

Comparative Efficacy of Water Indigo Carmine vs. Water or Air Method on Adenoma Detection Rate (ADR):

A Randomized Controlled Trial (RCT)

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Comparative Efficacy of Water Indigo Carmine Vs. Water or Air Method

Project Summary/Abstract

Detection and removal of colorectal adenomas is the recommended approach to the prevention of colorectal cancers (CRC). In separate studies we reported that water infusion in lieu of air insufflation (water method) provided a significantly higher overall adenoma detection rate (ADR) and proximal diminutive ADR than the usual method of air insufflation used during scope insertion. When indigocarmine was added to the water method, the dye highlighted small colonic lesions and significantly increased the overall ADR compared with historical cohorts examined by the water method alone or the conventional air method, as well as proximal diminutive ADR when compared with the water method alone. This proposal addresses the question of whether the water method (with or without indigocarmine) will result in a significantly higher proximal diminutive ADR compared with the air method alone in a RCT. The primary hypothesis asserts that a higher proportion with at least one proximal diminutive adenoma (ADR) will be found in the group randomized to the water + indigocarmine method compared with those randomized to the water method alone or the air method. Asymptomatic veterans referred for sedated colonoscopy for CRC screening at the Sacramento VAMC will be considered for enrollment. Over a 2.5 year recruitment period a total of 330 consented veterans will be randomized to confirm a 20% (34% - 14%) difference in proximal diminutive ADR in favor of the water group in the water vs. air comparison; and a 30% (64% - 34%) difference in favor of the indigocarmine + water method in the indigocarmine + water vs. water comparison. Consent covers agreement to undergo colonoscopy by the randomized methods, respond to pre- and post-colonoscopy questionnaires and allow the examination to be recorded for data analysis in a de-identified fashion. The PI, experienced in all three methods, will examine all enrolled patients. To ensure quality performance, all groups are expected to maintain the recommended overall ADR of 25% in male subjects and 15% in female subjects. Applicable human subject protection and adverse event monitoring procedures will be followed. Outcome data will be gathered and monitored prospectively and guarded by relevant data security measures. Appropriate evaluation with logistic regression and analysis of variance will be employed. Population studies showed that traditional air colonoscopy failed to eliminate post screening colonoscopy cancers or cancer mortality in the proximal colon. Even diminutive adenomas harbor significant dysplasia. A simple, inexpensive, easy-to-learn method of adding indigocarmine to the water method may increase the yield of proximal diminutive adenomas. A higher ADR may minimize the burden of interval CRC by decreasing missed adenomas. The long term goal is to perform further studies to determine if post screening colonoscopy interval cancers and cancer mortality in the proximal colon can be attenuated among the veteran population by the novel methods.

Project Narrative

Adenoma detection rate (ADR) is a quality indicator of colonoscopy performed for colorectal cancer screening. Population studies have shown that traditional air colonoscopy fail to eliminate post screening colonoscopy cancers or cancer mortality in the proximal colon. We aim to establish the superior effectiveness of combining chromoendoscopy with the water method in detecting more proximal diminutive adenomas during screening colonoscopy in sedated veterans. An improved adenoma detection rate associated with optical colonoscopy will minimize the risk of missed lesions. The improvement may translate into a remedy for the limitations of screening colonoscopy in the proximal colon. In other words, a higher adenoma detection rate may minimize the burden of post screening colonoscopy interval colorectal cancers among the veteran population.

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Facility

The Sacramento VA Medical Center has a total of 5 procedure rooms and we have state-of-art equipment for performing both air and water colonoscopy. We have conducted a number of pilot studies and completed several IRB approved RCTs to determine the effects of water colonoscopy on cecal intubation rate, medications requirement and patient satisfaction. All members of the supporting staff are familiar with the set up and techniques involved in the proposed study, and we have trained nursing staff familiar with the research requirements for study subjects and safety monitoring. We have a very good setup with pre-procedure open access colonoscopy classes to educate our patients, and an FOBT clinic that allows us to reach out to eligible patients and offer them the colorectal cancer screening modality of their choice. We have performed 1200 screening colonoscopies last year and we have sufficient number of subjects for recruitment into this very important study. The PI is experienced with air colonoscopy and also pioneered the development of the water method and the combined chromoendoscopy and water method for colonoscopy and has extensive experience with all of these methods for screening colonoscopy.

Equipment

Equipment available in GI unit for sedated screening colonoscopy include monitoring systems (IntelliVue MP40, Philips); high definition pediatric colonoscopes (Olympus PCF-H180AL), high definition monitors (HDTV), light source generator (CLV 180, Olympus, Tokyo, Japan), mavigraph for photography, water infusion pump (Endolav EL-100C, Cooper Surgical, Trumbull, CT).

(Funding is requested for a dedicated high definition pediatric colonoscope for the study patients).

Consumables and disposable accessories required for sedated screening colonoscopy for study patients include blood pressure cuffs, finger probe for oximetry, EKG leads, lubricant, backflow valves, connecting tubing, syringes, needle adaptor, suction device, biopsy forceps, biopsy specimen containers, injection needles, snares for polypectomy, polyp traps, polyp retrieval nets, hemoclips, reagents for preserving biopsies and polyps, reagent to solidify liquid feces in canister before disposal, and disposable chux for incontinence, disposable grounding pads for electrocautery, and food paddle for activating foot pump.

Digital recording and image capture system will be employed for study and control patients. Water at body temperature (37°C) maintained with a water bath [Cardinal Health, McGraw Park, IL] will be used.

Response to reviewers

Critique 1

1. **Significance:** Response: We agree with these comments on possible missed right-sided cancers. We have modified the study endpoint to focus specifically on the proximal diminutive adenomas which are potential precursors of colon cancer and can “easily” be missed because of their small size. Preliminary data (Table 5) indicates that we detect more proximal diminutive adenomas using the water method and water combined with chromoendoscopy further enhances the detection of proximal diminutive adenomas (Table 7).

2. Response: We agree with the reviewer. The water method with or without indigo carmine did appear to improved quality of bowel preparation in the withdrawal based on water exchange performed during the insertion phase to remove residual feces. Since this is under full control of the colonoscopist, it is a welcome addition to the colonoscopist’s armamentarium. To control for colonoscopist variability (a potential confounding factor in this early stage of development of the novel method), the PI (with a respectable track record of ADR, Tables 4, 6 and 7) will perform all the study colonoscopies. In a separate project, we’ll be simultaneously evaluating the hypothesis that fewer contractions during the withdrawal phase and less need for excessive distension of the colonic lumen (obviate stretched folds to hide lesions behind them). In this ACG funded new project we’ll evaluate the impact of the water method compared with the air method on the issue of “lesions may be hidden behind folds”. The indigo carmine staining brings out flat and small lesions, making them more easily identified. For these reasons, we speculate that the water method, with or without addition of indigo carmine optimizes colonoscopy method with minimal additional hardware or labor costs.

3. Response: Thank you for the positive comment. The crucial difference between the water method as we have described it as compared with all other descriptions of water infusion as adjuncts to air insufflation is that we turn off the air pump during scope insertion and water is infused to facilitate scope advancement until the cecum is reached. Without air we have to suction the dirty water with residual feces before infusion of clean water to clear the view. In addition to removing residual feces which can impair inspection of the mucosa, the water method has other advantages including lower medication requirement for patients receiving sedation medications, a higher success rate and completion with unsedated colonoscopy, a higher cecal intubation success rate and a greater ADR compared with the conventional air method.

4. **Approach:** Response: We have modified the study protocol to emphasize proximal diminutive adenoma detection as the primary outcome. Instead of involving multiple colonoscopists with variable ADRs, we propose to conduct a single investigator (PI) study. The PI is responsible for pioneering and developing the study method of water infusion in lieu of air insufflation (water method) and the combined chromoendoscopy and water method for screening colonoscopy. In addition, we have added the conventional air method as a control group to compare the results with that of the two investigative methods. We will focus mainly on the group of asymptomatic patients undergoing first time screening colonoscopy. Furthermore, we select the primary outcome as proximal diminutive adenoma detection rate which we consider most relevant in detection and prevention of right-sided colon cancer. We have limited the number of covariates and secondary outcomes. Sample size calculation reveals a total number of 330 subjects are needed (110 in each of three groups). Based on current workload data, we should be able to recruit the required number of patients and complete the study in the 2.5 year recruitment period.

5. Response: We understand it is difficult to blind the investigator and therefore will monitor the quality of the colonoscopy to insure that the three groups of patients are comparable and that the performance of the colonoscopist is consistent with community standard. We expect to maintain an overall ADR of >25% in the air method group as recommended for quality performance. We have just received ACG funding to perform analysis of the video recordings in our previous RCT to discover parameters (e.g. fewer or shorter duration of contractions during withdrawal) that may be associate with increased ADR. We are not proposing such formal analysis in this application because we have yet to develop the criteria for scoring these de-identified video recordings. To include such formal analyses in this proposal risks lowering the feasibility of achieving the proposed objective and weakening this application in the eyes of esteemed critical reviewers. Once these criteria are developed, however, we plan to request IRB approval to subject the recordings in this RCT to similar analysis.

6. **Response:** We thank the Reviewer for this constructive recommendation. We have added the air insufflation group as a control. The total number of subjects required for the study has been adjusted based on preliminary data related to the current primary outcome of proximal diminutive ADR.

7. **Innovation:** Response: We thank the Reviewer for the positive comment. The Editor and Associate Editor of Endoscopy (the premier endoscopy journal in Europe) share similar sentiments. They have invited the PI and co-investigators to contribute an article to the Innovation Forum summarizing our results as well as providing a detailed description of the “how to perform” aspect of the water method. Organizers at the 2011 DDW have invited members of the research team to present two State-of-the-Art Lectures at ASGE sessions.

8. **Investigators:** Response: The PI is responsible for pioneering and developing the water method and combined chromoendoscopy and water method and has extensive experience in conducting RCTs to evaluate the impact of the water method.

9. **Feasibility:** Response: We performed 1200 screening colonoscopies last year in our clinic at the Sacramento VA. The PI performed about 300 of these screening colonoscopies. We are in a favorable position to recruit the required number of subjects in a 2.5 year period.

10. **Budget:** Response: We have added the conventional air method as a control in the revised proposal and adjusted the budget appropriately.

Critique 2

1. **Significance:** Response: To address the important issues of missed right-sided lesions and screening colonoscopy does not affect the outcome of right-sided cancer, we have modified our study protocol to focus on the primary outcome of detection of diminutive (easy to miss) right-sided adenoma. In addition, we added conventional air insufflation as the control group.

2. **Approach:** Response: We appreciate the valuable suggestion and have included the conventional air insufflation method as a control group.

3. **Response:** We have added a control group receiving standard care using air insufflation.

4. **Response:** In addition to the Sacramento VA data, the Sepulveda VA data are presented in Tables 3 and 5. Data collected by our collaborator, Dr. Ramirez at the Phoenix VA, confirm the water method increases ADR (overall and in the proximal colon, particularly diminutive ones). The abstract will be presented at the DDW – ASGE Oral Session on Cutting Edge Colonoscopy Technology 2011. Thus, comparable observations demonstrating the water method to exert a positive impact on ADR have been forthcoming from three VA sites. To highlight the importance of the water method, this technique is being featured in two symposia in the upcoming DDW in May 2011 where the water method will be presented and discussed in special topic forum and symposium on cutting edge colonoscopy technology. Important publication including an Endoscopy Innovation Forum paper will be published. We have organized two Colorectal Cancer Screening Symposium at the Sacramento VAMC where the water method was presented and its application and benefits discussed.

