Original Article

Paired Comparison of Procedural Sequence in Same-day Bidirectional Endoscopy with Moderate Sedation and Carbon Dioxide Insufflation: A Prospective Observational Study

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ABSTRACT

Background/Aims: Same-day bidirectional endoscopy (BDE) is a commonly performed procedure, but the optimal sequence of the procedure with carbon dioxide insufflation is not well established. In this study, we investigated the optimal sequence for same-day BDE without polypectomy under moderate sedation and carbon dioxide insufflation in terms of sedation doses and colonoscopy performance. **Patients and Methods:** We performed a prospective observational study of 63 asymptomatic patients who were admitted for physical check-ups. A colonoscopy-esophagogastroduodenoscopy (EGD) examination was performed first and then an EGD-colonoscopy examination was performed within 1.5 years. **Results:** The total procedure time, procedure complexity, bowel preparation quality, cecal intubation time, colon polyp detection rate, and adverse events were similar between the two study groups. The total doses of fentanyl and midazolam were significantly higher for the colonoscopy-EGD group than that for the EGD-colonoscopy group (70.8 ± 9.6 μg vs. 56.6 ± 9.2 μg and 6.1 ± 1.3 mg vs. 4.6 ± 1.1 mg, $P < 0.0001$ and $P < 0.0001$, respectively). The recovery time to discharge was significantly longer for the colonoscopy-EGD group compared to the EGD-colonoscopy group (38.5 ± 3.9 min vs. 31.9 ± 3.2 min, $P < 0.001$, respectively). **Conclusions:** EGD-colonoscopy is the optimal sequence for same-day BDE. In this order, the procedures are better tolerated, the sedation doses are reduced, and the recovery time is shorter.

Key Words: Bidirectional endoscopy, carbon dioxide, colonoscopy quality, moderate sedation

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An esophagogastroduodenoscopy (EGD) and colonoscopy are commonly performed to evaluate patients for overt/occult gastrointestinal bleeding, iron-deficiency anemia, positive fecal occult blood tests, and abdominal pain.[1-7] The combination of both the procedures, i.e. bidirectional endoscopy (BDE), is also administered to asymptomatic patients during a physical check-up or cancer screening.[8,9] Same-day BDE is commonly used in clinical practice, and a national endoscopy database showed that BDE accounts for > 10% of all cases referred for gastrointestinal endoscopies in the United States.[10] The benefits of a same-day BDE compared to an alternate-day endoscopy are well-established and include reduced sedation doses, a shorter hospital stay, reduced medical costs, and expedited decision-making for patient care.[11,12]

The optimal sequence of performing a same-day BDE has not been well established. Anecdotal evidence from some endoscopists suggests that the gas insufflation required when performing an EGD makes the subsequent colonoscopy more difficult. As a result, in same-day BDE, the colonoscopy tends to be performed first followed by the EGD to avoid colonoscopy failure.[2,4,7] However, in a cohort of unsedated patients, two recent studies showed that EGD was perceived

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to be more stressful to patients when preceded by the colonoscopy.[13,14] The increase in the discomfort during the EGD examination when performed after the colonoscopy was also reported by another study abstract in subjects with moderate sedation.[15] When propofol-induced deep sedation was applied, lower propofol doses and better EGD tolerability were reported when the EGD was performed before the colonoscopy.[16] Nevertheless, a recent study demonstrated that there were no differences in the patients' discomfort and satisfaction regarding the procedure sequence.[17] Because carbon dioxide (CO_2) is absorbed across the intestines 160 times more rapidly than nitrogen and 13 times more rapidly than oxygen, which are the principal gas components of air,[18] CO_2 insufflation has been commonly used in modern colonoscopies to decrease abdominal discomfort during and following the procedure.[19-22] The aforementioned side effect of gas insufflation during EGD-colonoscopy sequence might be negligible when CO_2 insufflation is used. A same-day BDE study using CO_2 insufflation has not been reported in the literature. Therefore, we conducted a paired comparison analysis using moderate sedation and CO_2 insufflation on the procedural sequence of the same-day BDE.

