Date: 02/01/2021

Title: Comparing left colon mucus production by water versus saline infusion during water exchange colonoscopy: a prospective randomized controlled trial

Background

Water exchange (WE) colonoscopy is a standardized technique developed to achieve gasless colonoscope insertion. WE maximizes colon cleanliness and improve the adenoma detection rate (ADR).[1-3] The American Society for Gastrointestinal Endoscopy has recommended using sterile water during gastrointestinal endoscopy and this form the basis of standard protocol at most endoscopy units.[4] However, increased mucus production in the left colon is anecdotally observed during withdrawal of water-aided colonoscopy.[5]

In a recent pilot study, El Rahyel et al. reported normal saline infusion significantly reduced left colon mucus production compared to sterile water during water-aided colonoscopy.[6] This finding is promising for future WE practice. However, in that pilot study, the insertion method was not WE, the patients were not randomized, and the effect of saline infusion on serum electrolyte was not examined. Therefore, the provocative finding warrants validation.

The primary aims of this study are to compare the left colon mucus scores between colonoscopy using carbon dioxide (CO_2) insufflation and WE, and in those patients undergoing WE, the scores between groups using warm water versus warm mixed saline/water infusions during insertion. We hypothesize that the mucus scores would be lower when saline is used during WE insertion.

Methods

This will be a prospective, randomized, controlled trial comparing left colon mucus scores between CO_2 insufflation, WE insertion with water (WE water group), WE insertion with 1:1 mixed normal saline/water (WE 50% saline group), and WE insertion with 1:3 mixed normal saline/water (WE 25% saline group). The mucus score will be graded during withdrawal by blinded colonoscopists and research assistant. It will be conducted at Evergreen General Hospital in Taoyuan, Taiwan. Consecutive patients will be enrolled

from March 2021 to July 2022. A written informed consent will be obtained from all participating patients. The study has obtained approval from Institutional Review Boards and has been registered with *ClinicalTrials.gov* (NCT04769739).

Participants

Consecutive patients aged 20-75 years old undergoing colonoscopy for screening, surveillance, and positive fecal immunochemical test will be considered for enrollment. The exclusion criteria will include familial adenomatous polyposis and hereditary non-polyposis colorectal cancer syndrome, active inflammatory bowel disease, previous colonic resection, gastrointestinal bleeding, therapeutic colonoscopy (e.g., hemostasis, removal of large polyp), evidence of colonic obstruction based on pre-colonoscopy clinical evaluation, American Society of Anesthesiology classification of physical status grade 3 or higher, allergy to fentanyl or midazolam, mental retardation, pregnancy, and refusal to provide a written informed consent.

Randomization

Patients will be randomized in a 1:1:1:1 ratio to undergo CO_2 insufflation and WE insertions with either water infusion, 50% saline infusion, or 25% saline infusion. Randomization will be carried out by a computer-generated random sequence. Individual random sequences will be placed in an opaque envelope kept by an independent research assistant not directly involved in this study, which will be opened immediately before the procedure.

Bowel Preparation and Sedation

Patients will be instructed to eat low-residual foods for two days before colonoscopy. Oral and written instructions on the split-dose bowel preparation of 3 L polyethylene glycol will be provided. Colonoscopy will be performed with moderate sedation using intravenous fentanyl plus midazolam.

Colonoscopy Procedures

Colonoscopies will be performed by two board-certified colonoscopists who

have experience in WE (Chi-Liang Cheng, Yen-Lin Kuo). The colonoscopist is blinded as to whether water or mixed saline/water is being used. Standard colonoscopes (CF-Q260AL/I, CF-HQ290L/I; Olympus Medical Systems Corp., Tokyo, Japan) will be used.

Antispasmodic medication will be administered during colonoscopy examination if indicated. All infused fluids will be warmed to approximately 32-33 °C. CO_2 insufflation will be used for CO_2 group and during the withdrawal phase of the WE group. Colonoscopy will begin with the patients in the left lateral position. In the WE group, the air pump will be turned off before starting the procedure. During the insertion phase, air and residual water or feces in the rectum will be aspirated, and then the colon will be irrigated with warm fluid using a flushing pump (Olympus AFU-100; Olympus Corp.). There will be no restriction placed on the overall volume of fluid infused to achieve adequate cleansing. WE entails the infusion of fluid to open the lumen and suction of infused fluid sequentially. Air pockets, when encountered, will be aspirated. When the cecum is reached and after most of the fluid is suctioned to collapse the cecal lumen, CO_2 will be opened. Cecal intubation will be defined as the passage of the scope tip beyond the ileocecal valve with visualization of the medial wall between the ileocecal valve and the appendix orifice.

