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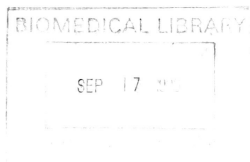
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Colonoscopic Evaluation of Immunochemical Fecal Occult Blood Test for Detection of Colorectal Neoplasia

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KEY WORDS: Colonoscopy; Colorectal neoplasia; Diagnostic accuracy; Immunochemical occult blood test

ABSTRACT

BACKGROUND/AIMS: This study was carried out to assess the validity of three testing methods of immunochemical occult blood according to the number of collection times as a means for colorectal cancer screening.

METHODOLOGY: Four thousand six hundred and eleven asymptomatic individuals, who received both an immunochemical occult blood test with a three-day method and colonoscopy during a medical check-up, served as subjects for this study. For evaluation of the desirable number of sampling times, we used the results of the first day for the 1-day method, the results of the first and second days for the 2-day method, and the results of three-consecutive days for the 3-day method. Sensitivities and specificities of these three testing methods were evaluated.

RESULTS: Sensitivities and specificities for colorectal cancer were calculated to be 56% and 97% for the 1-day method, 83% and 96% for the 2-day method, and 89% and 94% for the 3-day method, respectively, showing a significant difference in sensitivity between the 1-day and the 2-day methods, as well as the 3-day method ($p < 0.01$), and in specificity between the 1-day as well as the 2-day and 3-day methods ($p < 0.05$).

CONCLUSIONS: These findings indicate that the immunochemical fecal occult blood test is useful for the diagnosis of colorectal cancer, and that 2-day testing is recommended as a means of screening for colorectal cancer.

INTRODUCTION

The sensitivity and specificity of fecal occult blood tests for colorectal neoplasms are affected by the number of fecal collection times, and the 3-consecutive-days collection method is generally accepted as the method of choice in the guaiac-impregnated chemical fecal occult blood test (1-3). Sensitivity of chemical tests over 3 consecutive days has ranged in patients with symptomatic colorectal cancer from 26-95% (4-6).

The immunochemical fecal occult blood test for human hemoglobin was developed in an attempt to improve the performance of the guaiac-

impregnated chemical fecal occult blood test, and has been pointed out to have a higher level of sensitivity for colorectal bleeding than the guaiac-based occult blood test (7-9). In a separate article (10), we reported that the diagnostic accuracy for colorectal cancer was higher in an immunochemical test (Monohaem), than in the widely used chemical guaiac-based test (Hemoccult II).

However, in the immunochemical fecal occult blood test, there is no clear understanding of the optimal number of fecal collection times

necessary for the development of a more appropriate screening test with a high accuracy. For this reason, we conducted a comparative study to evaluate the desirable number of fecal sampling times using three testing methods for immunochemical fecal occult blood.

METHODOLOGY

Four thousand six hundred and eleven asymptomatic individuals who participated in the medical check-up for colorectal cancer served as the subjects for this study. Each subject was tested for 3 consecutive days by an immunochemical fecal occult blood test without dietary or medicinal restriction before conducting colonoscopy. The subjects were aged over 40 and mainly asymptomatic. Fecal smears from the subjects were collected at the laboratory within 1 day and tested immediately.

For evaluation of the desirable number of fecal collection times, we used the results of the first day for the 1-day method, the results of the first and second days for the 2-day method, and the results of the 3 consecutive days for the 3-day method. Sensitivities and specificities of these three testing methods were evaluated.

The principles and procedures of the immunologic slide Monohaem (Nihon Pharmaceutical, Japan), which was used in the present study, are as follows. Firstly, those being screened are asked to make a thin fecal smear on the test filter paper. If human hemoglobin is present in the fecal sample, it will participate in an antigen-antibody reaction with the monoclonal antibody in the filter paper. The reacted sample is then washed to remove components other than hemoglobin, and a color coupler is added. Oxygen is dissociated from hydrogen peroxide by the peroxidase-like activity of the human hemoglobin, which oxidizes tetramethylbenzidine, leading to the appearance of a green color. The presence of human

hemoglobin is thus indicated by the appearance of this green coloration. The procedures of this test are uncomplicated and the cost per slide for each test is approximately \$2.50.

Statistical analysis was performed using the Chi-square test, and a *p* value of less than 0.05 was defined as statistically significant.

RESULTS

Among 4611 participants in the medical check-up, 18 patients with colorectal cancer, 73 patients with colorectal adenomatous polyps and other colorectal diseases, such as inflammatory bowel diseases, diverticulosis and hemorrhoids, were diagnosed by colonoscopy. The immunochemical fecal occult blood test was positive in 10 patients with colorectal cancer and 22 patients with colorectal adenoma in the 1-day method, in 15 patients with colorectal cancer and 37 patients with colorectal adenoma in the 2-day method, and in 16 patients with colorectal cancer and 40 patients with colorectal adenoma in the 3-day method (Table 1).

