

# Indigocarmine added to the water exchange method enhances adenoma detection - a RCT

Joseph Leung<sup>1,2</sup>, Surinder Mann<sup>2</sup>, Rodelei Siao-Salera<sup>1</sup>, Catherine Ngo<sup>2</sup>, Randy McCreery<sup>1</sup>, Wilhemina Canete<sup>1</sup>, Felix Leung<sup>3</sup>

<sup>1</sup>Gastroenterology, Sacramento VA Medical Center, Sacramento; <sup>2</sup>Gastroenterology, UC Davis Medical Center; <sup>3</sup>Gastroenterology, Sepulveda ACC, VAGLAHS and David Geffen School of Medicine at UCLA, North Hills, CA

**Key words:** colon cancer screening, water method, indigocarmine, adenoma detection

**Abbreviations:** ADR, adenoma detection rate; NBI, narrow band imaging; SD, standard deviations; US, United States; VA, Veterans Affairs

**Purpose:** Chromoendoscopy with dye spray and the water method both increase adenoma detection.

**Hypothesis:** Adding indigocarmine to the water method will enhance further the effectiveness of the latter in adenoma detection.

**Methods:** Screening colonoscopy was performed with the water method (control) or with 0.008% indigocarmine added (study) by two endoscopists. Randomization was based on computer-generated codes contained in blocks of pre-arranged opaque sealed envelopes. High resolution colonoscopes were used. Upon insertion into the rectum, air was suctioned. With the air pump turned off, water was infused using a blunt needle adaptor connected to the scope channel and a foot pump to facilitate scope insertion until the cecum was reached. Residual stool causing cloudiness was suctioned followed by infusion of clear or colored water (water exchange) to facilitate scope passage with minimal distention of the colonic lumen. Upon seeing the appendix opening under water, water was suctioned and air was insufflated to facilitate inspection on scope withdrawal.

**Statistics:** Sample size calculation revealed 168 patients (84/group) needed to be randomized. Study was IRB-approved and registered (NCT01383265).

**Results:** There were no significant differences in mean age, gender distribution, BMI, and family history of colon cancer. Cecal intubation success rate was 100% in both groups. The overall adenoma detection rate was 44% (water only) versus 62% (water with indigocarmine), respectively ( $p=0.03$ ). One cancer was detected in each group.

**Conclusion:** In a RCT, indigocarmine at 0.008% concentration, added to the water method, significantly enhanced further the effectiveness of the latter in detecting adenomas.

## Introduction

Chromoendoscopy with target dye spraying has been used to outline the extent of mucosal lesions and in defining the possible underlying pathology of colonic lesions. In cases of underlying polyps, chromoendoscopy has been used to identify potential neoplastic lesions. However, it is a cumbersome technique as it uses a concentrated dye solution with subsequent washing before examination and biopsy. As a result, it has not become a popular or commonly practiced procedure except for research purposes.<sup>1</sup> The water method (with water exchange) has been shown to be superior to the conventional air method in screening colonoscopy. Patients were able to complete the colonoscopy with less sedative medication,<sup>2-5</sup> a higher proportion of patients were able to complete the procedure without medication when offered the option of on-demand sedation.<sup>6</sup> A review of published data on prospective RCTs involving water colonoscopy showed that water

method (with exchange) may be superior to water immersion in adenoma detection rate (ADR).<sup>7</sup> Our pilot retrospective study suggested that use of water method appeared to increase adenoma detection.<sup>8-9</sup> The addition of indigocarmine to the water method showed a significantly higher ADR compared to the water method using plain water and the conventional air method.<sup>10</sup> In this study, we performed a RCT to evaluate the potential benefits of adding indigocarmine to the water method compared to the standard water method in adenoma detection in patients undergoing screening colonoscopy. We test the hypothesis that with dye added to the water used in the water method, ADR can be enhanced. The study was approved by the Sacramento VA IRB and registered with ClinicalTrials.gov (NCT01383265).