Polyp search and resection will be performed during the withdrawal phase in all groups. Insertion polypectomy will not be performed. All proximal colon (defined as the colon segment proximal to the descending colon) polyps will be removed irrespective of their size and appearance. All diminutive polyps with hyperplastic appearance (based on narrow band imaging) in the rectosigmoid colon will be documented by photography and left alone. Polyp size will be determined by comparison with an opened biopsy forceps or a snare.

In all groups, the following information will be recorded: bowel preparation quality using the Boston Bowel Preparation Scale score; the total amount of sedative medications; the length of colonoscopy reaching cecum; the amount of fluid infused and suctioned during insertion and withdrawal phases; the insertion time; the withdrawal time; the need of abdominal compression and/or position change to assist colonoscopy insertion; and the overall polyp number,

size, histology and location.

Mucus scores

During the withdrawal phase of the colonoscopy, the blinded colonoscopist and another blinded research assistant will grade the amount of mucus produced in the left colon (descending colon, sigmoid colon, rectum) independently. No validated scoring system for the mucus production in the colon is available. We use a 5-point Colon Mucus Scale (CMS) (0-4 points), modified from the original colon mucus study by El Rahyel et al.,[6] to quantitate the amount of mucus production in left colon: score 0: no visible mucus; score 1: minimal amounts of clear mucus in thin streaks or strands; score 2: mild opaque mucus in thin strands; score 3: moderate opaque mucus in thicker clumps covering one side of surface; score 4: more opaque mucus in thicker clumps covering more views of lumen (Figure 1). Prior to beginning scoring, the colonoscopists and study assistant will review 10 videos and discuss their scores. After they have reached consensus on the 10 cases, scoring will be performed independently.

Outcomes

The primary outcomes are the left colon mucus scores using CMS between colonoscopy using CO_2 insufflation and WE, and, in those patients undergoing WE, the scores between groups using water versus 50% saline versus 25% saline. Secondary outcomes include procedure times (insertion and withdrawal times) and acute serum electrolyte abnormality in the WE saline groups. Patients assigned to the WE saline groups will receive measurements of the serum sodium, potassium, and chloride, which will be performed 20 minutes before and 60 minutes after the colonoscopy.

Sample size estimation

We performed an observational study focusing on left colon mucus production using CMS scoring system by unblinded colonoscopist and compared either full strength normal saline (normal saline group), 1:1 mixed normal saline/water (50% saline group), or 1:3 mixed normal saline/water

(25% saline group) during WE insertion in patients undergoing routine colonoscopies in December 2020. We compared these findings with the reference WE water group which was video recorded during our previous randomized controlled trial comparing right colon adenoma miss rate using WE and CO_2 insufflation.[7] The results showed that fluid containing saline significantly reduced the mucus production compared to water alone (Table 1).

The sample size estimation is based on the assumption that WE 50% saline infusion will reduce left colon mucus score compared to WE water infusion. Mucus score reduction to ≤ 1 is considered clinically significant. According to our preliminary data, we estimate the proportion of subjects with CMS score ≤ 1 to be 50% in the WE water group. The sample size needed to show the proportion of subjects with CMS score ≤ 1 that can be increased to 80% by WE 50% saline infusion at a 5% alpha error level with 90% power will be 68 patients per group. To account for dropouts, incomplete procedures, and inadequate preparation, an additional 10% will be enrolled. Therefore, a total of 300 patients (75 patients in each group) will be enrolled.

Statistical analysis

Categorical variables will be presented as numbers (percentages), whereas continuous variables will be expressed as the means ± standard deviations. Overall *P* values for categorical and continuous parameters will be obtained by Fisher's exact test and Kruskal-Wallis test, respectively. Pairwise comparisons among all groups were performed when the overall group effect was significant. Agreement between the blinded raters will be tested with Fleiss kappa. For mucus production quantity, the 2-category scale (minimal [score 0-1] vs. moderate [score 2-4]) will be examined. Potential risk factors for mucus production include female sex, lower body mass index, prior abdominal or pelvic surgery, poor bowel preparation, water as the infused solution, larger volume of infusion, and longer insertion time. Univariate and multivariate logistic regression analyses will be used to assess which of the demographic and procedural data are independent predictors of moderate mucus production. Factors with a *P* value < 0.1 on univariate analysis will be further entered in the multivariate logistic regression analysis. The odds ratio with 95% confidence

interval will be used to describe the influence of various factors on mucus production. All statistical analyses will be performed by using SAS version 9.3 or later (SAS Institute Inc., Cary, NC, USA). The criterion for statistical significance will be a *P* value <0.05.

