Title: Comparing right colon adenoma and hyperplastic polyp miss rate in colonoscopy using water exchange and carbon dioxide insufflation: A prospective randomized controlled trial

INTRODUCTION

Colonoscopy is currently regarded as the gold standard to detect and prevent colorectal cancer (CRC) [1]. It estimated to prevent about 76%-90% of CRC [2], but post-colonoscopy CRCs (PCCRCs) still occur. Recent case-control studies consistently demonstrated that protection by colonoscopy against right-sided colon cancer, ranging from 40% to 60%, was lower than the 80% protection attained in the left colon [3-5]. Of all PCCRCs, 58% were attributed to lesions missed during examination [6]. In a systematic review of tandem colonoscopy studies, a 22% pooled miss-rate for all polyps was reported [7]. Colonoscopy maneuvers helping to reduce miss-rate for all polyps, particularly in the right colon, have the potential to decrease the incidence of PCCRCs.

Water exchange (WE) colonoscopy is characterized by the gasless insertion to the cecum in clear water and maximizing cleanliness during insertion. WE colonoscopy has been shown to improve the overall adenoma detection rate (ADR), compared to air insufflation colonoscopy, in many prospective randomized controlled trials (RCTs) [8-13]. WE colonoscopy also has been shown to improve right colon ADR in RCTs [10-12] and meta-analyses [14,15]. In a pooled data from two multisite RCTs, WE also significantly increases right colon combined advanced and sessile serrated ADR as compared to air insufflation colonoscopy [16]. Decreased multitasking-related distraction from cleaning maneuvers has been the most recently identified explanation for the increase in ADR by WE [17]. The right colon is usually the worst prepared segment and proximal colorectal neoplasms with advanced histology

frequently are smaller than the ones in the left colon or have a nonpolypoid appearance [18,19]. Therefore, the adoption of WE in the right colon might be especially beneficial.

Traditionally, all CRC are believed to arise from the adenomas through the adenoma-carcinoma sequence. However, recent studies showed that 35% of CRC were derived from serrated lesions (SLs) [20], which include hyperplastic polyp (HP), sessile serrated adenomas/polyps (SSA/Ps) and traditional serrated adenomas [21]. The presence of SLs, even small and diminutive proximal HPs, has been reported to be associated with higher rates of synchronous advanced neoplasia [22,23]. Proximal HPs might also serve as precursors of cancer through DNA methylation and deficient DNA mismatch repair [24-26]. However, SLs tend to be pale and flat and pose a challenge for the endoscopists to detect them [27]. WE might come in handy for uncovering the proximal SLs through the above stated mechanisms.

The primary outcome of this study is the right colon combined adenoma miss rate (AMR) and hyperplastic polyp miss rate (HPMR) determined by tandem inspection of the right colon using WE or CO2 insufflation for screening, surveillance, or positive fecal immunochemical test (FIT) indications. The secondary outcomes are the overall ADR and other adenoma detection related metrics between the two colonoscopy methods.

METHODS

This will be a prospective RCT comparing CO2 insufflation and WE in terms of right colon combined AMR and HPMR by tandem inspection. It is originally designed as a multicenter study conducted in three community hospitals in Taiwan. Consecutive patients will be enrolled from April 2019 to October 2020. A written informed consent will be obtained from all participating patients. The study has obtained

ethical approval from the Joint Institutional Review Board of Taiwan (19-002-T-1) and has been registered with *ClinicalTrials.gov* (NCT03845933). Due to delay in obtaining IRB approval in two of the participating hospitals (Dalin Tzu-Chi Hospital obtained IRB approval in late May 2019 and has not recruited any patient; Taipei Medical University Hospital has not obtained IRB approval in early June 2019) and rapid recruitment of Evergreen General Hospital since April 2019, which has recruited and completed more than 90 patients in the end of May 2019, we have amended the study design from multicenter study to single center study and have obtained the approval of this amendment on July 19, 2019 from the Joint Institutional Review Board of Taiwan.

Participants

Consecutive patients aged 45 years or older undergoing colonoscopy for screening, surveillance, and positive FIT will be considered for enrollment [28]. Exclusion criteria will include familial adenomatous polyposis and hereditary non-polyposis CRC syndrome, personal history of CRC or inflammatory bowel disease, previous colonic resection, obstructive lesions of the colon, gastrointestinal bleeding, allergy to fentanyl or midazolam, American Society of Anesthesiology (ASA) classification of physical status grade 3 or higher (e.g. controlled congestive heart failure, stable angina, previous heart attack, poorly controlled hypertension, morbid obesity, chronic renal failure, bronchospastic diseases with intermittent symptoms), mental retardation, pregnancy, and refusal to provide a written informed consent.