The primary aim of this study was to compare the sedative doses and patient discomfort between the study groups who received a colonoscopy followed by an EGD (colonoscopy-EGD) or an EGD followed by a colonoscopy (EGD-colonoscopy) during a same-day BDE. The secondary aim was to assess colonoscopy performance, including the cecal intubation time and polyp detection rate between the two endoscopic sequences.

PATIENTS AND METHODS

Patients

This was a prospective, observational study conducted from August 2013 to August 2015 at the Evergreen General Hospital, Taiwan. Asymptomatic patients admitted to our physical check-up department for a same-day BDE examination within 2 consecutive years were enrolled. During BDE scheduling, patients provided: (1) a personal history of major comorbid diseases, (2) a past history of abdominal surgeries, and (3) a current medication list. Patient demographics and BDE findings were prospectively collected and stored in a central database. Patients with the following conditions were excluded: Previous gastrectomy or colectomy, inadequate bowel preparation, hot snare polypectomy for gastric or colon polyp, obstructive lesions of the colon, severe colitis, gastrointestinal bleeding, allergy to fentanyl or midazolam, American Society of Anesthesiology (ASA) classification of physical status grade 3 or higher, age < 18 years, and refusal to provide a written informed consent. The study was approved by the Institutional Review Board of Evergreen General Hospital.

Endoscopy procedures

Patients enrolled in this study underwent a BDE with the colonoscopy-EGD sequence in the first year of check-up and a BDE with the EGD-colonoscopy sequence in the second year of check-up. All BDE examinations were performed under moderate conscious sedation with fentanyl (United Biomedical; Taipei, Taiwan) and midazolam (Dormicum; Roche Pharmaceuticals, Basel, Switzerland) according to the current guidelines.[23,24] Moderate sedation was provided by gastroenterologists. CO_2 insufflation was used for all endoscopic procedures. Endoscopies were performed by two experienced endoscopists (CL Cheng, YL Kuo) who conducted more than 500 examinations annually. BDE examinations were performed with a standard upper endoscopy (GIF-Q260; Olympus Medical Systems Corp., Tokyo, Japan) and colonoscopy (CF-Q260AI or CF-Q260AL; Olympus Medical Systems Corp., Tokyo, Japan). All patients received 3-L polyethylene glycol (PEG; Klean-Prep, Helsinn Birex Pharmaceuticals Ltd., Dublin, Ireland) for bowel preparation. A split-dose of the PEG preparation was 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 was provided for the afternoon colonoscopy. The level of colon cleansing was prospectively scored at the time of the colonoscopy with the Boston Bowel Preparation Scale (BBPS). In this study, an excellent bowel preparation was defined as a total BBPS score of 8 or higher, a good preparation as a total score of 7, a fair preparation as a total score of 6, and a poor preparation as a total score of 5 or less. Cecal intubation time was defined as the time between the scope insertion and cecal intubation. Colonoscopy withdrawal time was defined as the duration between the time at which the cecum was reached and the time at which the scope was withdrawn from the anus.

A procedure score was used to define the complexity of the endoscopic procedures: Diagnostic procedure (score 0) and interventional procedure (score 1). Total procedure score ranged from 0 to 2 in each BDE examination. Interventional procedures included biopsy removal of polyps, biopsy histology for peptic ulcer/erosion, and a biopsy for colitis. Rapid urease test during the EGD examination was considered a diagnostic procedure.

Blood pressure, heart rate, and oxygen saturation were monitored and recorded during the endoscopic procedures. Supplemental oxygen by nasal cannula was provided when oxygen desaturation was detected by pulse oximetry. The duration of EGD and colonoscopy examinations, cecal intubation time, procedure complexity, and total sedative doses were recorded by a gastroenterology nurse after each BDE examination. The following adverse events were recorded during conscious sedation: (1) oxygen desaturation:

<90% persisting for more than 30 s; (2) hypotension: <90 mmHg systolic blood pressure for more than 30 s; (3) hypertension: >180 mmHg systolic blood pressure for more than 30 s; (4) tachycardia: >120 beats per minute, lasting more than 30 s; and (5) bradycardia: <50 beats per minute, lasting more than 30 s.

