Title: Impacts of inspection during instrument insertion on colonoscopy quality: A prospective randomized controlled trial

INTRODUCTION

Colonoscopy is considered the preferred modality for colorectal cancer (CRC) screening since it has both diagnostic and therapeutic capabilities. However, colonoscopy is not a perfect test. It misses a substantial number of neoplastic lesions [1,2]. In a systematic review of tandem (same-day back-to-back) colonoscopy, the pooled miss rate for polyps of any size was 22%, and the adenoma miss rate by size was 2.1% for ≥10 mm, 13% for 6-9 mm, and 26% for ≤5 mm, respectively [3]. Researches continue to explore methods to improve the polyp and adenoma detection during colonoscopy and many of them focus on the withdrawal phase of the examination [4-5]. Thus, colonoscopy is typically performed with rapid passage of the instrument through the loops and bends of the colon to the cecum and then performing a slow deliberate withdrawal. As a consequence, all removal of polyps is done when the instrument is pulled back.

Many experienced endoscopists recognized that small polyps seen incidentally but not removed during insertion are sometimes quite difficult to find during withdrawal. This may be due to different anatomical conformations of the colon during instrument insertion and withdrawal. The insertion and withdrawal phases may expose somewhat different sections of the mucosal surface to the colonoscope, and inspection on insertion and withdrawal are possibly complementary. Most endoscopists agree that advanced (≥10 mm) polyps should be removed only during withdrawal [6]. Whether smaller polyps (<10 mm) should be removed during insertion phase is controversial. Some studies showed that inspection and polypectomy during insertion phase reduced colorectal polyp/adenoma miss rate [7-9]. But other studies found that inspection and polypectomy during insertion phase offered no additional benefit on adenoma detection [10-12].

The adenoma detection rate (ADR) has become a validated quality indicator for colonoscopy; the higher the ADR of colonoscopists, the lower the risk of interval CRC and the lower the risk of dying from CRC [13-14]. However, the ADR may not provide a comprehensive assessment of the adequacy and thoroughness of colonoscopic

examination. Recent study has shown that the standard ADR cannot distinguish high versus low endoscopist performance [15]. Other secondary quality measures have been suggested to supplement the ADR and include the polypectomy rate (PR), the mean adenoma per procedure (MAP), the mean adenoma per positive procedure (MAP+), the mean additional adenomas detected beyond the first adenoma per positive procedure (ADR-Plus), and the proximal serrated polyp detection rate (PSP-DR) [15-21]. The impact of the inspection and polypectomy during insertion phase of colonoscopy upon these secondary quality indicators is not known.

The primary aim of this study is to compare the impact upon the colonoscopy quality (including ADR, PR, MAP, MAP+, ADR-Plus, and PSP-DR) of additional inspection and polypectomy during insertion as opposed to the traditional practice of careful inspection and polypectomy performed entirely during withdrawal in patients undergoing routine colonoscopy with moderate sedation for screening or surveillance indications. The secondary aim of this study is to compare the impact of such endoscopic strategy on procedure times, distraction during withdrawal, procedure difficulty, sedative doses, and intra-procedure abdominal pain.

METHODS

This is an investigator-initiated prospective randomized controlled study. The study will be conducted at Evergreen General Hospital, Taoyuan, Taiwan. We plan to enroll patients since October of 2017 and the study is expected to be completed within 18 months after patient enrollment. A written informed consent will be obtained from all patients.

Participants

Patients aged 45 years or older who are able to give informed consent and are scheduled for elective colonoscopy at Evergreen General Hospital are eligible for enrollment. Exclusion criteria are previous surgical resection of the colon or rectum, inflammatory bowel disease, polyposis syndrome, previously incomplete colonoscopy, obstructive lesions of the colon, inadequate bowel preparation (defined as Boston Bowel Preparation Scale [BBPS] score of 0 or 1 in any colon segment) [22,23], gastrointestinal bleeding, allergy to fentanyl or midazolam, American Society of Anesthesiology (ASA) classification of physical status grade 3 or higher, mental

retardation, pregnancy, and refusal to provide a written informed consent. Patients will be enrolled by the primary investigator or co-primary investigators.

