ORIGINAL ARTICLE

Propofol alone versus midazolam plus propofol for sedation in outpatient endoscopic procedures: A randomized controlled trial

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Background: Propofol and midazolam are the most commonly used sedatives in endoscopic procedures. The purpose of this study was to compare these two sedation regimens prescribed during outpatient endoscopy and colonoscopy procedures. **Materials and Methods**: In this randomized clinical trial, 242 low-risk anesthesia patients (American society of anesthesiologist [ASA] I–II) referred to the endoscopy and colonoscopy ward of Al-Zahra Hospital, Isfahan, from January to June 2025, were studied. Patients were divided into two groups: sedation with propofol (P) and midazolam + propofol (M + P). After the collection of data, they were analyzed through SPSS version 18 software. **Results:** In the procedures, the P group had lower systolic blood pressure (BP) readings ($P = 0.003$) and a lower respiratory rate (RR) ($P < 0.001$) compared to the control group. Heart rates were not different. Pain visual analogue scale scores were lower in the P group ($P = 0.012$), but endoscopist satisfaction scores and patient satisfaction scores were not different between groups. Recovery was lowered in the P group ($P < 0.001$). Even though the requirement for the booster dose was more variable – occurring more often in the P group with endoscopy ($P = 0.040$) and in the M + P group with colonoscopy ($P < 0.001$) – the average booster dose was equal ($P = 0.126$). A correlation was found between body mass index and the booster dose of propofol in the P group. **Conclusion:** Propofol supplementation with midazolam enhanced some of the physiological parameters, like RR and systolic BP stability. However, it was at the expense of prolonged recovery and increased pain experience. Propofol alone ensured quicker recovery and greater analgesia but needed increased monitoring as a result of larger physiological excursions.

Key words: Colonoscopy, endoscopy, midazolam, patient satisfaction, propofol

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INTRODUCTION

Colonoscopy and endoscopy offer significant diagnostic and therapeutic benefits, but they can be uncomfortable and stressful for many patients.[1] Anxiety often arises from a lack of information or fear of pain,[2,3] leading to avoidance and reduced satisfaction.[4,5]

Intravenous benzodiazepines are standard agents for sedation in endoscopy,[6-8] administered alone or with opioids.[9] Midazolam is preferred for its rapid onset, short duration, and amnesic effect.[10,11]

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Propofol, an ultra-short-acting hypnotic with sedative and amnesic effects but no analgesia, can lower cardiac output, systemic vascular resistance, and arterial pressure.[12] It may also cause respiratory depression and negative inotropy, reversible with dose adjustment. Propofol is used alone or with other agents; higher doses alone increase risks of hypotension, respiratory depression, and bradycardia. Combining with benzodiazepines can mitigate these effects and enhance amnesia.[13]

Although combination therapy is thought to prolong recovery, trials do not consistently confirm this. One

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study reported longer recovery with propofol alone than with combination therapy.[14] A meta-analysis of 1162 patients comparing propofol to benzodiazepine/opioid regimens found similar complication rates overall, though colonoscopy patients given propofol had fewer risks.[15]

Because prior studies show conflicting results between propofol monotherapy and combinations, this study aims to compare these regimens to identify the approach with fewer side effects and greater satisfaction for both patients and endoscopists.

MATERIALS AND METHODS

Study design and participants

This is a prospective, randomized, clinical trial comparing sedation with midazolam + propofol (M + P) and propofol (P) alone. The study was conducted at the Endoscopy and Colonoscopy Center of Al-Zahra Hospital, Isfahan, from January 2025 to June 2025.

This study was conducted on 242 patients. Consecutive eligible patients presenting to the Endoscopy and Colonoscopy Center during the study period were enrolled until the required sample size was achieved.

Inclusion criteria were adult patients (≥18 years), ASA I–II, undergoing elective outpatient endoscopy or colonoscopy. The exclusion criteria were known sensitivity or allergy to the study drugs, age <18 years, pregnancy or breastfeeding, risk of difficult intubation, history of obstructive sleep apnea syndrome, ASA physical status greater than III, use of sedatives and antidepressants, and history of complications in previous sedation, inadequate patient preparation during colonoscopy, presence of residual food in the stomach for endoscopy, severe hemodynamic changes, drug intolerance, and patients who need emergency intervention.

