Optimum Number of Stool Specimens Collected for Immunochemical Occult Blood Screening: A Cost-effectiveness Analysis

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Abstract

Background/Objectives : This study was carried out, from the viewpoint of cost-effectiveness, the optimum number of fecal specimens to collect for use in immunochemical occult blood testing as a means of screening for colorectal cancer.

Subjects and Methods: 3300 asymptomatic individuals were subjects of this study. They gave samples for an immunochemical fecal occult blood test, Monohaem and colonoscopy was carried out during a medical check-up. For evaluation of the optimal number of sampling specimens, the results of the first day of sampling, those of the first and second days, and those of the samples taken for three consecutive days were considered as a single-day method, a two-day method, and a three-day method respectively. The average costs per detection of one patient with colorectal cancer, and the detection rate and the false positive rate of these three fecal sample collection methods were evaluated.

Results: The average costs for one cancer case detected were calculated as $3630.68 for a single-day method, $3350.65 for a two-day method, and $4136.36 for a three-day method, respectively. The detection rate and the false positive rate were calculated as 47% and 3.5% for a single-day method, 82% and 4.7 % for a two-day method, and 88% and 5.3% for a three-day method, respectively, indicating a significant difference in the detection rate between a single-day and a two-day methods, as well as a single-day and a three-day methods($p<0.05$). No significant differences in the false positive rate among the three testing methods were observed.

Conclusions: This analysis suggests that a two-day fecal collection method is recommended in immunochemical occult blood screening by Monohaem from the aspects of cost-effectiveness and diagnostic accuracy.

Keywords: Colonoscopic Examination, Colorectal Cancer, Cost-effectiveness, Immunochemical Occult Blood Screening, Sample collection method

Introduction

Diagnostic accuracy of fecal occult blood test for colorectal neoplasms is influenced by the number of fecal specimens, and collection on three consecutive days is generally accepted method for the guaiac-impregnated chemical fecal occult blood test(1-3). Sensitivity of chemical tests with three consecutive days of collection has ranged from 26% to 95% in patients with sympomatic colorectal cancer(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 demonstrated to have a higher level of sensitivity for colorectal bleeding than the guaiac-based occult blood test(7-9). In a previous study(10), I also reported that the diagnostic accuracy for colorectal cancer was higher in an immunochemical test, Monohaem, than in a widely used chemical guaiac-based test, Hemoccult II.

The costs of these immunochemical tests are slightly more expensive than the guaiac-impregnated chemical test(9,10). Consequently, in large-scale screening program for colorectal cancer by the immunochemical occult blood test, special attention should be paid to the number of fecal specimens collected from the viewpoint of cost-effectiveness.

In the immunochemical fecal occult blood test, however, there is no clear understanding on the best number of fecal specimens to be collected in order to balance an appropriate screening test with optimal cost-effectiveness benefit and a high accuracy. For this reason, I conducted a comparative study to evaluate the desirable number of fecal specimens using an immunochemical fecal occult blood test, Monohaem.

Subjects and Methods

3300 asymptomatic people aged over 40 who participated in a medical check-up for colorectal cancer served as the subjects of this study. The six samples of three-consecutive days' stool from each subject were tested by an immunochemical fecal occult blood, Monohaem, without dietary or medicinal restriction according to the test principle before conducting colonoscopy. Fecal smears from the subjects were collected at the laboratory within a day and tested immediately. Meanwhile, all the participants received colonoscopic examination.

For the evaluation of the average costs per detection of one colorectal cancer case among the three fecal samples collection methods, I used the results of the first day to denote a single-day fecal collection method, the results of the first and second days as a two-day fecal collection method, and the results of the three consecutive days as a three-day fecal collection method. The costs of the immunochemical occult blood test as well as colonoscopy procedure were also calculated. The costs of colonoscopy procedure, here, were accounted for the expenditure of colonoscopic examination in the positive subjects of fecal occult blood test. In addition, the diagnostic accuracies were compared for these three fecal collection methods.

The principles and procedures of the immunochemical 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 oxidises tetramethylbenzidine, leading to the subsequent 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 was ¥400 (Japanese Yen), equivalent to US$3.64, approximately. The cost of colonoscopic examination for one person was ¥15,000, equivalent to US $136.36, approximately (according to the exchange rate of US $1.00=¥110 during the period of check-up).

