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ORIGINAL ARTICLE

Fecal Occult Blood Test in Patients on Low-Dose Aspirin, Warfarin, Clopidogrel, or Non-steroidal Anti-inflammatory Drugs

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Abstract
Aim To determine the effect of anticoagulants and antiplatelet medications on the positive-predictive-value of fecal occult blood test (FOBT).
Methods All patients who underwent a colonoscopy at our institution from 1995 to 2006 for a positive FOBT were identified. Medical records were searched, and patients were stratified into five groups selected a priori: low-dose aspirin, NSAIDs, warfarin, clopidogrel, or controls. The positive-predictive-value of FOBT for advanced colonic neoplasia was computed for each group.
Results During the study period, 1,126 patients underwent colonoscopy for a positive FOBT and met entry criteria. The average age of study participants was 69 years and most were men. The positive-predictive-value of FOBT for advanced colon neoplasia was significantly higher in the control group (30.5%) when compared to those on low-dose aspirin (20.5%; $p = 0.003$), NSAIDs (19.7%; $p = 0.003$), clopidogrel (7.3%; $p = 0.002$), or warfarin (20%; $p = 0.05$). The positive-predictive-value of FOBT was significantly lower for those on clopidogrel than those on low-dose aspirin ($p = 0.04$) and NSAIDs ($p = 0.05$), but not warfarin ($p = 0.08$). The positive-predictive-value for FOBT was similar for those on aspirin, NSAIDs, and warfarin. There was a linear trend between the number of number of positive FOBT cards and prevalence of advanced colon neoplasia ($p = 0.01$).
Conclusion Anticoagulants and antiplatelet medications lower the positive-predictive-value of FOBT for advance colonic neoplasia and should be stopped if clinically feasible prior to stool collection.

Keywords Colon cancer · FOBT · Occult blood · Screening · Fecal occult blood test

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Background

Despite the increasing use of direct colonoscopy, fecal occult blood test (FOBT) remains an extremely important part of colon cancer screening in the United States [1]. In a recent population-based survey of those ≥50 years of age, 18.7% reported having undergone FOBT during the preceding year [2]. FOBT is also the dominant colon cancer screening strategy for several large heath care systems, including the Veterans Affairs [3]. While the efficacy of FOBT in reducing colon cancer-related morbidity and mortality has been demonstrated in randomized trials, several questions regarding its effectiveness when applied to everyday clinical practice remain unanswered [1–3]. One of these is the accuracy of FOBT in patients on anticoagulants and antiplatelet medications, an issue that has become increasingly important with the widespread use of these medications. There is no consensus amongst experts if these medications need to be stopped before stool collection for FOBT is performed [4, 5]. Unnecessary restrictions on medications may adversely effect patient and physician compliance with FOBT. On the other hand, if anticoagulants and antiplatelet

medications increase the likelihood of bleeding from insignificant colonic lesions and lower the accuracy of FOBT for neoplasia, patients may undergo unwarranted colonoscopy. The objective of our study was to compare the positive predictive value of FOBT for advanced colonic neoplasia in patients on anticoagulants and antiplatelet medications with those who were not on these medications.

Methods

We searched the computerized colonoscopy database at the Minneapolis Veterans Affairs Medical Center from 1995 to 2006 and identified all patients who were referred for colonoscopy for a positive FOBT. Electronic medical records for study subjects were searched and information regarding patient characteristics, pharmacy profile, and colonoscopy findings was extracted. Age at the time of colonoscopy was used for analysis. Based on the patients' pharmacy profile on the date fecal occult blood testing was conducted, subjects were stratified into five groups selected a priori: low-dose aspirin group—patients prescribed aspirin $\leq$325 mg/day; non-steroidal anti-inflammatory (NSAID) group—patients prescribed aspirin >325 mg/day and or other NSAIDs at least three times a week; warfarin group—patients prescribed warfarin (patients prescribed aspirin $\leq$325 mg and warfarin were included in this group), clopidogrel group—patients prescribed clopidogrel at least three times a week; or control group—patients who were not prescribed aspirin, NSAIDs, warfarin or clopidogrel. Patients on warfarin and NSAIDs, warfarin and clopidogrel, or NSAIDs and clopidogrel were excluded from the analysis. We also excluded patients with overt gastrointestinal bleeding, iron deficiency anemia, familial adenomatous polyposis syndrome, hereditary non-polyposis colon cancer syndrome, and inflammatory bowel disease. Advanced colonic neoplasm, defined as invasive colon cancer, malignant polyp, polyp with high-grade dysplasia, villous adenoma, or tubular adenoma $\geq$10 mm served as the primary outcome measure [6]. FOBT was performed with Hemoccult II (Beckman Coulter, Incorporated, Fullerton, CA) or equivalent stool cards. All stool specimens were obtained using at-home test kits and were processed by trained pathology technicians without rehydration.