5. **Response:** We have limited the number of secondary outcomes. They include overall adenoma detection rate, cecal intubation success rate and sedation medication requirement. We will monitor a number of quality measures to insure the three groups of patients are comparable.

6. **Response:** The sample size calculation is based on the primary outcome of proximal diminutive ADR. Additional observations will be used as hypothesis-generating for future studies.

7. **Response:** Permission will be sought from the IRB to contact the patients at 30 days by phone and if patients report that they have had complications including ER visit or hospital admission, follow up data will be obtained (with the patients' permission) from the computerized patient record or from the local admitting hospital. It is important to track the 30 day complications since patients have been admitted to local hospital because of post procedural pain not associated with perforation but possibly due to the large amount of air insufflated especially in those who had air insufflation colonoscopy.

8. v) **Sample size:** Response: Based on more preliminary data collected in a RCT supported by the ASGE on ADR with the combined chromoendoscopy and water method, we have recalculated the number of subjects required for the study.

9. **Response:** We have decided to conduct a single investigator study to minimize the effect of variability in ADR between different colonoscopists. The study is set up to test the potential benefits of the

water method and the combined chromoendoscopy and water method compared with the conventional air method.

10. vi) **Bowel preparation:** Response: We'll standardize the bowel prep to follow the community standard of a split prep i.e. half the Golytely will be taken the evening before and the other half taken in the morning on the day of the procedure.

11. vii) **Blood tests:** Response: These data have been collected showing the water method did not alter serum electrolytes (Table 8), indicating it is a safe method. Patients in the proposed study will no longer be subjected to such burden.

12. viii) **Colonoscopes:** Revised: To obviate such concerns, only high definition variable stiffness pediatric colonoscopes from Olympus will be used.

13. ix) **Time:** Response: All study procedures will be recorded to aid in subsequent analysis.

14. (b) Response: Although a defined withdrawal time has been shown to improve the ADR, other studies have reported contradictory results. We will calculate the actual time taken for the examination as a quality measure to monitor for bias.

15. (c) Response: Prior studies indicated that a minimal withdrawal time of 6 minutes will improve overall ADR. Instead of mandating the 6 minute withdrawal time, we will monitor the cecal intubation time, withdrawal time and total procedure time, the time taken to remove polyps and suction water will be accounted for to determine the actual examination time.

16. x) **Randomization:** Response: We will recruit only asymptomatic patients eligible for screening colonoscopy and will not include any patients who are FOBT+ve. Therefore, stratification of the patient is not necessary.

17. Response: Per the Reviewers' suggestion, temporary exclusion will not be used.

18. **Feasibility:** Response: Total number of patients eligible for CRC screening is estimated at 2000 a year and we performed 1200 screening colonoscopy last year. About 80% of patients we approached were willing to participate in the previous sedated colonoscopy studies.

19. **Budget:** Response: Critical reviewers have raised concerns over the accuracy of the real time recordings. The DVD recording (e.g. biopsy duration, polypectomy durations etc) provides more objective and "accurate" measurements. Nevertheless, we have made adjustment (reduction) to the expenses for the study.

20. **Overall Evaluation:** Response: The clinical implication is detection of more adenomas may translate into fewer missed but potentially precancerous lesions. The revised application has added preliminary data to address the Reviewer's concerns.

Critique 3 Statistics

1. Response: The revised application involves a single colonoscopist and enrollment of only first time screening colonoscopy patients. The statistics section has been revised accordingly.

2. Response: see response above.

3. Response: The statistical analysis has been entirely rewritten. We investigate the primary hypothesis through logistic regression models. To follow up, we investigate how covariates affect the rate of adenoma detection. Our secondary analysis uses repeated measures regression models to investigate how secondary outcomes (adenoma size, adenoma location, etc) vary between the three methods.

4. Response: Because patients are sedated, and will be given additional sedation medication throughout the procedure if requested, we do not expect large numbers of drop-out (failure to complete colonoscopy). However, patients that do drop out will be retained and assigned a value of zero for the number of adenomas detected, if none is found in the examined segments.

5. Response: The analyses are designed to quantify the differences between the three treatment groups and to determine if they are significant. Additionally, we plan to account for the rate of colorectal cancer diagnoses in the estimation of the differences between the three tests.

Specific Aims

(a) Goal

Population studies showed that traditional air colonoscopy failed to eliminate post screening colonoscopy cancers or cancer mortality in the proximal colon. Even diminutive adenomas harbor significant dysplasia. A simple, inexpensive, easy-to-learn method of adding indigocarmine to the water method may increase the yield of proximal diminutive adenomas. A higher ADR may minimize the burden of interval CRC by decreasing missed adenomas. The current study evaluates the benefits of a combined chromoendoscopy and water method for screening colonoscopy in identifying proximal diminutive adenomas compared to the water method alone and the conventional air method. The long term goal is to perform further studies to determine if post screening colonoscopy interval cancers and cancer mortality in the proximal colon can be attenuated among the veteran population by the novel methods.

(b) Hypothesis

In patients undergoing optical colonoscopy for first time CRC screening, a higher proximal diminutive ADR (proportion of patients with at least one diminutive adenoma in the colon proximal to the splenic flexure) will be found in the group examined by combined chromoendoscopy (indigo carmine) with water method compared with water method alone or air method.

Primary outcomes: Proximal diminutive (<10 mm) adenoma detection rate.

Secondary outcomes: ADR (overall for entire colon and for proximal colon), cecal intubation success rate, sedation medications.

Co-variables: patient demographic variables [age, gender, BMI, co-morbidity, endoscopic findings, etc.], successful completion of split bowel preparation

(c) Specific Objectives

To compare the primary and secondary outcomes in a prospective RCT involving the combined chromoendoscopy with water method vs. water method alone and air method in asymptomatic patients undergoing first time outpatient screening colonoscopy.

Short title: Comparative efficacy of water & indigo carmine vs. water or air method on ADR – a RCT

Long title: RCT to compare proximal diminutive adenoma detection rate (ADR) of combined chromoendoscopy (Indigo carmine) with water infusion in lieu of air insufflation (water method) vs. water method alone or conventional air method in screening colonoscopy

(1) Rationale

Statement of the Problem

Optical colonoscopy is the final common pathway for all patients with positive colorectal cancer (CRC) screening tests. Several recent studies have reported that optical colonoscopy missed right-sided (proximal to the splenic flexure) colon cancers [1] and failed to reduce colon cancer mortality due to right-sided cancers [2] or reduce it at best by ~50% [3]. Methods under the immediate control of the colonoscopist at the time of screening colonoscopy are needed to remedy these shortcomings of optical colonoscopy to ensure maximum benefit for the healthy, asymptomatic individuals undergoing screening colonoscopy. This revised application seeks confirmation of pilot data showing chromoendoscopy combined with the water method enhances proximal adenoma detection rate (ADR, proportion of patients with a least one adenoma of any size) compared with the water method alone or conventional air method in patients undergoing optical colonoscopy for CRC screening.

Screening colonoscopy with early detection and removal of colonic neoplastic polyps or adenomas prevent a subset of these lesions to progress to become colon cancers. The major limitation to screening colonoscopy is missed lesions [4] which account for the variation in reported ADR [5]. Among patients undergoing resection for right-sided colon cancer, the cancer miss rate of screening colonoscopy has been reported to be 4.0% [1]. Although endoscopic methods are being evaluated for their ability to distinguish benign from neoplastic polyps, current practice still emphasizes complete removal of potentially neoplastic lesions.

Even polyps <10 mm can have a significant risk of neoplasia and clinical impression correlated poorly with neoplasia [6,7,8]. One report using chromoendoscopy suggests that adenomas missed by conventional air method are smaller (mean size 2.7 ± 1.0 mm) and more often right-sided [9]. Failure to clear the proximal colon may also result from incomplete colonoscopy because of inadequate bowel preparation. The residual fecal matter obscures adenomas (especially small ones) and prevents them from being identified and removed.

In addition to improved technology (e.g. high definition instruments) and bowel preparation methods (e.g. split-dose, patient education), missed lesions are potentially identifiable by enhanced observation with methods controlled by the colonoscopist (including slow withdrawal and examination behind folds). Towards this goal, the third-eye retroscope which enhances detection of proximal colon lesions [10,11,12] is an important new tool. The drawback is that the methodology is not widely available and requires substantial resources to set up and recurrent expenses for the disposable third eye.

Air insufflation to aid colonoscope insertion and examination of the colonic mucosa is convenient, logical and has been used since the invention of polypectomy [3]. The consistent miss rate and absence of mortality reduction from right-sided cancer, however, may be the result of inadequate bowel preparation due to poor patient compliance and incomplete examination. The presence of adherent stool on the mucosa, residual liquid and stool in the lumen, spasm of the colon, inability to hold the insufflated air and collapse of the colonic wall during withdrawal all contributes to inadequate examination. Setting aside the possibility of unique biology of right-sided cancers, modifications in optical colonoscopy methods are urgently needed to increase adenoma detection especially the proximal lesions.

Adenoma detection rates with air insufflation colonoscopy varied considerably. In one of the early studies employing the water method a trend towards a higher ADR in the water method group was recognized (37% vs. 26%) (Table 3) [14]. The observation prompted a retrospective analysis of 1178 cases of screening and surveillance colonoscopy performed by a single endoscopist (PI) at the Sacramento VAMC, which showed an overall ADR (presence of at least one adenoma) of 27% with air colonoscopy whereas that for the water method colonoscopy was 35% ($p=0.007$) (Table 4) [7]. In a subsequent combined analysis of two prospective RCT of air vs. water colonoscopy for screening and surveillance using scheduled unsedated colonoscopy [15] and on-demand sedation [16], more patients were found to have at least one diminutive adenoma in the proximal colon in the water method group than in the air group (28% vs. 14%, respectively, $p=0.0298$) (Table 5) [17]. At one of our collaborator's site (Phoenix VAMC), a quasi randomized study of screening patients using high definition equipment confirmed a significantly higher overall ADR with the water method ($n=177$) compared with the air method ($n=191$) (57% vs. 46%) ($p=0.03$). The odds of detecting an adenoma was 81%

higher with the water method (OR 1.81; 95% CI: 1.12-2.90) and independent of age, body mass index (BMI), current smoking and alcohol use, withdrawal time & quality of bowel preparation. In the proximal colon ADR was significantly higher in patients examined with the water method than with air method (46% vs. 35%) ($p=0.03$), particularly for adenomas <10 mm in size (38% vs. 25%) ($p=0.007$) [18]. These encouraging preliminary data reflect the potential benefits of water method colonoscopy. Our current research question is whether any further improvement in ADR can be made by additional modifications of the water method.

Previous studies have reported the benefits of chromoendoscopy with dye spray in enhancing the detection of colon adenomas [19]. Kahi et al. [20] recently reported that high definition (HD) colonoscopy alone can improve the detection of colonic polyps and that the addition of chromoendoscopy using 0.2% indigo carmine spray did not offer any significant additional benefit in detecting large adenoma. The use of high definition equipment and chromocolonoscopy did show a significant improvement in the detection of small <5 mm adenoma. In a separate performance improvement project, we performed screening colonoscopy with the combined chromoendoscopy (0.008% indigo carmine) and the water method using high resolution colonoscope. Intriguingly, we showed an overall ADR of 62% which was significantly higher (in a retrospective manner) than the water method alone (40%) [21,22]. Since our collaborator [18] has shown that water method and high definition equipment produced significantly higher ADR than high definition equipment and air method, the potential impact of combining chromoendoscopy with the water method and high definition equipment on adenoma detection in screening colonoscopy (vs. water method alone or air method alone in conjunction with high definition equipment) deserves to be evaluated in a RCT with a substantially larger sample size. Additional pilot data will be presented in the preliminary data section to support the call for such an evaluation.

