Chromoendoscopy with Indigo Carmine in Flexible Sigmoidoscopy Screening: Does it Improve the Detection of Adenomas in the Distal Colon and Rectum?

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Abstract

Background and aims. The aim of our study was to determine whether chromoendoscopy with indigo carmine significantly improves the detection of adenomas in the distal colon and rectum and therefore could become routine in flexible sigmoidoscopy screening. **Methods.** Between 2001- 2003, two sigmoidoscopies, the first conventional, the second with chromoendoscopy, were performed in a "back-to-back" design by two experienced endoscopists in a series of 55 patients. All lesions were classified with regard to position and size before and after staining, then endoscopically removed and referred to two experienced pathologists. **Results.** 55 patients, mean age 60 ± 9.8 (42-79) years, 34 (61.8%) men and 21 (38.2%) women were enrolled. After staining, 47 patients had 373 visible lesions, 306 (82%) < 3mm, 47 (12.6%) 3- 5 mm and 20 (5.4%) > 5 mm. Histologically, 215 (57.7%) were hyperplastic polyps, 27 (7.2%) adenomas and 131 (35.1%) other lesions. With chromoendoscopy, in 17 of the 47 patients (36.2%) 27 adenomas (15 ≤ 5 mm and 12 > 5 mm) were detected. Chromoendoscopy significantly improved the detection of adenomas ≤ 5 mm ($p<0.01$). Regarding the detection of adenomas larger than 5 mm, there was no significant difference between conventional sigmoidoscopy and chromoendoscopy. The chi-square test was performed for comparisons between the number of lesions detected by standard sigmoidoscopy and chromoendoscopy. **Conclusions.** Chromoendoscopy with indigo carmine allows the detection of significantly more adenomas ≤ 5 mm in the distal colon and rectum. Thus, flexible sigmoidoscopy with routine chromoendoscopy could become an option in colorectal cancer screening when colonoscopy is unavailable or not accepted by the patient.

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Key words

Chromoendoscopy- indigo carmine- flexible sigmoidoscopy screening- colorectal adenomas

Introduction

The most recent German and American guidelines recommend colonoscopy evaluation starting at the age of 50 years and repeated every 10 years if normal until the 75th year of life, as a standard procedure in colorectal cancer screening (1,2).

There is evidence that the acceptance and willingness of the broad symptom free population for screening colonoscopy (SC) is still very low. Only 40 % of all women and 18-20% of all men respond at present to the offer of regular screening for colorectal cancer (CRC) (3). Trying to find explanations, one study showed that the four most reported deterrents to SC were "volume of bowel preparation," "adequate analgesia," "no recommendation from primary physician," and "embarrassment" (4). Consequently, it is easily conceivable, despite the lack of any data for comparison, that patients would rather accept a less complicated screening method.

Examining the last 50 cm of the large intestine, flexible sigmoidoscopy, recommended every 5 years (1,2), has two main advantages: the bowel preparation consists of only two enemas and there is no need for sedation. It leads to a risk reduction for colorectal cancer of 60% in the following 10 years and of 44% for colon cancer only in the following 6 years (5-7). Furthermore, a prospective Norwegian study showed that sigmoidoscopy followed by colonoscopy in patients found to have adenomas decreased CRC incidence (8). However, the impossibility to examine the proximal colon is still an extensively discussed theme.

Indigo carmine is a contrast stain mainly used during magnifying colonoscopy for the "pit- pattern"- analysis, allowing the differentiation between neoplastic and non-neoplastic polyps on the basis of the Kudo criteria (9). It also may be helpful in the detection of small neoplastic lesions which are not visible by standard endoscopy (10).

The aim of the present study was to evaluate if indigo carmine significantly improves the detection of adenomas in the distal colon and rectum and, consequently, whether chromoendoscopy could become routine procedure in flexible sigmoidoscopy screening.