## Methods

As reported in our previous study,<sup>10</sup> plain water was used as control and the combined dye and water (study) method utilized a 0.008% indigocarmine solution (by adding 10 ml 0.8% indigocarmine to a liter of water) used with the standard water method.

Patients received usual bowel preparation including a low-

\*Correspondence to: Joseph W. Leung; Email: [jwleung@ucdavis.edu](mailto:jwleung@ucdavis.edu)  
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residue diet for 2 days before and 2 tablets of bisacodyl plus 1 gallon of Colyte (polyethylene glycol-electrolyte) on the day before colonoscopy given in two divided doses.<sup>2-4</sup> Informed consent was obtained from the patient after full discussion of the risk and benefits of the study. Patients who signed the consent were randomized according to a computer generated code contained in a series of sealed opaque envelopes. Premedication included a combination of intravenous Diphenhydramine, Fentanyl and Midazolam.<sup>2-4</sup> High resolution colonoscopes from Olympus were used.

### Water method

The air pump on the light source generator (CLV 180; Olympus, Tokyo, Japan) was turned off prior to insertion of the colonoscope. Warm water (at 37 °C) was infused using a peristaltic pump (Endolav EL-100C, Cooper Surgical, Trumbull, CT, USA) with a blunt needle adaptor inserted through the biopsy channel of the colonoscope. Upon scope insertion into the rectum, air was suctioned and water was infused using the needle adaptor and a paddle pump to facilitate the passage of the colonoscope with minimal distension of the colonic lumen. When air pockets were encountered, the air was suctioned to reduce looping and straightened the colon at the flexures, before further infusion of water. Water was suctioned during scope passage to keep a minimum amount of water in the colon upon scope insertion. When cloudiness of water secondary to residual stool was seen, the water was suctioned to remove the residual feces before water (clear or colored) was infused to identify the lumen to facilitate scope passage. The colonoscope was 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, using intermittent water infusion. Water exchange with suction and infusion in rapid sequence was performed to facilitate clear visualization of the lumen. To minimize suction of the mucosa into the endoscope channel the water infusion was started first followed by application of suction. The volume of water needed to clear the view (200 to 2000 ml) was kept to a minimum, but not restricted. The collapsed colonic lumen allowed the water to more adequately soak the colonic surfaces and remove the adherent stool from the colonic mucosa. The turbulence set up by the sequential infusion and suction of water in the collapsed lumen dislodged the residual feces from the surrounding mucosa in close proximity to the tip of the colonoscope. This maneuver made removal of the residual feces “easier” than washing with a single water jet in a dilated air filled colon. Most of the infused water was aspirated into the suction bottle rapidly instead of being left in the colon, and over-distension of the colon was obviated. If advancement failed, the assistant provided abdominal compression followed by changing the patient position if necessary. If the advancement was uninterrupted, no abdominal pressure or change in patient position was used. For the combined dye and water method, residual stool in the proximal colon (especially in patients with inadequate bowel preparation) changed the indigocarmine solution to a greenish color. Continuous exchange of the dirty water was performed until a clear blue color was seen. If the appendix opening was seen under water or when the cecum was

thought to be reached by external finger palpation, the air button was turned on to confirm the location. If the cecum had not been reached, failed intubation was recorded based on intent-to-treat (ITT) but colonoscopy was continued. Cecal intubation was defined as described above. Any residual water was suctioned on scope withdrawal to facilitate examination.

Intermittent air insufflation (air pump set at high flow) was used to distend the colon on scope withdrawal for inspection, biopsy and polypectomy. Washing of any residual stool covered mucosa was performed by water or in the combined method with diluted indigocarmine irrigation. Inspection of the mucosa including examination behind folds was performed systematically as needed. After turn around in the rectum, residual air in the colon was removed by suction.