Intervention and randomization

Patients will be randomly assigned by a research assistant, by using a computer-generated randomization sequence to undergo colonoscopy with either inspection and polypectomy during both insertion and withdrawal of colonoscope (study group) or inspection and polypecotmy entirely during withdrawal of colonoscope (control group). Randomization will be done via concealed allocation with a sealed envelope that designate study group or control group. The colonoscopist is not blinded to group assessment.

Procedure

Colonoscopies will be performed by two experienced colonoscopists by using a standard colonoscopy (CF-Q260AI or CF-Q260AL; Olympus Medical Systems Corp., Tokyo, Japan). All procedures are performed under moderate conscious sedation with fentanyl (United Biomedical, Taipei, Taiwan) and midazolam (Dormicum; Roche Pharmaceuticals, Basel, Switzerland) according to the current guidelines [24]. Carbon dioxide insufflation is used for all endoscopic procedures. All patients receive 3-L polyethylene glycol (PEG; Klean-Prep, Helsinn Birex Pharmaceuticals Ltd., Dublin, Ireland) for bowel preparation. A split-dose of the PEG preparation is provided for morning colonoscopy (2 L consumed in the evening before the colonoscopy and 1 L consumed in the early morning of the colonoscopy) and a same-day preparation is provided for the afternoon colonoscopy. The level of colon cleansing is prospectively evaluated with the BBPS score after all cleansing maneuvers are completed.

For patients in the study group, the colonic lumen is washed with saline and the fluid and debris are suctioned as the instrument is slowly inserted from rectum to cecum. Deliberate and systematic inspection of the colonic mucosa is performed with adequate luminal insufflations during both the insertion and withdrawal phases. Polyp size is determined by comparison with open colonoscopic biopsy forceps pushed against the polyp or, in some cases of pedunculated polyp by direct measurement after retrieval. Polyps with size <10mm are removed as they are identified on insertion and withdrawal. Polyps with size ≥10mm are removed only

during withdrawal.

For patients in the control group, deliberate mucosal inspection and polyp removal are performed exclusively on instrument withdrawal. During insertion, minimal mucosal inspection and insufflation are applied to efficiently advance the instrument into cecum. If a polyp is found during insertion, endoscopists are instructed to make a mental note of it and find it during withdrawal for polypectoymy.

Definition

Complete colonoscopy is defined as reaching and taking pictures of the cecum and ileocecal valve. Insertion time is defined as the time between the scope insertion and cecal intubation, including the time taken for mucosal clearing and polypectomy. Withdrawal time is defined as the duration between the time at which the cecum is reached and the time at which the scope is withdrawn from the anus, including the time taken for mucosal clearing and polypectomy. Total procedure time is the sum of insertion time and withdrawal time. The quality of bowel preparation is classified as excellent (BBPS score of 8 or higher), good (BBPS score of 7), or fair (BBPS score of 6).

The location of colorectal polyps is defined according to the anatomical distribution. The portion of the colon above the level of the splenic flexure is defined as the proximal colon. Diminutive polyp is defined for polyp with size ≤5mm. Small polyp is defined for polyp with size 6-9mm. Large polyp is defined for polyp with size ≥10mm. Adenomas include all adenomas and sessile serrated adenoma. Advanced adenoma is 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 is defined as the proportion of colonoscopies where at least one adenoma is found. Advanced ADR is defined as the proportion of colonoscopies where at least one advanced adenoma is found. PR is defined as the proportion of patients undergoing colonoscopy in whom at least one polyp is removed. MAP is defined as the total number of adenomas detected divided by the number of colonoscopies. MAP+ is defined as the total number of adenoma detected divided by the number of colonoscopies in which at least one adenoma is found. ADR-Plus is defined as the mean number of adenomas detected after the first adenoma in procedures in which at least one adenoma is found. PSP-DR is defined as the proportion of patients undergoing colonoscopy in

whom at least one serrated polyp (hyperplastic polyp, sessile serrated adenoma/polyp, traditional serrated adenoma) is identified proximal to the splenic flexure. The mean neoplastic polyp detection rate (MNP-DR) is defined as the total number of adenomas plus proximal serrated polyps (hyperplastic polyp, sessile serrated polyp) divided by the number of colonoscopies.