Recovery time from moderate sedation was assessed at 15 and 25 min after the BDE examination using the Aldrete scale.[25] The time interval between arrival at the recovery room and the time of discharge was recorded.

Evaluation of patient discomfort

The grade of the patient's discomfort, as perceived by the endoscopist, was rated after every endoscopy using a 10-point Likert scale: 0, no discomfort at all; 5, need for multiple additions of sedative agents during the procedure; and 10, abortion of the procedure because of the patient's agitation. After recovery, patients were asked to fill a standard questionnaire using a 10-cm visual scale to report the extent of discomfort.

Statistical analysis

The primary aim of the study was to evaluate whether there was a difference in the total dose of sedative agents between the two groups. Power calculation estimated that 60 patients in each group would ensure 90% power of detecting a mean of paired difference of 0.6 mg in the dose of midazolam (given a standard deviation of 1.4 mg) or 5.5 μg in the dose of fentanyl (given a standard deviation of 12 μg) with a two-sided significance of 5%. Summary statistics were presented as percentages in the case of categorical variables and as the means with standard deviations in the case of continuous variables. The paired *t*-test for continuous data and the McNemar test for binary data were used to compare the differences between the two study groups. All calculations were conducted using SAS version 9.3 software (SAS Institute Inc., Cary, NC, USA). The criterion for statistical significance was $P < 0.05$.

RESULTS

A total of 75 patients were enrolled in the study and 12 patients were excluded (six patients had inadequate preparation and six patients underwent a polypectomy during the BDE procedure). The 63 patients eligible for analysis underwent the colonoscopy-EGD sequence during the first BDE examination and the EGD-colonoscopy sequence during the second BDE examination. The mean duration between the two BDE examinations was 15 months (range: 12–18 months). There were no significant differences between the two study groups regarding age, body weight, body mass index, ASA classification status, or history of abdominal surgery [Table 1].

Table 2 shows the endoscopy and sedation related parameters between the two study groups. The durations required to complete the EGD, colonoscopy, and BDE procedures were similar between the two study groups. The total procedure score was comparable between the two study groups. The total dose of fentanyl was significantly higher in the colonoscopy-EGD group than that in the EGD-colonoscopy group (70.8 ± 9.6 μg vs. 56.6 ± 9.2 μg, $P < 0.0001$, respectively). In addition, the total dose of midazolam was significantly higher in the colonoscopy-EGD group than that in the EGD-colonoscopy group (6.1 ± 1.3 mg vs. 4.6 ± 1.1 mg, $P < 0.0001$, respectively). Correspondingly, the post-procedure recovery evaluation regarding 15-min Aldrete score revealed a significantly lower score in the colonoscopy-EGD group than that in the EGD-colonoscopy group (9.1 ± 0.7 vs. 9.5 ± 1.3, $P = 0.037$, respectively), and the recovery time for patient discharge was significantly longer in the colonoscopy-EGD group than that in the

Table 1: Patient demographics

	Colonoscopy-EGD BDE (*n*=63)	EGD-colonoscopy BDE (*n*=63)	*P*-value
Age, years	53.2±(9.1)	54.2±(9.1)	NS
Male, *n* (%)	38±(60.3)	38±(60.3)	NS
Weight, kg	68.1±(11.4)	68.5±(11.4)	0.182
BMI, kg/m²	25.0±(3.7)	25.2±(3.8)	0.147
ASA classification	1.7±(0.5)	1.7±(0.5)	NS
Abdominal surgery, *n* (%)	19±(30.2)	19 (30.2)	NS

