastrointest. Endosc.* 2005; **62**: 529–34.
10. Ge ZZ, Chen HY, Gao YJ, Hu YB, Xiao SD. The role of simeticone in small-bowel preparation for capsule endoscopy. *Endoscopy* 2006; **38**: 836–40.
11. Albert J, Gobel CM, Lesske J, Lotterer E, Nietsch H, Fleig WE. Simethicone for small bowel preparation for capsule endoscopy: A systematic, single-blinded, controlled study. *Gastrointest. Endosc.* 2004; **59**: 487–91.
12. Keuchel M, Hagenmèuller F, Fleischer D. *Atlas of Video Capsule Endoscopy*. Heidelberg: Springer Medizin, 2006.
13. Tang SJ, Zanati S, Dubcenco E *et al.* Diagnosis of small-bowel varices by capsule endoscopy. *Gastrointest. Endosc.* 2004; **60**: 129–35.
14. Lapalus MG, Ben Soussan E, Saurin JC *et al.* Capsule endoscopy and bowel preparation with oral sodium phosphate: A prospective randomized controlled trial. *Gastrointest. Endosc.* 2008; **67**: 1091–6.
15. Spina GP, Arcidiacono R, Bosch J *et al.* Gastric endoscopic features in portal hypertension: Final report of a consensus conference, Milan, Italy, September 19, 1992. *J. Hepatol.* 1994; **21**: 461–7.
16. McCormack TT, Sims J, Eyre-Brook I *et al.* Gastric lesions in portal hypertension: Inflammatory gastritis or congestive gastropathy? *Gut* 1985; **26**: 1226–32.
17. Kozarek RA, Botoman VA, Bredfeldt JE, Roach JM, Patterson DJ, Ball TJ. Portal colopathy: Prospective study of colonoscopy in patients with portal hypertension. *Gastroenterology* 1991; **101**: 1192–7.
18. Goulas S, Triantafyllidou K, Karagiannis S *et al.* Capsule endoscopy in the investigation of patients with portal hypertension and anemia. *Can. J. Gastroenterol.* 2008; **22**: 469–74.
19. Repici A, Pennazio M, Ottobrelli A, Barbon V, De Angelis C, DE Lio A. Endoscopic capsule in cirrhotic patients with portal hypertension: Spectrum and prevalence of small bowel lesions. *Endoscopy* 2005; **37**: A72.
20. Misra SP, Misra V, Dwivedi M. Effect of esophageal variceal band ligation on hemorrhoids, anorectal varices, and portal hypertensive colopathy. *Endoscopy* 2002; **34**: 195–8.
21. Gupta R, Saraswat VA, Kumar M, Naik SR, Pandey R. Frequency and factors influencing portal hypertensive gastropathy and duodenopathy in cirrhotic portal hypertension. *J. Gastroenterol. Hepatol.* 1996; **11**: 728–33.
22. Sarin SK, Govil A, Jain AK *et al.* Prospective randomized trial of endoscopic sclerotherapy versus variceal band ligation for esophageal varices: Influence on gastropathy, gastric varices and variceal recurrence. *J. Hepatol.* 1997; **26**: 826–32.
23. Tanoue K, Hashizume M, Wada H, Ohta M, Kitano S, Sugimachi K. Effects of endoscopic injection sclerotherapy on portal hypertensive gastropathy: A prospective study. *Gastrointest. Endosc.* 1992; **38**: 582–5.
24. Zargar SA, Javid G, Khan BA *et al.* Endoscopic ligation vs. sclerotherapy in adults with extrahepatic portal venous obstruction: A prospective randomized study. *Gastrointest. Endosc.* 2005; **61**: 58–66.

ORIGINAL ARTICLE

Single-balloon versus double-balloon endoscopy for achieving total enteroscopy: a randomized, controlled trial

Noriyuki Takano, MD, Atsuo Yamada, MD, Hirotsugu Watabe, MD, Goichi Togo, MD, Yutaka Yamaji, MD, Haruhiko Yoshida, MD, Takao Kawabe, MD, Masao Omata, MD, Kazuhiko Koike, MD

Tokyo, Japan

Background: Balloon endoscopy has been accepted as an effective tool for examining the small intestine. Two types of balloon endoscopy, single and double, are commercially available. The difference in performance between these 2 types of balloon endoscopy has not yet been elucidated.

Objective: To compare the yield of single-balloon endoscopy (SBE) and double-balloon endoscopy (DBE).

Design: Single-center, randomized, controlled trial.

Setting: University hospital in Tokyo, Japan.

Patients: Patients with suspected small-bowel disease.

Interventions: SBE and DBE.

Main Outcome Measurements: Outcomes were the total enteroscopy rate, diagnostic yield, complication rate, and clinical outcomes. Analysis was done by intent to treat.

Results: The study started in April 2008 and was terminated in April 2010 because of an obvious disadvantage for the SBE group. Thirty-eight patients were enrolled in the study; 18 patients were assigned to the SBE group and 20 to the DBE group. The total enteroscopy rate was 0% in the SBE group and 57.1% in the DBE group ($P = .002$). In terms of complications, the DBE group had 1 patient with Mallory-Weiss syndrome, and the SBE group had 1 patient with hyperamylasemia. There was no difference in the overall diagnosis rate between the SBE and DBE groups (61.1% vs 50.0%, $P = .49$). There was no difference in therapeutic outcome between the SBE and DBE groups (27.8% vs 35.0%, $P = .63$).

Limitations: Relatively small number of study patients.

Conclusions: Total enteroscopy is more easily performed with DBE than with SBE. (Gastrointest Endosc 2011; xx:xxx.)