### Statistics

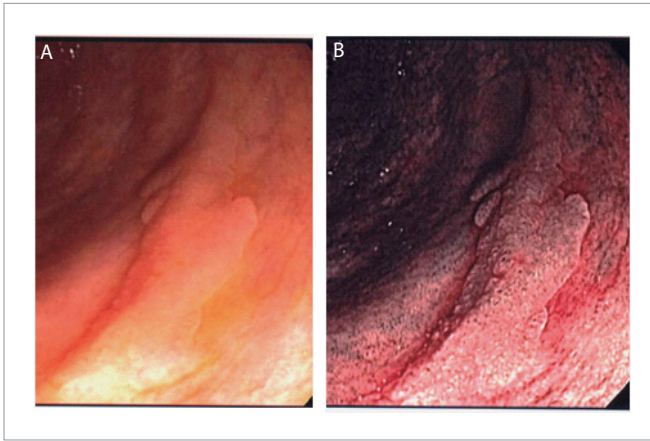
The ADR (defined as proportion of subjects with at least one adenoma of any size) in the study group (combined indigocarmine and water method) was compared with the water method using plain water. Power calculation indicated that 168 patients (84/group) were needed to be randomized. The tabulated data were analyzed using t-test and Fisher's exact test. A p value of <0.05 was considered to be significant.

## Results

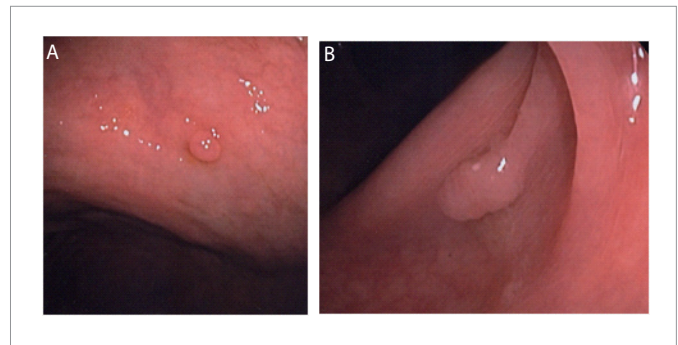
The results are presented in the tables. A total of 168 patients (84 in each group) were randomized. There were no significant differences in the mean age, gender distribution, BMI, and family history of colon cancer (**Table 1**). The cecal intubation success rate was 100% in both groups. The overall ADR was 37/84 (44%)(control with water only) versus 52/84 (62%)(study or combined dye plus water), respectively (p=0.03)(**Table 2**). One cancer was detected in each group.

## Discussions

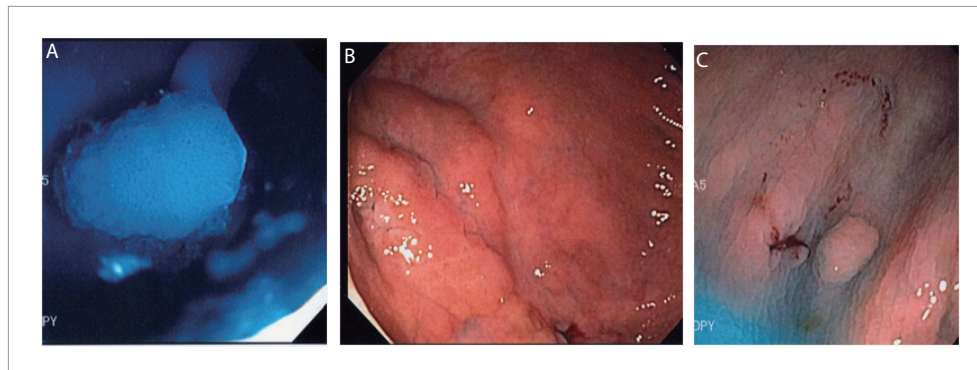
Canadian and German data indicated that colonoscopy failed to reduce incident cancers and cancer mortality in the right colon.<sup>11-13</sup> More recent US data have confirmed the same.<sup>14,15</sup> A plausible explanation is missed adenomas in the proximal colon during screening colonoscopy. Small lesions are more easily missed especially in the proximal colon. Different reasons may account for the high proximal missed rates. These include poor bowel preparation and failed cecal intubation. Despite an improvement in the overall bowel preparation score, split-dose bowel preparation did not improve overall adenoma detection. Adenoma detection rate, but not cecal intubation rate was an independent predictor of the risk of interval colorectal cancer after screening colonoscopy.<sup>16</sup> The impact of recent development in technology and techniques on ADR has been highly variable and inconclusive. These include colonoscopy performed with high-definition, wide-angle endoscope;<sup>17-21</sup> narrow band imaging;<sup>22-25</sup> transparent hood attached to the tip of the colonoscope<sup>23,26,27</sup> withdrawal time >6 min<sup>28,29</sup> or modified (e.g. split-dose) bowel preparation.<sup>30,31</sup> An optimal “colonoscopist-controlled” technique to enhance ADR and minimize “missed” right-sided lesions is