The grade of the colonoscopy difficulty is rated by the endoscopist using a 10-point Likert scale: 1, being extremely easy; and 10, being extremely difficult. Distraction during withdrawal phase is determined by the time of mucosal clearing and suction divided by the total withdrawal time and the total water volume required for mucosal claering. Patient's subjective assessment of discomfort during the procedure is graded by patients with a 10-cm visual scale: 0, being no pain; and 10: being extremely severe pain.

Statistical analysis

The primary aim of the study is to evaluate whether there is a difference in the ADR between the two study groups. We calculate the required sample size by using the assumption of a 40% ADR in the control group [25]. For the study to have 85% power to detect a 15% increase in ADR with a 5% significance level, the study needs 211 participants per group to achieve significance (two sided). To account for dropouts, incomplete procedures, and inadequate preparation, an additional 10% will be enrolled. Therefore a total of 464 patients (232 in each group will be enrolled. Summary statistics are presented as frequencies and percentages in the case of categorical variables and as the means with standard deviations in the case of continuous variables. Student's t tests for continuous factors, Wilcoxon rank sum tests for ordinal variables (such as polyp size), and Chi-square tests for categorical variable are uses to assess differences in demographic and clinical characteristics of patients in each group. All calculations are conducted using SAS version 9.3 or later (SAS Institute Inc., Cary, NC, USA). The criterion for statistical significance is P <0.05.

REFERENCES

1. Rex DK, Cutler CS, Lemmel GT, Rahmani EY, Clark DW, Helper DJ, Lehman GA, Mark DG. Colonoscopic miss rates of adenoma determined by back-to-back colonoscopies. Gastroenterology 1997;112:24-28.

2. Pickhardt PJ, Nugent PA, Mysliwiec PA, Choi JR, Schindler WR. Location of adenomas missed by optical colonscopy. Ann Intern Med 2004;141:352-359.
3. van Rijn JC, Reitsma JB, Stoker J, Bossuyt PM, van Deventer SJ, Dekker E. Polyp miss rate determined by tandem colonoscopy: a systemic review. Am J Gastroenterol 2006;101:343-350.
4. Barclay RL, Vicari JJ, Doughty AS, Johanson JF, Greenlaw RL. Colonoscopic withdrawal times and adenoma detection during screening colonoscopy. N Engl J Med 2006;355:2533-2541.
5. Butterly L, Robinson CM, Anderson JC, Weiss JE, Goodrich M, Onega TL. Amos CI, Beach ML. Serrated and adenomatous polyp detection increases with longer withdrawal time: results from the New Hampshire Colonoscopy Registry. Am J Gastroenterol 2014;109:417-426.
6. Theuerkauf jr FJ. Colonoscopy and polypectomy. Am Surg 1976;42:33-43.
7. Wildi SM, Schoepfer AM, Vavricka SR, Fruehauf H, Safroneeva E, Wiegand N, Bauerfeind P, Fried M. Colorectal polypectomy during insertion and withdrawal or only during withdrawal? a randomized controlled trial. Endoscopy 2012;44:1019-1023.
8. Ahn SB, Han DS, Bae JH, Byun TJ, Kim JP, Eun CS. The miss rate for colorectal adenoma determined by quality-adjusted back-to-back colonoscopies. Gut Liver 2012;6:64-70.
9. Patel NC, Islam RS, Umar SB, Gurudu S, Faigel DO, Leighton J, Ramirez FC. Polypectomy during the insertion phase of screening colonoscopy: how often does it occur, and what are the clinical impacts? Gastrointest Endosc 2013;77:AB506.
10. Hewett DG, Rex DK. Inspection on instrument insertion during colonoscopy: a randomized controlled trial. Gastrointest Endosc 2012;76:381-387.
11. Sanaka MR, Parsi MA, Burke CA, Barnes D, Church J, Rizk M, Zein N, Joseph R, Thota PN, Lopez R, Kiran RP. Adenoma detection at colonoscopy by polypectomy in withdrawal only versus both insertion and withdrawal: a randomized controlled trial. Surg Endosc 2015;29:692-699.
12. Ji JS, Lee SW, Lee JR. Comparison of adenoma detection by polypectomy during both insertion and withdrawal versus only withdrawal of colonoscopy: a randomized controlled multicenter trial. Ann Oncol 2016;27(suppl2):ii68??