The advent of capsule endoscopy (CE) has allowed us to examine the entire small intestine easily.[1] The number of capsules used for examinations has reached 1,000,000 all over the world.[2] As CE is performed more often, the indications for endoscopic intervention in the small intestine have increased. Another recent advance in small-bowel enteroscopy is double-balloon endoscopy (DBE).[3] DBE allows access to the small intestine for endoscopic interventions. DBE consists of an endoscope and a soft overtube. A latex balloon is attached to the tip of the endoscope and another to the tip of the overtube. Each balloon can be inflated and deflated by a pressure-controlled air pump system. Gripping the intestine by using balloon inflation prevents redundant loop formation and thus facilitates deep insertion of the endoscope. Recently, single-balloon endoscopy (SBE) was introduced.[4]

Abbreviations: BE, balloon endoscopy; CE, capsule endoscopy; DBE, double-balloon endoscopy; SBE, single-balloon endoscopy.

DISCLOSURE: *All authors disclosed no financial relationships relevant to this publication.*

0016-5107/$36.00
doi:10.1016/j.gie.2010.10.047

Received August 4, 2010. Accepted October 21, 2010.

Current affiliations: Department of Gastroenterology and Endoscopy and Endoscopic Surgery, University of Tokyo, Tokyo, Japan.

Reprint requests: Hirotsugu Watabe, MD, Department of Gastroenterology, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan.

SBE is simpler to perform than DBE because it has only 1 balloon at the tip of the overtube. However, the yield of SBE for small-bowel diseases remains unclear.[5] In this study, we aimed to compare the yield of SBE with that of DBE in a randomized, controlled trial.

Take-home Message

- Double-balloon endoscopy makes it easier to achieve total enteroscopy than single-balloon endoscopy. However, diagnostic and therapeutic yields are the same with either double-balloon or single-balloon endoscopy.

METHODS

Study protocol

Patients referred to the authors' institution with suspected small-bowel disease were candidates for study participation. Each study participant had at least 1 of the following conditions: obscure GI bleeding[6]; small-bowel tumor suspected by other diagnostic modalities including CT, magnetic resonance imaging, and CE; or inflammatory bowel disease. The exclusion criteria were undergoing only 1 route (oral or anal) balloon endoscopy (BE), having undergone a previous BE, and age younger than 20 years. One-route BE was planned when CE showed lesions located at the proximal jejunum (within 15 minutes after passing the pylorus) or distal ileum (within 15 minutes before reaching the cecum) or when CT showed lesions obviously located on the proximal side of the ligament of Treitz or distal ileum (up to approximately 20 cm from the ileocecal valve) or afferent loop of Roux-en-Y reconstruction.

The enrolled patients were randomly assigned at a 1:1 ratio to either the DBE or SBE group. Randomization was performed based on a computer-generated list of random numbers. The endoscopists and patients were not blinded to the group assignment.

The study was conducted according to the Declaration of Helsinki and approved by the ethics committee of our institution. The registration number of the study in UMIN-CTR (Japanese clinical trial registration scheme) is UMIN000000954. Written informed consent was obtained from each study participant.

Endoscopic procedure

Each BE was performed by an endoscopist who had performed at least 10 BEs. DBE was performed by using the EN-450T5 (FUJIFILM Medical Co, Ltd, Tokyo, Japan), and SBE was performed by using the SIF-Q260 (Olympus Medical Systems, Tokyo, Japan). We attempted to perform a BE bidirectionally, ie, via both oral and anal approaches. The order of approach was decided according to the site of suspected lesions detected by other diagnostic modalities. In patients with no information on the location of lesions before BE, we used the anal approach first. In cases in which the anal approach was used, patients were administered 2 L of polyethylene glycol solution before the procedure. All procedures were performed with the patients receiving pethidine hydrochloride as a sedative.

We tried to advance the endoscope as deeply as possible. When we met the following conditions, tattooing at the deepest position was performed and the endoscope was withdrawn: detection of a significant lesion, indication for endoscopic intervention, insertion time exceeding 90 minutes, or a request by the patient to stop the procedure. A secondary BE was performed the day after the first BE. However, we canceled the second BE in patients who had undergone an endoscopic intervention including hemostasis, polypectomy, and balloon dilation; those in whom the final diagnosis of a small-bowel disease had been established; those who had experienced procedure complications; and those who refused to undergo a second BE.

Complications

The following conditions were defined as endoscopy-related complications: hyperamylasemia (>3 times the upper limit of normal 24 hours after the procedure), GI tract perforation, hemorrhage requiring blood transfusion, pancreatitis (abdominal pain with hyperamylasemia requiring at least 2 days of unplanned hospitalization after the procedure [American Society for Gastrointestinal Endoscopy guidelines[7]]), and status that required hospitalization more than 2 days after the BE. To collect information on complications, each patient was followed for 2 weeks after the procedure.

Study endpoints

The primary outcome measurement of the current study was the success rate for total small-bowel observation, which was calculated for patients who underwent bidirectional BE. The secondary outcome measurements were as follows: complications during and after BE, endoscopic findings, and clinical outcomes. Those patients who underwent only 1 endoscopy because of characteristics of detected lesions were included only in the analysis of the secondary outcome measurements.

Statistical analysis

We calculated the number of patients needed to detect an effect size of 0.6, which corresponds to absolute difference of 30% in success rates assuming the average success rate of 50%, with a 2-sided type I error of 0.05 and a power of 90%. We planned 2 interim analyses: one for safety and general feasibility when approximately 20% of patients had been examined and the other for the probability of detecting a significant difference at the end of the study when approximately 50% of patients had been examined. According to the method of Pocock, sample size per group was calculated to be 14, 49, and 118 at first and second interim analyses and final analysis, respectively. To ensure that the overall type I error did not exceed 0.05, a significance level of .0101 was required in each analysis.