EGD: Esophagogastroduodenoscopy, BDE: Bidirectional endoscopy, BMI: Body mass index, ASA: American society of anesthesiology, NS: Not significant

Table 2: Endoscopy and sedation-related parameters between study groups

	Colonoscopy-EGD BDE (*n*=63)	EGD-colonoscopy BDE (*n*=63)	*P*-value
EGD duration, min	5.4±(1.2)	5.6±(1.0)	0.180
Colonoscopy duration, min	22.8±(3.6)	22.7±(3.2)	0.425
Total DBE duration, min	28.2±(3.7)	28.2±(3.3)	0.939
Total procedure score	1.3±(0.5)	1.3±(0.5)	0.658
Total fentanyl dose, μg	70.8±(9.6)	56.6±(9.2)	<0.0001
Total midazolam dose, mg	6.1±(1.3)	4.6±(1.1)	<0.0001
Aldrete score at 15 min	9.1±(0.7)	9.5±(1.3)	0.037
Aldrete score at 25 min	9.95±(1.9)	9.92±(0.3)	0.603
Time to discharge, min	38.5±(3.9)	31.9±(3.2)	<0.0001

Data represented as mean ± SD; EGD: Esophagogastroduodenoscopy, BDE: Bidirectional endoscopy

EGD-colonoscopy group (38.5 ± 3.9 min vs. 31.9 ± 3.2 min, $P < 0.0001$, respectively). There was no significant difference in the post-procedural recovery evaluations regarding the 25-min Aldrete score between the two study groups.

Table 3 shows the questionnaire results of patient discomfort during the BDE examination. Subjective discomfort with the EGD examination, as assessed by both the patient and endoscopist, was significantly higher in the colonoscopy-EGD group than that in the EGD-colonoscopy group. Subjective discomfort with colonoscopy examination, as assessed by both the patient and endoscopist, was similar between the two groups.

Table 4 summarizes the colonoscopy quality between the two study groups. Cecal intubation was achieved in all patients. The BBPS score, patients with excellent/good preparation, cecal intubation time, and colonoscopy withdrawal time were similar between the two study groups. No significant difference of polyp detection was found between the two study groups. However, more adenomas were detected in the colonoscopy-EGD group than that in the EGD-colonoscopy group (73% vs. 54%, $P = 0.023$, respectively).

Table 5 shows the adverse events related to conscious sedation in the study population. Similar proportions of patients in the two study groups experienced hypoxemia, hypertension, hypotension, and tachycardia. All these episodes were transient, did not necessitate termination of the examination, and were followed by a full recovery of the patients. Bradycardia did not occur in any patient.

Table 3: Patient tolerability between study groups

	Colonoscopy-EGD BDE (*n*=63)	EGD-colonoscopy BDE (*n*=63)	*P*- value
Discomfort score during EGD			
Endoscopist's assessment,	1.62±(0.96)	0.79±(0.86)	<0.0001
Patient's assessment,	1.16±(1.00)	0.56±(0.96)	<0.0001
Discomfort score during colonoscopy			
Endoscopist's assessment	1.90±(2.52)	1.82±(2.35)	0.308
Patient's assessment	1.81±(2.44)	1.79±(2.31)	0.382

Data represented as mean ± SD; EGD: Esophagogastroduodenoscopy, BDE: Bdirectional endoscopy

Table 4: Colonoscopy quality between study groups

	Colonoscopy-EGD BDE (n=63)	EGD-colonoscopy BDE (*n*=63)	*P*-value
BBPS score	7.3±(0.7)	7.2±(0.8)	0.606
Excellent/good preparation, *n* (%)	55±(87.3)	54±(85.7)	0.739
Cecal intubation, *n* (%)	63±(100)	63±(100)	NS
Cecal intubation time, min	8.3±(2.9)	8.2±(2.5)	0.538
Withdrawal time, min	14.5±(2.2)	14.5±(2.0)	0.672
Polyp detection, *n* (%)	59±(93.7)	58±(92.1)	0.564
Adenoma detection, *n* (%)	46±(73.0)	34±(54.0)	0.023

