Propofol compared with bolus and titrated midazolam for sedation in outpatient colonoscopy: a prospective randomized double-blind study CME

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Background and Aims: The safest and most efficient method of sedation for outpatient colonoscopy remains unclear. This study aimed to compare the efficiency and safety of bolus administration of midazolam compared with titrated administration and propofol administration for patients undergoing outpatient colonoscopy.

Methods: We randomly divided patients undergoing colonoscopy into the propofol group, bolus midazolam group, and titrated midazolam group. We compared total procedure time, induction time, recovery time, and discharge time among the 3 groups. We also compared patient satisfaction and the incidence of adverse events.

Results: In total, 267 patients (89 in each study group) were enrolled during the study period. Patients in the propofol group had a shorter total procedure time (39.5 vs 59.4 vs 58.1 minutes; $P < .001$), induction time (4.6 vs 6.3 vs 7.6 minutes; $P < .001$), recovery time (11.5 vs 29.5 vs 29.2 minutes; $P < .001$), and discharge time (20.6 vs 34.9 vs 34.7 minutes; $P < .001$) than patients in the bolus midazolam group and titrated midazolam group. Patients in the propofol group reported higher degrees of satisfaction than patients in the bolus or titrated midazolam plus meperidine groups (9.9 vs 9.6 vs 9.6 [$P = .007$] and 4.9 vs 4.7 vs 4.8 [$P = .008$], respectively). Adverse events were not significantly different between groups.

Conclusions: In this randomized trial, propofol was superior to bolus or titrated midazolam in terms of endoscopy unit efficiency and patient satisfaction during outpatient colonoscopy. (Clinical trial registration number: KCT0002805.) (Gastrointest Endosc 2021;93:201-8.)

Increasingly large numbers of colonoscopies are performed with the patient under sedation to relieve patient anxiety and discomfort. Many different sedatives and analgesics can be used to achieve appropriate levels of sedation depending on patient and procedural variables. Colonoscopies are generally performed with the patient under moderate sedation in which the patient maintains ventilatory and cardiovascular function and provides purposeful responses to verbal or light tactile stimulation.[1,2]

Midazolam and narcotics are frequently used as sedatives because of their efficacy, safety, cost, and efficiency in colonoscopy. Guidelines recommend that the doses of sedatives should be titrated accordingly to achieve a safe, comfortable, and technically successful endoscopic procedure.[1] However, a retrospective study compared bolus administration of fentanyl and midazolam with titrated administration[3] and found that bolus administration of sedatives shortened induction time and thus improved endoscopy unit efficiency and safety and decreased the amount of sedatives required compared with the titrated group.

The use of propofol for sedation during colonoscopy is increasing in frequency and has been shown to shorten

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induction and recovery times compared with a combination of midazolam plus narcotics, suggesting it improves endoscopy unit efficiency.[4,5] Currently, most guidelines recommend propofol as an option for sedation during colonoscopy.[6,7]

Bolus administration of midazolam and narcotics may improve unit efficiency compared with titrated administration and thus have similar efficiency to propofol administration. However, no prospective studies have compared bolus administration of midazolam with titrated administration or propofol administration. Thus, we performed a prospective study to compare the efficiency of these 3 methods of sedation during outpatient colonoscopy. We focused on whether propofol administration was superior to bolus administration of midazolam and whether there are differences between bolus and titrated administration of midazolam.

METHODS

Study population

This study was a randomized, double-blinded, prospective study from July 2018 to June 2019 in a tertiary referral center. Patients scheduled for colonoscopy and who agreed to participate in the study were enrolled. Patients were eligible to enter the study if they were aged ≥18 years and were scheduled for colonoscopy. Exclusion criteria were pregnancy, known hypersensitivity to any of the study medications or to either soy-based or egg-based products, and history of adverse events with previous sedation. These patients were randomly assigned to either bolus administration of propofol, bolus administration of midazolam and meperidine, or titrated administration of midazolam and meperidine. A statistical advisor generated a random sequence that was concealed in an envelope. A research assistant nurse opened the envelope and performed sedation accordingly. The induction and sedation maintenance of each group was performed by a qualified research nurse. Thus, both the patient and physician were blinded to the method of sedation.