**Figure 1.** Polyp seen with water method. A: Flat polyp (adenoma) in proximal colon; B: NBI view of same polyp.



**Figure 2.** Polyps seen with water method. A: Small cecal polyp; B: Sessile polyp in ascending colon.



**Figure 3.** Polyp seen with dye plus water method. A: Polyp seen under blue (indigocarmine) water; B: Large flat adenoma in proximal colon; C: Small polyp in ascending colon. Note the bluish color fluid filling the surface irregularities and outline of the polyps.

desirable. The water method (with water exchange) has been shown to increase overall ADR compared to the conventional air method and water immersion method where a combination of air and water was used during the examination.<sup>7</sup> The increased ADR may be a result of higher cecal intubation success rate as compared to the air method with a combined effect of warm water that reduces colon spasm and facilitates examination.

A major limitation of the conventional dye-spray chromoendoscopy method is poor bowel preparation. In these studies, proportion of patient excluded varied from 4%,<sup>32</sup> 5%,<sup>33</sup>, 8%<sup>34</sup> to 9%.<sup>17</sup> Intent-to-treat analysis would have dictated an adjustment (decrease) of the ADR reported in each of these studies by the proportion of patients excluded due to poor bowel preparation (see values in [ ] in **Table 3**). The results of the current report indicate that the water method with dye in the form of 0.008% indigocarmine added to the water method is feasible. A high overall ADR of 62% was achieved. The salvage cleansing effect of the water exchange, which is an integral part of the water method,<sup>5,9</sup> obviated the need to exclude any patients because of poor bowel preparation even when indigocarmine was added to the water. The water (with or without indigocarmine)

could provide cleansing of the colon with suboptimal bowel preparation. The water exchange reduces the amount of residual water and allows undistracted examination on scope withdrawal. Coupled with the dye serving as a surface contrasting agent, the diluted indigocarmine highlighted the surface irregularities and outline of mucosal lesions including polyps and enhanced the detection of adenomas.

Recent published rates of adenoma and cancer detection are summarized in **tables 3**. The ADR of 62% using the combined dye plus water method was similar to our previous reported pilot study and this was higher than those derived from studies using other modalities, even those obtained with high definition colonoscopes,<sup>17,18-20</sup> narrow band imaging (NBI)<sup>21,24,25</sup> or dye spray chromoendoscopy.<sup>32-34</sup>

Like the dye spray method, a similar limitation of the current study is inadequate bowel preparation as the residual stool turned the color of the blue water green. The presence of residual stool especially in the proximal colon required additional water irrigation and suction in order to maintain the blue color of the indigocarmine solution. The finding of more adenoma obviously will require additional time in performing biopsies or removal

**Table 1.** Patient demographic variables

	Water Method (n=84)	Indigocarmine added to Water Method (n=84)	p
Mean Age	58	58	ns*
Male/Female	81/3	76/8	0.2108**
BMI	28.9	29	ns*
Smoker	29 (35%)	38 (45%)	0.2073**
Family history of colon cancer	5	7	ns*

\*t-test; \*\* Fisher's exact test.

