A new immunochemical fecal occult blood test (Hemosure IFOBT) with two-consecutive stool sample testing is a cost-effective approach for colon cancer screening: Results of a prospective multi-center study in Chinese patients

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A B S T R A C T

BACKGROUND: Guaiac-based chemical Fecal Occult Blood Tests (CFOBT) have been widely used for colorectal cancer screening in Western countries. It is recommended that the test be performed on three-consecutive stool samples. The goal of this study was to determine the cost-effectiveness of a new immunochemical FOBT method (Hemosure IFOBT) for colon cancer screening in the Chinese population, and whether the new assay could reduce the number of samples needed for the test. In addition, a combined sequential method (SFOBT) in which the CFOBT was performed first, followed by the IFOBT, was also evaluated.

METHODS: A multi-center hospital based study was performed, involving five major hospitals in Beijing, China. A total of 324 patients with various indications for colonoscopic examination were enrolled in the study. Three consecutive stool samples were collected from each study subject for simultaneous CFOBT and IFOBT tests. A colonoscopic examination was performed after the FOBT tests for all subjects.

RESULTS: The Hemosure IFOBT method had a significantly lower positive rate in normal individuals than the CFOBT (10.8% vs. 24.5%, respectively, $X2=9.82$, $P<0.01$). Both CFOBT and IFOBT were quite effective in detecting multiple or large adenomas (>20mm) as well as cancer. With three consecutive samples, the positive rates in large or multiple adenomas were 61.5% for CFOBT and 69.2% for IFOBT ($P>0.05$) and the positive rates for cancer were equal at 95.9% by both methods. The hypothetical SFOBT decreased the positive rate in normal and colitis patients ($p<0.05$), but at the expense of missing 1 cancer (1 out of 47 = 2.1%) and 3 large adenomas (3 out of 26 =11.5%). IFOBT with two consecutive samples had higher positive rates than either CFOBT or SFOBT in cancer group (87.8% vs. 77.5% and 75.5%, respectively, $P<0.05$), with retained relatively high specificity (96.4%) and the lowest cost per cancer detected than any other test modalities.

CONCLUSION: Hemosure IFOBT has better specificity than CFOBT in normal populations, and the hypothetical SFOBT may further increase the specificity and reduce the cost. Overall, the new Hemosure IFOBT with two consecutive stool samples appears to be the most cost-effective approach for colon cancer screening in the Chinese population. Further studies are needed to confirm the findings of the screened population.

INTRODUCTION

In recent years, the incidence of colorectal cancer is increasing rapidly in China, especially in major metropolitan areas such as Beijing and Shanghai [1]. The exact reason for this is unclear. The problem of colorectal cancer (CRC) in China is further compounded by the fact that more than half of patients with CRC are diagnosed at the advanced stage, which may be at least partly due to the lack of implementing screening measures [2,3]. Based on the data from randomized, controlled trials from developed countries, population based screening of CRC may increase the detection rate of early cancer, thus increasing the long-term survival rate of patients [4,5,6,7].

In the United States, the Fecal Occult Blood Test (FOBT) is one of the most commonly recommended colorectal cancer screening methods by the National Cancer Institute, National Institute of Health and the American Cancer Society[8]. Currently there are two major types of FOBT tests: Chemical Fecal Occult Blood Test (CFOBT) and Immunochemical Fecal Occult Blood Test (IFOBT). The CFOBT method is relatively inexpensive, but generates a higher false-positive rate and often requires a restriction of certain food types before and during the time of fecal sample collection. In contrast the IFOBT has better specificity, but has a relatively higher cost[9]. For either CFOBT or IFOBT test, however, it is recommended that the test should be performed on three consecutive samples, and patients with any positive findings should be evaluated further[8].