(2) Background and Significance

(a) Background

Optical colonoscopy is considered the “gold” standard for CRC screening. The number of adenomas is a strong predictor of future colorectal cancer risk. Detection and removal of adenomas has been shown to reduce the incidence of colon cancers [23]. Adenoma detection rate, but not cecal intubation rate, is an independent predictor of the risk of interval colorectal cancer after screening colonoscopy [24]. Methods that enhance adenoma detection are desirable for all CRC screening programs. The U.S. Multi-Society Task Force recommended that endoscopists should detect adenomas in at least 25% of men and 15% of women age 50 years and older [25].

Missed lesions remain an unresolved issue weakening the effectiveness of screening colonoscopy despite advances in colonoscopic technology. In a study of 183 patients who underwent back-to-back colonoscopies the overall miss rate for adenomas was 24%, 27% for adenomas ≤ 5 mm, 13% for adenomas 6-9 mm, and 6% for adenomas ≥ 1 cm. The significant miss rates for adenomas <1 cm even with meticulous colonoscopy suggest the need for improvements in colonoscopic technology [26].

Advances in devices and optics continue to demonstrate missed adenomas; but not all of the advances in technology have been embraced as solutions [27,28,29,30]. The detection of missed lesions [31] is critical to improvement of quality.

Methods to enhance detection of mucosal pathologies have been tested. Chromoendoscopy with pancolonoscopic or targeted dye spray detected more diminutive [32] and missed adenomas at a cost of a longer withdrawal time [30]. Two reports from the same group described conflicting results regarding whether chromoendoscopy is an efficacious adjunct for detecting adenomas missed by white light inspection [9]. The routine application of chromoendoscopy using dye spray for CRC screening has not been uniformly endorsed [20,29].

Kahi et al. reported a prospective RCT comparing ADR using high definition (HD) chromocolonoscopy (with 0.2% indigo carmine spray) versus HD white light colonoscopy in 660 average risk patients undergoing CRC screening [20]. There was no significant difference in the number of advanced adenoma per patient or the number of advanced adenomas >10 mm per patient between the two groups. There was only a marginal

difference in the number of adenomas per patient. However, chromocolonoscopy did detect significantly more flat adenomas per patient and adenomas <5 mm in diameter per patient. No difference in finding of larger polyps suggested that dye spray did not improve the observation of obvious lesions using high definition scope. However, chromoendoscopy did reveal significantly more small adenomas which were reportedly more likely to be missed with optical colonoscopy alone [9,20].

In one study with an overall adenoma miss rate of 25%, auto fluorescence did not significantly reduce adenoma miss rate compared with high-resolution endoscopy. Both auto fluorescence and narrow band imaging (NBI) had a disappointing diagnostic accuracy for polyp differentiation, although auto fluorescence had a high sensitivity [22]. Narrow band imaging did not improve the miss rate compared to white light; the miss rate for advanced adenomas was less than 1% and for all adenomas was 12%. The neoplasm detection rates were similarly high using NBI or white light; almost half the study patients had at least one adenoma [28]. Thus, the efficacy of colonoscopes equipped with the newer generation of optics remains uncertain. There appears to be insufficient data to justify the added expense of widespread adoption of these modalities before more definitive evidence on effectiveness is available.

Table 1 shows data on ADR variability based on air method and standard definition instruments.

Table 1: Selected summary data - literature review (% patients with at least one adenoma)			
Indications	Total N	% Patients with Any Adenoma	Reference
Screening	3196	35.7%	[33]
Screening	3741	25.5%	[34]
Surveillance	1803	25%	[35]
FOBT +		29%	[36]
Screening	10034	15% (30 yr old), 35% (70 yr old); 24% (men), 17% (women); range 16%-41%	[37]
With or without fellows	309	37% (with fellows) vs. 23% (without)	[38]
Screening	660	48%	[20]
		Up to 48% with at least one adenoma	

Recent reports on ADR achieved with high definition colonoscopy are variable (Table 2). The unusually high ADR by a small number of expert colonoscopists [20] remain to be confirmed. Furthermore, these authors excluded 63 patients (10%) from the study due to poor bowel preparation and this may have artificially inflated ADR [20] compared with intent-to-treat (ITT) analysis. Had the analysis been performed with ITT and all excluded subjects were grouped under no adenoma detected, the ADR for HD white light would only range from 31% to 47% and that for HD + chromocolonoscopy would only range from 34% to 49%. A unique strength of the water method as described below is the augmentation or salvage of colon cleansing especially when a suboptimal bowel preparation is encountered during colonoscopy [14].

Table 2: Adenoma or Neoplasm Detection Rate			
Standard Definition (SD)	High Definition (HD)	Chromocolonoscopy	References
29%	37%		[39]
21.9%	24.7%		[40]
	41-57% (non ITT analysis)	HD 45-59% (non ITT analysis)	[20]
	[31%-47% (ITT analysis)]	[HD 34%-49% (ITT analysis)]	[20]
36%		SD 46%	[41]

The effectiveness of other measures in enhancing adenoma detection is controversial. Early studies of cap-assisted colonoscopy suggested a higher ADR with this simple, inexpensive and easy-to-learn method [42,43,44]. A RCT, however, failed to confirm the superior adenoma detection capability of cap-assisted colonoscopy - 30.5% cap-assisted and 37.5% regular colonoscopy ($p=0.018$) [45]. Inadequate bowel preparation limits cap-assisted colonoscopy as semisolid trapped inside the plastic hood hinder visualization of the mucosa [45]. A report of withdrawal time >6 minutes as a significant predictor of adenoma detection [46] was confirmed by an observational study by the same group using withdrawal time of >8 min [47], but not by another when compliance with mandated withdrawal time of >7 minutes was achieved [48]. A second examination by retroflexion in the proximal colon did not improve miss rate relative to that performed by a

forward view examination. The published data do not support the addition of routine right colon retroflexion [49]. The same research team, however, presented unblinded abstract data at the 2010 ACG meeting reporting a benefit (retroflexion detected an additional 68 polyps in 58 patients) [50]. Confirmation by other investigators is eagerly awaited. These unsettled issues suggest future studies may focus on randomized controlled comparisons of the efficacy and cost-effectiveness of the water method with or without chromoendoscopy with retroflexion, third eye retroscope examination in the right colon, or cap-assisted colonoscopy with or without the aid of the water method.

(b) Significance

The number of estimated new cases of CRC in the United States in 2010 are 102,900 (colon) and 39,670 (rectal); with 51,370 deaths (colon and rectal combined) [51]. Current preventive approach is based on the premise that most colorectal cancers arise in adenomas (adenoma-carcinoma sequence) [52]. Therefore detection and endoscopic removal of adenomas is a means of reducing the incidence of colorectal carcinomas [52].

The VA cooperative study showed colonoscopy to be effective in detecting and removing adenomas [33]. VA guideline recommends screening for adenomas and removal by optical colonoscopy for high and average risk individuals [53]. The Center for Disease Control estimated in 2004 that 43 million Americans are eligible for CRC screening [54]. One study reported that the rates of right-sided colon cancer are continuing to increase, especially in older individuals [55]. Interval cancers and missed adenomas limit the effectiveness of screening colonoscopy. Inadequate bowel preparation, failure to reach the cecum, colonoscopist characteristics (variability in cecal intubation success and ADR), and optimal withdrawal time (a marker of a quality performance) are factors that contribute to modulate these limitations. There is no consensus regarding the effectiveness of new equipment and approaches in overcoming the challenges (interval cancers and missed adenomas) besetting colonoscopists performing screening colonoscopy. Although tandem colonoscopy with or without retroflexion can discover missed adenomas, the approach requires a patient to undergo back- to-back examination which may be impractical in routine practice. Chromoendoscopy used during air colonoscopy is effective in identifying difficult-to-detect (e.g. flat or diminutive) lesions but the added time for dye spray has limited its widespread adoption. A simple, inexpensive, easy-to-learn method (e.g. water method) that incorporates the advantages of chromoendoscopy (e.g. addition of indigo carmine to outline flat and diminutive polyps in the proximal colon) to further increase the yield of screening colonoscopy may possibly minimize the risk of missed adenomas and attenuate the burden of interval cancers in patients who undergo optical colonoscopy for CRC screening.

Several trials are in the planning stage in the United States and in Europe to assess the efficacy of optical colonoscopy in preventing colon cancer. The reports in major medical journals raising serious questions about efficacy and effectiveness of screening colonoscopy in the proximal colon [1,2,3] serve the critical function of reiterating the reminder that colonoscopists need to improve colonoscopy technique in colon cancer prevention by screening colonoscopy. It is imperative that investigators contributing to these trials employ the most efficacious colonoscopy method. The traditional air method has clearly been shown not to be effective in the proximal colon [1,2,3]. While any screening is better than no screening, screening with a suboptimal method may ultimately defeat the purpose, undermine the efforts devoted to promoting screening and limiting the return on resources invested in the process.

Since the last submission, the water method has gained worldwide attention. In an invited Innovation Forum review in press in *Endoscopy* (the premier endoscopy journal in Europe) the impact of the water method (based on our observational and RCT data) to aid colonoscope insertion is narrated and critically discussed [56]. This paradigm shift from using air insufflation to water infusion exclusively demonstrates that the water method offers significant benefits. The seminal observation is recognized by educated peer reviewers who made the unusual request to have detailed description of the “how to” aspects of the water method added, in the words of the Editor and Associate Editor “We have some minor comments that aim at increasing the practical value of the paper for endoscopists who want to start using water infusion colonoscopy”. The accepted addition has been reproduced in the methods section of this application. Colleagues in other parts of the world also recognize the contribution of the water method with invited lecture: “The water method and adenoma detection” at the 8th Pan Arab Conference on Gastroenterology (Feb 8-10, 2011). Even in the United

States the initial reservation to regard the water method as a viable alternative to the conventional air method (because the observations were made only in male veterans and might not be generalizable to the general population) has given way to recognition of its plausible impact on minimizing discomfort and enhancing ADR. Members of the research team have been invited to present “A splash into water colonoscopy” at an ASGE Clinical Symposium, an oral presentation of a submitted abstract “The water method is associated with higher adenoma detection rate (ADR) - a head-to-head comparative study” and State-of-the-Art Lecture “Master Class- Warm Water Infusion ... for Colonoscopy” at the ASGE Cutting Edge Colonoscopy Techniques 2011 Topic Forum at the 2011 DDW.

(c) *Relevance to Veterans Health*

The use of screening colonoscopy increased from 24,955 in 1998 to 55,199 in 2003 at VHA facilities [57]. The number is expected to increase as a result of implementation of VHA Directive 2007-004 [53]. Our annual statistics at the Sacramento VAMC showed that we performed about 1200 screening colonoscopies last year, an estimated increase of over 400% since 2000. The trend will likely continue because the eligible age for screening colonoscopy has been lowered to 50 years.

