Dig Dis Sci (2007) 52:1009–1013
DOI 10.1007/s10620-006-9383-y

ORIGINAL ARTICLE

Performance Characteristics and Comparison of Two Fecal Occult Blood Tests in Patients Undergoing Colonoscopy

Marcia Cruz-Correa · Kathleen Schultz · Sanjay Jagannath · Mary Harris · Sergey Kantsevoy · Marshall Bedine · Anthony N. Kalloo

Received: 21 December 2005 / Accepted: 6 April 2006 / Published online: 16 February 2007

Abstract We investigated the use of a new type of FOBT (EZ-Detect) that uses the blood's pseudo-peroxidase activity as an enzymatic catalyst, in a one-step chromogen-substrate system performed by the patient. Asymptomatic patients ≥ 50 years old received three Hemoccult II (HO) cards and three EZ-Detect (EZ) packages to be used in three consecutive bowel movements. Sensitivity, specificity, positive predictive value, and negative predictive value for detection of colorectal neoplasia was calculated. The study included 207 patients, with a mean age of 58.9 years. Diagnostic accuracy for detection of adenomas was similar for the EZ and HO tests (66.7% vs. 71.0%; $P = 0.48$), while for advanced adenomas diagnostic accuracy for the EZ and HO tests was 86.0% vs. 94.2% ($P = 0.01$), respectively. Most patients preferred the EZ test (92% vs. 8%). We conclude that the EZ test has a diagnostic profile similar to that of the HO test for identification of adenomas; however, for advanced adenomas the diagnostic accuracy was slightly better for the HO. The EZ test was preferred by most patients, which may increase colorectal cancer screening compliance.

Keywords Colorectal cancer · Screening · Fecal occult blood testing · Diagnostic accuracy

M. Cruz-Correa · K. Schultz · S. Jagannath · M. Harris · S. Kantsevoy · M. Bedine · A. N. Kalloo (✉)
Department of Medicine, Johns Hopkins University School of Medicine,
1830 East Monument Street, Room 420, Baltimore, Maryland 21205, USA
e-mail: akalloo@jhmi.edu

M. Cruz-Correa
Department of Medicine, University of Puerto Rico Comprehensive Cancer Center,
San Juan, Puerto Rico 00936, USA

Introduction

Colon cancer is the second leading cause of cancer death in the United States for men and women combined (American Cancer Society, 2005). Therefore, devising effective screening programs is of paramount importance to decrease the morbidity and mortality of patients affected by this disease. The importance of screening is emphasized by the finding that patients with early colorectal cancer have a relatively high 5-year survival rate, whereas those with advanced disease have a significantly decreased 5-year survival rate [1]. One of the most common colorectal cancer screening modalities is fecal occult blood testing (FOBT), which detects premalignant adenomas and early-stage colon cancer [2, 3]. Three randomized, controlled clinical trials have shown that both annual screening and biennial screening for occult blood in the stool significantly reduce the incidence of and the mortality from colorectal cancer [4–6].

Despite the widespread use of FOBT in colorectal cancer screening, concerns remain regarding its sensitivity and specificity [7–9]. In fact, the sensitivity of the Hemoccult II (HO) test (Beckman Coulter; formerly SmithKline Diagnostics) has been reported to be as low as 26% for cancers and 13% for large adenomas [10]. Furthermore, the specificity of the HO test is reduced by dietary factors such as nonhuman hemoglobin and peroxidase-rich vegetables, which may cause false-positive results. Additionally, utilization of the current FOBT requires handling of stool by the patient, which may prove to be an obstacle for a significant number of patients. The ideal test would be one with a high sensitivity and specificity that is inexpensive and easy to use.