**Table 2:** Procedure-rated outcomes

	Water Method	Indigocarmine added to Water Method	p
Number of patients	84	84	
Cecal intubation success	100%	100%	ns*
Adenoma detection rate (ADR)	37/84 (44%)	52/84 (62%)	0.0302**
Cancer	1	1	ns*
Number of patients with normal biopsies	12	18	0.3139**

\*t-test; \*\* Fisher's exact test.

**Table 3:** Comparison of ADR in the current study and those reported in the literature

		Current report
ADR water method	44%	
ADR water method with indigocarmine added	62%	
Representative published overall ADR	ADR	Literature Reference
Narrow band imaging	23%	24
High definition colonoscopies	24.7%	20
Withdrawal time >6 min	28.3%	29
High definition colonoscopies	28.8%	19
Chromoendoscopy and standard colonoscope (after excluding 4% with poor bowel preparation)	33.6% [29.6%]	32
Chromoendoscopy and standard colonoscope (after excluding 5% with poor bowel preparation)	35.4% [30.4%]	33
High resolution colonoscope	42	37
White light and high definition colonoscope	41-57%	17
Narrow band imaging	51%	21
Chromoendoscopy and high definition colonoscope (after excluding 9% with poor bowel preparation)	55.5% [46.5%]	17
Narrow band imaging	57.3%	25
White light	58.3%	25
High definition colonoscope	60.4%	18
Chromoendoscopy (after excluding 8% with poor bowel preparation)	66.2% [58.2%]	34

Values in [ ] indicate results based on intent-to-treat analysis without excluding the patients with suboptimal bowel preparation.

of the lesions found. However, the dye plus water method did not appear to complicate the simple and easy approach of the water method. The diluted solution of indigocarmine did not interfere with examination under water. This combined method is compatible with conventional colonoscope (not requiring high definition or NBI) and minimizes set up cost.

Prevention of colorectal cancer by detection and removal of adenomas has been the recommended practice in the US for almost 20 years.<sup>35</sup> National guideline has recommended that endoscopists performing screening colonoscopy should detect adenomas in at least 25% of men and 15% of women age 50 years or older.<sup>36</sup> However, variability exists in the detection of adenomas by endoscopists (**Table 3**). Various methods have been

proposed to improve detection of neoplastic lesions including taking adequate time for examination on scope withdrawal.<sup>29</sup> However, adherence to mandated withdrawal time of >7 min did not increase ADR.<sup>28</sup> The use of chromoendoscopy with dye-spraying has been shown to improve ADR. Soetikno et al.<sup>37</sup> reported a neoplastic polyp detection rate of 42% using a targeted dye-spray technique with traditional air insufflation colonoscopy. Chromoendoscopy is particularly useful in the detection of non-polypoid colorectal adenomas.<sup>37</sup>

Targeted or pan-colonic dye staining during colonoscopy is cumbersome and requires the use of spray catheters<sup>1</sup> or injection of the dye and air into the working channel of endoscope to apply a uniform mist of the staining agent onto the mucosal. In

addition, the delivery of dyes via capsule and enemas has been described.<sup>38,39</sup> Implementation of chromoendoscopy, however, has not been adopted for routine use in screening and surveillance colonoscopy.<sup>1,40</sup> The combination of indigocarmine-the active component of dye spray chromoendoscopy with the water method further enhanced the benefits of the water method. The ADR of 62%, is much higher than the plain water method alone. This prospective RCT confirmed our pilot observation of the beneficial role of this combined method in adenoma detection. The provocative finding indicates a head-to-head comparison of air insufflation, water exchange and water exchange plus indigocarmine to evaluate the hypothesis that the combination of chromoendoscopy and water exchange yields the highest ADR deserves to be performed.

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### Disclosure

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