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Comparison of Synergistic Sedation with Midazolam and Propofol Versus Midazolam and Pethidine in Colonoscopies: A Prospective, Randomized Controlled Study

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Colonoscopy is a key procedure for the early detection of colorectal cancer. Despite its importance, the discomfort associated with colonoscopy often requires sedation, and the ideal sedation regimen remains to be determined. In this prospective randomized controlled trial, patients scheduled for colonoscopy were randomly assigned to two different sedation protocols. Group A received a combination of midazolam and propofol, while group B was given midazolam and pethidine. The study analyzed data from 51 patients, with 23 in group A and 28 in group B. The incidence of adverse events was similar across both groups. Additionally, no significant differences were observed in cecal intubation times or total procedure durations. Notably, group A had a lower frequency of required postural changes (1.0±0.7 vs. 1.5±0.7, p=0.02) and a reduced rate of manual compression (52.2% vs. 82.1%, p=0.02). There were no significant differences between the groups regarding subjective pain or overall satisfaction. Both sedation regimens were found to be safe and effective. The midazolam and propofol combination was associated with a smoother procedure, evidenced by fewer postural adjustments and less manual compression needed during colonoscopy.

Key Words: *Colonoscopy; Conscious Sedation; Endoscopy; Midazolam; Propofol*

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INTRODUCTION

Colorectal cancer is the leading cause of cancer-related deaths worldwide.[1] Colonoscopy is an important diagnostic tool for the early detection and treatment of colorectal cancer, and is widely used for colorectal cancer screening.[2] Early detection of colorectal cancer through screening colonoscopy reduces the incidence[3] and mortality rate of colorectal cancer.[4] However, patient discomfort and pain associated with the procedure can deter individuals from undergoing colonoscopy, even for cancer screening. Adequate sedation helps addresses these issues by alleviating patient anxiety and enhancing the comfort of both patients and endoscopists during the procedure.[5] Consequently, the use of sedation during colonoscopies is increasing in Korea.[6] Achieving successful sedative endoscopy entails finding a balance between patient comfort and safety, considering various factors such as patient characteristics, procedure-related variables, and continuous patient monitoring as fundamental principles.[7-9] While numerous sedation methods have been employed during endoscopy,[10-12] the optimal sedation approach remains undetermined. In Korea, most sedative colonoscopies are performed using either a combination of midazolam and pethidine or a combination of midazolam and propofol.[13]

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We aimed to identify a safe and effective sedation method for endoscopy. Traditional standard sedation combines midazolam (a hypnotic) and pethidine (an analgesic). A more recent approach involves the use of two hypnotics: midazolam and propofol (balanced sedation). To ascertain which method is superior, we conducted a prospective randomized controlled study to compare the two approaches.

MATERIALS AND METHODS

1. Patients

This study was conducted in accordance with the Declaration of Helsinki. The research protocol was approved by the Ethics Committee of Chonnam National University Hospital (Institutional Review Board Number: CNUH-2019-194; Approval date: July 19, 2019). This trial was registered on the International Clinical Trials Registry Platform (No. KCT0004225; registration date: August 21, 2019). Written informed consent was obtained from all participating patients.

The study included patients scheduled for colonoscopy under sedation at an outpatient clinic between July 2019 and June 2022. The exclusion criteria were: (1) age under <20 years or >75 years; (2) American Society of Anesthesiologists' Physical Status Classification (American Society of Anesthesiologists, ASA) score of ≥ 4 points;[14] (3) incomplete examination; (4) Liver cirrhosis; (5) Dialysis; (6) pregnancy; (7) chronic use of benzodiazepines or opioids; and (8) body weight <45 kg or >90 kg.

Patients in group A received midazolam (Bukwang Pharm., Seoul, Korea) and propofol (Hana Pharm., Seoul, Korea), while those in group B received midazolam and pethidine (Myungmun Pharm., Seoul, Korea). Patients in both groups received 2 or 3 mg of midazolam depending on their weight. Patients weighing ≥ 70 kg received 3 mg, while those weighing <70 kg received 2 mg. Pain assessments were performed at 5-min intervals during colonoscopy. The Visual Analog Scale (VAS) score (range, 0-10) was used to assess pain levels.

In group A, propofol 20 mg was administered as rescue therapy if the VAS score was ≥ 4. For scores of ≥ 7, pethidine 25-50 mg was also available as rescue therapy, with a maximum additional pethidine dose limited to 75 mg. In group B, patients experiencing pain were administered 25 mg of pethidine for VAS scores ≥ 4. In patients with a VAS score ≥ 7, pethidine 25-50 mg could be used as rescue therapy, with a maximum allowable additional dose limited to ≤ 75 mg.