EZ-Detect (EZ) is a type of FOBT that also uses the blood's pseudo-peroxidase activity as an enzymatic catalyst. However, there appear to be several advantages of the EZ FOBT system over the HO test. First, EZ uses a newer

chromogen-substrate system which is much faster that the regular guaiac system. Second, the test has all the chemicals impinged on the biodegradable tissue paper (tetramethylbenzine and peroxide), which allows patients to perform the test in the privacy of their homes and may increase patient compliance. Third, the color development of the test is clear and sharp, which should aid in the interpretation of results. Fourth, the chromogen-substrate system does not require very restrictive dietary or lifestyle guidelines, which may improve both compliance and diagnostic accuracy. The EZ test is designed to detect bleeding from the gastrointestinal tract; since the blood is primarily picked up on the outside of the stool, other sources of peroxidase such as raw vegetables (usually imbedded within the stool) and sources of blood such as raw meat (usually denatured through the digestion process) do not affect the process. Use of ASA and NSAIDs is discontinued, as it may induce lower gastrointestinal bleeding, resulting in a false-positive result. Unfortunately, there are limited published data, and no previous clinical trial on the efficacy of this particular FOBT has been published [11, 12]. In view of the potential advantages of using EZ as a screening FOBT, we conducted a head-to-head comparison of EZ with the standard HO test to determine the diagnostic accuracy for colorectal cancer screening. The primary objectives were to compare detection rates for colonic neoplasia (adenomas or advanced neoplasia) and to determine patients' test preferences.

Methods

Study design, rationale, and procedures

We conducted a cross-sectional study of consecutive patients referred to an academic gastrointestinal practice (Johns Hopkins Outpatient Endoscopy Unit and Johns Hopkins Greenspring Endoscopy Unit). HO was chosen for comparison with EZ because it is the only FOBT proven to reduce the incidence of and risk of death from colorectal cancer and is the most widely used guaiac-based test. Patients scheduled for a colonoscopic examination were given three HO cards and three EZ packages to be used during the week prior to the colonoscopic examination in three consecutive bowel movements (both the HO and the EZ tests were used with each bowel movement). All subjects received oral and written instructions to complete both tests. For the HO test patients were instructed to use the three cards in three consecutive bowel movement, sampling two different areas of the stool and applying each separately to the two panels of each HO card. The completed cards were mail to the investigators for analysis.

For the EZ test, patients were instructed to administer, read, and record the results in a diary (according to the manufacturer's recommendation). The EZ test consisted of a biodegradable paper (test tissue) coated with a chromogenic dye (tetramethylbenzidine; TMB) and peroxide. The chemical solution is printed on the paper in the form of a cross. When the test tissue touches the toilet water surface after a bowel movement, if there is blood hemoglobin present, it will liberate oxygen from the peroxide, which in turn oxidizes the colorless dye (TMB) to a blue-green color (peroxide + hemoglobin water → oxygen → oxygen + unoxidized TMB [colorless] → oxidized TMB [blue-green color]). The completed diary was then mailed to the investigators along with the three completed HO cards. All tests were conducted in a blinded fashion; the colonoscopy was performed without knowledge of the results of the HO or EZ.

Patients were instructed to eat a low-peroxidase-containing diet for 1 week before the colonoscopy (before and during the time of FOBT). Medications such as aspirin, other NSAIDs, and vitamin C were stopped for 1 week before colonoscopy. The HO cards were developed by nonrehydrated analysis and read independently by two investigators consistently with the manufacturer's instructions and guidelines. If there was a conflict in the interpretation of a result, both investigators reviewed the case and reached an agreement.

Colonoscopy was performed with standard preparation (polyethylene glycol [Golytely; Braintree Corp.] or liquid Fleet Phospho-soda [Fleet Corp.]) and sedation, using standard Olympus colonoscopes. The endoscopist documented the extent of the colon that was visualized and the quality of the bowel preparation. Completion of colonoscopy up the cecum with adequate visualization of the colonic mucosa was required. The size and location of any lesions were recorded. The colonoscopic examination and pathology reports were used to determine histological diagnosis. For a patient to be included in the analysis, all three HO cards (six panels) had to be completed, all three EZ results had to be recorded on the diary card, and a complete colonoscopy up to the cecum was required.

Study population

Eligible subjects were asymptomatic patients 50 years of age or older who were having a colonoscopy and who were able to sign informed consent. Exclusion criteria included gastrointestinal bleeding within the preceding month, frequent hematochezia (defined as more than one episode of bright red per rectum per week), change in bowel habits, recent onset of abdominal pain, prior resection of any part of the colon, iron-deficiency anemia, inflammatory bowel disease, known radiation proctitis, and known infectious colitis. Clinical and demographic information was obtained by direct interview and review of the medical records. The study was approved by the Johns Hopkins Institutional Review Board; all

subjects signed informed consent prior to participation in the study.