The proposed study using combined chromoendoscopy and the water method will address the need to find an improved technique for performing screening colonoscopy for veterans who chose this option for CRC screening. The water method for optical colonoscopy was first introduced to overcome the limitation of discomfort and technical difficulty due to distension and lengthening of the colon by air insufflation. As shown in the preliminary data section below the water method with or without combination with chromoendoscopy produces a significant impact in increasing ADR.

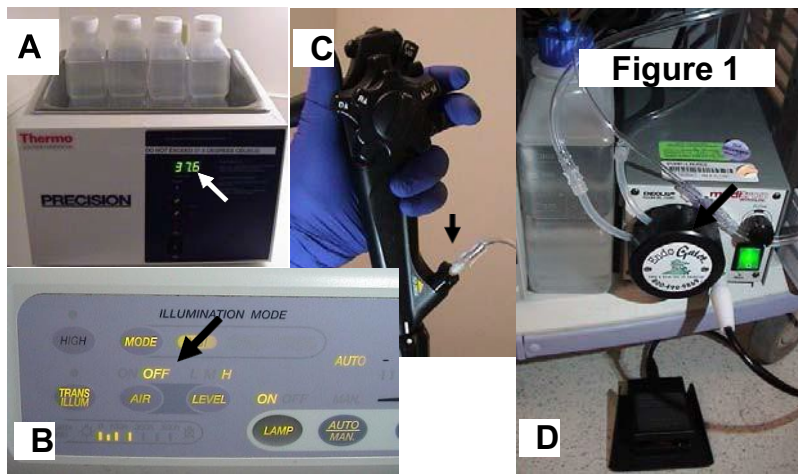
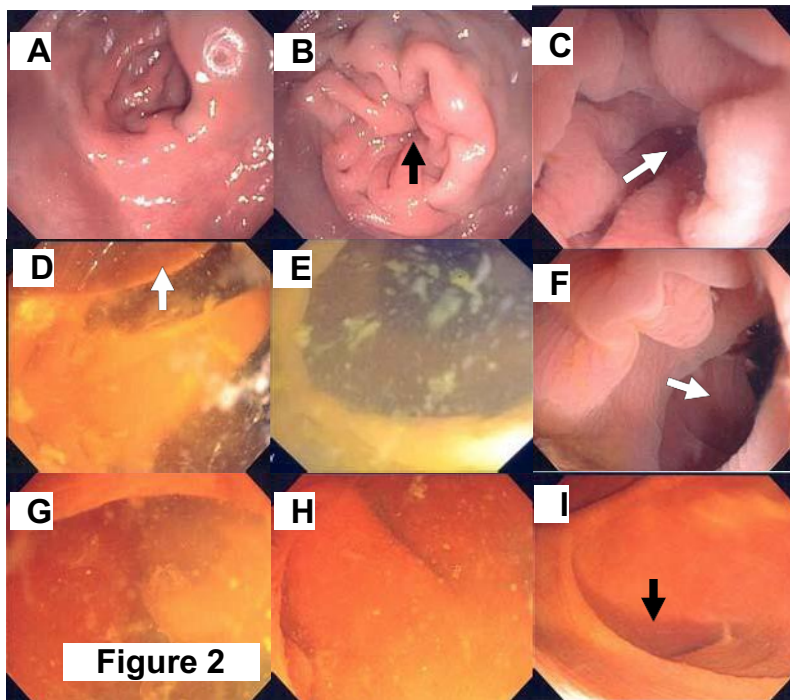
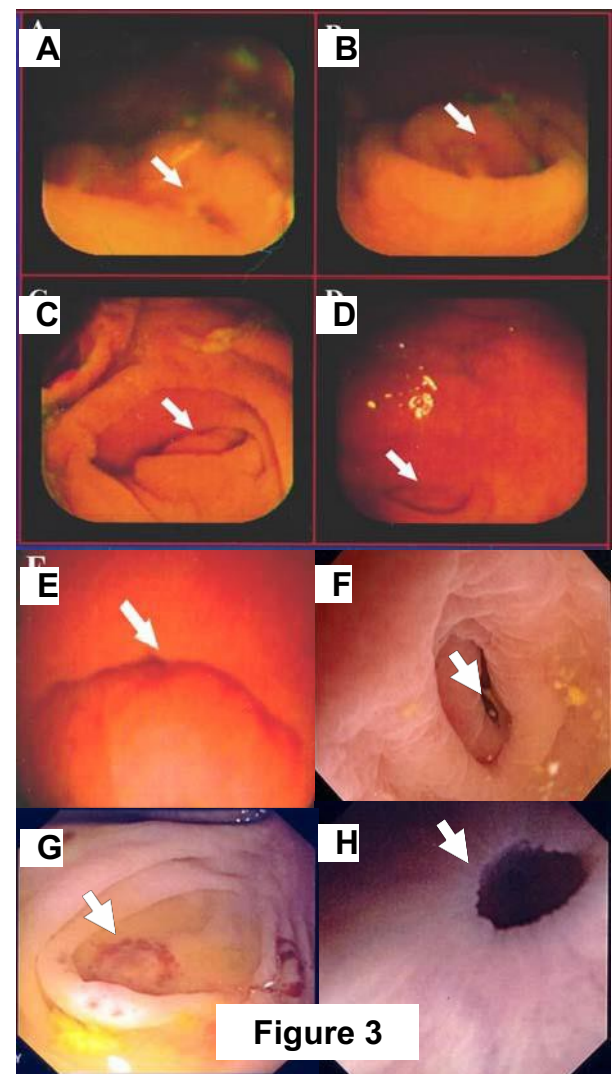
This proposal which involves a larger number of patients undergoing screening colonoscopy will focus on the important issue of diagnostic yield (ADR and increased detection of easy-to-miss right-sided diminutive adenomas). A comparison of the combined chromoendoscopy and water method versus the water method alone or the conventional air method in sedated veterans will be assessed to allow the observations to be generalized to other VA sites. The proposed study enhances the VHA's multiple missions. Increase in the number of veterans receiving colonoscopy meets the VACO recommendation on using colonoscopy for CRC screening. A higher detection rate of adenomas and cancers improves the quality of care. Validation of an improved (water) method with or without chromoendoscopy will contribute to the VHA's research mission. Publication of the efficacy of the improved water method will serve VHA education function.

We observed a significantly higher overall ADR [7] and proximal diminutive ADR [17] in screening patients examined with the water method. The addition of indigo carmine to the water method further increased overall ADR in pilot studies [22] and proximal diminutive ADR in an on-going RCT supported by the ASGE. Increased proximal diminutive ADR may translate into fewer missed colorectal cancer precursors. The VA Clinical Merit Review Committee deserves credit to have supported confirmation of the water method with or without chromoendoscopy as the simple, inexpensive and easy to learn approach (a solution to the problem of missed right-sided cancers and adenomas) for future studies and programs devoted to CRC screening in the United States and elsewhere.

(3) *Work Accomplished*

Detailed description of the water method - from Innovation Forum paper (56)

While we do not endorse any particular component illustrated in Figure 1, the equipment set up is self-explanatory. Bottles of water are placed in the water bath set at 37.6° (Figure 1A). The switch for the air pump is in the off position (Figure 1B). The warm water is infused via the colonoscope scope channel with the help of a tube and a blunt tip adaptor (Figure 1C). The water pump with a foot paddle switch is tested to confirm effective delivery. A digital rectal examination is performed to exclude obstruction. After lubrication, the tip of the scope is inserted through the anus. If the rectum contains pre-existing air (Figure 2A) all the air is removed by suction to collapse the colon around the colonoscope (Figure 2B) to increase the chance that the tip will be

**Figure 1****Figure 2****Figure 3**

pointing in the direction of the “future” lumen. The endoscope is advanced to abut the slit-like lumen or where the folds converge. The foot paddle switch is triggered briefly to infuse water directed at the potential opening ahead. The water opens the lumen (Figure 2C), if the orientation of the tip is correct. Incorrect orientation will not lead to opening of the lumen ahead, and water infusion is stopped. The tip of the colonoscope is pulled away from the mucosa slightly and redirected. The water infusion is briefly repeated. The water infusion assists in identification of the lumen for advancement of the colonoscope through the colon without excessive distension. The colonoscope is advanced by a series of to and fro, back and forth, or repeated insertion and withdrawal motions of the shaft of the colonoscope with a torque in the direction of the expected lumen, and intermittent water infusion to seek the lumen. All residual air pockets encountered at flexures and redundant segments (Figure 2D, white arrow) will be removed by suction (based on the rationale described above). Since air could not be used to find the lumen, suspended residual feces obscuring the view (Figure 2D, black arrow) is suctioned and replaced by clean water. The turbulence set up by the simultaneous infusion and suction in the collapsed lumen dislodged the residual fecal matter from the surrounding mucosa in close proximity to the tip of the colonoscope (Figure 2E). This maneuver appears to make removal of the residual fecal matter “easier” than by washing with a single water jet in a dilated air filled colon. Water exchange continues until the colonic lumen is visualized again (Figure 2F). Most of the infused water in fact was aspirated into the suction bottle instead of remaining in the colon during insertion to minimize over-distension. To avoid suction of the mucosa, the sequence of events for this maneuver is to start the water infusion first, followed by application of suction. Adjustment of the level of suction by trial and error may be necessary. The volume of water needed to clear the view is kept to a minimum, but not restricted. To ensure adequate visualization during the insertion phase a range of volumes [200 ml (clean colon) to 2000 ml (dirty colon)] may be necessary. If advancement

fails, the assistant will provide abdominal compression or the patient will change position to facilitate passage of the colonoscope. If the advancement is uninterrupted, no abdominal pressure or change in patient position needs to be employed. Cecal intubation is suggested by appropriate movement of the endoscopic image on the monitor screen when the right lower quadrant was palpated, or ~90 cm of the colonoscope was in the colon in the short configuration, or the appendix orifice under water is visualized after adequate water exchange is implemented to convert a dirty (Figure 2G) to an improved (Figure 2H) and eventually clean (Figure 2I) cecum. The appearance of the appendix opening may vary (Figure 3). Some appear as concentric rings in a water filled but non distended cecum (Figure 3A to 3C) as the tip of the scope moves away from the appendix opening. After air distension, the usual crescent shape of the appendix opening can be confirmed (Figure 4 D). It may take on a slit-like appearance (Figure 3E) or a diverticular-like opening with depth (Figure 3F). In some instances, after several attempts to advance the colonoscope in different directions, but the appendix opening cannot be identified, arrival in the cecum is suggested by seeing red suction marks (Figure 2G). The cecum is then distended by air to confirm visualization of the ileocecal valve and the appendix orifice (cecal intubation). Figure 3H shows a true diverticular opening that should be avoided. During withdrawal sufficient air was insufflated to permit examination behind folds, biopsy and polypectomy.

B. The data related to impact of the water method and combined water method and chromoendoscopy on ADR

Table 3 shows the uncontrolled, non randomized, consecutive group experience on ADR in the scheduled unsedated patients undergoing screening, surveillance or diagnostic colonoscopy. When the traditional air method was used, ADR was 26%. When the water method was used, ADR was 37%, a trend towards an increase [14].

Table 3: Unsedated [14]	2005-06 Air (n=62)	2006-07 Water (n=63)
ADR	26%	37%

The observation prompted us to review a data base of two groups of sedated screening patients (Table 4). From 2000 to 2006, the air method yielded an ADR of 27% in 680 patients. From 2006 to 2009, the water method yielded an ADR of 35% in 495 patients ($p<0.05$, Fisher's exact test) [7].