2. Quality control of colonoscopy

The endoscopy team comprised experienced physicians, each having at least two years of experience and having performed over 500 procedures. All team members were certified as qualified endoscopists by the Korean Society of Gastrointestinal Endoscopy (https://gie.or.kr/eng/). Vital signs, including blood pressure, were monitored at 5-min intervals, with continuous pulse oximetry. Patients received a continuous oxygen supply of 2 L/min through a nasal cannula throughout the procedure and during the subsequent recovery phase. Pain assessments were conducted every 5 min during colonoscopy. In the post-endoscopy recovery area, patient readiness for discharge was assessed every 5 min using a Modified Aldrete score, with a score of 10 points satisfying readiness for discharge. The patient satisfaction survey was administered to patients meeting the discharge criteria in the recovery room.[14]

3. Physician survey

We examined the degree of procedural difficulty, drug dosages administered during the procedure, successful cecal intubation, time taken to reach the cecum, total procedural time, patient movement and coughing during the procedure, bowel preparation scale score using the Boston bowel preparation scale,[15] changes in oxygen saturation, highest and lowest blood pressure measurements, and maximum and minimum heart rates. Additionally, we also documented any procedure-related adverse events, whether manual compression was required during endoscope insertion, and whether postural changes were needed.

4. Patient survey

The VAS score was used to evaluate the maximum and average pain reported by patients during colonoscopy. Additionally, we measured discomfort experienced in the recovery phase after colonoscopy, the likelihood to request the same sedation regimen in future colonoscopies (%), the percentage of patients willing to recommend the same medications to others (%), and their comfort level at discharge compared with their initial arrival at the hospital (%).

5. Safety profiles

Hypoxia was defined as a drop in oxygen saturation below 90% for more than 10 s. Hypotension was defined as systolic blood pressure <90 mmHg. Tachycardia was defined as a heart rate exceeding 120 bpm, whereas bradycardia was defined as a heart rate below 50 bpm.

6. Randomization and blindness

The enrolled patients were randomly assigned to either the midazolam plus propofol group (group A) or the midazolam plus pethidine group (group B) at a 1:1 ratio. Randomization was conducted with a block size of four, and the allocation details were securely sealed. The Randomization was generated using a web service (www.randomizer). An investigator (YL) confirmed the randomization outcomes. This study was conducted in a single-blind manner with the patients being blinded to the treatment they received, while the physicians were not blinded.

7. Sample size calculation and statistical analysis

The sample size was calculated assuming there would be no difference in blood pressure reduction between the two groups. According to previous reports, blood pressure

reduction was observed in 37.5% of patients in the midazolam plus propofol group and in 30.3% of patients in the midazolam plus pethidine group.[11] If there is a true difference in favor of the standard treatment of 7.2% (37.5% vs. 30.3%), then 56 patients are required to be 70% confident that the upper limit of a one-sided 90% confidence interval will exclude a difference in favor of the standard group of more than 30%. We used the following web service (https://www.sealedenvelope.com/power/binary-noninferior/) for sample size calculation. Differences in continuous variables between groups A and B were assessed using independent t-tests. Discrete variables were presented as counts and percentages, and their differences were analyzed using a χ^2 test or Fisher's exact test, as appropriate, for between-group comparisons. Statistical significance was set at p=0.05. Data were subjected to statistical analyses using SPSS version 25.0 (IBM Corp, Armonk, NY, USA).

RESULTS

A total of 61 patients provided informed consent to participate in the study. Among them, 5 patients were excluded due to not meeting the inclusion criteria (chronic renal disease [n=1], body weight>90 kg [n=1], Age<20 [n=2], Age>75 [n=1]). Thus, randomization was performed on the remaining 56 patients who met the inclusion criteria. This led to 28 patients in group A and 28 patients in group B. However, 5 patients from group A withdrew their consent during the course of the study. Consequently, the study was carried out with a final sample of 23 patients in group A and 28 patients in group B (Fig. 1). There were no significant differences between the two groups in terms of age, sex, body weight, body mass index, ASA score, history of abdominal operations, presence of diabetes, hypertension, or Boston Bowel Preparation Scale scores (Table 1). In group A, the mean dose of propofol was 35.2±18.3 mg. In group B, the mean dose of pethidine was 28.1±10.6 mg. Additionally, in group A, one patient was administered rescue therapy with 25 mg of pethidine. The doses of midazolam were 2.3±0.5 mg and 2.4±0.5 mg in groups A and B, respectively (p=0.37).