Dependent and independent covariates

The primary outcomes of the study were the *sensitivity, specificity, positive predictive value* (PPV), and *negative predictive value* (NPV) of the EZ and HO tests for colorectal neoplasia. A positive HO test was defined as having at least one of six panels in the three HO cards; similarly, a positive EZ test was defined as having at least one of three positive results. A negative test was defined as having negative results in all six panels of HO cards or in the three EZ tests. Diagnostic accuracy of EZ and HO was determined separately for the complete cohort and for those individuals who had screening colonoscopy. Additionally, the diagnostic accuracy of EZ and HO was evaluated for all adenomas and for advanced adenomas (≥ 10 mm in diameter or with villous component or dysplasia) separately. Finally, we evaluated the patients' test of choice (EZ vs. HO) and explored the reasons associated with their choice.

Statistical analysis

Descriptive statistics were used to characterize the database including means, median, and percentiles. Hypothesis testing was performed with chi-square or Fisher's exact test, as appropriate. We calculated sensitivity [true positives/(true positives + false negatives)], specificity [true negatives/(true negatives + false positives)], PPV [true positives/(true positives + false positives)], NPV [true negatives/(true negatives + false negatives)], diagnostic accuracy [(true positive + true negative)/total]. McNemar's test was used to compare the ability of the EZ and HO test to identify subjects with colonic neoplasia (adenomas or colorectal cancer). No interim analyses were performed. Sample size was predetermined on the basis of the assumption that the EZ and HO tests had sensitivities for the detection of colonic neoplasia of at least 40% and 20%, respectively. Given this assumption, the enrollment of 56 subjects with colonic neoplasia would provide the study with a statistical power of 80% to detect a significant difference at a two-sided α level of 0.05 with the use of McNemar's test. Statistical analysis was performed using STATA 8.0.

Results

Between September 2002 and June 2003, 235 eligible subjects were invited to enroll in this investigation and 28 (11.9%) declined to participate. A total of 207 subjects agreed to participate and completed the colonoscopy, both FOBTs, and the clinical questionnaire. Table 1 reports the clinical and demographic characteristics of the study participants. The medical indications for colonoscopic examination were routine screening for age ≥ 50 years (61%), history of adenomas (15%), history of colonic cancer (5%), and family history of cancer (19%). Sixty-nine percent (144) of colonoscopies showed no pathology, while 30.4% (63) had adenomatous polyps, and none had colorectal cancer. Eleven percent (7/63) of the adenomas were advanced adenomas.

Table 1 Demographic characteristics of study participants ($N = 207$)

	N (%)
Gender	
Female	131 (63.3)
Age, yr (mean ± SD)	65.5 ± 11.2
Race	
White	141 (68.1)
Black	63 (30.4)
Other	3 (1.5)
Reason for colonoscopy	
Screening	126 (60.9)
History of polyps	32 (15.4)
History of colon cancer	10 (4.8)
Family history of colon cancer	39 (18.9)

Diagnostic accuracy of tests

Complete cohort

We first evaluated the performance of the EZ and HO tests in the complete cohort of patients (Table 2). For detection of adenomas the EZ and HO tests had a sensitivity of 14.3% vs. 6.3%, specificity of 89.6% vs. 99.3%, PPV of 37.5% vs. 80%, and NPV of 70.5% vs. 70.8%, respectively. The diagnostic accuracy for detection of adenomas was similar for the EZ and HO tests (66.7% vs. 71.0%; $P = 0.48$). For detection of advanced adenomas EZ and HO tests had a sensitivity of 14.3% vs. 0%, specificity of 88.5% vs. 97.5%, PPV of 4.2% vs. 0, and NPV of 96.7% vs. 96.5%, respectively. The diagnostic accuracy for detection of advanced adenomas for the EZ and HO was 86.0% vs. 94.2% ($P = 0.01$).