The barriers for colon cancer screening in less developed countries such as China include not only the lack of financial resources, but also the inconvenience of the sampling method, for example the need to collect multiple stool samples. Thus, there is a need to find the most cost-effective method and optimal sampling approach for colon cancer screening. In an attempt to reduce the cost barrier for colorectal cancer screening in China, a new IFOBT test (Hemosure IFOBT) that is easier to perform and considerably cheaper than IFOBT tests currently available in western countries, has been developed and used in clinical settings. To take a step further, we also developed a protocol termed "Sequential Fecal Occult Blood Test" (SFOBT), which combines the CFOBT and IFOBT tests together[3,10,11]. In SFOBT, with three consecutive samples, CFOBT is first tested on the first sample, and if it is positive, the result is confirmed by IFOBT. For negative CFOBT or positive CFOBT but negative IFOBT, the same sequence is repeated for the second and third sample. Only patients with at least one positive CFOBT, which is confirmed by IFOBT, are further evaluated by colonoscopy.

The goal of this multi-center study was to perform a direct comparison of the cost-effectiveness of the 3 FOBT protocols (CFOBT, IFOBT and SFOBT) for Chinese patients in

an effort to determine the optimal method and number of samples needed for population based colon cancer screening in China.

MATERIALS AND METHODS

Patient population

The study was carried out in 5 hospitals: Beijing Army General Hospital, First Hospital of Beijing University, Beijing Haidian Hospital, 309 Hospital of People's Liberation Army, and Second Hospital of Beijing University. The patients who underwent colonoscopy for variety indications in these 5 hospitals were recruited from Nov.2003 to Feb.2004. There were no age, sex, or race restrictions. After obtaining an inform consent, each patient was instructed to collect three consecutive stool samples prior to colonoscopy. The patients were excluded from the study if they did not provide 3 consecutive stool samples or if the appropriate procedure of FOBT was not followed according to the protocol provided in the test kit. The Clinical Trial Ethics Committees of each participating hospital approved the study.

Performing FOBT tests

For the convenience of patients, no specific restriction of diet was requested. All submitted stool samples were tested for CFOBT and IFOBT simultaneously, according to the procedures provided by the manufacturers (CFOBT kits were produced by Baso Tech. Lt. Comp in China and IFOBT were provided by Wanhua-Puman Biol. Tech Lt. Comp in China). In practice, SFOBT was a sequential method combining CFOBT and IFOBT, i.e., with CFOBT performed first; IFOBT would only be performed for the sample that was positive for CFOBT. Therefore, SFOBT was interpreted as positive only if both tests were positive. However, in this study, since CFOBT and IFOBT were performed simultaneously on all samples, the data for SFOBT was generated hypothetically based on the two test results (CFOBT and IFOBT), rather than a separate test procedure itself.

Colonoscopic examination

Colonoscopy was performed on all participants after the 3 FOBT tests. An experienced gastrointestinal physician performed all colonoscopic examinations. No significant adverse events associated with colonoscopy were ever noted on the study subjects. A complete colonoscopy was defined as an endoscope reaching the cecum. A biopsy was taken from any lesions suspected for tumors or inflammation.

Histopathological examination

Surgery was performed for those diagnosed with CRC. One pathologist from each hospital examined the biopsy samples from the respective hospitals. The stage of cancer was determined according to the standard protocol. Advanced colonic neoplasm was defined as an adenoma > 2 cm in diameter or villous adenoma, adenoma with moderate to severe dysplasia or carcinoma.

Statistical analysis

Sensitivity was calculated as a number with a true positive test/(number with a true positive + a false-negative test). Specificity was calculated as a number with a true negative test/(number with a true negative test + number with a false-positive test). Colonoscopy with histopathology findings were used as the gold standard. The X^2 test was used to test the significance of difference among different FOBT methods. The correlation coefficient was calculated between the magnitude of adenoma and positive rate of FOBT. $P<0.05$ was considered statistically significant and all tests were two-tailed.95% confidence intervals were calculated using methods for proportions.