Table 4: Sedated colonoscopy [7]	2000-06 Air (n=683)	2006-09 Water (n=495)
ADR	27%	35%*
* $p<0.05$, Fisher's exact test.		

Table 5 shows when the combined secondary outcome data of ADR of two RCT [15,16] were assessed taking all screening, surveillance and diagnostic cases (all comers), the diminutive ADR in the proximal colon was significantly higher with the water method (28% vs. 14%) [17].

Table 5: ADR in the proximal colon [17]			
Two RCT (All comers)	Air (N=90)	Water (N=92)	p*
Proximal colon diminutive	13 (14%)	26 (28%)	0.0298
Frequency (%). ADR, adenoma detection rate (proportion with at least 1 adenoma). *Fisher's exact test.			

In a retrospective comparison of ADR for screening cases the water + chromoendoscopy method produced a significantly higher ADR than the water method alone [22] (Table 6).

Table 6 Retrospective comparison of ADR for screening colonoscopy	Water method (n=51)	Water + Chromoendoscopy (n=51)
Overall ADR (patient with at least 1 adenoma)	40%	62% ^a
Data as mean (SD); ^a vs. water; $p<0.05$, Chi square test		

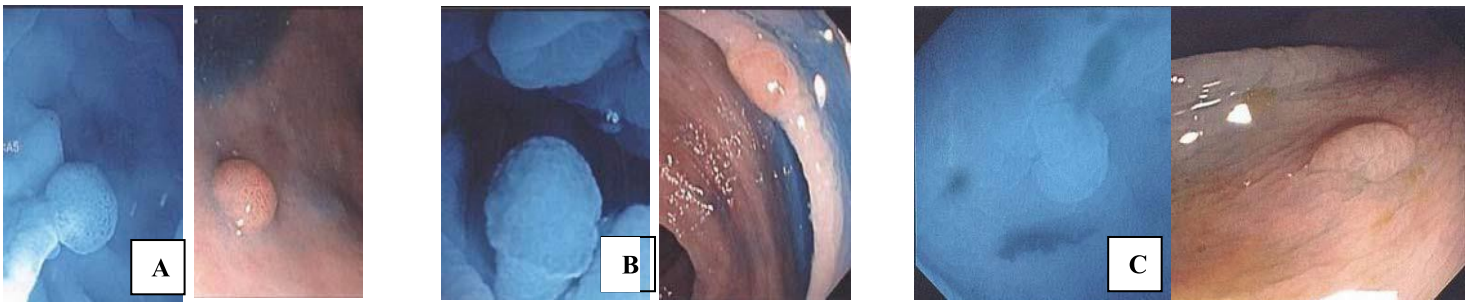


Figure 4: Same diminutive polyps (A, B, C) seen in lumen filled with blue water (left panel) or air (right panel). Note the blue staining of the mucosa permits the diminutive polyps to “stand out” in the air filled colon. A. 5 mm tubular adenoma in ascending colon, B. 6 mm tubular adenoma in proximal ascending colon, C. 5mm tubular adenoma in proximal transverse colon.

Preliminary analysis of an ongoing RCT (supported by an ASGE clinical research grant) on water method vs. water + chromoendoscopy, the overall ADR in the entire colon, in the proximal colon and the diminutive ones in the proximal colon were all significantly higher in the water + chromoendoscopy method group compared with the water group (unpublished pilot data) (Table 7). Examples are shown in Figure 4.

Table 7: Comparison of ADR by the water method and water + chromoendoscopy method				
Method	Number of patients with at least one adenoma			Number of patients in group
	Overall in entire colon	Overall in proximal colon	Diminutive ones in proximal colon	
Water	14 (48%)	10 (34%)	10 (34%)	29
Water + chromoendoscopy	22 (79%)	19 (68%)	18 (64%)	28
p*	0.0277	0.0173	0.0348	

*Fisher's exact test.

7. To address effect of the water method on serum electrolytes levels, patients in a prospective RCT comparing the water and air methods had blood taken before and after the procedure. Blood samples (2 ml each) were drawn within 5 to 10 min before and after colonoscopy for measuring the serum Na⁺ and K⁺ levels using the Istat machine (for bedside measurement of serum electrolytes) [58]

Table 8: Effect of water method on serum electrolyte levels					
		Before Colonoscopy		After Colonoscopy	
Method	N	K ⁺ meq/l	Na ⁺ meq/l	K ⁺ meq/l	Na ⁺ meq/l
Water	25	3.7 (0.3)	140 (2.4)	3.8 (0.4)	140 (3.1)
Air	32	3.8 (0.4)	138 (2.7)	4.0 (0.4)	138 (2.4)

There were no significant differences between the serum Na⁺ and K⁺ levels [mean (SEM)] before and after colonoscopy in either the air or the water group (Table 8). Thus, serum electrolyte levels are well preserved after large volume water exchange in the colonic lumen used with the water method. The water method is a safe modality for examination of the colon in this regard.

8. To address the concern that patients may retain excess water with the water method, the volume of water infused during colonoscopy and suctioned by the end of the procedure were compared in 37 patients examined recently. With the exchanging of dirty water by suctioning and infusion of clean water to aid scope insertion the mean volume of water suctioned was 2013 ± 614 ml compared with a mean infused volume of 1817 ± 679 ml. The total volume suctioned was more (mean 196 ml) than the volume of water infused for the procedure. The comparison indicates that with adequate suction removal of residual feces and purge as well as infused water during insertion, the patients do not retain excess water.

Table 9 shows the bowel prep scores reflecting improvement following water exchange (N=37).

Table 9	Mean Bowel Prep Score (max=4)
Insertion	2.3
Withdrawal	3.3
Bowel prep score during insertion and withdrawal: 4=excellent, 3=good, 2=fair, 1=poor (see definitions below)	

Bowel Prep Score for water colonoscopy on scope insertion when the colon is filled with water

Excellent (4)	The water allows clear visualization of the lumen and mucosa with no fecal content
Good (3)	The water allows visualization of the lumen and mucosa with minimal fecal content
Fair (2)	Discolored water limits visualization of lumen or mucosa with presence of fecal content
Poor (1)	Presence of solid fecal matter that prevents visualization of the lumen or mucosa

Bowel Prep Score on scope withdrawal when colon is filled with air (based on CORI database)

Excellent (4)	Good visualization of the mucosa with no residual stool content
Good (3)	Minimal stool without affecting the examination
Fair (2)	Presence of residual stool or discolored fluid that affects examination of mucosa
Poor (1)	Presence of solid stool that interferes with examination of the mucosa

CORI, clinical outcomes research initiative

(4) Work Proposed

(a) Study type descriptor.

Prospective randomized controlled trial (RCT) at a single VA site (Sacramento VA Medical Center)

(b) Research design, methods and procedures to be used to accomplish the specific aims.

Pre-colonoscopy Evaluation

When a primary care consultation request to perform a colonoscopy is received the veteran's CPRS record will be reviewed. Veterans without contraindications for routine sedated colonoscopy will be invited to attend the colonoscopy class or given usual colonoscopy instructions for preparation for colonoscopy by telephone. In addition a letter will be provided to describe the study and provide the veteran a phone number to call if s/he is interested in participating. When the veteran calls, the research coordinator will mail the veteran a set of the consent form. Also as part of our CRC screening program, we contact and offer screening service for veterans who become eligible (age 50) by mail through our FOBT clinic (a special set up to triage patients eligible for CRC screening). Those who respond will be invited to attend the open access colonoscopy class to discuss CRC screening and colonoscopy. During open access colonoscopy classes, after the usual pre- colonoscopy instructions are provided to the veterans, they will be informed of the study. The consent form will be distributed to those who express interest. One week before the scheduled examination, all patients will be reminded of the pre-colonoscopy instructions by phone. Instructions for use and the objective of the split dose purge preparation to ensure clear rectal output at the end of the purge will be reiterated.

Bowel preparation

The purge (using split prep with Golytely) will be standardized for all patients to minimize differences in the quality of bowel preparation in the study and control groups. Trained support staff will provide the instructions to minimize variations in patient compliance. Although patient compliance is frequently beyond the control of the colonoscopist, efforts will be made (e.g. telephone reminders by trained research staff) to encourage proper compliance.

Patients take low residue diet for 2 days and clear liquids for 1 day prior to the colonoscopy. They will fast overnight before the examination. Sips of water for meds after midnight will be allowed. Purge preparations (in the form of split prep) on the day before colonoscopy currently in use include 2 tablets of Bisacodyl in the morning and 2 L (1/2 gallon) of Golytely (Braintree Laboratories Inc., Braintree, MA) to be taken in the evening (6-8 pm). In the morning of the day of colonoscopy, patients will consume the second portion of the split prep (2 L) upon arrival (7 am) at the endoscopy unit. The process (7-9 am) will be supervised by the research

coordinator to ensure completion of the prep. This avoids the concern expressed by patients over the burden of having to get up in the middle of the night to complete the bowel prep. Examination will be performed 2 hours after completion of drinking of the bowel prep.

Published assessment scales link the amount of residual water in the colonic lumen with suboptimal preparation [59]. Since the water method employs water infusion from the start of the examination, we developed a scoring scale to assess the quality of bowel preparation: Excellent (score 4) – the water allows clear visualization of the lumen and mucosa with no fecal content, Good (score 3) – the water allows visualization of the lumen and mucosa with minimal fecal content, Fair (score 2) – discolored water limits visualization of the lumen or mucosa with presence of fecal content, Poor (score 1) – presence of solid fecal matter that prevents visualization of the lumen or mucosa. During the withdrawal phase, the usual local practice of flushing stool covered surfaces with water injected through the colonoscope channel is performed for the air insufflation group to evaluate the underlying mucosa. For the water method groups, air is insufflated after reaching the cecum to aid inspection and any residual water in the colonic lumen will be suctioned during withdrawal. Assessment of the bowel preparation on withdrawal include Excellent (score 4) - good visualization of the mucosa with no residual stool content, Good (score 3) - minimal stool covering the mucosa without affecting the examination, Fair (score 2) - presence of residual stool that affects observation that requires water irrigation for clearance or incomplete examination due to residual discolored fluid or liquid stool, Poor (score 1) - presence of solid stool that interferes with examination of the mucosa.

Methods on the day of the procedure

During the two hours after completing the second portion of the split prep, the coordinator will review the study consent form with the patients to ensure all questions they may have are adequately addressed prior to signing of the study consent form. Signed informed consent for the study will be obtained on the day of colonoscopy from all participants.

Initial sedation protocol with minimal sedation to minimize sedation-related complications

Patients will receive intravenous premedication prior to the procedure. In general, sedation will begin with 1 mg midazolam, 25 µg fentanyl, and 50 mg diphenhydramine.

Randomization

Block randomization using computer-generated random numbers will be used to ensure random, balanced allocation to the three study arms. The randomly assigned treatment options are contained in sequentially numbered, sealed opaque envelopes. A sealed envelope will be opened immediately before the procedure, and the assigned intervention will be performed accordingly. The endoscopist will be blinded to the assignment until the randomization envelop is opened. Patients will be blinded to the randomization. The monitor will be blocked from the patient's view by using a towel to cover the patient eyes on scope insertion (acceptable to patients in the several RCT conducted at the Sacramento VA site).

