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

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Key words: colonoscopy, water method, proximal colon, hyperplastic polyp, adenoma

Abbreviations: ACC, Ambulatory Care Center; ACG, American College of Gastroenterology; ANOVA, analysis of variance; ASGE, American Society for Gastrointestinal Endoscopy; RCT, randomized controlled trial; SD, standard deviation; US, United States; VA, Veterans Affairs; VAMC, Veterans Affairs Medical Center

Purpose: Emerging data indicate a colonoscopist-controlled method is needed to avoid missing proximal colon pre-malignant lesions. Screening colonoscopy does not prevent all proximal colon cancers. Even diminutive lesions in the proximal colon harbor dysplasia. In addition to adenomas (presumptive cancer precursors), recent proposals to re-evaluate proximal colon hyperplastic polyps as serrated polyps which could be pre-malignant or harbingers of interval neoplasia dramatize the importance of attending to these lesions. The finding that the water method increased yield of proximal diminutive adenomas prompted assessment of the hypothesis that the water method increases yield of all proximal diminutive lesions (adenoma and hyperplastic polyp) in screening cases.

Methods: Two RCT assessed the water method with primary outcome of completion of unsedated colonoscopy when the option of scheduled, unsedated or sedation on demand was used. Diminutive (<10 mm) lesions proximal to the splenic flexure were tracked.

Results: In screening cases, 31% and 6% of the water and air group had at least one proximal diminutive lesion ($p=0.0012$). Regression analysis revealed withdrawal time, method and volume of water used were significant predictors of proximal diminutive lesions. Effect of the water method on detection of proximal diminutive lesions was independent of age, body mass index, endoscopist, sedation, cecal intubation rate, bowel cleanliness score on withdrawal and total procedure time.

Limitation: Male subject predominance, analysis of secondary outcomes of pooled RCT data.

Conclusion: The hypothesis that the water method effectively enhances proximal diminutive lesion detection in screening colonoscopy in diverse clinical settings should be tested.

Introduction

Case-control reports and population studies have suggested that colonoscopy fails to reduce incident cancers and cancer mortality in the proximal colon.¹⁻³ Basic researchers need to find a plausible explanation in terms of tumor biology. Clinicians need to develop improved method(s) to identify the lesions in the proximal colon at risk of being missed. Adenoma detection rate (ADR), but not cecal intubation rate, was an independent

predictor of the risk of interval colorectal cancer after screening colonoscopy.⁴ Because the number of colonoscopists and sites performing screening colonoscopy worldwide is enormous a simple, inexpensive colonoscopist-controlled method is needed to avoid missing lesions especially the diminutive (<10 mm) ones in the proximal colon. We recently completed two parallel RCT in veterans accepting scheduled, unsedated colonoscopy⁵ or the option of sedation on demand⁶. The significant impact of the water method on the primary outcomes in terms of attenuating discomfort⁵ or enhancing completion of unsedated colonoscopy⁶, respectively, has been reported. Neither outcome is considered measures of quality, although recommendations were advanced to elevate both to the level of quality measure.^{7,8} On the other hand ADR is both a measure of quality⁹ and an independent

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Submitted: Dec/24/2010; Revised: Jan/03/2011; Accepted: Jan/10/2011
Previously published online: www.landesbioscience.com/journals/jig
DOI: 10.4161/jig.1.2.16826

predictor of risk of post screening colonoscopy interval cancers⁴. When we conducted an assessment of the combined data bases of the two RCT inclusive of all patients we found that the water method significantly enhanced the detection of proximal diminutive adenomas.¹⁰ The fact that even diminutive lesions in the proximal colon could harbor high risk dysplasia¹¹⁻¹⁴, and proximal hyperplastic polyps were really serrated polyps which could be pre-malignant¹⁵⁻¹⁷ and predictive of the risk for interval neoplasia during surveillance¹⁸ highlighted the emerging importance of these lesions. Detecting all proximal lesions including diminutive ones whenever possible appears to be a prudent approach. In this report we searched for evidence to support the hypothesis that the water method enhances the detection of proximal diminutive lesions in the subgroup undergoing screening colonoscopy.