Screening cohort

Evaluation of diagnostic accuracy among individuals who underwent screening colonoscopy showed similar results for both EZ and HO (Table 3) compared to the complete cohort. For detection of adenomas the EZ and HO tests had a sensitivity of 17.6% vs. 8.8%, specificity of 88.0% vs. 100%, PPV of 35.3% vs. 100%, and NPV of 74.3% vs. 74.8%, respectively. The diagnostic accuracy for detection of adenomas was similar for the EZ and HO tests (69% vs. 75%; $P = 0.40$). For detection of advanced adenomas the EZ and HO tests had a sensitivity of 25% vs. 0%, specificity

Table 2 Diagnostic accuracy of FOBT among all study participants ($N = 207$)

	Polyps		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
	Yes	No				
All adenomas						
EZ-Detect						
Positive	9	15	14.3	89.6	37.5	70.5
Negative	54	129				
Hemoccult II						
Positive	4	1	6.3	99.3	80.0	70.8
Negative	59	143				
Advanced adenomas						
EZ-Detect						
Positive	1	23	14.3	88.5	4.2	96.7
Negative	6	177				
Hemoccult II						
Positive	0	5	0	97.5	0	96.5
Negative	7	195				

Note. Results were positive if any of the three cards was positive and negative if all three cards were negative

of 86.5% vs. 97.5%, PPV of 5.9% vs. 0%, and NPV of 97.2% vs. 96.7%, respectively. The diagnostic accuracy for detection of advanced adenomas among the screening group for EZ and HO was 84.9 % vs. 94.4% ($P = 0.03$), respectively.

Test preference

Participants were asked to rate their preference between the EZ and the HO test. Most patients preferred EZ to HO (81% vs. 8%; $P < 0.001$), while 11% reported no preference. The most common reasons reported among the participants who preferred the EZ test ($N = 169$) were as follows: pleasant/cleaner test (81.5%), easier test (79.7%), and faster/not having to wait for result (63.7%). The most common reason reported among the participants who preferred the HO test ($N = 16$) was that the instructions for the HO test were easier to understand than those for the EZ test (88.7%).

Discussion

In this endoscopy-controlled investigation we prospectively compared the diagnostic accuracy of two FOBTs as a screening test for colorectal neoplasia in an asymptomatic population. Overall, the results demonstrated that the EZ and HO tests have a similar diagnostic profile for the detection of adenomas, while the HO test had increased diagnostic accuracy in the evaluation of advanced adenomas. The EZ test had numerically higher sensitivities for identifying all adenomas and advanced adenomas compared with the HO test. The HO test had numerically higher specificities in all categories examined (all adenomas and advanced adenomas) in the complete and the screening cohorts. However, there was no statistical significant difference in the overall diagnostic accuracy of the EZ and HO tests when evaluating adenomas in both the complete cohort and the screening cohort.

Our results are similar to those of previous FOBT studies reporting sensitivities for adenomas in the range of 13% to

Table 3 Diagnostic accuracy of FOBT among patients with screening colonoscopy ($N = 126$)

	Polyps		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
	Yes	No				
All adenomas						
EZ-Detect						
Positive	6	11	17.6	88.0	35.3	74.3
Negative	28	81				
Hemoccult II						
Positive	3	0	8.8	100	100	74.8
Negative	31	92				
Advanced adenomas						
EZ-Detect						
Positive	1	16	25	86.7	5.9	97.2
Negative	3	106				
Hemoccult II						
Positive	0	3	0	97.5	0	96.7
Negative	4	119				

Note. Results were positive if any of the three cards was positive and negative if all three cards were negative

26% [7, 8]. Previous studies have shown that the sensitivity of FOBT is very low in patients who only have adenomas [13, 14]. In our cohort advanced adenomas were present in only 3% of participants. The number of positive results (both true-positive and false-positive) in our study was rather low despite our deliberate attempt to increase the prevalence of disease by including individuals with a history of cancer, adenomas, and a family history of cancer. One factor that might have contributed to the low positive rate was the exclusion of active colonic disease such as gastrointestinal bleeding, frequent hematochezia, and known history of inflammatory bowel disease. While the number of positive results was low overall, there were more false-positive results in the EZ than in the HO test. Since subjects were instructed to adhere to a restricted diet during FOBT and since the EZ test uses a chromogen-substrate system that does not require very restrictive dietary guidelines, it is unlikely that dietary indiscretions accounted for the false-positive results observed. One factor that may have contributed to the high number of false-positive results in the EZ test was that the EZ test was self-administered and read by the patient (in accordance to the manufacturer's instructions). However, despite this slight increase in the false-positive rate in the EZ test, the overall diagnostic accuracy for adenomas was similar for EZ and HO test.