Sample size calculation

The required sample size was estimated using G*Power software (version 3.1.9.7) was developed by the Institute of Experimental Psychology, Heinrich Heine University Düsseldorf, Düsseldorf, Germany, based on a two-tailed independent samples *t*-test. Assuming a moderate effect size (Cohen's d = 0.5), a significance level of $\alpha = 0.05$, and a statistical power of 80% ($1-\beta = 0.80$), the minimum required sample size was calculated to be 102 participants per group. To account for potential dropouts and missing data, we increased the sample size to 121 participants per group. A 15% dropout rate was assumed, consistent with prior clinical trial methodology.[16]

This adjustment ensures adequate power for detecting clinically relevant differences between groups.

Blinding and allocation concealment

Blinding and allocation concealment randomization were performed using Random Allocation Software. Block randomization with a fixed block size of four was used to ensure an equal allocation into two groups (1:1 ratio).

To ensure allocation concealment, group assignments were placed in sequentially numbered, opaque, sealed envelopes prepared by an independent researcher not involved in patient recruitment or outcome assessment. These envelopes were opened by the anesthesiologist immediately before sedation. The endoscopist, data collectors, and statisticians remained blinded to group allocation throughout the study. Patients were also blinded to the study due to the similar form of the drugs.

Sedation protocols

An anesthesiologist performed all sedation protocols. In the P group, 40–60 mg of propofol (1.5 mg/kg) was administered intravenously. In the M + P group, 2.5 mg of midazolam was administered to all patients, along with 0.25–0.5 mg/kg of propofol. In both groups, 10 mg of propofol was administered repeatedly to maintain a moderate level of sedation as needed by the clinical judgment of the anesthesiologist. After ensuring that the patient was adequately sedated, endoscopy and colonoscopy were initiated. These were recorded by a research assistant who was blinded to the group assignment of each patient.

Monitoring and data collection

All procedures were performed by one gastroenterologist. The procedure was performed using a Fujifilm 590 device.

Variables include age, gender, weight, height, body mass index (BMI), comorbidities, ASA physical status, mean time to reach Aldrete score 10 after anesthesia, scope time, mean procedure time, mean patient satisfaction score, mean endoscopist satisfaction score, complications, mean recovery time, heart rate (HR) per minute, respiratory rate (RR) per minute, blood pressure (BP) (systolic), oxygen saturation (SpO_2) percentage, and dose of booster sedative doses. Cases were recorded every 5 min from the start of anesthesia induction until discharge.

The Aldrete score is a tool used to assess the recovery of patients after anesthesia. The Aldrete Score includes five main criteria: Motor activity, respiration, circulation, level of consciousness, and skin color. Each criterion is scored from 0 to 2, and the total score ranges from 0 to 10. A higher score indicates better recovery for the patient.

The definition of variables is summarized in Table 1.

Table 1: Definition of variables

Variables	Definition	Type
Recovery time (min)	Time from completion of procedure until Aldrete score=10	Continuous
Scope time (min)	calculated from the time the scope is inserted until it is removed	Continuous
Time to discharge (min)	Time from sedative injection to discharge from the recovery unit	Continuous
Propofol dose (mg)	Total amount of propofol administered	Continuous
Complications	Any adverse event, including nausea, vomiting, aspiration, abdominal pain, bradycardia, hypotension	Binary
Booster dose requirement	Administration of additional propofol doses to maintain sedation	Binary
Patient satisfaction	VAS score from 0 (not satisfied) to 10 (completely satisfied)	Continuous
Endoscopist satisfaction	VAS score from 0 (not satisfied) to 10 (completely satisfied)	Continuous
Pain score (VAS)	VAS 0=no pain, 10=worst pain	Continuous
Vital signs	Heart rate, respiratory rate, systolic blood pressure, SpO_2 measured every 5 min	Continuous

VAS=Visual Analog Scale

Visual analog scale (VAS) is a 10 cm ruler with the word "no pain" written on the left end and the word "worst pain" written on the right end. The person marks the line according to the amount of pain they have experienced. Endoscopist and patient satisfaction will be determined based on the same VAS, with 10 being considered complete satisfaction and 0 being regarded as complete dissatisfaction.

The Ramsay score has been used to assess the level of consciousness while receiving sedatives. Scoring is done from 1 to 6. According to the anesthesiologist, the Ramsay score was maintained between 3 and 4 during the procedures.

Ethical considerations

The study protocol was approved by the Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1403.465) and the Iranian Registry of Clinical Trials (IRCT20250217064758N1). The study was conducted in accordance with the Declaration of Helsinki, and all patients provided written informed consent.