RESULTS

Of the 324 patients that participated in the study, there were 50 colorectal cancer, 60 chronic colitis, 60 colorectal adenomas, 15 hemorrhoids, and 139 normal colons. Table 1 shows the clinical and demographic information of the patients. Among the 324 patients enrolled in the study, 186 were men and 137 were women. The mean age was 53.47±15.3 years and the age range was 18 to 68 years old (Table 1). The FOBT tests and colonoscopy were performed successfully on all except one patient with colon cancer, in whom the IFOBT test did not follow the protocol appropriately and thus was excluded from the analysis.

Table 2 presents the results of positive findings based on three consecutive samples in different groups of patients. The IFOBT method had a significantly lower positive rate in normal individuals than the CFOBT (10.8% vs. 24.5%, respectively, X2=9.82, $P<0.01$). The positive rates in colitis/hemorrhoid, adenomas of various sizes, and cancer groups were similar with two methods ($P>0.05$). Both methods were quite effective in detecting multiple or large adenomas (>20 mm) as well as cancer. The positive rates in large or multiple adenomas were 61.5% for CFOBT and 69.2% for IFOBT ($P>0.05$) and the positive rates for cancer were equal at 95.9% by both methods. As expected, the sequential method (SFOBT) further decreased the positive rate in normal and colitis groups ($P<0.05$) compared to the IFOBT method, however, it was at the expenses of missing 1 cancer (1 out of 47 = 2.1%) and 3 large adenomas (3 out of 26 = 11.5%).

Table 3 shows the results when only two consecutive stool samples were tested. The positive rate of IFOBT was higher than either CFOBT or SFOBT in the cancer group ($P<0.05$ by Chi-square test), with retained relatively low positivity in normal (5.6%).

We further compared the sensitivity and specificity of different FOBT protocols with two versus three consecutive samples in detecting CRC or adenoma plus CRC (Table 4). Because the same number of true negatives were used for the calculation, the specificities for "CRC" only or "adenoma + CRC" were the same. For IFOBT, a slight decrease of sensitivity (87.8-% vs. 95.9% for CRC and 65.1% vs. 69.7% for "adenoma + CRC", $P>0.05$ for both) but increased specificity was observed when two versus three consecutive samples were used. For SFOBT, the decrease of sensitivity was significant (75.7% Vs 93.8% for CRC and 49.5% Vs 65.1% for "adenoma + CRC", $P<0.05$ for both), and its specificity was not changed significantly (98.5% Vs 94.2% and 86.4% Vs 83.6%, $P>0.05$ for both), when three versus two consecutive samples were used. In addition, IFOBT had slightly better sensitivity to detect adenomas than SFOBT with two stool samples.

Table 5a shows the relationship of positive detecting rates of three FOBT protocols (CFOBT, IFOBT, and SFOBT) with tumor stages in cancer groups, when three-consecutive samples were used. The performance was similar for all three protocols. The detection rate was 60% for the patients with cancer of Dukes' stage A (3 out of 5) and 100% for patients with Stage B to D cancers. SFOBT missed one of the un-staged cancers.

The cost per each cancer detected was estimated for three different protocols, with one, two, and three consecutive samples. For the sake of simplicity, only the costs of the FOBT test (0.65 Chinese Yuan/test For CFOBT and 2.0 Chinese Yuan/test for IFOBT) and colonoscopy (300 Chinese Yuan/test) were included in the calculation, whereas other costs were not considered (for example cost for sample collection, shipping, etc.). The cost was adjusted by equalizing the number of cancers detected for each type of test (47 cases for three consecutive stool samples, and 43 cases for two consecutive stool samples). As shown in Table 6, we found that the cost/cancer detected was the lowest using SFOBT (906.4 Chinese Yuan per cancer detected) when three consecutive stool samples were used. However, with two consecutive samples, the cost/cancer detected was lowest when using the IFOBT (727.7 Chinese Yuan per cancer detected). When only one stool sample was used, the CFOBT or SFOBT failed to be positive in over 40% cancer patients, whereas the IFOBT was negative in 25% of cancer patients. The cost savings; however, was not substantially different from the two sample testing.