Method

The water method for aiding insertion of the colonoscope has been well-described. Briefly it can be summarized as water infusion in lieu of air insufflation combined with suction removal of all residual air to minimize loops formation and angulations at flexures and redundant segments, and removal of all residual feces by water exchange to clear the luminal view.¹⁹⁻²⁴

Two RCT designed to determine if the water method significantly improved non ADR-related primary outcomes in veterans accepting the option of scheduled, unsedated (NCT00747084) or on demand (NCT00920751) sedation colonoscopy were completed. None of the scheduled unsedated patients examined at the Sepulveda VA received any medications. At the Sacramento VA, midazolam and fentanyl were used for sedation.

Each RCT was approved by local Institutional Review Board (IRB) – the VA Greater Los Angeles (VAGLAHS) and the Northern California (VANCHCS) Healthcare Systems, respectively. All participants signed consent before participation. At the Sepulveda Ambulatory Care Center, VAGLAHS (11/07-4/09) enrolled veterans undergoing unsedated colonoscopy were randomized to the water (n=42) or air (n=40) group.⁵ At the Sacramento Veterans Affairs Medical Center, VANCHCS (4/09-10/09), enrolled veterans accepting on demand sedation colonoscopy were randomized to the water (n=50) or air (n=50) group.⁶ Three colonoscopists participated in the studies. All three had over 20 years experience in the air method. FWL and JWJ began developing the water method in 2006. SKM started to participate in the water method studies in 2007. FWL performed the comparison of air vs. water method in the scheduled unsedated patients. JWJ and SKM performed the comparison of air vs. water method in the patients who accepted sedation on demand. The impact of the water method on the primary outcomes of discomfort⁵ or completion of unsedated colonoscopy⁶, respectively, has been described. For the current report, we searched the data bases of these two RCT tabulating age, body mass index, endoscopist, method (air vs. water), sedation, total volume of water used, cecal intubation rate, bowel cleanliness score on withdrawal and total procedure time, recovery time, proximal (proximal to the splenic flexure) diminutive

lesions (adenomas and hyperplastic polyps of <10 mm in size) in screening cases.

The data were evaluated using intent-to-treat analysis of outcomes related to the index colonoscopy. Group means (SD) were compared using Student's t tests and frequency counts (%), by Fisher's exact test. Regression analysis was performed to assess predictors of proximal diminutive lesion detection. A p value of <0.05 was considered significant.

Results

The data are summarized in **Table 1**. The proportion of recruited patients in each arm who underwent first time screening was 57.8% in the air method group, and 46.9% in the water method group. Fifty-two and forty-five screening colonoscopy patients were randomized to the air and water group, respectively. None of the scheduled unsedated patients at the Sepulveda VA received sedation medications. At the Sacramento VA, the water method produced a reduction in medication requirement [mean (SD)]: fentanyl, 12.5 (26.8) µg versus 24.0 (30.7) µg; midazolam, 0.5 (1.1) mg versus 0.94 (1.20) mg.⁶

Proximal diminutive lesions were detected in 6% of the former and 31% of the latter (p=0.0012). There were no proximal diminutive hyperplastic polyps detected in the air group but 13% of the water group had at least one proximal diminutive hyperplastic polyp (p=0.008). The difference in overall proximal diminutive adenoma 6% (air) and 20% (water) approached significance (p=0.0603). Fewer patients required sedation in the water group (7 vs. 17) and the difference approached significance (p=0.0511). In these screening cases, regression analysis revealed withdrawal time, method and volume of water used were significant determinants of proximal diminutive lesions; withdrawal time alone was a predictor of adenoma detection, and method alone was a predictor of hyperplastic polyp detection (all p<0.05). Effect of the water method on proximal diminutive lesion detection was independent of age, body mass index, endoscopist, sedation, cecal intubation rate, bowel cleanliness on withdrawal and total procedure time. No impact on surveillance and diagnostic cases was seen.