Dietary restrictions but no change in medications prior to stool collection were recommended, but compliance was not verified. Our institutional review board approved this study.

Data Analysis

One-way ANOVA was used to compare continuous variables, and Chi-square test was used to compare categorical variables across the five study groups. Positive predictive value of FOBT for advanced colonic neoplasia was computed for each study group. Positive predictive value was defined as the proportion of patients with positive FOBT who had advanced colonic neoplasia. The study was powered to detect a 15% difference in the prevalence of advanced colon neoplasia between patients on warfarin and controls, assuming a 25% prevalence of advanced colon neoplasia in controls. Logistic regression models were created with advanced colonic neoplasia as the dependent variable. Study groups were entered into the model as independent class variables. These models were then used to adjust for difference in age and prevalence of co-morbid illness between the study groups.

Results

During the study period, 1,126 patients underwent colonoscopy at the Minneapolis Veterans Affairs Medical Center for a positive FOBT and met study criteria. Of these, 215 patients were included in the low-dose aspirin group, 218 patients in the NSAIDs group, 85 patients in the warfarin group, 41 patients in the clopidogrel group, and 518 patients in the control group. Table 1 shows the baseline characteristics of the study subjects stratified by study group. The study groups were similar with regard to age and gender. As expected, there were significant differences between the study groups with regard to the prevalence of hypertension, diabetes, and coronary artery disease.

The positive predictive value of FOBT for advanced colon neoplasia was significantly higher in the control group (30.5%) when compared to those on aspirin (20.5%; $p = 0.003$), NSAIDs (19.7%; $p = 0.003$), clopidogrel (7.3%; $p = 0.002$), or warfarin (20%; $p = 0.05$) (Fig. 1; Table 2). The positive predictive value of FOBT was significantly lower for those on clopidogrel than those on aspirin ($p = 0.04$) and NSAIDS ($p = 0.05$), but did not reach statistical significance when compared to those on warfarin ($p = 0.08$). The positive predictive value for FOBT was similar for those on aspirin, NSAIDS and warfarin. Table 2 also shows the positive predictive value of FOBT for other colonic lesions. A similar trend, with the positive predictive value of FOBT being highest for those in the control group was noted for most other colonic lesions as well. Of the 85 patients in the warfarin group, seven patients were also on warfarin and low-dose aspirin. The positive predictive value of FOBT for the 78 patients on warfarin alone was 19.4%, and not significantly different from the warfarin group as a whole (20%), and therefore these patients were reported together.

Study subjects were stratified by the number of positive fecal occult blood test cards (Table 3). There was a linear

Table 1 Baseline characteristics of study subjects

	Aspirin $n = 264$	NSAIDs $n = 218$	Clopidogrel $n = 41$	Warfarin[a] $n = 85$	Controls $n = 518$	p-value
Age in years	68.6 ± 10	67.1 ± 11	68.2 ± 9.8	70.7 ± 9.7	68.2 ± 10.1	0.09
Gender—males	99.6% (263)	98.2% (214)	97.6% (40)	98.8% (84)	97.5% (505)	0.3
Hypertension	73.1% (193)	61.5% (134)	85.4% (35)	56.5% (48)	56.8% (294)	<0.001
Diabetes	45.1% (119)	30.3% (66)	46.3% (19)	42.4% (36)	23.9% (124)	<0.001
Coronary disease	51.5% (136)	32.1% (70)	68.3% (28)	42.4% (36)	11.6% (60)	<0.001
Lung disease	22.3% (59)	14.7% (32)	12.2% (5)	16.5% (14)	18.1% (94)	0.2