References

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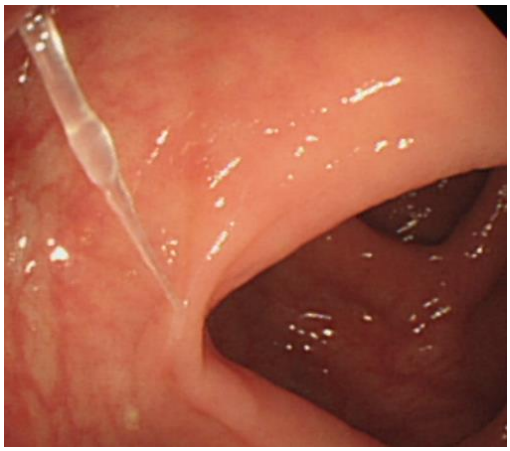
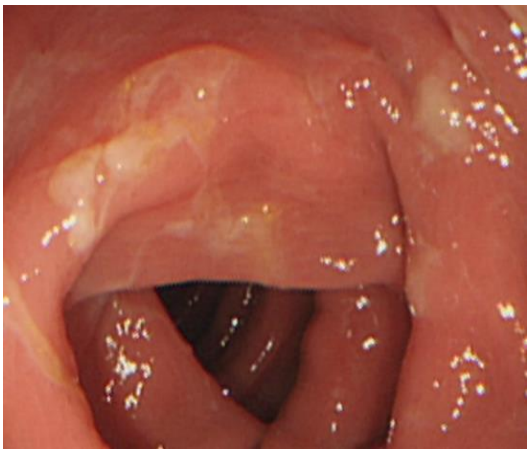
Figure 1. Left Colon Mucus Scale (CMS) scores

Score 1



Score 2



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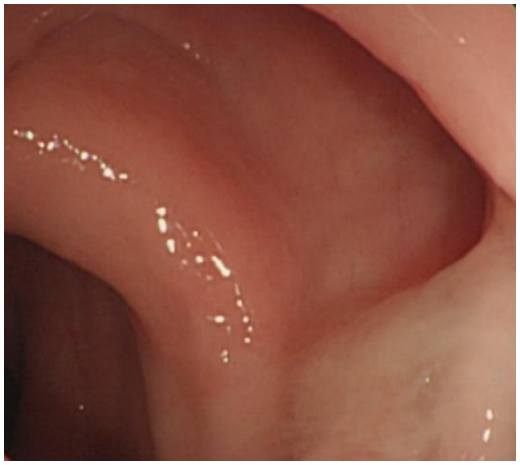

Score 4

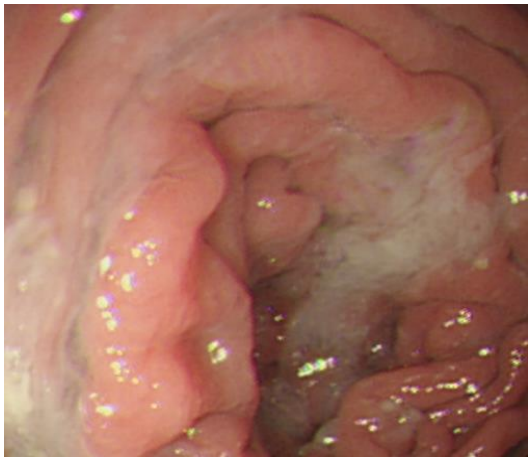

Table 1. Left colon CMS score* by unblinded endoscopists during WE colonoscopy

Variable	WE/normal saline (n=17)	WE/50% saline (n=17)	WE/25% saline (n=17)	WE/ water (n=17)	*P*-value
CMS score, mean (SD)	0.35 (0.49)	0.94 (0.66)	1.06 (0.83)	1.88 (0.78)	<0.0001
Patients with CMS score ≤1, n (%)	17 (100)	14 (82)	13 (77)	4 (24)	<0.0001

*Colon Mucus Scale (CMS) score: No mucus (score 0); Minimal amounts of clear mucus in thin streaks or strands (score 1); Mild opaque mucus in thin strands (score 2); Moderate opaque mucus in thicker clumps covering one side of the surface (score 3); More opaque mucus in thicker clumps covering more views of the lumen (score 4).