Patients and methods

Experimental design

Between 2001-2003, 55 patients were enrolled in the study at the Department of Internal Medicine Regensburg, Germany, after informed consent had been obtained. Exclusion criteria were: absence of a written consent, pregnancy, coagulation disorders with high risk for gastrointestinal bleeding, already diagnosed colorectal inflammatory diseases, adenomas or carcinoma. Bowel preparation consisted of two enemas administered two hours before the examination. No sedatives or antispasmodics were required. High-resolution CF-Q160AL colonoscopes (Olympus Optical Co. Hamburg) were used during the study. Each patient received consecutively two sigmoidoscopies by two different, very experienced endoscopists, in a "back-to back" design. During the first examination in a standard view, all detected protruding lesions were classified with regard to size (category I: < 3 mm; category II: 3- 5 mm; category III: > 5 mm) and position (cm from anal verge). The second sigmoidoscopy was performed by an examiner blinded for the results of the first one.

15- 20 ml of 0.27% indigo carmine solution was applied on the entire examined colorectal mucosa using a special polyethylene spray catheter (PW-205 L; Olympus Optical Co. Hamburg), which allowed a circular and intense staining distribution. Thereby, all protruding mucosal changes were classified again using the same criteria and then were endoscopically removed. Two experienced pathologists independently classified the findings as adenomas, hyperplastic polyps or other lesions (inflammatory or non-specific changes). Dysplasia in adenomas was divided into low and high grade according to the Vienna classification (11).

Statistics

The chi-square test was performed for comparisons between the number of lesions detected by standard sigmoidoscopy and chromoendoscopy. Differences with a p value < 0.05 were considered to be statistically significant.

Results

Fifty-five patients, mean age age 60 ± 9.8 (42-79) years, 34 men and 21 women underwent sigmoidoscopy in the standard view and consecutively chromoendoscopy. Eight patients had a mucosa of normal appearance even after staining.

There were 382 protruding lesions found in 47 patients at both standard sigmoidoscopy and chromoendoscopy. One lesion from the category 3-5 mm turned out to be a carcinoid tumour and was visible already in the conventional view.

Before the dye application, 104 lesions were found in 30 patients, while 25 had a mucosa of normal appearance. Histology showed adenomas in 16 (15%) lesions, hyperplastic polyps in 66 (64 %) and inflammatory/non-specific changes in 22 (21%) ones.

After indigo carmine spraying, 373 protruding lesions were found in 47 patients, 27 (7%) adenomas, 215 (58%) hyperplastic polyps and 131 (35%) inflammatory/non-specific changes.

In the 25 cases with mucosa of normal appearance prior to staining, chromoendoscopy revealed lesions in 17 patients, mostly hyperplastic polyps and only 6 adenomas, of which 4 were ≤ 5 mm.

Indigo carmine significantly improved the detection of lesions in the size categories I (< 3 mm) and II (3- 5 mm) (Fig.1).

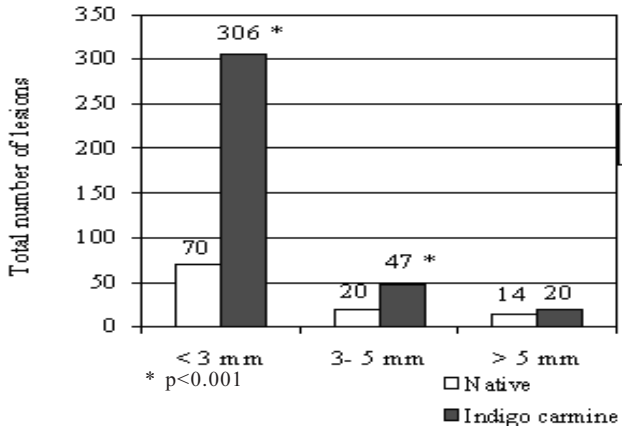

Fig.1 The total number of lesions, classified by size, before and after staining.

Histologically, chromoendoscopy significantly improved the detection of adenomas, hyperplastic polyps and inflammatory/non- specific lesions (p< 0.001) (Fig.2).