Statistical analysis

Data were analyzed using SPSS 18 (SPSS Inc., Chicago, IL, USA). Normality of continuous variables was assessed using the Shapiro–Wilk test and Q–Q plots. For normally distributed variables, parametric tests (independent *t*-test and Pearson correlation) were used; for skewed data, nonparametric tests (Mann–Whitney *U*-test and Spearman correlation) were applied. Continuous variables are expressed as mean ± standard deviation and categorical variables as counts (%). Repeated measures data, such as vital signs (BP, HR, RR, and SpO_2), were analyzed using repeated measures ANOVA with the Greenhouse–Geisser correction when sphericity was violated. Linear mixed-effects models (LMMs) were additionally used when adjustment for covariates such as BMI and procedure type was required, or when data were unbalanced across time points. Thus, repeated measure ANOVA was applied for balanced data with complete measurements, and LMMs were employed to account for within-subject variability and covariate effects. Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for binary outcomes (e.g., complications, booster dose). Logistic regression models used the M + P group as the reference category. Adjustments for BMI and procedure type were applied in all models. Repeated measures analyses were reported with Holm–Bonferroni corrections. For significant group × time interactions, pairwise comparisons at each time point were performed with Holm-Bonferroni adjustment.

The primary outcome was the recovery time until the Aldrete score reached 10. Secondary outcomes included hemodynamic parameters, need for booster dose, pain (VAS), satisfaction, and adverse events. To control for multiple comparisons, Holm–Bonferroni or Benjamini–Hochberg False discovery rate (FDR) corrections were applied as appropriate. Results are presented as mean differences or ORs with 95% CIs. Statistical significance was set at $P < 0.05$ (two-sided).

Descriptive statistics such as mean and standard error and percentage were used to describe data. Then, the data were analyzed by analytical statistics (*t*-test, Chi-square, and Pearson correlation). The significance level (*P* value) was set at 0.05.

RESULTS

In this study, 245 people were evaluated for inclusion in the study, of whom three did not consent to receive medication other than midazolam and were excluded from the study. The patient flow chart is shown in Figure 1.

A total of 242 patients were randomized equally into two groups (121 in propofol [P] and 121 in midazolam + propofol [M + P]). Baseline demographic characteristics were generally balanced, except for the distribution of procedure type (endoscopy vs. colonoscopy), which differed significantly between groups ($P = 0.034$). Therefore, all subsequent analyses were adjusted for both BMI and procedure type.

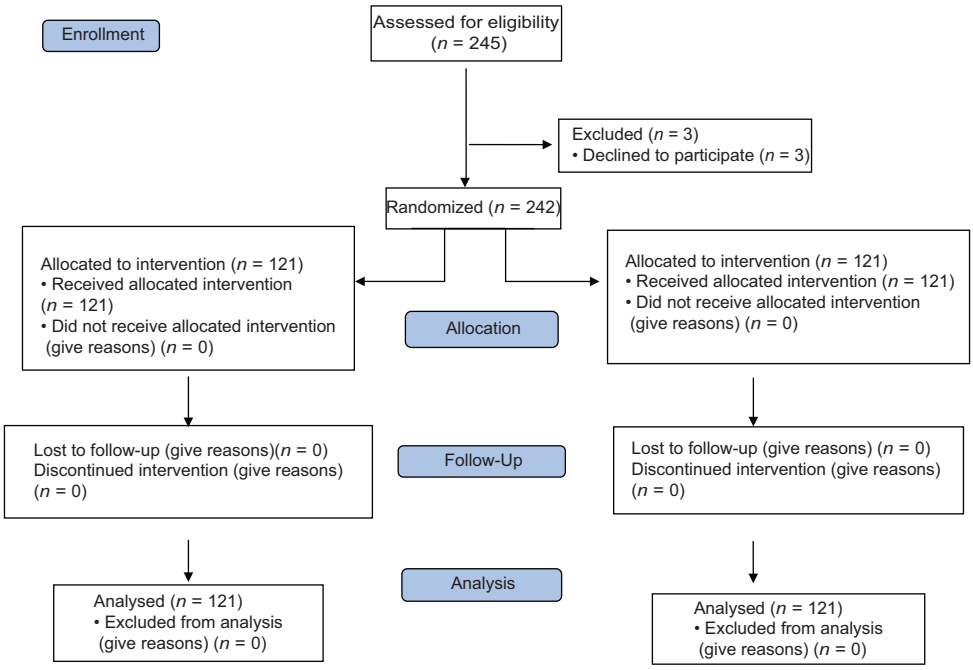

Figure 1: Consolidated standards of reporting trials (CONSORT) participant flow diagram