[a] Seven patients in the warfarin group were also on low-dose ASA

NSAIDs, Non-steroidal anti-inflammatory drugs; Age given as mean ± standard deviation; *percentages and numbers in parenthesis* are counts; *Hypertension*, systolic BP > 140 mmHg or diastolic > 90 mmHg, or use of anti-hypertensives; *Diabetes*, fasting blood plasma glucose level of 126 mg/dl or higher on >1 occasion; *Coronary disease*, history of myocardial infarction, angina, or congestive heart failure; *Lung disease*, chronic obstructive lung disease, asthma, or pulmonary fibrosis

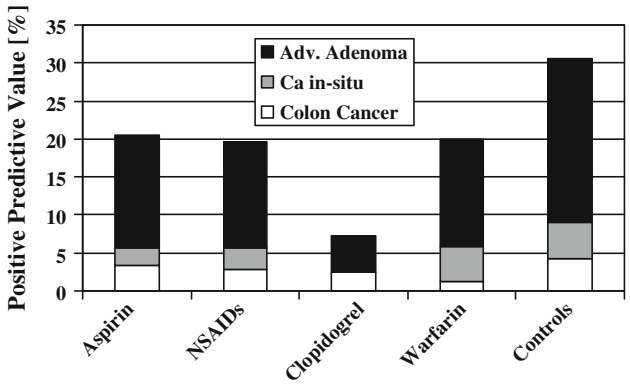

Fig. 1 Comparison of the positive predictive value of FOBT for advanced colonic neoplasia between study groups. *Adv. Adenoma* advanced adenoma, *Ca in situ* carcinoma in situ, *Aspirin* low-dose aspirin group, *Warfarin* seven patients in this group were also on low-dose aspirin

trend between the number of number of positive stool cards and positive predictive value of FOBT ($p = 0.01$). A comparison was also made between colon cancer stage at the time of diagnosis between patients on anticoagulants and antiplatelet medications and controls. No statistically significant difference between the groups was noted (Table 4).

We used logistic regression to adjust for differences in the prevalence of co-morbidities amongst study groups. First we entered coronary artery disease, lung disease, hypertension, and diabetes as independent variables into a logistic regression equation. Advanced colonic neoplasia served as the dependent variable (outcome). Only coronary artery disease was found to be independently associated with advanced colonic neoplasia (odds ratio = 0.64; 95% CI, 0.44–0.93; $p = 0.02$). Logistic regression models were then generated to compare study groups after adjusting for the presence of coronary artery disease (Table 5). The odds of finding advanced colonic neoplasia at colonoscopy done for positive FOBT were similar and indistinguishable from an odds ratio of 1 for those in the aspirin, NSAID, and warfarin groups. The odds of finding advanced colonic neoplasia were 70% lower for those in the clopidogrel group, however, these results were not statistically significant (odds ratio 0.3; $p = 0.07$).

Table 2 Positive predictive value of fecal occult blood test for colonic pathology

	Aspirin (%) $n = 264$	NSAIDs (%) $n = 218$	Clopidogrel (%) $n = 41$	Warfarin[a] (%) $n = 85$	Controls (%) $n = 518$
Advanced neoplasia	20.5 (54)	19.7 (43)	7.3 (3)	20.0 (17)	30.5 (158)
Colorectal cancer	3.4 (9)	2.8 (6)	2.4 (1)	1.2 (1)	4.2 (22)
Advanced adenoma	14.8 (39)	14.2 (31)	4.9 (2)	14.1 (12)	21.4 (111)
A.V.M.	2.3 (6)	1.8 (4)	2.4 (1)	8.2 (7)	5.6 (29)
Colitis	0.8 (2)	3.2 (7)	2.4 (1)	5.9 (5)	2.7 (14)
Ulcers	0.8 (2)	2.3 (5)	0.0 (0)	0.0 (0)	1.4 (7)

[a] Seven patients in the warfarin group were also on low-dose ASA

Numbers in parenthesis are counts

NSAIDs non-steroidal anti-inflammatory drugs; *A.V.M.* arterio-venous malformations; Colitis includes radiation proctitis