The study protocol was approved by the Institutional Review Board of the Ethics Committee of the Catholic University College of Medicine, Korea before initiating this study (approval number: OC16EISI0050). This trial was registered with the International Clinical Trials Registry Platform (no. KCT0002805).

Sedation protocol

In the propofol group (Fresofol MCT, 150 mg/15 mL/A; Fresenius-Kabi Korea, Seoul, Korea), induction of sedation started with an initial .5-mg/kg (.05-mL/kg) bolus administered intravenously, followed by titration with .25-mg/kg (.025-mL/kg) boluses. Bolus administration of midazolam and meperidine was based on the bolus dosing nomogram previously reported.[3,8] Titrated administration consisted of administering incremental doses of midazolam and meperidine every 2 to 3 minutes per American Society of Anesthesiologists guidelines until sedation was believed to be adequate to begin the procedure. The research assistant nurse assessed the depth of sedation during the procedure using the Ramsay sedation scale.[9] If the Ramsay sedation scale score was <3, additional medication was titrated at 2- to 3-minute intervals for achievement or maintenance of a sedation scale score of 3 to 4.

Colonoscopy protocol

Bowel preparations were completed with split-dose polyethylene glycol before colonoscopy. All colonoscopic procedures were performed using a high-definition colonoscope (CF-H260AL; Olympus Optical Co, Tokyo, Japan) without caps by 3 experienced endoscopists (J.S.K., C.W.H., and D.W.M.). A research nurse checked the procedure-related time points and the occurrence of adverse events. After completion of the procedure, patients were transferred to a recovery room and monitored with continuous electrocardiography, pulse oximetry, and blood pressure recordings. A recovery nurse assessed full recovery and readiness for home discharge (defined as blood pressure and heart rate within 20% of the baseline, oxygen saturation greater than 90% [on room air], and ability to stand at the bedside without assistance).

Outcome measures

The primary outcome was total procedure time (sedative administration to discharge), which is associated with the overall efficiency of the endoscopic unit as a result of the 3 protocols. We also analyzed induction time (sedative administration to successful sedation), total colonoscopy time (scope in to scope out), recovery time (scope out to full recovery), discharge time (scope out to discharge), and sedation time (sedation start to full recovery). Secondary outcomes were adverse events (such as hypotension, tachycardia, bradycardia, or hypoxia) and patient experience.

Adverse events

Hypotension was defined as mean arterial pressure <90 mm Hg during the procedure and a 25% decrease from the baseline. Tachycardia was defined as heart rate >100 beats/min during the procedure and a 25% increase from the baseline. Bradycardia was defined as heart rate <60 beats/min during the procedure and a 25% decrease from the baseline. Hypoxia was defined as oxygen saturation of <90% during the procedure.

Patient satisfaction survey

After the procedure, a survey was given to patients before discharge. The survey included 4 questions regarding colonoscopy, which provided information on patient satisfaction (by use of the visual analog scale and

Likert scale), degree of sedation, recommendation to others, and how their experience compared with previous experiences of colonoscopy.

Sample size calculations

Using data from previous studies,[4,5] we calculated a sample size for detecting a 20% decrease in total procedure time in the propofol group compared with the titrated midazolam group. We assumed that the bolus midazolam group would have a similar decrease as the propofol group. With an α value of .05 and power of 80%, the number of patients per group was 85. Assuming a 5% dropout rate, the final number of patients was 89 per group.

Statistical analysis

All continuous variables are expressed as the mean ± standard deviation, whereas categorical variables are presented as absolute values and percentages. The χ^2 or Fisher exact test was used to compare categorical variables. To compare the means among 3 groups, a 1-way analysis of variance with a post hoc (Tukey's method) test was used. Statistical significance was determined by $P < .05$. All statistical analyses were performed using SPSS version 20.0 for Windows (SPSS Inc, Chicago, Ill, USA).

RESULTS

Baseline patient characteristics

Two hundred sixty-seven patients were enrolled and underwent colonoscopy. They were randomly assigned to the propofol (n = 89), bolus administration of midazolam plus meperidine (n = 89), or titrated administration of midazolam plus meperidine (n = 89) groups. All recruited patients were enrolled, and no patients were excluded or dropped out.