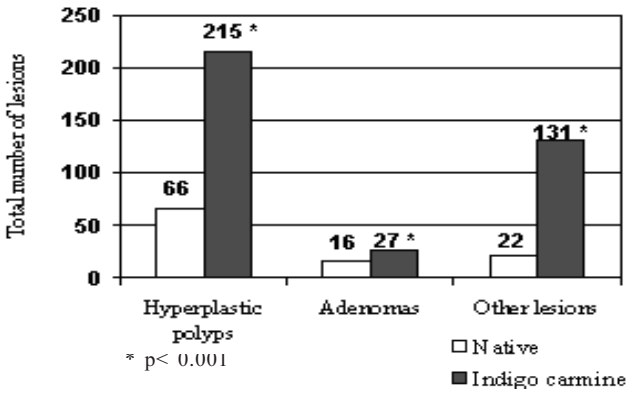

Fig.2 Histological classification of all lesions found before and after staining.

Seventeen (36.2%) patients had adenomas. In 5 (29.4%) of the cases, the neoplastic polyps could be detected only after staining, while in 12 (70.6%) of them, adenomas were already identified by standard sigmoidoscopy. Regarding the size classification, indigo carmine significantly improved

the detection of adenomas for category II, while for the categories I and III, there was no significant difference between standard sigmoidoscopy and chromoendoscopy (Fig.3). Considering all adenomas ≤ 5 mm, significantly more were identified by indigo carmine compared to the standard view ($p<0.01$).

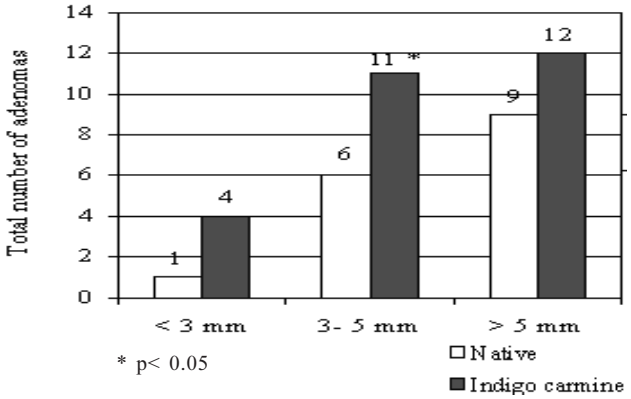

Fig.3 The total number of adenomas, classified by size, before and after staining.

From all the protruding lesions revealed only by indigo carmine, the percentage of neoplastic polyps was 1% for category I (< 3 mm) , 19% for category II (3-5 mm) and 50% for category III (> 5 mm). Histologically, no polyps with high-grade dysplasia or cancer were found after dye application.

Discussion

There are many studies which report, on the basis of "back-to-back" conventional colonoscopies, a miss rate for polyps of 27% for adenomas ≤ 5 mm and 6% for lesions ≥ 10 mm (12). More recently, it was found that a significant number of neoplastic lesions are overlooked, including 12% of all adenomas, regarding 17% of all patients (13), respectively 11% of the lesions ≥ 10 mm (14).

In a randomized controlled trial on 259 patients, 124 examined using chromoendoscopy and 135 by standard colonoscopy, significantly more adenomas < 5 mm and significantly more patients presenting 3 or more adenomas were found after dye application (15). In a more recent randomized study, comparing pan-colonic with targeted indigo carmine staining during colonoscopy, pan-chromoscopy significantly ($p<0.01$) increased the detection of adenomas smaller than 4 mm and also increased the number of patients with ≥ 3 neoplastic polyps (16). Considering the patients with ≥ 3 adenomas at high risk, the most recent ASGE guidelines concerning the surveillance management after polipectomy recommend repeat colonoscopy after 3 years in these cases, while in patients with ≤ 2 small, tubular adenomas (< 1 cm) and only low-grade dysplasia, colonoscopy should not be performed earlier than 5 years (2).