Statistical analysis was performed by McNemar's test and two-tailed P value of less than 0.05 was defined as statistically significant.

Results

Seventeen patients with colorectal cancer were diagnosed by colonoscopy. Positive cases of an immunochemical fecal occult blood test were 125(3.8%), 168(5.1%), and 191(5.8) in a single-day, a two-day, and a three-day methods, and the patients with colorectal cancer detected by colonoscopic examination were 8, 14, and 15 in a single-day, a two-day, and a three-day methods (Table 1). In 17 patients where colorectal cancer was detected, there were 10 cases of Dukes stage A, 6 cases of Dukes stage B and 1 case of Dukes stage C. Lesion sites included 3 in rectum, 8 in sigmoid colon, 3 in transverse colon and 3 in ascending colon.

The costs of the immunochemical fecal occult blood test and colonoscopy were calculated as $12000.00 and $17045.45 in a ingle-day method, $24000.00 and $22909.09 in a t wo-day method, and $36000.00 and $26045.45 in a three-day method, respectively. The costs of colonoscopy here were the

expenditure of colonoscopic examination on all positive subjects of fecal occult blood test. According to these results, the average costs per case were calculated as $3630.68 for single-day testing, $3350.65 for two-day testing, and $4136.36 for three-day testing, respectively (Table 2).

Colonoscopy revealed 9 false negatives and 117 false positives in a single-day method, 3 false negatives and 154 false positives in a two-day method, and 2 false negatives and 176 false positives in three-day method (Table 3). Accordingly, the detection rate and the false positive rate were calculated as 47% and 3.5 for a ingle-day method, 82% and 4.7% for a two-day method, and 88% and 5.3 for a three-day method, respectively, showing significant differences in the detection rate between a single-day method and a two-day method($P<0.05$), and between single-day method and three-day method($p<0.05$), and no significant differences in the false positive rate among three fecal collection methods (single-day versus three-day, $P=0.07$) (Table 4).

Discussion

Cost-effectiveness analysis aim to evaluate the net cost of providing a service and also to measure the outcomes obtained. The method commonly used is to calculate the cost per specified health effect of a technology in a program, for example, costs per life year gained or costs per case identified, and compare this cost-effectiveness ratio with the ratios from other interventions. It is a common understanding that the lower the ratio, the more "cost-effective" the intervention. In cost-effectiveness analysis of screening program for cancer, there are many direct, indirect, and intangible costs, such as screening, diagnosis, treatment, and non-medical costs or additional costs(11-15).

In this study, in an attempt to clarify the optimum number of times to collect stool specimens, I limited the components of the costs to the fecal occult blood test, and colonoscopy procedure for the positive subjects of fecal occult blood test. The average costs calculated in this study were $3630.68 for a single-day method, $3350.65 for a two-day method, and $4136.36 for a three-day method. These results show that a two-day testing method is the least expenditure and is recommended as the optimum cost-effective approach for the immunochemical occult blood screening by Monohaem.

Physiological gastrointestinal bleeding has been estimated to be 0.32 ± 0.09 mg/g stool(16), 0.1-0.2mg/g stool(17). The lower the theshold value of the immunochemical fecal occult blood test, the higher the number of positive cases that will be detected in the actual screening. In the immunochemical test, Monohaem, for human hemoglobin employed in this study, a high antibody titer with the cut-off point 0.02mg/g stool is used. Accordingly, the positivity rate of 5% in a two-day method is higher than that of the guaiac-impregnated Hemoccult test(10), and a large proportion of the screened population will have a positive test result following their annual screening. Higher positive rate of fecal occult blood test increases cancer detection, but it also increases false positive cases detected in the colonoscopic examination. If this high positivity rate is a serious limiting factor for wide scale screening of colorectal cancer, reconsideration of the threshold value of this test might be necessary as a trade-off between sensitivity and specificity.

The value obtained for the average costs per case is affected by the accuracy of the immunochemical occult blood test. Sensitivity analysis determines the degree to which uncertainty surrounding the costs and outcomes in the model

affects the conclusion of the analysis. In this analysis, critical parameters, both costs and health outcomes, are varied over a broad range to determine if the preferred strategy changes. The detection rates in this study were evaluated as 47% in a single-day method, 82% in a two-day method and 88% in a three-day method, indicating a significant difference in the test sensitivity between a single-day method and a two-day method, and between a single-day method and a three-day method. In addition, there were no significant differences in the detection rates and false positive rates between a two-day and a three-day methods. The cost of a two-day method for one case of colorectal cancer identified was substantially lower than that of a three-day method ($3350.65 versus $4136.36).