Colonoscopy

Before the start, during and after the examination, upper arm blood pressure, finger oximetry, and cardiac rhythm will be monitored to document complications, if any (e.g. hypotension, hypoxia, arrhythmias) with monitoring systems (IntelliVue MP40, Philips). The PI will perform all study cases for this protocol to obviate limitations in variability of endoscopist performance. At the beginning of the examination, the patient will lie in the left lateral position with the hip flexed. After digital rectal examination to exclude obstruction or anal lesions, the colonoscope will be inserted. For all patients, application of abdominal compression, change in patient position, loop reduction maneuvers will be employed at the clinical discretion of the colonoscopist (usual practice). All adjunct maneuvers will be recorded. Rescheduling due to poor bowel preparation or failed procedure will be recorded.

Control method

1. Conventional air insufflation method will be used.

Study methods

1. Usual water method will be used (as described below).
2. The usual water method combined with chromoendoscopy (0.008% indigo carmine).

Cecal intubation is arrival in the cecum and visualization of the appendix orifice (Figure 3) and/or ileal cecal valve (in patients with appendectomy) under water, subsequently confirmed after air insufflation. The time of insertion, cecal intubation, findings and time of withdrawal from the rectum will be recorded by endoscopic photographs [60] using standardized equipment. A digital video recording of the entire procedure is taken to provide objective documentation/verification of time intervals and endoscopic findings.

Sedation protocol during colonoscopy

The pain score (0=none, 10=most severe) is assessed at all stages of the colonoscopy. At intervals of 2-3 minutes the nurse will ask the patient if s/he needs more medication and the pain score. If the pain score is ≥ 2 , the endoscopist will perform maneuvers to minimize the pain such as reducing loops by shortening of the colonoscope, suction of colonic content as well as abdominal compression. When asked by the nurse if s/he wants additional medications, the patient has the option of declining or accepting the pain medications offered. If the patient approves receiving additional medication, 25 μ g of fentanyl or 1 mg of midazolam will be administered. All medications will be documented [16].

Gold standard to ensure no lesions are missed (quality control)

To reduce the rate of missed polyps, colonoscope withdrawal time will be maintained at >6 minutes [46] in all groups, even though there is some controversy over this specific recommendation [47,48]. Patients who fail cecal intubation will undergo CTC [61,62]. These patients will be considered failures of cecal intubation based on intent-to-treat analysis for the index colonoscopy.

Colonoscopist

A single colonoscopist (PI) who has been responsible for developing the pilot data at the Sacramento VAMC will perform all of the study cases in this single center study to obviate the confounding factor of variations in ADR amongst colonoscopists.

- a. Intervention/treatment/services to be compared

Equipment: High definition variable stiffness pediatric colonoscopes (Olympus), water infusion pump (Endolav EL-100C, Cooper Surgical, Trumbull, CT), suction device, biopsy forceps, snares for polypectomy, video and photographic instruments will be used for the study. The same instruments will be employed for both the study and control patients. Water at body temperature (37°C maintained by water bath) will be used.

The air insufflation method: Patient is placed in the left lateral position, after a rectal examination, the colonoscope is inserted gently into the rectum and advanced slowly using minimal air insufflation to distend the lumen for proper orientation. If looping occurs or if advancement fails, the assistant will provide abdominal compression or the patient's position will be changed to facilitate scope passage. The scope is inserted until the cecum is reached and the appendix opening and/or ileocecal valve identified. On withdrawal, air is insufflated to distend the lumen for visualization and water irrigation is used to mobilize any adherent feces covering the mucosa. Residual feces in the lumen will be removed by suction. Biopsy or polypectomy is performed where indicated. Retroflexion is performed in the rectum and air is suctioned upon completion of the colonoscopy and prior to removal of the scope from the rectum.

The water method: The air button is turned off before scope insertion. Water is infused intermittently using a peristaltic pump via a tube fitted with a blunt needle adaptor through the biopsy channel. For warm water, water temperature will be maintained at 37°C using a water bath. Residual pocket of air will be suctioned to minimize looping and angulations. Water is infused to distend the lumen to facilitate scope advancement. When the luminal water becomes turbid due to residual feces, the dirty water will be suctioned (to minimize over distension) and clean water is infused until the colonic lumen is visualized again. In the absence of luminal air, the technique of water exchange helps to remove the residual stool covering the mucosa. No specific limit will be set for the volume of water to be used. Depending on the amount of residual feces, our preliminary data showed a range of 200 (clean colon) to 2000 ml (dirty colon) was necessary to ensure adequate visualization of the lumen throughout the examination. Air will not be insufflated until the cecum is reached [56]. If advancement fails, the assistant will provide abdominal compression or the patient's position will be changed to facilitate scope passage. Specifically, if advancement of the colonoscope is uninterrupted, no abdominal pressure or change in patient position will be used. Cecal intubation is suggested by appropriate movement of the endoscopic image on the monitor screen when the right lower quadrant is gently palpated, or ~90 cm of the colonoscope is in the colon in the short configuration, or visualization of the appendix orifice and or ileocecal valve under water.

If the cecum is believed to have been reached, but the usual landmarks are not recognizable, more water is infused to distend the cecum to aid visualization of the appendix opening. The volume of infused water, the use of position change and abdominal compression will be recorded. Once the appendix opening is visualized, air insufflation will be used to distend the cecum to confirm touching of the cecal floor with visualization of the ileocecal valve and/or the appendix orifice (cecal intubation). Thereafter, usual air insufflation will be used to facilitate suctioning of residual colonic content (mostly water and residual feces) and mucosal inspection, biopsies or polypectomy during endoscope withdrawal. All polyps (including diminutive ones in the right colon) will be removed and tissue submitted for pathological evaluations. When multiple diminutive polyps (predominantly hyperplastic) in the rectum are identified and recorded; a limit of one biopsy will be taken (to minimize time burden on study subjects).

Reassuringly, water enemas using equivalent volumes were not associated with significant fluctuations in serum electrolytes [63]. Preliminary data did not show any significant change or differences in the serum electrolytes level before and after the water infusion (Table 8) [58]. With the suction of dirty water and then infusion of clean water during scope advancement, the actual amount of water within the colon at any time during scope insertion is much less than the total volume of water used to facilitate scope passage.

The combined chromoendoscopy with indigo carmine and water method: As used in pilot study, the technique is identical to the water method above except we add 10 ml of 0.8% indigo carmine solution into a liter bottle of sterile water to make up a solution of 0.008% indigo carmine [22].

b. Population to be studied

Inclusion criteria: asymptomatic veterans scheduled for first time screening colonoscopy and agree to be randomized will be enrolled.

Exclusion criteria: patients who decline to be randomized, non screening cases.

c. Unit(s) of analysis (Table 10).

Table 10: Primary and secondary outcome variables

Measures	Details
Primary Outcome	
Proximal diminutive adenoma	1 = yes, 0 = no
Primary covariates	
Demographic variables	Age, gender, BMI, ethnicity
Volume of water (ml)	ml used during colonoscopy
Cecal intubation time*	Time from anus to cecum (appendix opening, ileocecal valve seen)
Withdrawal time*	Time from cecum to anus
Total procedure time*	From insertion of colonoscope to removal from the anus
Completion of split preparation	Yes = 1, no = 0
Secondary covariates	
Colon cancer	Colon cancer discovered during exam (Yes = 1, no = 0)
Sedation medications	Type, initial dose, additional doses during colonoscopy based on patient pain score and request
Secondary Outcomes	
Size of adenoma*	mm measured by open forceps
Anatomical location of adenoma	rectum, sigmoid, descending, splenic, transverse, hepatic, ascending, cecum
Located behind a fold*	Yes = 1, no = 0
Morphology of lesion*	Polypoid or flat
Pathologic diagnosis of the biopsy or snared polypectomy specimen	Adenoma (with or without advanced features), hyperplastic polyp, serrated adenoma
Immediate complications	Perforation, bleeding, hypoxia, hypotension, arrhythmia
Complications up to 30 days	Perforation, bleeding, hypoxia, hypotension, arrhythmia, severe abdominal pain requiring ER visit and/or admission to hospital

* Documented during colonoscopy and objective confirmation by digital video record of endoscope clock.

Record keeping: A digital image capturing system will be used to record the procedure to document the procedure times (insertion, arrival in the cecum, biopsy, polypectomy, end of examination), confirmation of cecal intubation (visualization of the appendix orifice and/or the ileocecal valve) and the findings during the withdrawal phase (recorded by the research assistant). The digital images will bear no personal identifier.

d. Sampling strategy

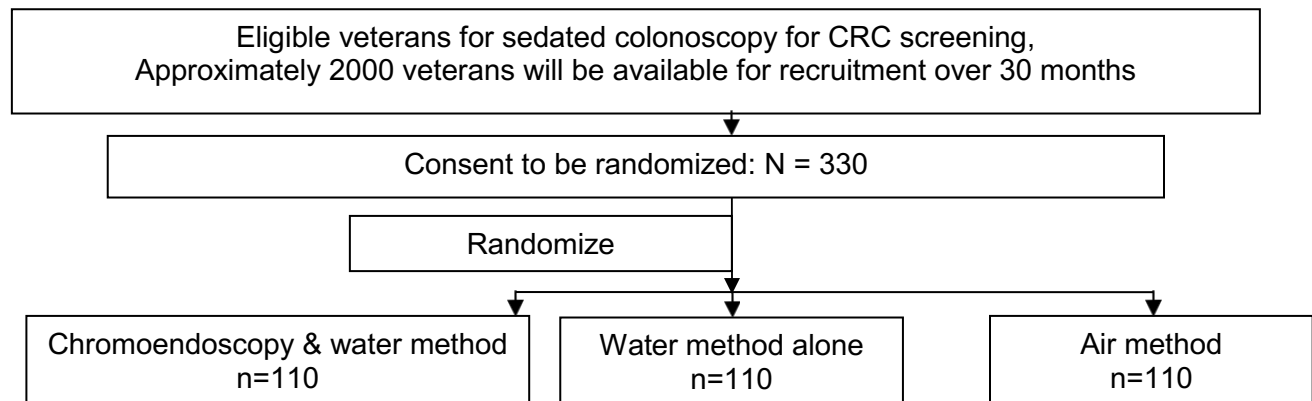
The consent covers agreement to allow the colonoscopist to randomize the method to aid colonoscope insertion and examination (chromoendoscopy with water vs. water method vs. air insufflation), and to video record and photograph the procedure for analysis.

In order to accommodate the patients and allow them time to complete the split bowel preparation in the morning of the procedure, the study procedures will be scheduled as late morning and early afternoon cases as this will give the patients more time to complete the bowel preparation.

Sample size calculation

The study will utilize proximal diminutive ADR as the primary outcome. Based on prior preliminary data (Tables 5 and 7), the proximal diminutive ADR is estimated to be 14%, 34%, and 64% for air, water and combined water with chromoendoscopy, respectively. The sample size needed to detect the smallest difference (between 0.14 and 0.34) is 103 per group ($\alpha = 0.05$, power 0.80), for a total of 309. To allow for possible sample loss (e.g. due to poor bowel prep), we plan to randomize 330 subjects with 110 in each group. With these samples we can significantly determine these differences, which are equivalent to 2.5 to 3 time greater observable risk between tests.

Flow Chart Based on CONSORT Guideline:

**(c) Subject recruitment.**

Screening

Patient sources will include referral from primary care providers, clinical reminder on CPRS, pre-colonoscopy clinic when patients choose colonoscopy and review of colonoscopy clinic schedule to identify eligible screening patients for study. Chart review will be performed by the research coordinator for selection of patients suitable to be recruited.