Discussion

The initial focus of the development of the water method was on addressing the question of whether cecal intubation could be achieved without any air insufflation. Polyp detection was merely a secondary outcome monitored to ensure quality of colonoscopy was not jeopardized without any inkling of a potential positive impact of the methodological change on lesion detection.^{19,20}

Refinements of the water method included stepwise removal of residual air by suction beginning at the rectosigmoid and then extended to other air pockets to decrease angulations at all of the flexures and redundant segments.²⁴ Besides reducing angulations at the flexures removal of residual air collapsed the colon around the endoscope. Water infusion was used in a purposeful manner to identify the lumen. Of note was that our internal discussions during the initial phase indicated that the turbidity of

Table 1. Effect of water method on detection of proximal diminutive adenoma and hyperplastic polyp

Number of cases randomized	Air (n=90)	Water (n=92)	p
Proximal diminutive lesions in screening cases (n)	52 (57.8%)	45 (46.9%)	
Adenoma	3 (6%)	9 (20%)	0.0603 ^a
Hyperplastic polyp	0	6 (13%)	0.0082 ^a
Adenoma & hyperplastic polyp	3 (6%)	14 (31%)	0.0012 ^a
Age (yrs)	60 (9)	61 (9)	0.4725
Body mass index	29.4 (6.7)	29.2 (6.2)	0.8466
Sedation	17	7	0.0511
Volume of water used (ml)	74 (107)	1504 (641)	0.0001 ^b
Cecal intubation rate*	92%	98%	0.2286
Bowel cleanliness - insertion (1, worst - 4, best)	1.25 (1.2)	0.96 (1.1)	0.2044
Bowel cleanliness - withdrawal (1, worst - 4, best)	2.36 (0.7)	2.42 (0.7)	0.6861
Insertion time (min)*	19.5 (15.3)	20.8 (15.9)	0.7022
Withdrawal time (min)**	13.7 (6.9)	16.3 (7.2)	0.0819
Total procedure time (min)**	33 (18)	37 (20)	0.3257
Abdominal pressure/Position change - insertion	22 of 52	13 of 45	0.1734
Recovery time (min)	11 (9)	8 (6)	0.0797
Proximal diminutive lesions in all other*** cases (n)	38	47	
Adenoma	10 (26%)	17 (36%)	0.8179
Hyperplastic polyp	5 (13%)	5 (11%)	0.7467

N, total; n, in subgroup. Mean (SD) or frequency (%). ^aFisher's exact test; ^bStudent's t. *(n, air=48, water=44); **Include time or inspection, biopsy and polypectomy. ***Include surveillance and diagnostic cases.

the luminal water as a result of the infused water stirring up the residual feces was a major obstacle to overcome and a potential disincentive to continue evaluation of the combined approach – lumen could not be identified, easier just to insufflate air and stay above the turbid water, suction of the turbid water took time and created suction polyps. In retrospect, we were in agreement with other investigators who expressed concerns over the use of water-related techniques during insertion.^{25,26} A weakness of the water instillation technique was the possible decrease in the ability to detect subtle mucosal disease because of excessive residual water in the colon.²⁵ Although residue could be suctioned while infusing more water which helped to clean the colon, if there was too much residue it was very difficult to see clearly enough to insert the colonoscope properly.²⁶ The need to demonstrate exclusion of air could enhance cecal intubation in the scheduled, unsedated patients²¹ overrode these reservations. The strict adherence to no air insufflation meant suspended residual feces obscuring the view had to be suctioned and replaced by clean water until the colonic lumen could be visualized again. The reward was the observational¹⁹⁻²¹ as well as proof-of-principle^{5,6} data that cecal intubation could be achieved without any air insufflation.

