Chromocolonoscopy for colorectal cancer screening: Dive into the Big Blue

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Chromoendoscopy involves the use of special stains to help identify and characterize lesions in the gastrointestinal tract. Dyes can be classified as absorptive or contrast; indigocarmine is one of the most commonly used agents in the latter category. The underlying principle is that the dye pools temporarily in abnormal mucosal areas without actively staining crypts, allowing the delineation of lesion contour and morphology. Indigocarmine is non-toxic, inexpensive, and is technically straightforward to apply.¹ The concentration of the dye used is variable but has ranged from 0.1% to 0.5% in the recent literature.²⁻⁷ This concentration range appears to offer the best compromise between adequate contrast effect, and not interfering with visualization due to excessive darkening of the mucosa. A clean, well-prepped bowel is a sine qua non for the effective use of chromoendoscopy. Chromoendoscopy has been shown to improve the yield of colonoscopy for flat and depressed colorectal neoplasms in patients with ulcerative colitis, and in certain high-risk patients (personal or family history of colorectal cancer, presence of symptoms). In one of the earliest RCTs of pan-colonic indigocarmine chromoendoscopy versus standard colonoscopy, Brooker et al. found more diminutive (<5 mm) adenomas in the proximal colon and more patients with 3 or more adenomas in the chromocolonoscopy group.² Hurlstone and colleagues conducted a similar study, which was controlled for lavage effect and extubation time to minimize potential bias.³ Chromoendoscopy allowed the identification of more diminutive adenomas, more lesions in the right colon, more patients with 3 or more adenomas, and more patients with high-grade dysplasia and cancer. Conversely, Le Rhun and colleagues found that pan-colonic chromocolonoscopy improved the detection of

flat adenomas and hyperplastic polyps, but not overall adenoma detection.⁵

These findings have spurred interest in investigating the potential role of pan-colonic indigocarmine in routine average-risk screening situations. Our group conducted a multicenter randomized controlled trial, comparing the adenoma yield of high-definition chromocolonoscopy to high-definition white light colonoscopy in 660 average-risk patients undergoing their first screening colonoscopy.⁸ The adenoma detection rate (ADR) (55.5 % vs. 48.4 %, $P=0.07$), and the number of adenomas per patient (1.3 vs. 1.1, $P=0.07$) were marginally higher in the chromocolonoscopy group. There were no significant differences in the number of advanced adenomas per patient. Chromocolonoscopy detected significantly more flat adenomas per patient (0.6 vs. 0.4, $P=0.01$), adenomas <5 mm in diameter per patient (0.8 vs. 0.7, $P=0.03$), and non-neoplastic lesions per patient (1.8 vs. 1.0, $P<0.0001$). The increased adenoma yield in the chromoendoscopy arm appeared to be endoscopist-dependent. While mean examination time was pre-set and not significantly different between the 2 study arms, total procedure time was significantly longer for patients randomized to chromoendoscopy (about 31 minutes, compared to 22 minutes). This was not unexpected, because the technique we used involved spraying 0.2% indigocarmine administered by a reusable spraying catheter through the colonoscope accessory channel; this was performed segmentally during withdrawal and pools of excess dye had to be suctioned before examination. More recently, Pohl and colleagues described a variation on this method which significantly improved procedure time.⁶ This involves continuous gentle spraying of 0.4% indigocarmine via

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Abbreviations: ADR, adenoma detection rate

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a dye-spraying catheter during withdrawal. The advantage of this technique is that it allows adequate staining while minimizing the accumulation of pools of excessive dye which require suctioning, and essentially changes a multi-step segmental method to a one-step continuous one. In this RCT, a total of 1008 patients were randomized to pan-colonic chromoendoscopy or standard colonoscopy, about half of which were for screening indications. The ADR and mean number of adenomas per patient were significantly higher in the chromoendoscopy group (46.2% versus 36.3%, $p=0.002$, and 0.95 versus 0.66, $P<0.001$). The withdrawal time (11.6 versus 10.1 minutes) and total procedure time (16.6 versus 12.8 minutes) were significantly longer in the chromoendoscopy group. Similar to our study, chromoendoscopy benefited some endoscopists more than others, and the increment in adenoma yield was mostly due to small lesions without high-grade dysplasia. Both studies also illustrated the fact that chromoendoscopy requires adequate bowel preparation; the exclusion rates due to unsatisfactory bowel preparation were 8% and 13%, respectively.

A method which would combine chromoendoscopy's potential for improved adenoma detection, while minimizing some of its drawbacks such as lengthy procedure time, labor-intensity, and dependence on bowel preparation, would be attractive. In principle, combining chromoendoscopy with the water method cleverly bridges all of these issues: the water exchange can ameliorate the prep, the dye can be applied to the entire colon simultaneously with water during insertion, and adenoma yield could be increased with indigocarmine.

In this issue of *JIG*, Leung and colleagues report the results of an RCT comparing colonoscopy using the water method alone to water with indigocarmine.⁹ In a group of 168 US veterans undergoing screening colonoscopy, the adenoma detection rate increased from 44% in the water arm to 62% ($p=0.03$) in the water-indigocarmine

arm. These findings are intriguing, and are similar to a previous study published by the same group of investigators.¹⁰ In that study, data collected prospectively in a performance improvement program (non-randomized) showed ADRs in the air, water, and water-indigocarmine methods of 36%, 40%, and 62%, respectively. In the present RCT, the number of patients randomized was 84 per group, which is presumably based on the former pilot study. The markedly improved ADR is the most striking finding but is difficult to explain. The indigocarmine concentration which was used was 0.008%, which is much lower than what has been used in recent studies. This concentration was chosen on the basis on preliminary work done by the investigators to find an optimal indigocarmine concentration which would allow visualization of the colonic lumen during insertion, and not hamper the water method.¹⁰ However, the resulting effluent is dilute and at this low concentration, the dye does not pool effectively and mucosal contrast highlighting is faint. Additional details regarding the characteristics of the excess adenomas found in the water-indigocarmine group would have helped clarify whether the dye contributed independently to the increased ADR; for example, finding more diminutive and flat adenomas as well as non-neoplastic lesions in the chromoendoscopy group would be consistent with what is expected based on the literature. It is also not clear whether the increment in adenoma yield is primarily due to finding more patients with at least one adenoma, or due to finding more adenomas per patient, or a combination of these two factors. The two patient groups were adequately randomized and comparable with respect to demographic and clinical features. However, additional factors may have influenced the ADR, such as different withdrawal or examination times, differences in operator technique, ascertainment bias, or other unmeasured confounders. As with all studies comparing endoscopic techniques, the

issue of observational bias has also to be kept in mind; additional larger studies of water-chromoendoscopy, possibly with a range of indigocarmine concentrations, in different medical centers and by different operators, would help clarify the impact of this technique on adenoma yield.

The investigators should be commended for conducting novel research which is outside-the-box of traditional paradigms, and often in the face of limited resources. The new technique appears promising, but additional confirmatory studies are required before we all start submerging our colonoscopes into the Big Blue.

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