Table 3 Risk of advanced colonic neoplasia based on the number of positive fecal occult blood test cards

No. of positive FOBT cards	No. of subjects	PPV for advanced colonic neoplasia (%)
1 of 3	789	15.60
2 of 3	197	21.80
3 of 3	130	22.30
>3[a]	10	30.00

p for trend = 0.007

[a] Few patients inadvertently received >3 cards

FOBT Fecal occult blood test; *PPV* positive predictive value

Table 4 TNM cancer stage stratified by study groups

	Stage I (%)	Stage II (%)	Stage III (%)	Stage IV (%)
Control group	27 (4)	53 (8)	20 (3)	0 (0)
Others	48 (10)	14 (3)	23 (5)	10 (2)

Fisher's exact test $p = 0.2$

Stage, TNM cancer stage; *Others*, subjects in aspirin, NSAIDs, clopidogrel and warfarin groups

Numbers in parenthesis are counts

Table 5 Unadjusted and adjusted odds for the diagnosis of advanced colonic neoplasia stratified by study group

	Odds ratio	p-value	95% CI
Unadjusted odds ratios			
Aspirin	0.8	0.18	0.5–1.1
NSAIDs	0.8	0.17	0.5–1.1
Clopidogrel	0.2	0.05	0.05–0.9
Warfarin	0.7	0.25	0.4–1.3
Controls	1	NA	NA
Odds ratios adjusted for prevalence of coronary artery disease			
Aspirin	0.9	0.5	0.6–1.3
NSAIDs	0.8	0.2	0.5–1.2
Clopidogrel	0.3	0.07	0.06–1.1
Warfarin	0.7	0.3	0.4–1.4
Controls	1	NA	NA

NSAIDs non-steroidal anti-inflammatory drugs; *CI* confidence interval

Discussion

We found that anticoagulants and antiplatelet medications lowered the positive predictive value of FOBT for advanced colonic neoplasia. Clopidogrel, when compared to aspirin, NSAIDs, and warfarin, appeared to have the most negative effect on the positive predictive value of FOBT.

FOBT remains the only colon cancer screening strategy supported by evidence from multiple randomized controlled trials [7–9]. Further, cost-effectiveness analyses show that FOBT is highly cost-effective [10]. The estimated cost per year of life gained by annual FOBT is $13,581, well within the $40,000 benchmark established by the United States federal government. The cost of cancer detection for a FOBT-based colon cancer screening program results predominantly from the initial colonoscopy that is required for the evaluation of a positive FOBT, and from subsequent surveillance colonoscopies in those who are found to have an adenomatous polyp. Therefore, even a modest decrease in the positive predictive value of FOBT may result in a dramatic increase in costs. In an effectiveness- and economic-impact analysis, Helm et al. [11] projected the results of the Minnesota and Funen FOBT trials to the United States population at-risk. They found that a 26% difference in the proportion of positive FOBT tests noted between the Minnesota and Funen FOBT trials results in an estimated $15.7 billion increase in over all cost of cancer detection.

For FOBT to remain a cost-effective and viable national screening strategy, the test itself should be standardized. There is still no agreement regarding recommendations for FOBT in patients on anticoagulants and antiplatelet medications. The lack of consensus in this area is reflected in the design of the three pivotal FOBT clinic trials: Mandel et al. recommended that study participants stop aspirin 24 h before and during stool collection: Kronborg et al. recommended that study participants stop all non-steroidal anti-inflammatory drugs 3 days before stool collection; and Hardcastle et al. did not recommend any change in medications [7–9].

While most experts agree that NSAIDs (including low-dose aspirin) increase gastrointestinal blood loss, it remains uncertain as to whether the increase is sufficient to result in a false-positive FOBT. Our study found that non-steroidal anti-inflammatory drugs (including low-dose aspirin) substantially lower the positive predictive value of FOBT and should therefore be stopped prior to stool collection. Our results are supported by those of Greenburg et al. [12] who studied asymptomatic individuals and found a positive FOBT in 0 of 25 controls, 7 of 50 using low-dose aspirin, and 3 of 25 using warfarin. In a study of healthy volunteers, Fleming et al. [13] found fecal blood levels up to five times the normal level in those using aspirin and consuming moderate amounts of alcohol. However, our results contradict those of Norfleet, who found no evidence of occult blood in the stool of 27 volunteers who were given 1,300 mg of aspirin [14]. In a prospective study conducted at a Veterans Affairs hospital, investigators found that aspirin users and non-users with positive FOBT were equally likely to have findings at colonoscopy that could

explain occult bleeding [15]. This study was limited by a small sample size in the control group ($n = 58$) and was different from ours in that the authors included right-side colitis and vascular malformations along with neoplastic lesions in the primary outcome.