Table 1 compares the demographic and basic characteristics of the 3 study groups. The mean age was 61, 58, and 59 years in the propofol group, bolus midazolam group, and titrated midazolam group, respectively. There were no significant differences in basic characteristics such as age, sex, body mass index, smoking history, alcohol intake, or comorbidities among the 3 groups. Screening was the most common indicator for colonoscopy in all groups, followed by abdominal symptoms and polyp surveillance. The propofol group received a mean dose of 82.4 ± 30.1 mg, the bolus midazolam group a mean dose of 4.8 ± 1.5 mg midazolam and 50 mg meperidine, and the titrated midazolam and meperidine group 4.4 ± 1.5 mg midazolam and 50 mg meperidine. There was no significant difference in dose per unit weight between the bolus and titrated midazolam groups (Table 2).

Endoscopy unit efficiency measures

Patients administered propofol, bolus midazolam plus meperidine, and titrated midazolam plus meperidine had total procedure times of 39.5 minutes, 59.4 minutes, and 58.1 minutes, respectively. The propofol group had a significantly shorter total procedure time than the bolus and titrated midazolam group ($P < .001$). Induction time was significantly shorter in the propofol group than in the bolus and titrated midazolam groups. (4.6 vs 6.3 vs 7.6 minutes; $P < .001$). After completing the colonoscopy, patients in the propofol group required less time to reach full recovery (11.5 vs 29.5 vs 29.2 minutes; $P < .001$) and were discharged sooner (20.6 vs 34.9 vs 34.7 minutes; $P < .001$). Induction time in the bolus group was significantly shorter than that in the titrated group (6.3 vs 7.6 minutes; $P < .001$). Colonoscopy withdrawal time was not significantly different among the 3 groups (9.9 vs 11.8 vs 10.1 minutes, respectively; $P = .110$) (Table 3 and Fig. 1).

Adverse events

Twenty-five minor adverse events occurred during the procedures. There was no significant difference in the incidence of significant hypotension, bradycardia, tachycardia, or hypoxia in the 3 groups (Table 4). We plotted changes in vital signs of patients using line plots (Fig. 2). As shown in Figure 2, the oxygen saturation was always maintained above 90% and heart rate remained between 60 and 100 beats/min in all groups.

Patient satisfaction survey

Patient survey findings are displayed in Table 5. Administration of bolus propofol, bolus midazolam plus meperidine, and titrated midazolam plus meperidine resulted in patient satisfaction scores of 9.9, 9.6, and 9.6 when using the visual analog scale and 4.9, 4.7, and 4.8 when using the Likert scale, respectively. Patient satisfaction was significantly higher in the bolus propofol group ($P < .01$). In the assessment of the degree of sedation, more than half of the patients in the propofol group rated this as being "adequate," whereas most patients in the bolus and titrated midazolam groups reported it to be "excessive." In addition, patients in the bolus propofol group reported that their experience was better than a previous colonoscopy experience, mostly with midazolam and meperidine.

DISCUSSION

In this randomized controlled trial, we found that propofol sedation for colonoscopy improved endoscopy unit efficiency by allowing a faster onset to colonoscopy state and a quicker recovery, which resulted in reducing the total procedure time compared with bolus or titrated sedation using midazolam and meperidine. Although there was no difference in safety, we found that patient satisfaction in the propofol group was higher than that in the bolus or titrated midazolam groups. The bolus midazolam group was faster in induction time than the titrated group,