The most desirable method to assess the diagnostic accuracy of a screening test is to conduct both a screening test and close examination of all asymptomatic subjects in the community. However, the feasibility of carrying out such a study on a large scale is poor owing to the operational difficulties and thus a cross-sectional study in the hospital such as that employed here is recommended as the best alternative to investigate the validity of a screening test. The present study also provides information about the accuracy of a screening test, but has limitations compared with the above population-based study.

In terms of cost-effectiveness of the immunochemical occult blood screening, a comparative study between the immunochemical and chemical tests shows that the average costs required to detect one colorectal cancer case by an immunochemical fecal occult blood test, Monohaem method, is one-third lower than those by the guaiac-impregnated Hemoccult Ⅱ test(18). In addition, two studies in Japan suggest that the immunochemical fecal occult test followed by colonoscopy is most cost-effective in the screening for colorectal cancer(19,20).

One note of caution should be added; this comparison may not always be valid since the costs of colonoscopy differs among different countries and in some countries differing average costs would be obtained. Indeed, the cost-effectiveness of immunochemical versus guaiac-based screening cannot usually be generalized across different studies and countries as it depends on the technical minutiae of the specific test circumstances.

In conclusion, the present economic analysis suggests that a two-day fecal collection method described herein is the optimum procedure when carrying out Monohaem test as a means of screening for colorectal cancer. To reconfirm the findings of the present study, however, it would be necessary to conduct a larger population-based prospective study using appropriate methods.

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Table 1 Results of immunochemical fecal occult blood testing and colonoscopy

Ⅰ. No. of examinees	3300
Ⅱ. No. of positive occult blood cases (Ⅱ/Ⅰ)	191 (5.8%)
A. Single-day method	125 (3.8%)
B. Two-day method	168 (5.1%)
C. Three-day method	191 (5.8%)
Ⅲ. No. of detected cancer (Ⅲ/Ⅰ)	17 (0.5%)
A. Single-day method	8 (0.2%)
B. Two-day method	14 (0.4%)
C. Three-day method	15 (0.5%)

Table 2 Comparisons of average costs per one patient with colorectal cancer detected for the three fecal collection methods of immunochemical fecal occult blood screening

	Fecal collection methods		
	Single-day	Two-day	Three-day
Ⅰ. Screening costs (A×B)	$12000	$24000	$36000
A. Fecal occult blood test	$3.64(¥400)	$7.27(¥800)	$10.91(¥1200)
B. No. of screenees	3300	3300	3300
Ⅱ. Examination costs (A×B)	$17045.45	$22909.09	$26045.45
A. Diagnostic examination	$136.36 (¥15000)	$136.36 (¥15000)	$136.36 (¥15000)
B. No. of examinees	125	168	191
Ⅲ. Total costs (Ⅰ+Ⅱ)	$29045.45	$46909.09	$62045.45
Ⅳ. No. of detected cancer	8	14	15
Ⅴ. Average costs per one case detected (III/IV)	$3630.68	$3350.65	$4136.36

Table 3 Results of immunochemical fecal occult blood screening for colorectal cancer stratified by three fecal collection methods

Colorectal cancer	Fecal collection methods								
	Single-day			Two-day			Three-day		
	+	−	Total	+	−	Total	+	−	Total
+	8	9	17	14	3	17	15	2	17
−	117	3166	3283	154	3129	3283	176	3107	3283
Total	125	3175	3300	168	3132	3300	191	3109	3300

Table 4 Comparisons of detection rate and false positive rate among three fecal collection methods in immunochemical fecal occult blood screening

Accuracy	Fecal collection methods		
	Single-day	Two-day	Three-day
Detection rate (%)	8/17 (47.1)*	14/17 (82.4)	15/17 (88.2)
False positive rate (%)	117/3283 (3.5)	154/3283 (4.7)	176/3283 (5.3)

*: $p<0.05$ for difference in detection rate between single-day method and two-day method, and between single-day method and three-day method.