DISCUSSION

The ultimate goal of cancer screening is to reduce the incidence and mortality of the disease by detecting cancer at its earliest possible stage so that the progression of the disease can be interrupted[12]. The FOBT has widely been used as an effective screening tool for colon cancer in Western countries. Prospective, randomized controlled trials have demonstrated a 15% to 33% reduction in colorectal cancer mortality with FOBT screening[5,6,7,13]. There are currently two major types of FOBT: chemical and immunochemical tests. The chemicals-based test (CFOBT) reacts positively to pseudoperoxidase activity of heme in the feces and is not specific for human blood. False positive tests can be due to the presence of plant and animal materials. In contrast the immunochemical fecal occult blood test (IFOBT) is designed to detect the human hemoglobin and is also specific for blood in the large intestines rather than for blood originating from other sources higher up in the gastrointestinal tract[14]. Studies have shown that the IFOBT has better specificity than CFOBT in cancer detection in western countries and in Japan[9,14,15]. However, there has been no head to head comparison reported in the Chinese population in mainland China. Furthermore, while three serial samples are generally recommended for the screening, there has been few studies that analyzed the cost effectiveness of the optimal number of samples that are needed for screening with various types of FOBT.

This study compared directly the sensitivity and specificity of traditional chemical Guaiac-based FOBT (CFOBT) and a new immunochemical based FOBT (Hemosure IFOBT) developed by a Chinese company for the detection of colon cancer and adenomas in Chinese patients referring for colonoscopy. In addition, we also examined a combined sequential protocol hypothetically, i.e., CFOBT followed by IFOBT for CFOBT-positive samples (SFOBT). With SFOBT, only samples when both tests were positive, was a positive score given. A colonoscopy was performed for all subjects and used as the gold standard. With three consecutive stool samples, the study showed that SFOBT and IFOBT had favorable specificity for colon cancer detection over CFOBT (94.2% and 89.2% versus 75.5%), with the similar sensitivity (93.8% and 95.9% Vs 95.9%, $P>0.05$). With two consecutive samples, IFOBT had a higher sensitivity (87.8%) and specificity (96.4%) than either CFOBT or SFOBT.

Using the colonoscopy as the gold standard, the overall reported sensitivity of CFOBT for colon cancer detection is around 80% and specificity in the range of 85-94% (for review see reference[14]). For IFOBT, the sensitivity is in the range 80 to 87% and the specificity of 87 to 97% [14, 16, 17]. Our results showed that CFOBT test has substantially lower specificity, but had a similar level of sensitivity than what had been reported previously in similar studies probably due to the fact that the Chinese diet often contains components that may cause a false positive CFOBT[19]. The finding that the IFOBT has a substantially higher

specificity than the CFOBT test in our study supports this hypothesis.

The rate of a very small polyp being cancerous may be only 1 in 500, that for a l cm diameter polyp is around 10% and that for a polyp over 2cm may be 50%[18]. Table 2 showed with three consecutive samples, the positive rate of adenomas was similar for all 3 methods (41.0% for CFOBT, 48.3% for IFOBT, and 41.6% for SFOBT). With two-consecutive samples (Table 3), the positive rate for IFOBT remained at 46.7%, however, the positive rate for SFOBT was only 28.3%, significantly lower than that of IFOBT ($P<0.05$). In fact, SFOBT did not detect any small adenomas less than 0.5 cm.

The American Cancer Society Guidelines do not recommend a combined IFOBT and CFOBT approach for colon cancer screening in United States. We, over the years, have adopted the combined SFOBT approach in clinical and population based screening of colon cancer in part of China as a cost-saving gesture. This is proposed with the assumption that with three consecutive stool samples, CFOBT has at least the same, or better, sensitivity but lower specificity (possibly due to the Chinese diet) than IFOBT to detect significant colonic neoplasia (large adenoma and carcinoma) than IFOBT. Although the findings from the current cross-sectional study do not show significant differences in positive rates for cancer patients, it is entirely possible that in the actual screening process and with a large sample size, the CFOBT might have lower sensitivity than CFOBT, especially for adenomas. Another potential problem with the SFOBT approach is the fact that some CFOBT formats used sample cards submitted by the patient, not the actual stool sample, thus IFOBT may not be able to perform on the card.