Contacting patients

The research coordinator will implement the following. Initial presentation/inform patients of study will take place via telephone contact or during open access colonoscopy class. Patients interested in participating in the study will receive either mailing (those contacted by phone) or hand-out (during educational sessions) of the explanatory information and consent form to review. The phone number to call the research coordinator for questions will be provided. Those expressing interest during the educational sessions will receive a separate briefing conducted by the research coordinator after colonoscopy class regarding details of the study. Patient identifiers (name and contact phone number) will be recorded to track and document acceptance or refusal.

Day of procedure

The research coordinator will review the study with the patient and obtain informed consent. Thereafter the investigator will review the indication for colonoscopy with the patient, exclude any previously overlooked contraindication, perform the necessary physical examination, discuss and address patient questions and have the patient sign the usual clinical informed consent for the colonoscopy procedure.

(d) Description of base population and groups to be studied and method of randomization.

The base population will include patients who are referred for colonoscopy. The indication includes screening of otherwise healthy asymptomatic individuals between the ages of 50 to 75 years. After informed consent is provided by the patient, and immediately before insertion of the colonoscope, the patient will be randomized as described above.

(e) Justification of endpoints, and procedures and links between questions, data, and endpoints.

Adenoma detection and adequate removal is crucial to the prevention of CRC. We postulate that missed adenomas due to incomplete examination associated with low cecal intubation rate or poor bowel preparation obscuring the lesions are potentially remediable by the water method and that the use of chromoendoscopy will further enhance detection of flat lesions and less obvious (diminutive) polypoid lesions. To avoid confounding issues related to bowel preparation, all patients will be given instruction for a split prep using Golytely [64,65] with slight local logistical modifications as described above.

In addition to further improving bowel preparation, the water method has been reported to enhance cecal intubation, possibly by obviating elongation of the colon when air insufflation is used (56). It improves bowel preparation from suboptimal to adequate, possibly by optimizing the soaking effect of the water on residual fecal matter adherent to the colon wall and improves visualization. The magnification under water and observing lesions that are not flattened with air distension and stretching of the colonic wall helps with the examination. These effects potentially increase the extent of the colonic mucosa that can be examined thereby avoiding missing lesions. These combined features of the water method contribute to a more complete examination during withdrawal of the colonoscope and may mediate improved detection of adenomas. These effects are more pronounced in the right-sided lesions as the proximal colon is more prone to be affected by intubation failures and inadequate bowel preparation in the cecum and ascending colon. The addition of chromoendoscopy which highlights the outline and surface irregularities of the mucosa further enhances the detection of flat and small lesions.

Examination under water may be difficult with poor preparation as the residual stool alters the color and turbidity of the water and in cases with chromoendoscopy combined with the water method, turning the water green instead of blue and impairing visibility. Our experience indicated that water exchange by intermittent suctioning of dirty water and infusion of clean water will improve the visualization of the colonic lumen. Which patient will have poor preparation, however, is unpredictable. To overcome this unavoidable problem, we have adopted this colonoscopist-controlled approach of water exchange to remove any residual stool to improve the endoscopic examination. Since quality colonoscopy is ultimately the responsibility and pride of the colonoscopist, a method that is under his/her direct control during colonoscopy is the focus of our investigation.

(f) Data collection methods, intervals, and follow-up procedures:

Follow up care after the procedure

The research coordinator will call the patients after the colonoscopy at 24 hours to conduct the post procedural evaluation including any complications and to document patient satisfaction and address any questions or concerns from the patients (routine care applicable to all research subjects). Patients are advised to contact the research team or local emergency department if they notice any post procedural discomfort or pain. Patient will be contacted by phone at 30 day to document any adverse events including post procedural complications that may lead to emergency department visits or hospitalization.

The colonoscopist will review the pathology report of all lesions biopsied or removed and will notify the patients by mail of the results and the future follow up plan. Patients are generally advised to follow up with their primary care provider unless they have a complication or a significant pathology i.e. malignant polyp that requires further management discussion and referral.

Prospective data gathering (Table 11).

Table 11: List of quality measures, their purposes, and when the data will be collected.			
Data to be monitored ^a (purpose)	Baseline	During Recover	Up to 30 days
Findings – polypoid and flat lesions (primary and secondary outcomes)	X		
Cecal intubation (secondary outcome)	X		
Total medications during colonoscopy (secondary outcome)	X		
Maximum pain score during colonoscopy (quality measure)	X	X	
Additional medications during colonoscopy (quality measure)	X		
Demographic data interview & record review (co-variables)	X		
Medical and surgical history (co-variables)	X		
Complications - emergency department visit, hospitalization (co-variables)			X

(g) General analytic plan (statistical analysis):

Primary Hypothesis.

In patients undergoing sedated colonoscopy for screening, when all polypoid and flat lesions including diminutive ones proximal to the splenic flexure are removed by polypectomy or biopsy, the patients examined by the combined chromoendoscopy and water method will be found to have a higher proportion of individuals with at least one proximal diminutive adenoma compared with the water method alone or air insufflation method for aiding insertion of the colonoscope.

Statistical Analysis: We will summarize the variables collected by calculating the frequencies of the categorical variables [such as number of patients with at least one proximal diminutive adenoma (proximal diminutive ADR), number of adenomas detected, adenoma location, adenoma size, gender, ethnicity, etc) and calculating the mean and standard deviation of the continuous variables (such as adenoma size, volume of water used, age, BMI, etc)].

To investigate differences in ADR, we will use logistic regression models, with an outcome that is a binary variable denoting whether each subject had one or more diminutive proximal adenomas. These models will allow us to quantify the differences between the three tests and determine if the differences are statistically significant. We will account for demographic characteristics (age, gender, BMI, ethnicity, etc) and investigate how other primary covariates (procedure time, volume of water used in study, etc) affect the rate of adenoma detection. Following, we will investigate the effects of secondary covariates (colon cancer detected, sedation medications) on adenoma detection rates.

As a secondary analysis, we will investigate how the secondary outcomes vary among the three tests. We will use repeated measures ANOVA and logistic regression models to quantify the differences between tests and to determine if they are statistically significant.

Pitfalls and solution

The report by Kahi et al. [20] did not demonstrate a significant difference in the adenoma detection between chromoendoscopy with HD scope and HD white light colonoscope alone. The failure to demonstrate a significant difference may be the result of a type II error. The authors did state that they would require upward of 800 patients in order to show a significant difference.

The time consuming procedure of dye spraying may also be a deterrent to the routine use of chromoendoscopy. However, our pilot data using combined chromoendoscopy and water method with high resolution colonoscopes did demonstrate a much higher ADR and with the additional benefits of the water method over the conventional air technique, it would be prudent to evaluate the potential impact of this combined method in enhancing adenoma detection in routine CRC screening.

The significance of small adenoma in the future development/advancement to CRC remains controversial and needs to be addressed. Most of the current publications referred to identification of relatively larger adenoma. In previous RCT, our experience suggested that small polyps and adenoma are better visualized using the water method with or without chromoendoscopy. Indeed, Kahi et al. [20] also reported a significantly higher detection of <5 mm adenomas and flat adenomas in the chromoendoscopy group suggesting that dye staining enhances the appearance of small lesions. Air distension tends to stretch the colonic mucosa making small lesions less obvious under white light examination. A combined chromoendoscopy and water method reveals the small lesions by outlining their contour and highlighting mucosal abnormalities (Figure 4). Improved visualization allows the biopsy or removal of these small lesions. The water method enhances the observation of small lesions especially those on the right side which are more likely to be missed due to poor preparation and failed cecal intubation.

A number of genetic and environmental factors influence the growth and progression of small adenoma [66]. One recent study reported that of the 3291 colonoscopies performed, 1235 colonoscopies yielded a total of 1933 small or diminutive adenomatous polyps. Advanced histology including carcinoma was found in 10.1%

5-10 mm adenomas and in 1.7% of ≤ 4 mm adenomas [67]. It is logical to expect that with the adenoma-cancer sequence concept, a proportion of small polyps can grow/evolve to become dysplastic and eventually cancer. Therefore even small lesions especially those on the right side should be biopsied or removed because of the potential risk of future malignancy [7,8]. Once detected on screening colonoscopy and confirmed pathologically, the finding (adenomas or flat lesions) would change the recommendation for subsequent surveillance. The lack of mortality reduction by optical colonoscopy for right-sided cancer has not been explained and this may be related to miss lesions. These considerations justify the detection and removal of diminutive lesions during optical colonoscopy, especially those in the right colon. However, only long term follow up studies will be able to show if removal of the right-sided small adenomas will prevent future development of colon cancer. We will continue to follow this cohort of patients when they return for surveillance colonoscopy or with symptoms of colorectal cancer.

The presence of poor bowel preparation could limit examination. The presence of stool could change the color of the indigo carmine solution turning it green instead of blue color. We emphasize the need for suction removal of the dirty water from the colonic lumen before infusion of clean (colored) water to clear the view for visualization and enhance the staining effects of indigo carmine. Dye staining serves to highlight the contour and contrast between the polyp and adjacent mucosa thus improving observation of the lesions.

Other issues

Issues related to expectation. Expectation of benefit (e.g. finding more lesions) cannot be avoided by the colonoscopist who is not blinded. We'll monitor changes in process variables (variables that reflect the presumed mechanism of treatment, e.g. cecal intubation documented by photograph of the appendix orifice and or cecal folds, withdrawal time, rate of adenoma detection (e.g. control group should meet the quality standard of having an ADR of 25% in male patients undergoing screening).

Issues related to blinding of endoscopist. The colonoscopist and nurse cannot be blinded to treatment allocation and the primary outcome of proximal diminutive ADR. Randomly selected (10% of total determined by the statistician) coded digital records will be reviewed by independent paid observers to confirm agreement of lesions, cecal intubation, times (endoscopic clock) of insertion, cecal intubation and total withdrawal of the colonoscope. For secondary outcomes, to compensate for increased risk of investigator bias, this study will be designed to use independent, blinded evaluators, whenever indicated, for assessment of outcome(s). No analysis will be started until all patients have completed evaluation to avoid biasing the colonoscopist, who may change the approach if it is known that one group is doing better or worse than the other.

Issues related to male dominance in enrollees. While patients of both sexes will be enrolled, it is likely that there will be a predominance of male enrollees. This is unavoidable because the VA population consists of 95% male and 5% female.

Issue related to differential dropout rate. Since sedation is provided for all groups of patients, we expect the patient tolerance will be similar. Any dropouts will be retained in the data analysis (intent-to-treat) and labeled treatment failures (no adenomas in the unexamined segment) to avoid any differential dropout rate to seriously bias outcomes.

Issues related to the water techniques used to insert the colonoscope lack standardization. The insertion technique for the water method will be standardized (56) by having the air pump turned off until the cecum is reached. Air pockets are suctioned on scope insertion. Dirty water is suctioned before clean water is infused to facilitate scope advancement and to minimize the volume of water inside the patient in case the patient becomes incontinent. Close attention will be paid to keep record of these variables to detect unavoidable variations.