The effect of warfarin on occult gastrointestinal blood loss and the accuracy of FOBT have been less extensively evaluated. In a study of 128 patients with positive FOBT taking warfarin, Kewenter et al. [16] concluded that the positive predictive value of FOBT was too low to permit its use as a screening tool in this population. Contradictory results were reported by another study that found that the positive predictive value of FOBT was the same in warfarin users when compared to an age- and gender-matched control group of warfarin non-users [17]. It is not clear why the results of this study differ from ours, as both were done on subjects with very similar demographics. One possibility is that in this study, 48% of those in the control group were on NSAIDS compared to only 14.8% in the warfarin group ($p < 0.001$). We speculate that NSAIDS may have lowered the positive predictive value of FOBT in the control group, resulting in no difference being detected between the two study groups. In our study, 7 of 85 patients in the warfarin group were also on low-dose aspirin. We found no significant difference in our results when these seven patients were excluded from the analysis. As defined by the study protocol, final results were reported with these seven patients included in the warfarin group.

We are not aware of any other study that has evaluated the effect of clopidogrel on FOBT for colon cancer screening. We found the positive predictive value of FOBT in those using clopidogrel was only 7.3%. This was substantially lower than that observed in other study groups. Platelets pay a central role in mucosal healing throughout the gastrointestinal tract [18]. Clopidogrel blocks the activation of platelets by irreversibly binding to ADP receptors, and may substantially impair mucosal healing. In a study of 30 healthy volunteers, the addition of clopidogrel to naproxen was associated with an increase of the mean daily blood loss from 1.75 ± 1.40 to 6.83 ± 9.32 ml/day [19]. While we excluded patients on both clopidogrel and NSAIDs from our study, it has been well documented that up to 36% of asymptomatic volunteers may have gastroduodenal ulcers or erosions [20]. It is possible that clopidogrel had the dual effect of impairing healing and promoting bleeding from these otherwise insignificant gastrointestinal lesions, resulting in an increase in false-positive FOBT. An alternative explanation of our findings is that patients using clopidogrel were also using other medications or had other medical conditions that resulted in increased gastrointestinal occult blood loss and thus lowered the positive predictive value of FOBT, and that clopidogrel was simply a confounder in that relationship. This appears to be unlikely since we tested and adjusted for all statistically significant confounders in our final logistic regression model, and still found that clopidogrel use was associated with a lower positive predictive valve for FOBT. The retrospective nature of our analysis does not allow us to firmly establish a cause-and-effect relationship between clopidogrel use and lower positive predictive valve for FOBT, but our data raise that possibility.

Several limitations of our study warrant further discussion. First, our study has all the inherent shortcomings of a retrospective analysis. We attempted to mitigate this by defining our study groups and outcomes a priori. Further, a retrospective design allowed us to collect data on a large number of patients, including a control group that was not using anticoagulants or antiplatelet medications. Second, we did not perform colonoscopy on patients who had a negative FOBT, and were therefore not able to report on the influence anticoagulants and anti-platelet drugs may have had on the sensitivity and specificity of FOBT. We also did not study the effect alcohol or other drugs may have had by themselves or by their interaction with anticoagulants and anti-platelet drugs on FOBT. Third, almost all study subjects in our study were elderly and male, reflecting the United States veteran population served by our institution. Fourth, we used Hemoccult II or equivalent cards to perform FOBT, and therefore our results may not be applicable to the newer immunologic-based occult blood assays.

In conclusion, we found that anticoagulants and antiplatelet medications reduced the positive predictive value of FOBT for advanced colonic neoplasia. We recommend that if clinically feasible, these medications should be stopped prior to stool collection for FOBT.

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