Table 2: Demographic characteristics

Variables	Propofol (*n*=121)	Propofol + midazolam (*n*=121)	*P*
Age (years)⁺	50.08±16.89	51.54±15.11	0.481
Gender (male), *n* (%)	52 (43)	40 (33.1)	0.073
BMI (kg/m²)⁺	26.34±5.59	27.60±5.47	0.078
ASA grade (1), *n* (%)	60 (49.6)	52 (43)	0.183
Medical history (yes), *n* (%)	61 (50.4)	69 (57)	0.219
Procedure (endoscopy), *n* (%)	59 (48.8)	44 (36.4)	0.034

⁺Mean±SD. SD=Standard deviation; BMI=Body mass index; ASA=American Society of Anesthesiologists

As shown in Table 2, the randomization procedure successfully produced groups that were well-balanced at baseline for most demographic and clinical characteristics, including age, gender, BMI, ASA physical status, and medical history. However, a chance imbalance was observed in the distribution of procedure type (P = 0.034), with a higher proportion of endoscopic procedures in the P group. To account for this imbalance and for the clinical relevance of BMI in drug response, all subsequent analyses of primary and secondary outcomes were adjusted for both procedure type and BMI using appropriate statistical models. This adjustment ensures that these baseline differences do not confound the estimated effects of the sedation regimen.

In comparing vital signs in the two groups [Figure 2], repeated measures ANOVA showed a significant group × time interaction for systolic BP (P < 0.003). *Post hoc* pairwise comparisons adjusted with the Holm–Bonferroni correction revealed that systolic BP during the procedure was significantly lower in the propofol group. At the same time, no difference was observed at baseline or at the end of the procedure.

For RR, repeated measures ANOVA also showed a significant group × time effect (P < 0.001). Holm–Bonferroni-adjusted comparisons indicated that RR was lower in the propofol group during the procedure but not at baseline or after the procedure.

SpO_2 demonstrated significant differences between groups across all time points (P < 0.001 by repeated measures ANOVA). Holm–Bonferroni *post hoc* testing confirmed consistently lower SpO_2 values in the propofol group.

No significant differences were found in HR between the groups at any time point (P > 0.05 by repeated measures ANOVA).

No significant difference was observed in patient and endoscopist satisfaction between the two groups based on the VAS (P = 0.297 and 0.688, respectively). Still, the patient's pain assessment based on the same scale shows that it was significantly lower in the P group than in the other group (P = 0.012). There was no difference in complications, such as aspiration, nausea, vomiting, and abdominal pain, between the two groups (P = 0.500).

Table 3 compares several times based on the type of procedure. The only significant difference between the two groups in terms of endoscopic timings was the recovery time, which was shorter in the P group. There was a substantial difference between the two groups at all stages during colonoscopy, with the P group taking less time. The