There are few data in the literature regarding the use of chromoendoscopy during flexible sigmoidoscopy, most of the publications focusing on colonoscopy. In a study evaluating the effect of indigo carmine application on the last 30 cm of the distal colon and rectum after colonoscopy was performed in 74 patients, 58 lesions were found in 30 patients in the standard view and 176 mucosal changes in 46 cases after staining (17). Kiesslich *et al* determined in their on the pit-pattern-classification focussed issue, the detection rate of lesions after spraying the indigo carmine on the last 30 cm of colonoscopically normal appearing mucosa (18). They found that, from 48 patients with mucosa of normal appearance prior to staining, chromoendoscopy revealed 178 lesions in 27 patients. In contrast to these data, we identified 104 protruding lesions in 30 patients by conventional sigmoidoscopy, and 373 mucosal changes in 47 patients after dye application. The great difference between the total number of lesions found in the two mentioned studies as compared to our results, is very likely due to the significantly higher number of inflammatory/non-specific mucosal changes showed by us. Kiesslich *et al* did not mention such lesions, and Lee *et al* mentioned them only as "hyperplastic or inflammatory" (17). It is interesting the fact that, considering hyperplastic polyps and inflammatory/non-specific lesions as one category, our results regarding the percentage of these mucosal changes from all detected protrusions, are very similar to those of the other two publications [89.8% (Lee) respectively 92.7% (Kiesslich) versus 92.8%% (our study)].

Regarding the total number of adenomas detected after staining, there are some differences between our data and those of the Corean and German study: 18, respectively 13 adenomas in 46, respectively 27 patients (17,18) versus 27 neoplastic polyps in 17 patients in our case. This discrepancy is mainly due to the fact that we calculated all adenomas identified after dye application, including those already observed in the standard view. Considering the adenomas revealed by chromoendoscopy exclusively in patients without neoplastic polyps prior to staining, we found 6 neoplastic polyps in 5 patients. Thus, in our study, chromoendoscopy mostly increased the number of detected adenomas in patients already showing such mucosal changes in the standard view (12 cases).

Our findings may reveal the practical role of chromoendoscopy, considering the importance of the number of adenomas identified on flexible sigmoidoscopy in the decision to perform colonoscopy, although this subject is still controversial (1,2). Winawer *et al* consider that a single, small distal tubular adenoma may increase the risk for proximal advanced neoplasia slightly or not at all (19,20). On the other hand, patients with ≥ 3 (19,21) or even ≥ 1 (22) distal adenomas are at a high risk of developing advanced proximal neoplasia. Nevertheless, the actual guidelines still recommend colonoscopy after at least one adenoma has been revealed by sigmoidoscopy (1,2).

We could not confirm the data of Brooker *et al* and Hurlstone *et al* (15,16), who found a significantly higher number of patients having ≥ 3 adenomas after dye application, but this could be due to the considerably larger

cohort of patients who underwent chromoendoscopy in those studies (n=124 respectively n=128), compared to our study (n= 55) and to the fact that their subjects were examined by total colonoscopy.

We also could not identify any adenoma larger than 5 mm having high grade dysplasia. These data confirm the findings of Lee *et al* (17), while Kiesslich *et al* found one distal adenoma with high-grade intraepithelial neoplasia (18). Other studies suggest that such lesions are most likely to be identified in the right colon (15, 16).

Although not constantly monitorized, dye application prolonged the extubation time with 12 minutes on average compared with conventional sigmoidoscopy. This is not unusual, considering firstly the necessary time to remove all the lesions and secondly the fact that all experimented endoscopists involved had a reduced experience with chromoendoscopic techniques. As might be expected, this aspect will improve with the increasing of the training curve.

In conclusion, in our experience, chromoendoscopy with indigo carmine during flexible sigmoidoscopy was safe, less complicated, but relatively prolonging the extubation time. After staining, significantly more lesions were identified, mostly hyperplastic polyps and inflammatory/non-specific lesions. Regarding adenomas, chromoendoscopy significantly improved the detection of polyps $\leq$ 5 mm. It mainly increased the number of adenomas in patients already showing such lesions in the standard view, although the number of patients with $\geq$ 3 neoplastic polyps was not significantly higher after dye application. Neither did we identify distal adenomas with high-grade dysplasia. Thus, routine indigo carmine application in flexible sigmoidoscopy screening could become a good option, especially when colonoscopy is unavailable or not accepted by the patient.

Conflict of interest

None to declare.