Randomization

Patients will be randomized in a 1:1 ratio to undergo either the CO2 insufflation colonoscopy (CO2 group) or WE colonoscopy (WE group). Randomization will be carried out by a computer-generated random sequence. Stratification based on

colonoscopists and colonoscopy indications (screening, surveillance, and positive FIT) will be performed. Individual random sequence 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 (Polyethylene glycol solution) will be provided to all patients. Colonoscopy will be performed without sedation or with moderate sedation (intravenous fentanyl plus midazolam). Moderate sedative agents will be administered by endoscopists.

Colonoscopy Procedures

Colonoscopies will be performed by two board-certified colonoscopists (Chi-Liang Cheng, Yen-Lin Kuo). Standard colonoscopes (CF-Q260AL/I; Olympus Medical Systems Corp., Tokyo, Japan) will be used. All colonoscopists have performed more than 1000 conventional colonoscopies. Hands-on coaching by a WE expert (Felix W. Leung) to standardize the WE method has been completed. Each colonoscopist has or will have completed 100 cases of WE learning curve. Felix W. Leung will be involved in the study design, data analyses, and report preparation, but not in patient enrollment. All the colonoscopic procedures will be recorded.

Antispasmodic medication will not be administered during colonoscopy examination. CO2 insufflation will be used for CO2 group and 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 water (32C-35C) using

flushing pumps (Olympus AFU-100; Olympus Corp.). There will be no restriction placed on the overall volume of water infused to achieve adequate cleansing. Suction and infusion of water will be performed sequentially because the endoscope has only one channel. Air pockets, when encountered, will be aspirated. When the cecum is reached and after most of the water is suctioned to collapse the cecal lumen, CO2 will be opened. In the CO2 group, colonoscopy is performed in the usual fashion, with minimal insufflation required to aid insertion. Cleaning in the CO2 group will be performed entirely during withdrawal. In the CO2 group, suction marks will be deliberately produced in the hepatic flexure and cecum to mimic the same marks frequently produced by the WE technique. 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.

Upon arriving at the cecum, CO2 insufflation will be used in both groups and the scope will be withdrawn from the cecum to the hepatic flexure, with inspection of the mucosa at the same time. All polyps identified will be resected and sent for pathology evaluation. The most distal part of the hepatic flexure will be marked by a forceps biopsy and then the scope will be reinserted into the cecum by the first endoscopist using CO2 insufflation. A tandem inspection of the right colon will then be performed by a second endoscopist blinded to the insertion method in both study groups. All polyps found herein will be counted as the missed polyps. After the second withdrawal to the mark of distal hepatic flexure, the remainder of the colon will be examined in a standard manner by the first endoscopist. To assess the adequacy of blinding, the second endoscopist will be asked at the end of tandem right colon examination to guess which insertion method has been used. If less than 66% of these answers are correct, then adequate blinding will be considered to have

been achieved.

Polyp search and resection will be performed during the withdrawal phase in both groups. Insertion polypectomy will not be performed. All proximal 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 both groups, the following information will be recorded: bowel preparation quality using the Boston Bowel Preparation Scale (BBPS) score [29]; the total amount of sedative medications (in procedures with sedation); the length of colonoscopy reaching cecum; the amount of water infused and suctioned during insertion and withdrawal phases; the procedure time taken for insertion and withdrawal for the first examiner; the procedure time taken for tandem right colon inspection; the need of abdominal compression and/or positon change to assist colonoscopy insertion; the overall polyp number, size, histology and location; the missed right colon polyp number, size, histology and location.

Definition

Screening colonoscopy will be defined as either asymptomatic patients undergoing their first colonoscopic examination or patients with a history of negative screening colonoscopy undergoing their 5-year or 10-year follow-up examinations. Surveillance colonoscopy will be defined as patients with a history of colon polyps undergoing their follow-up examinations. Complete colonoscopy will be defined as successful cecal intubation. Insertion time will be defined as the time between the scope insertion and cecal intubation. Three stopwatches will be used to record the time taken for mucosal cleaning (water infusion and suction), mucosal inspection, and

polyp treatment respectively. Withdrawal time will be defined as the time from cecal intubation to the time when the colonoscope is withdrawn from the anus, including the time taken for mucosal cleaning, mucosal inspection, polyp biopsy and polypectomy. Total procedure time will be the sum of insertion time and withdrawal time. Three stopwatches will be used to record the time taken for mucosal cleaning, mucosal inspection, and polyp treatment, respectively, during the tandem right colon examination. Total duration of tandem right colon examination will be defined as the time of repeated examination from cecum to hepatic flexure by the blinded examiner, including the time taken for mucosal clearing, inspection and polyp treatment. Near-complete removal of infused water during insertion of WE is defined as ≥90% removal of infused water. Inspection times by the first and second endoscopists will be recorded. Comparable inspection times in the study and control groups will support the use of equivalent withdrawal inspection methods.