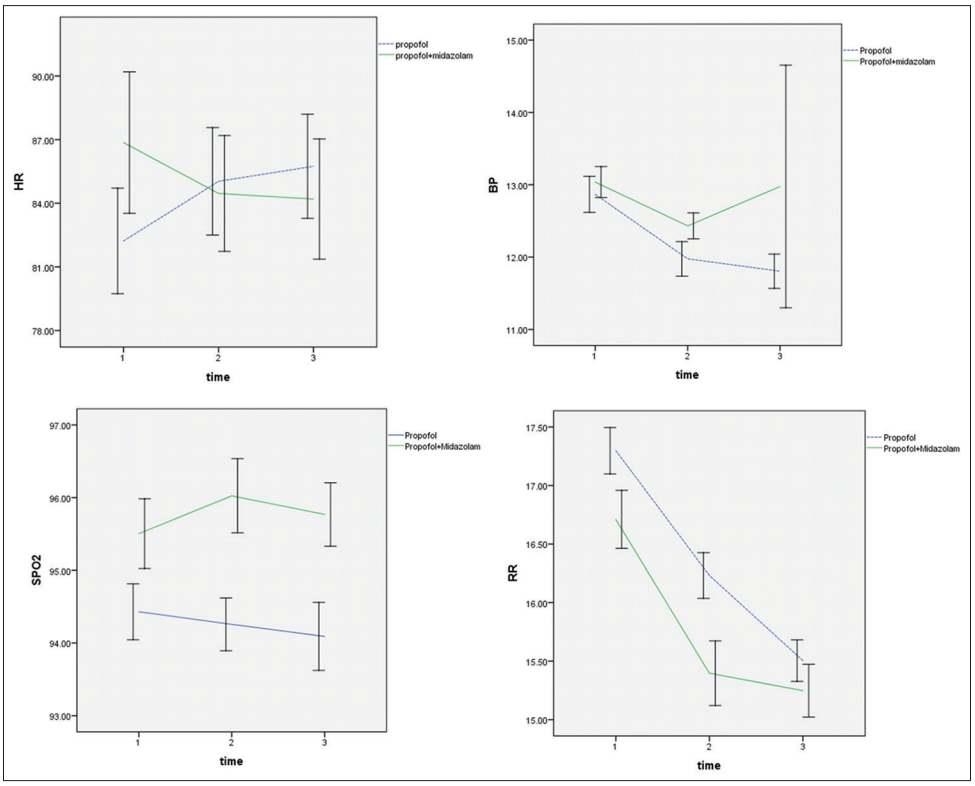

Figure 2: Systolic blood pressure in mm Hg, respiratory rate, oxygen saturation percentage,heart rate at different stages of colonoscopy and endoscopy. 1: Baseline (before the start of procedure); 2: During the procedure; 3: At the end of procedure. Error bar: 95% confidence interval

Table 3: Analysis based on type of procedure

Variables	Endoscopy			Colonoscopy		
	Propofol (*n*=59)	Propofol + midazolam (*n*=44)	*P*	Propofol (*n*=62)	Propofol + midazolam (*n*=77)	*P*
Time of scope+	7.00±3.27	7.64±2.68	0.295	11.97±2.45	13.62±5.11	0.014
Time to discharge+	7.80±3.34	8.95±3.09	0.076	12.58±2.58	14.71±5.04	0.006
Time of recovery+	1.63±0.90	3.34±2.60	<0.001	1.29±0.63	2.45±1.04	<0.001
Aldrete time+	1.63±0.90	3.02±1.33	<0.001	1.29±0.63	2.45±1.04	<0.001
Booster dose of propofol (mg)+	37.6±29.4	50.0±36.6	0.069	17.4±20.4	22.5±17.4	0.126
Giving booster dose of propofol (yes/no), *n* (%)	58 (98.3)	38 (86.4)	0.040*	33 (53.2)	63 (81.8)	<0.001

+Mean±SD, **P*=*P*-value. SD=Standard deviation

Alderte score was similarly lower in the P group in both endoscopy and colonoscopy.

Regarding whether to receive an additional dose, in endoscopy, more patients in the P group require a booster dose, while in colonoscopy, more booster doses are needed for the M + P group. However, the booster dose of propofol in the two groups did not differ in terms of the average dose in the two procedures.

A significant positive correlation was observed between BMI and the required booster dose of propofol in both endoscopy ($r = 0.801$, $P < 0.001$) and colonoscopy ($r = 0.379$, $P = 0.002$) when propofol alone was used. In contrast, no significant correlation was found in the midazolam–propofol combination group for either procedure.

Table 4 provides a concise summary of the primary and secondary outcomes comparing P with M + P, highlighting differences in recovery time, time to discharge, propofol dose, complications, and booster dose requirement. A comparison of the two subgroups in the primary outcome is also provided at the end of the table.

DISCUSSION

This investigation assessed the impact of the combination of midazolam + propofol (M + P) versus propofol (P) alone on several aspects of the procedure. The results indicated that the decrease in systolic BP was less in the M + P group during the procedure. Furthermore, although RR varied between groups during and before the procedure, this variation was not significant after the procedure, demonstrating a lesser

Table 4: Adjusted linear regression analysis of outcomes

Category/outcome	Group P (*n*=121), mean±SD	Group M + P (*n*=121), mean±SD	Adjusted effect estimate (95% CI)	*P*
Primary outcome				
Recovery time (min)⁺	1.63±0.90	3.34±2.60	−1.71 min (−2.30 to −1.12)	<0.001
Secondary outcomes – continuous				
Time to discharge (min)⁺	8.45±3.10	10.68±4.12	−2.23 min (−3.40 to −1.06)	<0.001
Propofol dose (mg)⁺	52.1±11.6	46.3±10.8	+5.98 mg (5.36 to 6.59)	<0.001
Secondary outcomes – binary				
Complications (any), *n* (%)	6 (5.0)	7 (5.8)	OR=1.14 (0.42–3.05)	0.801
Booster dose requirement, *n* (%)	23 (19.0)	36 (29.7)	OR=0.62 (0.39–0.97)	0.037
Subgroup analyses – procedure type				
Endoscopy – recovery time (min)⁺	1.55±0.85	3.26±2.55	−1.71 min (−2.30 to −1.12)	<0.001
Colonoscopy – recovery time (min)⁺	1.71±0.92	2.87±1.80	−1.16 min (−1.50 to −0.80)	<0.001