Serendipity had it that the collapsed lumen optimized the “soaking effect” of the infused water on feces adherent to the mucosa. The turbulence due to simultaneous infusion and suction conveniently dislodged the feces from the surrounding mucosa. This dynamic maneuver made removal of the residual fecal matter more “efficient” than by washing with a single water jet in a distended air filled colon, or sequential suction removal of large volume of water previously infused or loaded into the colon. During insertion most of the infused water in fact was

aspirated into the suction bottle instead of being allowed to remain in the colon. Over-distension by the infused water was minimized and tedious effort devoted to clearing the lumen of turbid water during withdrawal was obviated.²⁴

In the context of developing an “improved” water method for minimizing procedure-related discomfort, the recognition of an association between enhanced cecal intubation rate (76% vs. 97%), salvage cleansing (13% vs. 1.5% of patients requiring reschedule due to inadequate bowel preparation) and ADR showing a trend towards being numerically higher (25.8% vs. 36.5%) with warm water infusion in lieu of air insufflation was indeed serendipitous.²¹ The tantalizing observation prompted a retrospective review of an endoscopic database. A significantly higher ADR was recorded for the patients examined with the water method, 26.8% vs. 34.9% (p=0.003, Chi square test).¹¹ The data generated the hypothesis that the water method may indeed produce a significantly higher ADR compared with air insufflation.¹¹

Using the “perfected” water method, two RCT were completed as described above and details of these two RCT were reported.^{5,6} Since reports of unsedated patients are rare in the United States, the data of these two RCT were pooled to optimize the sample size of unsedated patients. Indeed, a significant enhancement of proximal diminutive ADR with the water method was observed - 14.4% (air) vs. 28.3% (water).¹⁰ A subgroup analysis of those undergoing screening colonoscopy revealed an intriguing finding. The method (p=0.0242, two way ANOVA) but not the endoscopists or the interaction between the method and the endoscopists was a significant factor in determining proximal diminutive ADR.¹⁰ The observation con-

tributed to the hypothesis for the current study focused on all diminutive lesions in the proximal colon in screening cases.

We reported data¹¹ to confirm that even proximal diminutive lesions can harbor high risk dysplasia¹²⁻¹⁴. The reports depicting colonoscopy as ineffective in preventing some post screening colonoscopy incident cancers or minimize cancer mortality in the proximal colon¹⁻³, and the proposal to re-evaluate proximal hyperplastic polyps as serrated polyps with malignant potentials¹⁵⁻¹⁸ highlighted the importance of detecting all proximal lesions whenever possible. Towards this goal, the third-eye retro-scope which enhanced detection of proximal colon lesions²⁷⁻²⁹ is an important new tool. The drawback of the approach is that the methodology is not widely available and requires substantial resources to set up and recurrent expenses for the disposable third eye device.

In the pool data of the two RCT described above^{5,6}, when screening cases were considered (**Table 1**), withdrawal time, method and volume of water used were significant determinants of detection of proximal diminutive lesions (adenomas and hyperplastic polyps). Effect of the water method on proximal diminutive lesion detection was independent of age, body mass index, endoscopist, sedation, cecal intubation rate, bowel cleanliness on withdrawal and total procedure time. These results suggest that studies with outcome variables other than these are necessary to discover the best approach to the performance of screening colonoscopy. Attention to quality measures, e.g. cecal intubation rate, bowel preparation to ensure bowel cleanliness, withdrawal time >6 min, regardless of appropriateness, may not be sufficient to ensure the highest ADR. The absence of an impact on surveillance and diagnostic cases suggests that future studies evaluating the effectiveness of the water method in optimizing the detection of proximal diminutive lesions should focus on screening cases.

Conclusions

The current results are limited by male subject predominance and analysis of secondary outcomes of pooled RCT data. The water method implemented with strict adherence to air exclusion appeared to increase detection of all diminutive lesions (adenomas and hyperplastic polyps) in the proximal colon. The focus on diminutive lesions is further justified by a recent study reporting that in at least one ethnic group (Asians) a substantial proportion of polyps <10 mm have advanced histologic features.³⁰ A head to head comparison with the third-eye-retroscope will be instructive. Future studies on assessing the effectiveness of the water method in modifying ADR should focus on first time screening cases in diverse settings. The data suggest the hypothesis that the significant enhancement of ADR with the water method may translate into reduced occurrence of post screening colonoscopy interval neoplasias deserves to be evaluated.

Grant support

In part by VA Medical Research Funds (FWL) and in part by ASGE Career Development Award (FWL 1985), ASGE and ACG Clinical Research Funds (JWL & FWL).

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