References

1. Schmiegel W, Pox C, Adler G et al. S3-Guidelines Conference "Colorectal carcinoma" 2004. Z. Gastroenterol. 2004; 42: 1129-1177.
2. Davila RE, Rajan E, Baron TH, et al. ASGE guideline: colorectal cancer screening and surveillance. Gastrointest Endosc 2006; 63: 546-557.
3. Eickhoff A, Maar C, Birkner B, Riemann JF: Colorectal cancer in Germany. Means for prevention and early detection: implications for laiety and physicians. Internist 2003; 44: 278, 281-286.
4. Harewood GC, Wiersema MJ, Melton LJ 3rd. A prospective, controlled assessment of factors influencing acceptance of screening colonoscopy. Am J Gastroenterol 2002; 97: 3186-3194.
5. Newcomb PA, Norfleet RG, Storer BE, Surawicz TS, Marcus PM. Screening sigmoidoscopy and colorectal cancer mortality. J Natl Cancer Inst 1992; 84: 1572-1575.
6. Muller AD, Sonnenberg A. Prevention of colorectal cancer by flexible endoscopy and polypectomy. A case-control study of 32,702 veterans. Ann Intern Med 1995; 123: 904-910.
7. Selby JV, Friedman GD, Quesenberry CP Jr, Weiss NS. A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. N Engl J Med 1992; 326: 653-657.
8. Thiis-Evensen E, Hoff GS, Sauar J, Langmark F, Majak BM, Vatn MH. Population-based surveillance by colonoscopy: effect on the incidence of colorectal cancer. Telemark Polyp Study I. Scand J Gastroenterol 1999; 34: 414- 420.
9. Kudo S, Tamura S, Nakajima T, Yamano H, Kusaka H, Watanabe H. Diagnosis of colorectal tumorous lesions by magnifying endoscopy. Gastrointest Endosc 1996; 44: 8- 14.
10. Kida M, Kobayashi K, Saigenji K. Routine chromoendoscopy for gastrointestinal diseases: indications revised. Endoscopy 2003; 35: 590-596.
11. Schlemper RJ, Riddell RH, Kato Y, et al. The Vienna classification of gastrointestinal epithelial neoplasia. Gut 2000; 47: 251- 255.
12. Rex DK, Cutler CS, Lemmel GT, et al. Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. Gastroenterology 1997; 112: 24-28.
13. Bensen S, Mott LA, Dain B, Rothstein R, Baron J. The colonoscopic miss rate and true one-year recurrence of colorectal neoplastic polyps. Polyp Prevention Study Group. Am J Gastroenterol 1999; 94: 194-199.
14. Pickhardt PJ, Nugent PA, Mysliwiec PA, Choi JR, Schindler WR. Location of adenomas missed by optical colonoscopy. Ann Intern Med 2004; 141: 352-359.
15. Brooker JC, Saunders BP, Shah SG, et al. Total colonic dye-spray increases the detection of diminutive adenomas during routine colonoscopy: a randomized controlled trial. Gastrointest Endosc 2002; 56: 333-338.
16. Hurlstone DP, Cross SS, Slater R, Sanders DS, Brown S. Detecting diminutive colorectal lesions at colonoscopy: a randomised controlled trial of pan-colonic versus targeted chromoscopy. Gut 2004; 53: 376-380.
17. Lee JH, Kim JW, Cho YK, et al. Detection of colorectal adenomas by routine chromoendoscopy with indigocarmine. Am J Gastroenterol 2003; 98: 1284-1288.
18. Kiesslich R, von Bergh M, Hahn M, Hermann G, Jung M. Chromoendoscopy with indigocarmine improves the detection of adenomatous and nonadenomatous lesions in the colon. Endoscopy 2001; 33: 1001-1006.
19. Winawer S, Fletcher R, Rex D, et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale-Update based on new evidence. Gastroenterology 2003; 124: 544-560.
20. Winawer SJ. Screening sigmoidoscopy: can the road to colonoscopy be less travelled? Ann Intern Med 2003; 139: 1034-1035.
21. Atkin WS, Morson BC, Cuzick J. Long-term risk of colorectal cancer after excision of rectosigmoid adenomas. N Engl J Med 1992; 326: 658-662.
22. Levin TR, Palitz A, Grossman S, et al. Predicting advanced proximal colonic neoplasia with screening sigmoidoscopy. JAMA 1999; 281: 1611-1617.