Our results showed that the two sample based Hemosure IFOBT is the most cost-effective approach than other protocols. While numerous studies have examined the various FOBT tests, few directly analyzed the optimal number of samples needed for the screening. This is important for not only the cost-effectiveness consideration, but also for the consideration of subject compliance in regarding stool sample collection, which is also a major barrier for colon cancer screening [3]. A study from Wong in Hong Kong Chinese population also demonstrated the effectiveness of two sample format of IFOBT method using a different product, the Magstream 1000/Hem SP from Japan[17]. However, the IFOBT used in their study had a different format, and there was no data from Wong's study for three samples. It should also be noted that there are different formats of IFOBT throughout the world, and whether they all have similar testing characteristics, remain to be a question.

Taken together, our study showed that Hemosure IFOBT has a better specificity than the

CFOBT in colonoscopically normal populations. Whereas the hypothetical SFOBT approach with three consecutive stool samples may further increase the specificity and reduce the cost, overall, the IFOBT with two consecutive stool samples appears to be the most cost-effective approach of colon cancer screening. Further prospective trials will be needed to confirm such an observation.

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Contributors

S Li (principal investigator), HH Wang, J Hu, N Li, Y Liu, Z Wu, Y Zheng, HG Wang, K Wu, H Ye, and J Rao all participated in the conception and design of the study, acquisition and interpretation of the data, and drafting and review of the report.

Conflict of Interest Statements

We declare that we have no conflict of interest.

Acknowledgements

We thank Wanhua-Puman Biol.Tech Lt Company for providing IFOBT kits for the study

Table 1. Subjects demographics and clinical information

Characteristics		N
Sex:	Male	186
	Female	137
Age:	Mean + SD	53.5 + 15.3
	Range	18-68
Clinical Indications for Colonoscopy		323
Suspicious for colon cancer		37
History of colon cancer		10
History of polyps		34
Abdominal pain		62
Diarrhea		40
Blood stool		80
Asymptomatic		46
Other		14

Table 2. Positivity of various FOBT tests by colonoscopic findings based on three consecutive stool samples

Protocols	N	CFOBT (%)	IFOBT (%)	SFOBT (%)
Colonoscopic findings				
Normal	139	34 (24.5)	15 (10.8)*	8 (5.8)*
Colitis & Hemorrhoid	75	41 (54.7)	47 (62.6)	27 (36%)#
Adenoma				
<5 mm	12	3 (25.0)	4 (30.0)	3 (25.0)
5-10 mm	14	4 (28.6)	3 (21.4)	3 (21.4)
10-20 mm	8	4 (50.0)	4 (50.0)	4 (50.0)
>20 mm or multiple	26	16 (61.5)	18 (69.2)	15 (57.7)
Cancer	49	47 (95.9)	47 (95.9)	46 (93.8)
Total	323			

P<0.01 compared to CFOBT1 method
#P<0.05 compared to IFOBT method

Table 3. Positivity of various FOBT test by colonoscopic findings based on two consecutive stool samples

Protocols	N	CFOBT (%)	IFOBT (%)	SFOBT (%)
Colonoscopic findings				
Normal	139	16 (11.5)	5 (5.6)	2 (1.5)*
Colitis & Hemorrhoid	75	35 (46.7)	42 (56)	27 (36)
Adenomas				
<5mm	12	3 (25)	4 (33.3)	0 (0)
5- 10mm	14	4 (17.4)	3 (21.4)	2 (14.3)
10-20 mm	8	4 (50)	4 (50)	4 (50)
>20 mm or multiple	26	14 (53.8)	17 (65.4)	11 (42.3)
Cancer	49	38 (77.5)	43 (87.8)*	37 (75.5)
Total	323			