An important aspect of this comparison study was to explore patients' preferences between the two FOBTs. Since compliance with CRC screening is low, improving the acceptability of a test may result in increase colorectal cancer screening [15]. Most of our study participants preferred the EZ test to the HO test. The EZ test was preferred, as it was felt to be more hygienic and simple than the HO test. We can hypothesize that providing an easier, more acceptable test with an accuracy similar to that of the other FOBTs might result in increased compliance with colorectal cancer screening. However, the population evaluated in this investigation was chosen from among those patients who were already scheduled to undergo a colonoscopic examination, hence limiting the generalizability of our findings. Although our results point to a similar diagnostic accuracy of both FOBTs, the restricted sample size and low prevalence of colorectal neoplasia constitute limitations to the study conclusions.

In summary, in this prospective head-to-head endoscopy-controlled investigation, the EZ and HO tests exhibited a similar diagnostic profile for the detection of all adenomas, while the HO test demonstrated a slight improvement in the diagnostic profile of advanced adenomas. The majority of study patients preferred EZ test to HO test, which may result in increased compliance with colorectal cancer screening. The EZ test provides an alternative methodology for FOBT colorectal cancer screening.

Acknowledgments This work was supported by Grant K07 CA092445 (to M.C.C.) and supported in part by an unrestricted grant from the Sol Hubert Trust (supplied EZ-Detect packages). None of the authors are on the Advisory Boards or Speaker Bureaus for the Sol Hubert Trust.

References

1. Bresalier RS, Kim YS (1998) Malignant neoplasms of the large intestine. In: Feldman M, Sleisenger MH, Scharschmidt BF, (eds.) Gastrointestinal disease, 6th ed. WB Saunders, Philadelphia, pp 1906–1939
2. Kronborg O, Fenger C, Olsen J, et al. (1996) Randomized study of screening for colorectal cancer with faecal-occult-blood test. Lancet 348:1467–1471
3. Allison JE (2005) Colon cancer screening guidelines 2005: The fecal occult blood test option has become a better FIT. Gastroenterology 129:745–748
4. Mandel JS, Bond JH, Church TR, et al. (1993) Reducing mortality from colorectal cancer by screening for fecal occult blood. N Engl J Med 328:1365–1371
5. Hardcastle JD, Chamberlain JO, Robinson MH, et al. (1996) Randomized controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet 348:1472–1477
6. Mandel JS, Church TR, Bond JH, et al. (2000) The effect of fecal occult-blood screening on the incidence of colorectal cancer. N Engl J Med 343:1603–1607
7. Liberman D, Sleisenger MH (1996) It is time to recommend screening for colorectal cancer? Lancet 348:1463–1464
8. Liberman DA (1990) Colon cancer screening. The dilemma of positive screening tests. Arch Intern Med 150:740–744
9. Greenberg PD, Bertario L, Gnauck R, et al. (2000) A prospective multicenter evaluation of new fecal occult blood tests in patients undergoing colonoscopy. Am J Gastroenterol 95:1331–1338
10. Collins JF, Lieberman DA, Durbin TE, et al. (2005) Veterans Affairs Cooperative Study #380 Group. Accuracy of screening for fecal occult blood on a single stool sample obtained by digital rectal examination: a comparison with recommended sampling practice. Ann Intern Med 142(2):81–85
11. Tate JJ, Northway J, Royle GT, et al. (1989) Evaluation of a "DIY" test for the detection of colorectal cancer. J R Soc Med 82:388–390
12. Hou SI, Chen PH (2004) Home-administered fecal occult blood test for colorectal cancer screening among worksites in Taiwan. Prev Med 38:78–84
13. Ahlquist DA, Wieand HS, Moertel CG, et al. (1993) Accuracy of fecal occult blood screening for colorectal neoplasia. A prospective study using Hemoccult and HemoQuant test. JAMA 269:1262–1267
14. St John DJB, Young GP, Alexeyeff MA, et al. (1993) Evaluation of new occult blood tests for detection of colorectal neoplasia. Gastroenterology 104:1661–1668
15. Smith RA, Cokkinindes V, Eyre HJ (2004) American Cancer Society guidelines for early detection of cancer. Ca Cancer J Clin 54(1):41–52