EGD: Esophagogastroduodenoscopy, BDE: Bidirectional endoscopy, BBPS: Boston bowel preparation scale, NS: Not significant

Table 5: Conscious sedation-related adverse events between study groups

	Colonoscopy-EGD BDE (*n*=63)	EGD-colonoscopy BDE (*n*=63)	*P*-value
Hypoxemia, *n* (%)	2±(3.2)	2±(3.2)	1.0
Hypertension, *n* (%)	0±(0)	1±(1.6)	0.317
Hypotension, *n* (%)	24±(38.1)	20±(31.7)	0.157
Tachycardia, *n* (%)	2±(3.2)	3±(4.8)	0.317
Bradycardia, *n* (%)	0±(0)	0±(0)	NS

EGD: Esophagogastroduodenoscopy, BDE: Bidirectional endoscopy, NS: Not significant

DISCUSSION

In this prospective, paired comparison study, we found that patients required a lower total dose of fentanyl and midazolam and a shorter recovery time when the EGD-colonoscopy sequence was used in the BDE examination. We also found that the EGD was better tolerated by patients when it was performed first. The total duration of procedures, the complexity of endoscopic procedures, and sedation-related adverse events did not differ significantly between the EGD-colonoscopy and the colonoscopy-EGD groups. To the best of our knowledge, this is the first study of patients undergoing a same-day BDE under moderate sedation with a fentanyl/midazolam combination and gas insufflations with CO_2.

In our study, the mean total doses of moderate sedation with fentanyl and midazolam were significantly higher in the colonoscopy-EGD group than that in the EGD-colonoscopy group ($P < 0.0001$ and $P < 0.0001$, respectively). The finding was in agreement with a previous study using deep sedation with propofol. Hsieh *et al*.[16] reported that lower propofol doses were needed when a same-day BDE was started with the EGD (124 mg vs. 135 mg, $P = 0.024$, respectively). However, in another same-day BDE study using moderate sedation with meperidine/midazolam, Carter *et al*.[17] found that there was no significant difference in the total doses of additional midazolam between the colonoscopy-EGD and

the EGD-colonoscopy groups (1.41 vs. 1.14 mg, $P = 0.67$, respectively). In the study, meperidine 50 mg and midazolam 2.5 mg were provided for every patient in both BDE groups during the initial preparation phase, and the authors did not analyze the difference of total meperidine and midazolam doses between the two study groups. The advantage of the EGD-colonoscopy sequence in our study could be explained by the endoscopy nature and the pharmacologic profile of drugs used for endoscopic sedation. In the current study, the average durations of the EGD and colonoscopy examinations were approximately 5.5 and 23 min, respectively. After intravenous administration, the onset of effect of fentanyl is 1–2 min, the peak effect is achieved within 3–5 min, and the duration of effect is 30–60 min.[23] After intravenous administration, the onset of midazolam's effect is 1–2 min, the peak effect is achieved within 3–4 min, and the duration of its effect is 15–80 min.[23] In patients undergoing the EGD-colonoscopy sequence of the BDE examination, the sedative agents posed their peak effect when the EGD was completed, and they remained pharmacologically effective during most of the colonoscopy. Accordingly, only small doses of sedative agents were needed during the colonoscopy examination. However, in patients undergoing colonoscopy-EGD sequence, the effect of sedative agents had already waned when the colonoscopy was completed, and thus, more doses were needed for the upcoming EGD examination.