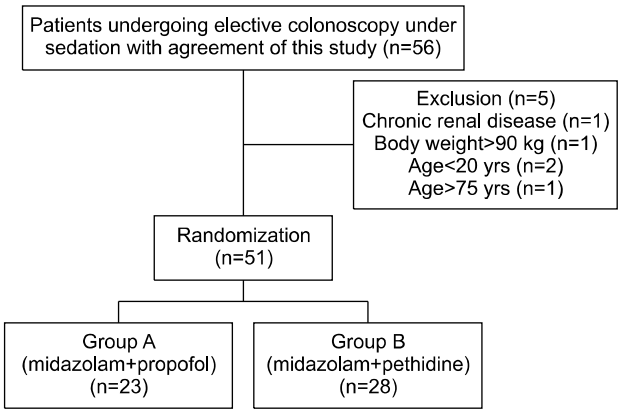

FIG. 1. Flow chart and study protocol.

None of the patients experienced hypoxia. Hypotension was observed in two patients (8.7%) in group A, while it was not observed in group B (p=0.20). Tachycardia occurred in 17.4% and 7.1% of patients in groups A and B, respectively (p=0.39). Cecal intubation was successfully achieved in all patients, with similar cecal intubation times of 9.1±11.9 min in group A and 9.1±6.5 min in group B (p=0.99). There were no significant differences in the total procedure time or degree of patient movement. However, the frequency of positional changes (1.0±0.7 vs. 1.5±0.7, p=0.02) and the use of manual compression (52.2% vs. 82.1%, p=0.02) were significantly lower in group A compared to group B. No significant differences were observed in procedural difficulty, colonic polyp detection, and time to discharge (Table 2).

Patient survey results revealed no statistically significant differences in the mean or maximum pain during the endoscopy procedure, mean pain felt in the recovery room, preference for using the same drugs for the next endoscopy, willingness to recommend the same sedative medication to others, or comfort level upon discharge (Table 3).

TABLE 1. Comparison of baseline characteristics between groups A (propofol plus midazolam) and B (midazolam plus pethidine)

	Group A (n=23)	Group B (n=28)	p-value
Age (years)	59.2±10.9	63.2±5.9	0.11
Female	9 (39.1)	18 (64.3)	0.07
Body weight (kg)	60.6±10.1	60.5±12.0	0.98
BMI (kg/m^2)	22.4±2.6	23.7±3.3	0.14
ASA score	1.2±0.4	1.4±0.6	0.07
Abdominal operation history	6 (26.1)	7 (25.0)	0.93
Diabetes	2 (8.6)	5 (17.9)	0.34
Hypertension	4 (17.4)	9 (32.1)	0.23
Boston bowel preparation scale	8.5±1.1	8.3±1.0	0.35
Rescue therapy	1 (4.3)	2 (7.1)	0.70
Midazolam (mg)	2.3±0.5	2.4±0.5	0.37
Propofol (mg)	35.2±18.3	0	<0.01
Pethidine (mg)	1.6±6.3	28.1±10.6	<0.01

Data was expressed as mean±SD or n (%). ASA: American Society of Anesthesiologists, BMI: body mass index, SD: standard deviation.

TABLE 2. Safety and efficacy of the propofol plus midazolam (group A) and midazolam plus pethidine (group B) regimes

	Group A (n=23)	Group B (n=28)	p-value
Hypoxia	0	0	-
Hypotension	2 (8.7)	0	0.20
Tachycardia	4 (17.4)	2 (7.1)	0.39
Bradycardia	0	0	-
Cecal intubation	23 (100)	28 (100)	-
Cecal intubation time (min)	9.1±11.9	9.1±6.5	0.99
Total procedure time (min)	20.1±12.4	19.7±8.5	0.89
Movement of the patients (VAS)	1.3±1.3	1.3±1.3	0.98
Position change	19 (82.6)	26 (92.9)	0.39
Position change frequency	1.0±0.7	1.5±0.7	0.02
Manual compression	12 (52.2)	23 (82.1)	0.02
Difficulty of procedure (VAS)	2.2±2.3	3.3±2.0	0.08
Colon polyp detection	9 (39.1)	15 (53.6)	0.30
Detected polyp count	1.0±1.5	1.9±2.2	0.18
Time to satisfy discharge criteria (min)	24.9±9.7	28.1±14.6	0.37

Data was expressed as mean±SD or n (%). SD: standard deviation, VAS: visual analog scale.