TABLE 1. Baseline characteristics of patients

Characteristics	Propofol group (n = 89)	Bolus midazolam/meperidine group (n = 89)	Titrated midazolam/meperidine group (n = 89)	*P* value
Age, y	60.9 ± 9.4	57.7 ± 14.0	59.3 ± 12.2	.200
Sex				.400
Male	42 (47.2)	51 (57.3)	46 (51.7)	
Female	47 (52.8)	38 (42.7)	43 (48.3)	
Body mass index, kg/m^2	23.8 ± 2.7	24.4 ± 3.5	24.1 ± 3.0	.415
Comorbidities				
Hypertension	32 (36.0)	31 (34.8)	32 (36.0)	.984
Diabetes	13 (14.6)	11 (12.4)	13 (14.6)	.882
Cerebrovascular disease	0 (.0)	0 (.0)	2 (2.2)	.133
Cardiovascular disease	7 (7.9)	5 (5.6)	3 (3.4)	.428
Renal disease	0 (.0)	1 (1.1)	1 (1.1)	.604
Liver disease	0 (.0)	0 (.0)	0 (.0)	.999
Pulmonary disease	1 (1.1)	0 (.0)	0 (.0)	.604
Current smoker	10 (11.2)	20 (22.5)	10 (11.2)	.053
Current alcohol user	27 (30.3)	30 (33.7)	22 (24.7)	.414
American Society of Anesthesiologists class				.663
I	53 (59.6)	50 (56.2)	47 (52.8)	
II	36 (40.4)	39 (43.8)	42 (47.2)	
III	0 (.0)	0 (.0)	0 (.0)	
Previous abdominal surgery	27 (30.3)	22 (33.7)	32 (36.0)	.265
Colonoscopy indication				.554
Screening	53 (59.6)	51 (57.3)	56 (62.9)	
Polyp surveillance	6 (6.7)	10 (11.2)	11 (12.4)	
Abdominal symptoms	30 (33.7)	28 (31.5)	22 (24.7)	
Bowel preparation				.610
Excellent	9 (10.1)	10 (11.2)	15 (16.9)	
Good	71 (79.8)	65 (73.0)	60 (67.4)	
Fair	7 (7.9)	9 (10.1)	10 (11.2)	
Poor	2 (2.2)	5 (5.6)	4 (4.5)	
Cecal intubation rate, %	100	100	100	

Values are mean ± standard deviation or n (%) unless otherwise defined.

but there was no difference in recovery and discharge time or in overall dose of midazolam.

Midazolam administration, in combination with narcotics, is considered to be the criterion standard for sedation and has been used widely during colonoscopy. Multiple studies have demonstrated that the use of midazolam and narcotics combined during colonoscopy is efficient and safe.[4,10-14] In addition, published data on the optimal method of dosing for these drugs demonstrated that bolus administration of midazolam plus meperidine is more efficient and requires a lower dose than titrated administration.[3,8] However, no prospective study has compared the 2 methods.

Propofol during colonoscopy has been shown to shorten induction and recovery times compared with combinations of midazolam and narcotics, suggesting it improves the efficiency of endoscopy units.[4,5] However, in the main trials evaluated by meta-analyses,[15,16] midazolam and narcotic combinations were only administered by titration. To the best of our knowledge, no prospective studies have compared bolus administration of midazolam plus meperidine with bolus administration of propofol during colonoscopy.

In the present study, induction time, recovery time, discharge time, and total procedure time were significantly shorter in the propofol group than in the bolus and titrated midazolam plus meperidine groups. These results are consistent with those of previous studies comparing propofol with midazolam plus meperidine for colonoscopy.[4,5]

TABLE 2. Doses of medication received

Medication	Propofol group (n = 89)	Bolus midazolam/meperidine group (n = 89)	Titrated midazolam/meperidine group (n = 89)	*P* value
Propofol				
Total, mg	82.4 ± 30.1			
mg/kg	1.36 ± .61			
Midazolam				
Total, mg		4.8 ± 1.5	4.4 ± 1.5	.052
mg/kg		.076 ± .030	.069 ± .028	.115
Meperidine				
Total, mg		50 ± .0	50 ± .0	
mg/kg		.78 ± .15	.80 ± .12	.227

Values are mean ± standard deviation.

TABLE 3. Efficiency measures of each method

Parameter	Propofol group (n = 89)	Bolus midazolam/meperidine group (n = 89)	Titrated midazolam/meperidine group (n = 89)	*P* value
Total procedure time, min	39.5 (37.6-41.2)	59.4 (56.9-62.0)	58.1 (56.1-60.4)	<.001
Induction time, min	4.6 (4.4-4.9)	6.3 (5.9-6.8)	7.6 (7.2-8.2)	<.001
Total colonoscopy time, min	14.3 (13.0-15.6)	17.8 (15.6-20.1)	15.8 (14.3-17.4)	.022
Recovery time, min	11.5 (10.5-12.7)	29.5 (28.8-30.2)	29.2 (28.2-30.5)	<.001
Discharge time, min	20.6 (19.4-21.7)	34.9 (34.1-35.7)	34.7 (33.6-35.9)	<.001
Sedation time, min	30.3 (28.6-32.2)	53.8 (51.3-56.4)	52.6 (50.6-54.8)	<.001
Cecal intubation time, min	4.6 (3.9-5.3)	6.1 (5.2-7.2)	5.2 (4.6-6.0)	.032
Withdrawal time, min	9.9 (8.7-11.0)	11.8 (10.2-13.5)	10.1 (9.0-11.3)	.110

Values are mean (95% confidence interval).