*P<0.01 compared to CFOBT

Table 4. Sensitive and specificity of various FOBT tests for adenomas and colorectal cancers (CRC) with two- or three-Consecutive Samples

	CFOBT	IFOBT	SFOBT
Two Consecutive Samples			
Sensitivity (% + 95% CI)			
Adenoma	41.7 (29.2-54.1)	46.7 (34.0-59.3)	28.3 (16.9-39.4)
Adenoma+CRC#	57.8 (48.5-67.1)	65.1 (56.2-74.1)	49.5 (40.0-58.9)$^{+/++}$
CRC only	77.5 (65.8-89.2)	87.8 (78.6-97.0)	75.5 (63.5-87.5)$^{+}$
Specificity (%)			
Adenoma	76.2 (70.4-81.9)	78.0 (72.5-83.6)	86.4 (81.8-91.0)
Adenoma+CRC	76.2 (70.4-81.9)	78.0 (72.5-83.6)	86.4 (81.8-91.0)$^{++}$
CRC only	88.5 (79.6-97.4)	96.4 (91.2-100.0)	98.5 (95.1-100.0)
Three Consecutive Samples			
Sensitivity (%)			
Adenoma	45.0 (32.4-57.6)	48.3 (35.7-61.0)	41.6 (29.2-54.1)
Adenoma + CRC	67.9(59.1-76.7)	69.7(61.1-78.4)	65.1(56.2-74.1)
CRC only*	95.9 (90.3-100.0)	95.9 (90.3-100.0)	93.8 (87.0-100.0)
Specificity (%)			
Adenoma	64.9 (58.6-71.4)	71.0 (65.0-77.1)	83.6 (78.7-88.6)
Adenoma + CRC	64.9 (58.6-71.4)	71.0 (65.0-77.1)	83.6 (78.7-88.6)
CRC only	75.5 (63.5-87.5)	89.2 (80.5-97.9)	94.2 (87.7-100.0)

* Compares "CRC" versus "normal + other diseases (colitis/hemorrhoid)"

Compares "adenoma + cancer" versus "normal + other diseases (colitis/hemorrhoid)"

+ P <0.05 compare to IFOBT

++ P < 0.05 compare to CFOBT

Table 5a Results of various FOBT tests vs. colorectal cancer stage with 3 consecutive stool samples

	Stages				
Methods	Dukes'A	Dukes'B	Dukes'C	Dukes'D	Unstaged
CFOBT					
Positive	3	15	16	4	9
Negative	2	0	0	0	0
IFOBT					
Positive	3	15	16	4	9
Negative	2	0	0	0	0
SFOBT					
Positive	3	15	16	4	8
Negative	2	0	0	0	1

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Table 5b Results of various FOBT tests vs. colorectal cancer stage with 2 consecutive stool Samples

	Stages				
Methods	Dukes'A	Dukes'B	Dukes'C	Dukes'D	Unstaged
CFOBT					
Positive	2	13	14	3	6
Negative	3	2	2	1	3
IFOBT					
Positive	2	14	15	4	8
Negative	3	1	1	0	1
SFOBT					
Positive	2	13	13	3	6
Negative	3	2	3	1	3

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Table 6. Cost analysis of various FOBT methods (CFOBT, IFOBT, and SFOBT) with one, two or three consecutive samples

Methods	Times	FOBT (+) cases			Colonoscopy	Total Cost	Cost/ca
		Ca*	Non-ca	Other			
CFOBT	3	47	34	78	159	48323.9	1028.3
	2	38	16	40	94	28619.9	796.6
	1	29	12	29	70	21210.0	845.1
IFOBT	3	47	15	86	148	46338.0	985.9
	2	43	5	52	100	31292.0	727.7
	1	35	1	31	67	20746.0	693.1
SFOBT	3	46	8	74	128	40967.9	906.4
	2	37	2	41	80	25711.9	755.2
	1	28	1	27	56	17656.0	742.1

- Adjusted cost/cancer detected (in Chinese Yuan)

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