TABLE 3. Patient satisfaction with the sedative endoscopy in group A (propofol plus midazolam) and group B (midazolam plus pethidine)

	Group A (n=23)	Group B (n=28)	p-value
Pain during endoscopy (VAS)			
Mean pain	1.6±1.2	1.7±1.3	0.77
Maximum pain	3.1±2.2	3.4±2.1	0.66
Average pain experienced in the recovery room (VAS)	0.5±1.3	0.6±1.1	0.67
Willingness to use the same drugs for the next endoscopy (%)	97.0±10.6	95.0±10.4	0.51
Willingness to recommend the current sedation method to others (%)	97.4±10.5	95.0±10.0	0.41
Comfort level at discharge (%)	95.7±10.8	90.7±17.6	0.23

Data was expressed as mean±SD or n (%). SD: standard deviation, VAS: visual analog scale.

DISCUSSION

Colonoscopy is pivotal for the early detection of colorectal cancer, reducing the incidence of colorectal cancer, and ultimately lowering mortality rates.[3,4] Nevertheless, patient preparation for colonoscopy, involving a low-residue diet and the consumption of approximately 1-4 L of bowel preparation solution,[16,17] alongside the discomfort experience during the procedure, often present significant barriers to patient compliance. Managing patient discomfort during a colonoscopy is a key challenge, as it directly impacts the willingness of individuals to undergo this procedure. Sedative endoscopy aims to reduce procedure-related discomfort and alleviate pain, ultimately lowering the barriers to colonoscopy.[18]

To date, various combinations of medications are used for sedative colonoscopy, but there is no clear consensus on which combination best balances patient safety, comfort, and procedural ease for physicians. Padmanabhan et al.[19] compared propofol alone to a combination of midazolam and analgesics in colonoscopy, and found that patients receiving propofol had higher satisfaction levels and fewer memories of being awake during the procedure. Schroeder et al.[12] reported greater overall patient satisfaction with propofol alone compared to a combination of midazolam and fentanyl. Patients in the midazolam plus fentanyl group reported greater pain and procedural difficulty, and the time spent in the colonoscopy suite was slightly shorter in the propofol group. There were no significant differences in cecal intubation rate, recovery time, or adverse events.[12] A meta-analysis of 19 studies involving 2,512 patients comparing propofol to traditional sedation agents for colonoscopy found that propofol resulted in faster recovery and discharge, shorter sedation and ambulation times, and improved patient satisfaction without increasing complication rates.[20] In a study comparing propofol alone with propofol combined with midazolam, the synergistic effects of midazolam and propofol reduced the propofol dosage required and improved patient recovery.[21] According to Wang's[22] study, cardiopulmonary complications did not significantly differ between the group that used a combination of propofol and midazolam and the group that used propofol alone. However, the combination therapy did contribute to reducing the propofol dosage.

Similar to our study, another study comparing midazolam plus pethidine with midazolam plus propofol reported shorter recovery times in the midazolam plus propofol group.[11] Our study showed that the discharge times

were 24.9±9.7 min for group A and 28.1±14.6 min for group B, with the latter group having a longer recovery time, although this difference was not statistically significant (p=0.37). We also observed no significant differences in safety issues, such as hypoxia, hypotension, and tachycardia, between the two groups. Additionally, the cecal intubation times were similar. However, group A required fewer position changes for colonoscope insertion and less manual compression than group B; while there was a numeric difference indicating that the procedure may have been slightly more challenging in group B, this difference was not statistically significant.

Difficulties in colonoscope insertion can arise, often due to factors like high or very low body mass index, history of abdominal surgery, or female sex.[23] These difficulties can lead to pain and reduced patient satisfaction, requiring additional measures such as external manual compression or changing the patient's position to facilitate insertion.[24] The group using midazolam and pethidine encountered more difficulties during colonoscopy and required more frequent manual compression and changes in patient posture. The need for additional personnel to perform external compression or assist with postural changes during colonoscopy is a potential drawback. However, despite this potential drawback, considering that the average pain and patient satisfaction were similar in both groups, the results showed that both midazolam plus pethidine and midazolam plus propofol are safe and effective sedation options for colonoscopy, depending on the clinical context.

Our study had several limitations. Although we conducted a randomized controlled trial, the sample size in each group was relatively small, limiting the subgroup analyses. Additionally, being a single-center study and the inability to blind physicians in a single-arm study are limitations. Nevertheless, this study contributes valuable insights into the comparative effects of midazolam plus propofol and midazolam plus pethidine sedation for colonoscopy, highlighting good safety profiles for both methods.

In conclusion, both sedation methods demonstrated comparable safety profiles and yielded satisfactory outcomes. Notably, the combination of midazolam plus propofol proved more effective by reducing the need for patient repositioning and manual compression during colonoscopy.

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CONFLICT OF INTEREST STATEMENT

None declared.

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