Compared with the previous studies,[4,5] a small dose of propofol were administered in this study, but the results such as induction time, recovery time and total procedure time were not different. In addition, this study showed that propofol was superior to midazolam plus meperidine in endoscopy unit efficiency, regardless of the method of midazolam and meperidine administration.

We found that bolus midazolam compared with titrated administration showed no significant difference in the efficiency or safety of the endoscopy unit. Our results are somewhat different from those of Finn et al,[3] who conducted a retrospective study comparing bolus and titrated administration of midazolam and fentanyl for colonoscopy. In their results, they found that the bolus group had a shorter induction time and required a lower dose of sedative. In our study, induction time in the bolus midazolam group was shorter than that in the titrated midazolam group. However, there were no significant differences in total procedure time or dose of sedative required between these 2 groups. Although the total colonoscopy time was longer in the bolus midazolam group than that in the titrated midazolam group, the difference was not statistically significant, and there was no significant difference in total procedure time between these 2 groups even when it was excluded.

Previous studies have reported that propofol sedation has some disadvantages, including severe respiratory depression, hypotension, and bradycardia.[17,18] However, in the present study, the number of patients with oxygen desaturation or cardiac dysfunction was not greater in the propofol group than in the bolus or titrated midazolam groups. These results are consistent with data collected in a prospective study by Sato et al[19] in which consecutive outpatients underwent colonoscopy with propofol sedation. No adverse events were reported in 32,550 patients who underwent up to a maximal dose of 200 mg propofol. In addition, in contrast to previous studies,[3] there were no significant differences in the incidence of adverse events between any of the 3 groups. These results support guidelines that do not mention the method of administration but instead advise the use of sedatives that maximize patient comfort while minimizing risks.[20]

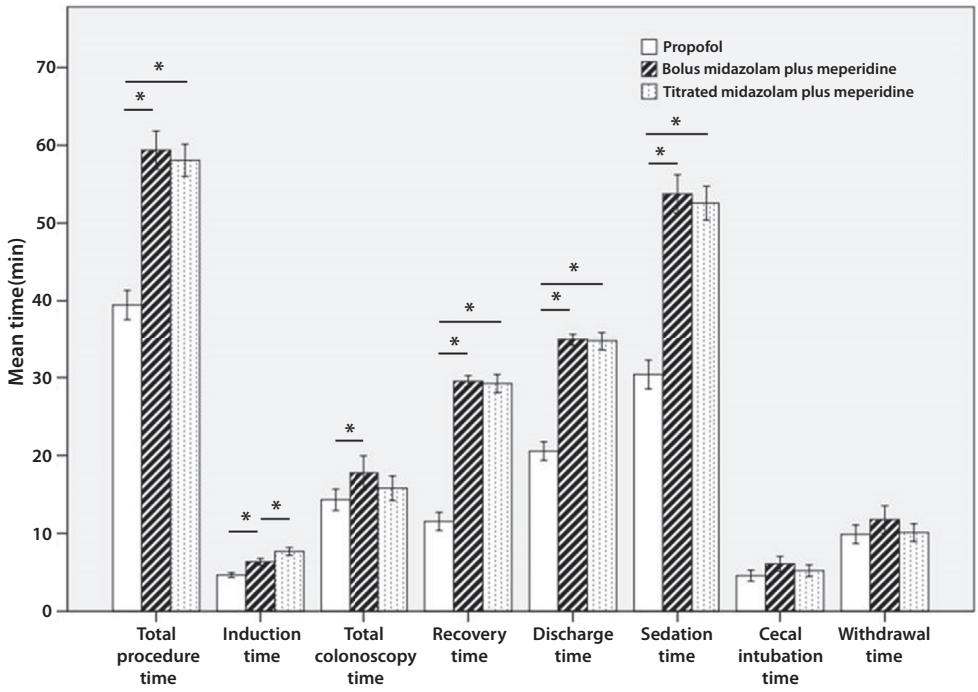

Figure 1. Measurements of endoscopy unit efficiency as a result of the 3 sedation methods. *Black error bars* are 95% confidence intervals. *$P < .05$.