On the basis of these results, sensitivities of an immunochemical fecal occult blood test for colorectal cancer and colorectal adenoma were calculated to be 55.6% and 30.1% for the 1-day test, 83.3% and 50.7% for the 2-day test, and 88.9% and 54.8% for the 3-day test. Specificity was 97.1% for the 1-day test, 96.0% for the 2-day test, and 93.9% for the 3-day test, showing a significant difference in sensitivity for colorectal cancer between the 1-day and the 2-day tests, as well as the 3-day test (*p* < 0.01). There was also a significant difference in specificity between the 1-day as well as the 2-day and 3-day tests (*p* < 0.05) (Table 2). However, there were no differences in sensitivity between 2-day and 3-day testings, or in specificity between 1-day and 2-day testings.

In patients with colorectal cancer, Duke's stages included 9 cases of Duke's stage A cancer, 6 cases of Duke's stage B cancer, and 3 cases of Duke's

TABLE 1 Results of Three Testing Methods of Immunochemical Fecal Occult Blood during Medical Check-up

Results of colonoscopy	Results of immunochemical fecal occult blood tests					
	One-day method		Two-day method		Three-day method	
	+	-	+	-	+	-
Colorectal cancer	10	8	15	3	16	2
Colorectal adenoma	22	51	37	36	40	33
Normal	131	4389	180	4340	275	4245

TABLE 2 Comparison of Diagnostic Validity among Three Testing Methods in an Immunochemical Fecal Occult Blood Test

Diagnostic validity	Testing methods		
	One-day method	Two-day method	Three-day method
Sensitivity			
Colorectal cancer	55.6*	83.3	88.9
Colorectal adenoma	30.1**	50.7	54.8
Specificity (%)	97.1	96.0	93.9***

* $p < 0.01$ for difference in sensitivity for colorectal cancer between the one-day fecal collection method and the two-day as well as the three-day fecal collection methods.

** $p < 0.01$ for difference in sensitivity for colorectal adenoma between the one-day fecal collection method and the two-day as well as the three-day fecal collection methods.

*** $p < 0.05$ for difference in specificity between the three-day fecal collection method and the one-day as well as the two-day fecal collection methods.

stage C cancer. Lesion sites included 3 rectum, 9 sigmoid colon, 1 descending colon, 2 transverse colon, and 3 ascending colon.

DISCUSSION

High diagnostic validity is essential for a desirable cancer screening test, and various types of study design can be used to evaluate the diagnostic accuracy of a cancer screening test, such as a follow-up study after screening, a retrospective study of patients with cancer, and a prospective study to perform both a screening test and a close examination test (11). Among these, the last approach is recommended as the most desirable method of investigating the accuracy of the screening test. In this study, we used a medical check-up-based prospective approach. Sensitivities and specificities of the immunochemical fecal occult blood test in this investigation were found to be 56% and 97% for the 1-day method, 83% and 96% for the 2-day method, and 89% and 94% for the 3-day method, respectively. These results compared favorably with the results of the chemical tests reported so far (7-9), substantiating the view that immunochemical tests have a higher accuracy than chemical tests and showing that 2-day testing is recommended as the optimal approach for colorectal cancer screening.

Sensitivity and specificity of fecal occult blood tests are affected by the cut-off value as well as fecal collection times. Physiologic blood loss from the gastrointestinal tract has been estimated to be 0.3mg/g stool (12) and 0.1-0.2mg/g stool (13). The lower threshold value of the occult blood test produces the higher positivity rate and the lower specificity. In an immunochemical test for

human hemoglobin employed in this study, the cut-off point was 0.2mg/g stool and a high antibody titer was used. Accordingly, the 5% positivity rate of the 2-day method is higher than that of the guaiac-impregnated Hemoccult test with the 3-day method (10), and a large proportion of the screened population will have a positive test result in the actual screening. If this high positivity rate is a serious limiting factor for the wide scale screening program of colorectal neoplasia, reconsideration of the threshold value of this test might be necessary on the basis of the trade-off association between sensitivity and specificity.

Although this study design is more reliable for evaluating the diagnostic value of this test, the feasibility of conducting a study by this method on a large scale is not high owing to operational difficulties. Thus, the subjects in this medical check-up-based study seem to be adequate enough for evaluating the diagnostic value of the immunochemical occult blood test for colorectal neoplasms. To confirm the findings of this study, however, it would be necessary to conduct a larger population-based prospective study using these methods.

Theoretically, two factors may lead to a negative fecal occult blood test result in colorectal neoplasms, even if bleeding from the lesions exists: 1) slight hemorrhage or intermittent bleeding from the disease; and, 2) inappropriate site of fecal sampling. It has been pointed out that slight or intermittent bleeding is the possible cause of a negative test result in the study of colorectal polyps (10,11) and that, particularly in rectal cancers, blood can adhere to part of the feces (12,13). Therefore, depending on

the characteristics of bleeding or the site of stool sampling, different mechanisms may yield a negative result.

In conclusion, our findings suggest that the immunochemical fecal occult blood test is

effective for the diagnosis of colorectal cancer, and that the 2-day fecal collection method is the most desirable in immunochemical occult blood testing as a means of screening for colorectal cancer.

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