⁺Mean±SD. SD=Standard deviation; CI=Confidence interval; OR=Odds ratio; M + P=Midazolam⁺propofol; P=Propofol

decrease in the M + P group. Measurement of HR revealed reduced rates at the beginning of the P group. Still, this difference was eliminated during and after the procedure, with a subsequent rise in HR compared to M + P. SpO_2 values were always varied between groups throughout, thus rendering the values noncomparable directly.

A study by Zhang *et al*. indicated that propofol produced a greater decrease in BP compared to midazolam, consistent with the findings of the present study, which support the use of combination therapy for hemodynamic stability.[17] Wang *et al*., in a meta-analysis, established that propofol produced less hypotension and hypoxia compared to classical drugs such as midazolam in colonoscopy, contrary to the findings of the present study.[18] In a similar vein, Kim *et al*. also had higher hypotension and tachycardia with P alone, but these were nonsignificant; reduction in SpO_2 was identical in both groups, unlike our current findings.[19]

Side effects were few in general but more marked in the P group, with bradycardia being most frequent, consistent with our results of cardiovascular instability in P alone.[20] On the contrary, Popa-Ion *et al*. reported a higher frequency of bradycardia and hypotension in the M + P group. They concluded that P alone was better in terms of parameters such as quicker recovery and higher hemodynamic stability.[21] Opposite to this, Yamamoto *et al*. had significantly fewer cardiovascular events and lower hemodynamic instability in the M + P group than in the P alone.[22]

Satisfaction ratings of both endoscopist and patient were also high in both groups in our study, as seen by Julián Gómez *et al*., who saw no significant differences in satisfaction.[20] Marginally higher satisfaction with P was seen by Akbulut *et al*., but this did not achieve statistical significance.[23] Kim *et al*. saw no significant differences in satisfaction in endoscopists, patients, or nurses between the P and M + P groups.[19]

Despite the low complication rates, which were comparable between the groups, pain scores were lower in the P group. Lower pain scores were noted by Molina-Infante *et al*. in the M + P group, albeit without a difference in complication rates, with partial agreement to our observations.[24]

Procedure time was comparable between the two groups on endoscopy, but less in the P group when colonoscopy was performed. Significantly, discharge time and attainment of an Aldrete score of 10 were lower in the P group for both procedures, based on both raw data and after adjustment for confounders. Popa-Ion *et al*. also found earlier awakening in the P group, which they thought was due to lingering effects of benzodiazepine sedatives in the M + P group.[25] Agrawal *et al*. also observed shorter recovery times in the P group even with the same procedure times, confirming our finding.[26] Molina-Infante *et al*. presented significantly earlier restoration with P but equal discharge time, again consistent with our results.[24]

Despite the observation that the mean booster dose of propofol was not significantly different between the two groups, the number of patients requiring a booster varied: Fewer in the M + P group during endoscopy, but more in the P group during colonoscopy. One of the salient aspects of the present study was the association between the booster dose of propofol and BMI. The booster dose and BMI in the P group also possessed a very strong positive association, especially for endoscopy ($r = 0.801$, $P < 0.001$). Still, for the M + P group, the latter was very poor or insignificant. This implies that midazolam supplementation decreases BMI-associated variation in propofol need – a result underemphasized in the literature and potentially informing more patient-tailored propofol dosing.

The study was limited. Only ASA I and II patients were studied, whereas other studies enrolled higher-ASA-age or higher-risk patients with similarly benign safety

profiles.[20,24] Second, benzodiazepine euphoria potentially distorted greater satisfaction scores in the M + P group and biased subjective results.

CONCLUSION

In summary, although the midazolam–propofol combination offers greater hemodynamic and respiratory stability during gastrointestinal endoscopy, it is associated with increased recovery times and higher patient-reported pain. Propofol alone yields faster recovery and better analgesic effects but necessitates closer monitoring based on its physiologic effects. Individualization of sedation protocol according to procedure type, patient BMI, and priority of recovery could potentially maximize clinical impact and patient satisfaction.

Limitations

Although these data are statistically significant, their clinical significance requires studies that determine the minimal clinically important differences at recovery times, etc., to examine the clinical significance of these findings.

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Conflicts of interest

There are no conflicts of interest.

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