TABLE 4. Adverse events of each method

Medication	Propofol group (n = 89)	Bolus midazolam/meperidine group (n = 89)	Titrated midazolam/meperidine group (n = 89)	*P* value
Bradycardia	4 (4.5)	5 (5.6)	3 (3.4)	.932
Tachycardia	0 (.0)	1 (1.1)	0 (.0)	1.000
Hypotension	1 (1.1)	0 (.0)	1 (1.1)	1.000
Desaturation	3 (3.4)	3 (3.4)	4 (4.5)	1.000

Values are n (%).

Like previous studies,[21,22] patients in the propofol group reported greater satisfaction than those in the bolus or titrated midazolam groups. In addition, compared with the previous colonoscopy experience that mainly administered midazolam plus meperidine, patients in the propofol group reported more satisfaction. Although patients in all groups indicated a high satisfaction score (approximately 9/10), more patients reported an excessive degree of sedation in the bolus and titrated midazolam groups than in the propofol group. This may be related to the combination of midazolam and meperidine leading to deeper levels of sedation and a prolonged recovery.[6]

The strength of our study is that it is the first prospective study to compare the efficacy and safety of propofol with bolus and titrated administration of midazolam plus meperidine in patients undergoing colonoscopy. Although previous studies have compared sedation with bolus propofol and titrated midazolam plus meperidine, this study also compared administration of midazolam plus meperidine in bolus form. Furthermore, this study included the largest sample size of any prospective study to date pertaining to this area.

Our study has several limitations. First, it is difficult to ensure that the endoscopist was completely blinded to the sedative administered to the patient. Second, this study involved 3 highly experienced endoscopists performing colonoscopies at a tertiary care referral hospital. Therefore, our results may not directly translate to those obtained by endoscopists with a different experience level in other healthcare environments. Third, it is difficult to generalize these results in high-risk groups or therapeutic endoscopy because the subjects of this study were healthy outpatients. Fourth, the sample size was calculated based on 2 previous studies comparing propofol and titrated midazolam because there were no previous studies comparing propofol administration and bolus midazolam. For this reason, our sample size may have been underpowered to demonstrate the differences among the 3 groups,