13. Kaminski MF, Regula J, Kraszewska E, Polkowski M, Wojciechowska U, Didkowska J, Zwierko M, Rupinski M, Nowacki MP, Butruk E. Quality indicators for colonoscopy and the risk of interval cancer. N Engl J Med 2010;362:1795-1803.
14. Corley DA, Jensen CD, Marks AR, Zhao WK, Lee JK, Doubeni CA, Zauber AG, de Boer J, Fireman BH, Schottinger JE, Quinn VP, Ghai NR, Levin TR, Quesenberry CP. Adenoma detection rate and risk of colorectal cancer and death. N Engl J Med 2014;370:1298-1306.
15. Wang HS, Pisegna J, Modi R, Liang LJ, Atia M, Nguyen M, Cohen H, Ohning G, van Oijen M, Spiegel BM. Adenoma detection is necessary but insufficient for distinguishing high versus low endoscopist performance. Gastrointest Endosc 2013;77:71-78.
16. Williams JE, Holub JL, Faigel DO. Polypectomy rate is a valid quality measure for colonoscopy: results from a national endoscopy database. Gastrointest Endosc 2012;75:576-582.
17. Gohel TD, Burke CA, Lankaala P, Podugu A, Kiran RP, Thota PN, Lopez R, Sanaka MR. Polypectomy rate: a surrogate for adenoma detection rate varies by colon segment, gender, and endoscopist. Clin Gastroenterol Hepatol 2014;12:1137-1142.
18. Lee TJ, Rutter MD, Blanks RG, Moss SM, Goddard AF, Chilton A, Nickerson C, McNally RJ, Patnick J, Rees CJ. Colonoscopy quality measures: experience from the NHS Bowel Cancer Screening Programme. Gut 2012;61:1050-1057.
19. Aniwan S, Orkoonsawat P, Viriyautsahakul V, Angsuwatcharakon P, Pittayanon R, Wisedopas N, Sumdin S, Ponuthai Y, Wiangngoen S, Kullavanijaya P, Perknimitr R. The secondary quality indicator to improve prediction of adenoma miss rate apart from adenoma detection rate. Am J Gastroenterol 2016;111:723-729.
20. Kahi CJ, Li X, Eckert GJ, Rex DK. High colonosopic prevalence of proximal colon serrated polyp in average-risk men and women. Gastrointest Endosc 2012;75:515-520.
21. Fayad NF, Kahi CJ. Quality measures for colonoscopy: a critical evaluation. Clin Gastroenterol Hepatol 2014;12:1973-1980.
22. Lai EJ, Calderwood AH, Doros G, Fix OK, Jacobson BC. The Boston bowel preparation scale: a valid and reliable instrument for colonoscopy-oriented research. Gastrointest Endosc 2009; 69: 620-625.

23. Clark BT, Protiva P, Nagar A, Imaeda A, Ciarleglio MM, Deng Y, Laine L. Quantification of adequate bowel preparation for screening or surveillance colonoscopy in men. Gastroenterology 2016;150:396-405.
24. Vargo JJ, DeLegge MH, Feld AD, Gerstengerger PD, Kwo PY, Lightdale JR, Nuccio S, Rex DK, Schiller LR. Multisociety sedation curriculum for gastrointestinal endoscopy. *Gastrointest Endosc.* 2012;76:e1-e25.
25. Lee TJ, Rutter MD, Blanks RG, Moss SM, Goddard AF, Chilton A, Nickerson C, McNally RJ, Patnick J, Rees CJ. Colonoscopy quality measures: experience from the NHS Bowel Cancer Screening Programme. Gut 2012;61:1050-1057.