The smaller doses of total sedative agents are rationally related to a shorter recovery time. In our study, the average recovery time for patient discharge was significantly shorter for the EGD-colonoscopy group compared to the colonoscopy-EGD group (31.9 min vs. 38.5 min, $P < 0.0001$, respectively). However, the finding was different from a previous report in which propofol was used for deep sedation. Hsieh *et al*.[16] demonstrated that a lower overall dose of propofol was required for patients with EGD-colonoscopy sequence, but the recovery time to leaving did not differ between the EGD-first and the colonoscopy-first groups (15.2 min vs. 15.3 min, $P = 0.954$, respectively). The reason for such a discrepancy could be explained by the pharmacologic profile between propofol and fentanyl/midazolam. Propofol is highly lipid soluble and has an onset of action equivalent to one arm-brain circulation (i.e., 30–45 s).[23] Propofol is metabolized rapidly in the liver with peak effect achieved within 1–2 min and duration of effect of 4–8 min. Because of its short half-life of action, patients receiving propofol could be discharged at an earlier time. It is likely that the benefit of lower propofol dose was offset by its short-acting pharmacologic profile.

In same-day BDE, gas insufflation during the first procedure may affect the examination of the second procedure. Cho *et al*.[13] found that the quality of the EGD was influenced by the sequence of the procedures. Moreover, some endoscopists believed that gas insufflation during EGD may make a subsequent colonoscopy more difficult. With the introduction of CO_2 insufflation, the aforementioned negative influence of gas insufflation during the first endoscopic procedure could be minimized. In our study, we found that the colonoscopy quality, including cecal intubation rate, cecal intubation time, and polyp detection rate, were similar regardless of which examination was performed first [Table 4]. The colon adenoma detection rate being significantly lower in the EGD-colonoscopy group than in the colonoscopy-EGD group could be explained by our study design. The EGD-colonoscopy sequence of the BDE was performed an average of 18 months after the colonoscopy-EGD sequence, and thus, the colon adenomas were theoretically fewer than the first BDE study.

Similar to the results of previous studies, analysis of patient and endoscopist questionnaires revealed that patients experienced greater subjective discomfort with the EGD when they underwent the colonoscopy-EGD sequence compared to the EGD-colonoscopy sequence.[13,14] Poor tolerance to esophageal intubation and inadequate sedation were two major reasons for such discomfort. In both the colonoscopy-EGD and EGD-colonoscopy groups, most doses of midazolam were provided during the first examination (64 and 80%, respectively). In the colonoscopy-EGD group, the mean dose of midazolam provided in the colonoscopy study was 3.9 mg and the mean dose of midazolam added in the EGD study was 2.2 mg. Because of the long procedure time of the colonoscopy, midazolam's effect had started to wane when EGD was performed. However, the maximum dose of midazolam for endoscopic sedation is approximately 6 mg, based on guideline suggestions, which limits the addition of a midazolam dose during the EGD examination.[22,23] In the EGD-colonoscopy group, the mean dose of midazolam provided in the EGD study was 3.7 mg and the mean dose of midazolam added in the colonoscopy was 0.9 mg. With adequate sedation during the EGD examination and less midazolam needed in the colonoscopy examination, patients in the EGD-colonoscopy group had lower sedative doses and a shorter recovery time.

A major strength of our study is that we provided CO_2 insufflation during BDE examination, which has not been reported in previous studies. Another strength is the paired comparison study design in which each patient is used as his/her own control, and thus, the individual differences became irrelevant. A major limitation is that it is designed as one sequence (i.e., colonoscopy-EGD followed by EGD-colonoscopy), rather than a crossover study design, and therefore, the period effect cannot be evaluated. Another limitation is the lack of patient randomization. Selection bias and decreased comparability between groups may have

occurred. Another limitation was that the physician was not blind to the sequence of the endoscopic procedures. Moreover, the procedures were performed by experienced endoscopists, so the results may vary for less experienced endoscopists.

CONCLUSION

Our study demonstrated that the EGD-colonoscopy sequence is the best choice for a same-day BDE with moderate sedation and CO_2 insufflation. Patients with the EGD-colonoscopy sequence tolerated the procedures better, needed less sedative doses, and had a shorter recovery time. The sequence of BDE procedures did not affect the colonoscopy quality. Further prospective, randomized controlled studies are warranted to confirm our observational study results.

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Conflicts of Interest
There are no conflicts of interest.

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