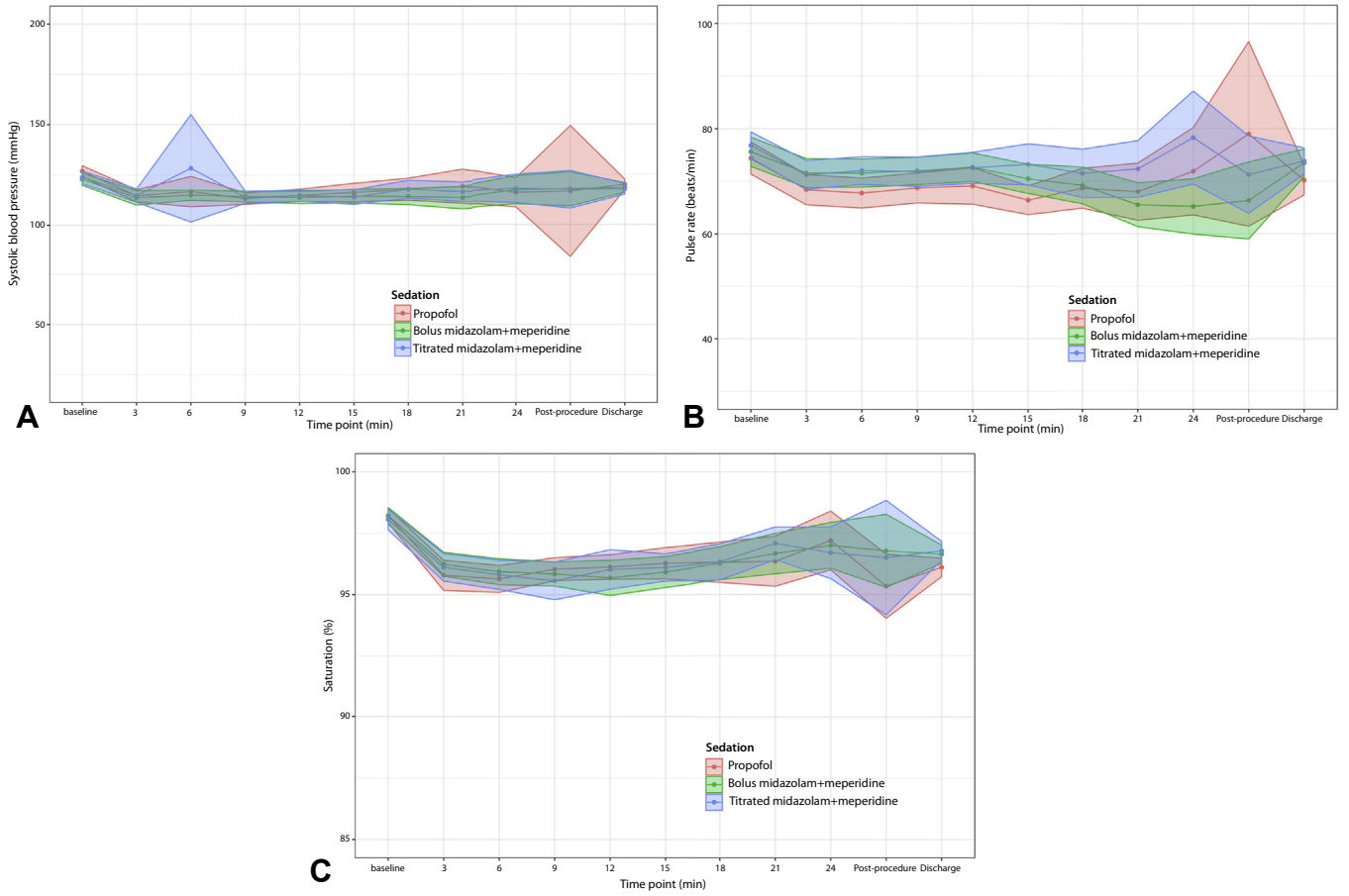

Figure 2. Changes in patient (**A**) systolic blood pressure (mm Hg), (**B**) heart rate (beats/min), and (**C**) oxygen saturation (%) determined at different stages of the study. Measurements were taken before sedative administration (baseline) and every 3 minutes after initiation of sedation during colonoscopy, postprocedure, and at discharge.

TABLE 5. Patient survey findings

Parameter	Propofol group (n = 89)	Bolus midazolam/meperidine group (n = 89)	Titrated midazolam/meperidine group (n = 89)	*P* value
Patient satisfaction				
Visual analog scale	9.9 ± .4	9.6 ± .7	9.6 ± .7	.008
Likert	4.9 ± .3	4.7 ± .6	4.8 ± .5	.007
Degree of sedation				<.001
More	37 (41.6)	72 (80.9)	75 (84.3)	
Adequate	48 (53.9)	11 (12.3)	11 (12.3)	
Less	4 (4.5)	6 (6.7)	3 (3.4)	
Recommend to others				.362
Yes	87 (97.8)	89 (100)	87 (97.8)	
No	2 (2.2)	0 (.0)	2 (2.2)	
Compared with previous colonoscopy				.015
Better	29 (45.3)	20 (27.8)	18 (24.3)	
Same	35 (54.7)	48 (66.7)	49 (66.2)	
Worse	0 (.0)	4 (5.6)	7 (9.5)	

Values are mean ± standard deviation or n (%).

especially between bolus midazolam and titrated midazolam. In addition, our study showed propofol administration by endoscopists to be safe and efficient during outpatient colonoscopy. However, this may not be applicable in Western countries where propofol is administered by anesthesiologists and is associated with increased costs. Finally, we administered meperidine instead of fentanyl, which is reported to have a faster recovery time relative to that observed with meperidine.[23] Nevertheless, we do not anticipate that these limitations will significantly affect the efficiency of the endoscopy unit or the incidence of adverse events, which are the main outcomes of this study.

In conclusion, bolus administration of propofol as a sedative for outpatient colonoscopy is superior to bolus and titrated administration of midazolam plus meperidine in terms of procedural efficiency and patient satisfaction. In addition, bolus midazolam shortened induction time compared with that in the titrated group. This study could be used as evidence for guidelines on conscious sedation for outpatient colonoscopy.

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