(I) Publication from Last Funding Period (Pertinent Publications)

RESEARCH PAPERS - PEER REVIEWED

- Leung JW, Mann S, Leung FW. Option for screening colonoscopy without sedation – a pilot study in United States veterans. *Alimentary Pharmacology and Therapeutics* 2007; 26(4):627-631.
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- Granados-Savatgy L, Bradham DD, Blohm L, Siao-Salera R, Leung JW, MD, Leung FW. Cost benefit analysis and cost estimating: sedated vs. unsedated colonoscopy at one VAMC. *Am J of Clin Med* 2010;7(3):147-150.
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- Leung FW, Leung JW, Siao-Salera RM, Mann SK, Guy Jackson G. The water method significantly enhances detection of diminutive lesions (adenoma and hyperplastic polyp combined) in the proximal colon in screening colonoscopy - data derived from two RCT in US veterans. *J of Interv Gastroenterol*. In press, 2011.
- Leung JW, Ransibrahmanakul K, Toomsen L, Mann SK, Siao-Salera RM, Felix W, Leung FW. The water method combined with chromoendoscopy enhances adenoma detection. *J of Interv Gastroenterol*. In press, 2011.
- Leung FW, Leung JW, Mann SK, Friedland S, Ramirez FC. Innovation Forum - The water method significantly enhances the outcome of colonoscopy in sedated and unsedated patient. *Endoscopy*. In press, 2011.

Human Subjects

(1) Risk to Subjects

(a) Human Subjects Involvement and Characteristics: Risks common to all forms of colonoscopy (sedated or unsedated, irrespective of the clinical study) include: pain, bloating, medication reaction, bleeding, perforation, intravenous site reaction and rarely death. Sedated colonoscopy has a 1.1% risk of cardiopulmonary events (hypotension, hypoxia, arrhythmia). Death occurs in less than 0.003%.

Inclusion criteria: asymptomatic veterans scheduled for routine screening colonoscopy and agree to be randomized will be enrolled. Exclusion criteria: patients who decline to be randomized, emergent colonoscopy, evidence of colonic obstruction based on pre-colonoscopy clinical evaluation, previous history of colonic operations, hemostasis procedure, surveillance of inflammatory bowel disease, unable to give consent. Other exclusion criteria were current participation in other studies, a history of colonic surgery, a medical condition that could increase the risk associated with colonoscopy (active cardiac or pulmonary disease or other serious disease) or that would preclude a benefit from colonoscopic screening (cancer or any terminal illness), a prosthetic heart valve, anticoagulant therapy, nonmedical problems (psychiatric disorders, lack of transportation, homelessness or lack of support at home, or excessive use of alcohol), and a need for special precautions in performing colonoscopy (i.e., antibiotic prophylaxis).

(b) Sources of Material: The patients' existing medical records in CPRS which contain demographic data such as age, sex, identification number, list of associated medical illnesses, medications will be reviewed. The patients' responses to the questionnaire designed for this study, the results of colonoscopy and pathology reports are specific information obtained for research purposes.

(c) Potential Risks:

Risks related to the clinical study:

Questionnaire: Inconvenience, embarrassment about revealing feelings related to the colonoscopy.

Other risks: Potential risks include confidentiality risk regarding medical and personal information. A breach of confidentiality is not anticipated due to the security procedures for research data.

Physical Risks: Water infusion in lieu of air insufflation has no known physical risks. Blood draw for checking serum electrolytes may be associated with pain and bruising at the puncture site and minimal risk of infection. Indigocarmine may be associated with nausea and itchiness but there is no reported side effect in previous studies involving the use of indigocarmine as dye staining in colonoscopy.

Psychological Risks: Water infusion in lieu of air insufflation has psychological risks of anxiety.

Social Risks: Water infusion in lieu of air insufflation has no known social risks.

Economic Risks: Water infusion in lieu of air insufflation has no known economic risks.

(2) Adequacy of Protection from Risks

(a) Recruitment and Informed Consent: For recruitment, the following will be presented to all patients attending pre-colonoscopy education class or by mail. Patients will be informed of the study and control methods of sedation and the use of water infusion in lieu of air colonoscopy with dye (study method) or without dye (study method) or conventional air colonoscopy (control method). The doctors will be conducting a study to determine if the study methods have any advantage over the control method. All patients who present to their scheduled elective colonoscopy will be invited to participate.

Participation will involve giving consent to be assigned in a random manner (according to a random list of codes generated by the computer) to one of the three ways of undergoing the examination. There will be questionnaires to be answered by all the participants.

(b) Protection against Risk:

Minimizing risks through study design:

Risk from time spent in responding to questionnaires: All questionnaires will be kept as concise as possible to minimize the time required to complete them.

Risk from discomfort associated with colonoscopy: Experienced endoscopists will perform and trained personnel will assist in the performance of the colonoscopy.

In addition, the following measures will be implemented to minimize risks for the subjects:

1. Enrollment of subjects will adhere to the inclusion and exclusion criteria.

2. The subjects will be given instructions to notify the study personnel if they have any concerns or untoward symptoms. They will be given the name and phone number of the site investigator and coordinator. An alternative number to one of the research team members will be given to subjects if they are not available. If an adverse event associated with the study should occur, the patients can contact one of the research team members, who will arrange appropriate and timely evaluations.

3. Subjects will be informed of new findings that may affect their decision to remain in the study.

4. VA good clinical practice guidelines will be followed.

5. VA information security measure will be implemented: Written documents and records will be coded so that the identity of the patient is protected. When not in use by the research team, these documents, records and codes will be placed in a locked file cabinet. Key access is available to members of the research team only. All computerized data will be placed in password protected computers. Password access will be available to members of the research team. These procedures are likely effective in protecting confidentiality.

(3) Potential benefit of the Proposed Research to the Subject and Others.

There are no known benefits to the research subjects.

(4) Importance of the Knowledge to be gained.

The result of the study may reveal if the additional dye staining (chromoendoscopy) is more or less efficacious, or no difference compared with the water method or the conventional air method in terms of finding more lesions (polypoid or flat lesions - hyperplastic and adenomatous polyps or cancers).

Therapeutic alternatives: All subjects in the study method group can undergo colonoscopy using the conventional air method.

Risk/Benefit analysis: The risks for both groups are time spent in responding to questionnaires. The potential benefits for society are that we will gain RCT data to support or not the use of water infusion (with or without dye staining) colonoscopy performed for colorectal cancer screening.

Comprehension of the information provided: Only subjects who can read and understand the consent are enrolled. The consent form will be provided to the patient in advance of the colonoscopy (e.g. by mail, as handout at the time of pre-colonoscopy class) to enable the patient to have time to read over the descriptions, to seek other opinions and to discuss with family members or friends. The subject is asked questions and feedback is elicited to ensure that the subject is aware of the consent including risks and benefits. The questions are as follows:

Directions: Make a subjective judgment regarding item 1 below. Ask the patient question 2 through 7. The evaluator may select the appropriate language to use in formulating the questions in order to assist the subjects' understanding.

Questions:

1. Is the subject alert and able to communicate with the examiner? ☐ Yes ☐ No

2. Ask the patient to name at least two potential risks incurred as a result of participating in the study.

3. Ask the patient to name at least two things that will be expected of him/her in terms of patient cooperation during the study.

4. Ask the patient to explain what he/she would do if he/she decides that they no longer wish to participate in the study.

5. Ask the patient to explain what he/she would do if he/she is experiencing distress or discomfort.

6. Ask the patient if participation in this research is voluntary. ☐ True ☐ False

7. Ask the patient whether he/she could get a second opinion regarding his/her care because his/her doctor is also a researcher and these two roles can be in conflict sometimes. ☐ True ☐ False

I hereby certify that the above patient ☐ Is, ☐ Is Not, able to communicate and able to give acceptable answers to items 2, 3, 4, 5, 6 and 7 above.

Evaluator

Date

Information withheld from subjects: None

Inclusion of women and minority: Every effort appropriate to the settings will be made to include women and minority in this study.

(5) Safety and Monitoring.

This study is a MODERATE risk clinical project with the potential of uncommon serious adverse events or unanticipated problems involving risks to participants.

The study methods both utilize water infusion in lieu of air insufflation with sedation, with the addition of dye to the combined chromoendoscopy and water method. Indigocarmine has been used and recommended in the literature for chromoendoscopy to enhance detection of colon polyps.

Exclusion criteria for safety include patients who decline to participate, unable to give informed consent or complete the questionnaires due to language or other difficulties.

All patients will be seen by one of the site investigators or the research staff prior to enrollment.

After participant enrollment, one of the site investigators will review blood pressure, cardiac rhythm and pulse oximetry (oxygenation) safety parameters prior to participant enrollment.

A study physician will be available on site for managing adverse events.

The site investigators will monitor study subjects for adverse events during the study.

Monitoring for pain in both study and control method groups will be carried out as follows: During the examination (with the colonoscope tip in the rectum, sigmoid colon, splenic flexure, transverse colon, hepatic flexure, ascending colon and cecum) or at 2-3 minute intervals, the patient will be asked to report pain on 10 point scale (0 = no pain, 10 = maximum pain) and for those who receives sedation, patient will be asked if additional medications are needed for control of pain. Additionally, if a pain score of ≥ 2 is recorded, medications will be offered. In either instance, the patient can decline or accept the medication depending on whether the pain is tolerable or not.

Monitoring for blood pressure, cardiac rhythm and pulse oximetry (oxygenation) will be maintained throughout the entire colonoscopy. Devices with automatic alarms used on a routine basis for all colonoscopy patients will be employed. Any alarm signals will be attended to immediately by a member of the research team and appropriate action will be taken to resolve any safety issues.

The identity of the subjects will be coded so that the data sheet with patient information will be de-linked from the patient identification. The coded video recording does not contain any patient identifier. The code will be kept in separate locked location and password access-protected computer (shared drive on the VA computer). When not in use by member of the research team all hard copies of coded patient information will be locked in file cabinet in designated location with locked access (e.g. investigators' office). All patient data transferred to computerized spread sheets will be stored in computers protected by password. Password access will be available to members of the research team only. At designated time after completion of the study (e.g. after publication of results), all stored data will be destroyed or erased. These measures are taken to comply with HIPAA requirements. The site investigators will review any complications and bring the occurrence to the attention of the Institutional Review Board.

Description of how adverse events are graded:

The main interventions are conventional method versus study methods. A grading scale will be used to describe adverse events if the need arises: 1=mild, 2=moderate, 3=severe, 4=life-threatening, 5=fatal. The attribution scale is 1=definitely not related, 2=probably not related, 3=possibly related, 4=probably related, 5=definitely related to the study interventions.

Plan for adverse event reporting:

The site PI will review all adverse events.

The site PI will promptly report any serious adverse events or unanticipated problems involving risks to study subjects in accordance with regulations: reportable adverse effects arising from any research procedures will be submitted promptly to the IRB. Although they are not anticipated to occur, deaths will be reported within 24 hours to the IRB. Unanticipated problems or Serious Adverse Events in research subjects will be reported to the IRB within 5 working days of awareness of the event and written reports will be submitted to the IRB no later than 15 calendar days after the event.

All reportable adverse events will be compiled, and reported in summary form, on an annual basis to the IRB, and at the conclusion of the study.

Performance and frequency of safety reviews:

The site investigators will perform safety reviews for all patients enrolled in this study on a weekly basis. The site PI of the study is responsible for carrying out continuous monitoring of accrual, data quality, and adverse events. The local study monitoring team will review the accumulating data regarding overall safety and efficacy of treatments employed in the trial. The study monitoring team will meet (twice a year) to review adverse events and subject safety issues.