All colonic polyps removed during procedures will be sent for histological examination with clear labeling of location and sequences of colonoscopy. The location of colonic polyps will be defined according to the anatomical distribution. Right colon will be defined as cecum, ascending colon, and hepatic flexure. Proximal colon will be defined as right and transverse colon. Diminutive polyps will be defined as polyps with size ≤5 mm. Small polyps will be defined as polyps with size 6-9 mm. Large polyps will be defined as polyps with size ≥10 mm. Adenomas will include all adenomas and sessile serrated adenoma. Advanced adenomas will be defined as those lesions with one of the following criteria: 1) lesions larger than 10 mm in diameter; 2) lesions with a villous component; 3) lesions with high-grade dysplasia; and 4) lesions with invasive features.

ADR will be defined as the proportion of colonoscopies with at least one adenoma.

Advanced ADR will be defined as the proportion of colonoscopies with at least one advanced adenoma. Mean adenoma per procedure (MAP) will be defined as the total number of adenomas detected divided by the number of colonoscopies. Mean adenoma per positive procedure (MAP+) will be defined as the total number of adenoma detected divided by the number of colonoscopies in which at least one adenoma is found. Mean additional adenomas detected beyond the first adenoma per positive procedure (ADR-Plus) will be defined as the mean number of adenomas detected after the first adenoma in procedures in which at least one adenoma is found.

Lesions detected on the tandem right colon examination will be used for the calculation of adenoma or polyp miss rate. Right colon AMR and hyperplastic polyp miss rate (HPMR) will be calculated as the number of adenomas and hyperplastic polyps missed in the first right colon examination divided by the total number of adenoma and hyperplastic polyps detected during both the first and tandem right colon examinations.

Study Outcomes

The primary outcome is the right colon combined AMR and HPMR. Secondary outcomes include right colon AMR, right colon HPMR, overall ADR, right colon ADR and HPDR after the first examination, combined right colon ADR and HPDR after the first and tandem examinations, overall advanced ADR, right colon advanced ADR, overall MAP, right colon MAP, overall MAP+, right colon MAP+, overall ADR-Plus, and right colon ADR-Plus. Procedure related parameters, including bowel cleansing, insertion and withdrawal times, duration of tandem right colon examination, volume of water infused and aspirated during insertion and withdrawal, and number of abdominal compressions and/or position change, are also evaluated.

Sample size estimation

The sample size estimation is based on the assumption that WE colonoscopy reduces right colon combined AMR and HPMR compared to conventional CO2 insufflation colonoscopy. We estimate the overall right colon combined AMR and HPMR in the CO2 group to be 30% [30,31]. According to our previous study, the average detected number of right colon adenoma and hyperplastic polyp is 0.8 per subject after first right colon examination [32]. To show a clinically important improvement of AMR reduction by the WE colonoscopy, we assume that WE colonoscopy should reduce the AMR by 15%. With a statistical power of 80% and a two-side significance level of 0.05, 131 patients will be needed in each study arm. To account for dropouts, incomplete procedures, and inadequate preparation, an additional 10% will be enrolled. Therefore, a total of 292 patients (146 patients in each group) will be enrolled.

Statistical analysis

Summary statistics will be presented as frequencies and percentages in the case of categorical variables and as the means with standard deviations (SD) in the case of continuous variables. Analysis will be performed by using an Intention-to-treat (ITT) approach. Interim analysis will be performed after enrollment of 131 patients. Student's *t*-test for continuous factors, Wilcoxon rank sum test for ordinal variables (such as polyp size), and Chi-square test for categorical variables will be used to assess differences in demographic and clinical characteristics of patients in each group. Factors associated with adenoma detection by the first examiner will be identified by univariate analysis. Factors with a *P* value <0.1 on univariate analysis will be further entered into forward stepwise logistic regression analysis. The adjusted odds ratio with 95% confidence interval (CI) will be used to describe the

influence of various factors on adenoma detection. 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 *P* value <0.05.

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