

Estimation of the Median Effective Dose of Propofol for Colonoscope Insertion in Adult Patients: A Prospective Dose-Finding Study

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Abstract

Aim: To estimate the median effective dose (ED₅₀) of propofol required to achieve well-tolerated and motionless colonoscope advancement through the rectosigmoid junction in adult patients undergoing colonoscopy. **Methods:** This prospective dose-finding study was conducted from September 12, 2025 to October 15, 2025. Adults aged <65 years, ASA I–III, and BMI <30 kg/m² undergoing elective colonoscopy were included. Intravenous bolus propofol was given using a modified Dixon up-and-down method, starting at 1.5 mg/kg with 0.1 mg/kg stepwise adjustments. After induction, a 2-minute observation allowed peak effect assessment. Success (MOAA/S ≤2 without pain, movement, or verbal response) prompted a 0.1 mg/kg dose decrease for the next patient; failure prompted an increase. Crossovers were defined as changes from success to failure or vice versa. **Results:** After eight crossover points, the study concluded at the 27th patient. The estimated ED₅₀ of propofol for successful colonoscope insertion was 1.026 mg/kg (95% CI, 0.735–1.317 mg/kg). **Conclusion:** This study estimated the ED₅₀ of propofol required for well-tolerated and motionless passage of the colonoscope through the rectosigmoid junction in selected adult patients. These findings may contribute to individualized initial bolus dose titration and provide preliminary data for future confirmatory studies with larger and more diverse populations.

Keywords: Propofol; sedation; median effective dose; colonoscopy; endoscopy

1. Introduction

Colonoscopy is an essential procedure for the diagnosis and treatment of gastrointestinal diseases and has become increasingly common worldwide¹. Performing gastrointestinal procedures under sedation has evolved into a standard clinical practice². Sedation during colonoscopy has been shown to enhance procedural quality, increase success rates, and improve patient satisfaction¹. An optimal sedation regimen for colonoscopy should ensure rapid onset, maintain cardiopulmonary stability, minimize adverse effects, and allow prompt recovery for early discharge³. Although various sedative agents can be used either alone or in combination, propofol remains the preferred drug for endoscopic procedures^{4,5}. When used as a single agent, it is most often administered in intermittent bolus doses⁶. This approach has been associated with faster recovery and a lower incidence of

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hypotension⁷. The rapid onset and short recovery time of propofol confer distinct advantages over other agents⁸. Moreover, propofol has been associated with stable sedation, improved patient cooperation, and a similar or reduced incidence of complications^{9–11}. However, its narrow therapeutic window and the absence of a specific antagonist remain important limitations^{6,12,13}. At higher doses, propofol may cause cardiorespiratory depression, whereas inadequate doses can result in insufficient suppression of airway reflexes, procedural pain, failed endoscope insertion, or body movements that interrupt the procedure^{6,12,13}. The depth of sedation and the likelihood of adverse events increase in a dose-dependent manner^{6,7}.

Previous dose-finding studies have evaluated propofol requirements in different endoscopic procedures, such as upper gastrointestinal endoscopy and gastroduodenoscopy, mostly using sequential allocation approaches such as the Dixon up-and-down method^{6,14,15}. These studies have provided important data regarding propofol dose requirements for specific patient populations and endoscopic procedures^{6,14}. However, the optimal initial bolus dose of propofol required for well-tolerated and motionless passage of the colonoscope during the initial stage of the procedure, particularly at the rectosigmoid junction, has not yet been clearly defined in adult patients. In clinical practice, the initial dose is often adjusted empirically based on clinician experience or center-specific routines, which may increase the risk of patient movement and procedural discomfort when the dose is insufficient, or the risk of respiratory depression and hypotension when excessive doses are administered. This study aimed to determine the median effective dose (ED₅₀) of propofol required for well-tolerated and motionless advancement of the colonoscope to the rectosigmoid junction in patients aged 18–65 years.

2. Methodology

2.1. Study Design

This study was designed as a prospective dose-finding trial using the Up-and-Down Sequential Allocation Method. Ethical approval (Approval Number: KAEK/09.bI.03) was obtained from the Kocaeli University Clinical Research Ethics Committee on May 15, 2025, in accordance with the Declaration of Helsinki. The trial was registered at <https://www.clinicaltrials.gov> (NCT07166640) on August 25, 2025, prior to participant enrollment. The study was conducted in the Endoscopy Unit of University of Health Sciences Kocaeli City Hospital, a tertiary referral hospital in Kocaeli, Türkiye, between September 12, 2025 and October 15, 2025. Written informed consent was obtained from all participants after they were fully informed about the study protocol.

2.2. Participants

Male and female patients aged 18 to 65 years, classified as American Society of Anesthesiologists (ASA) physical status I–III and scheduled for colonoscopy, were enrolled after providing written informed consent.

Patients were excluded if they declined participation; had known allergies to propofol, soy, peanuts, or egg white; had a body weight below 40 kg or a body mass index (BMI) greater than 30 kg/m²; experienced acute or chronic pain; had chronic alcohol use; were taking antipsychotic, antidepressant, or hypnotic medications; had a diagnosis of obstructive sleep apnea or a STOP-Bang score ≥ 3 ; had a history of anorectal disease (e.g., hemorrhoids, anal fissure, or anal fistula) or malignancy; had uncontrolled hypertension (blood pressure $\geq 180/110$ mmHg); had severe hepatic or renal dysfunction; were experiencing acute respiratory tract infection or chronic respiratory disease; or had a history of colorectal surgery.

2.3. Randomization and Blinding

Due to the nature of the study, neither randomization nor blinding was performed.

2.4. Anesthetic Technique and Dose-Finding Methodology

Upon arrival in the endoscopy suite, patients underwent standard anesthetic monitoring, including pulse oximetry, electrocardiography, and non-invasive blood pressure measurement. Capnography was used in all cases. A peripheral intravenous line was established using a 20- or 22-gauge cannula, and 1000 mL of Ringer's lactate solution was administered. Preoxygenation was performed for 3 minutes with oxygen delivered at a flow rate of 5 L/min via nasal cannula, and oxygen supplementation at the same rate was maintained throughout the procedure. In accordance with routine practice, patients were positioned in the left lateral decubitus position. Following adequate preoxygenation, sedation was induced with intravenous propofol (2,6-diisopropylphenol; Propofol-PF 1%, Polifarma® Pharmaceutical Industry, Türkiye) administered over 20 seconds.

The Dixon "up-and-down" sequential design was adopted in this study to estimate the effective dose^{16,17}. This stepwise method determines the drug dose administered to each subsequent patient based on the response of the preceding one and is widely used in clinical pharmacology^{16,17}. The initial propofol dose for the first patient was set at 1.5 mg/kg, as previous endoscopic dose-finding studies using the Dixon up-and-down method had also selected this starting dose^{18,19}. This choice was further supported by our routine clinical experience. Thereafter, the propofol dose for each subsequent patient was adjusted according to the response of the previous patient, with incremental or decremental changes of 0.1 mg/kg; this step size was selected based on previous dose-finding studies using the Dixon up-and-down method in endoscopic sedation^{18,19}. Anesthetic management was performed by specialist anesthesiologists (B.G. and A.S.). After induction, a 2-minute interval was allowed to achieve maximum drug effect⁶. At the start of colonoscopy, the depth of sedation was assessed using the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale²⁰. According to this scoring system: 5 = responds readily to name spoken in normal tone; 4 = responds lethargically to name spoken in normal tone; 3 = responds only after name is called loudly; 2 = responds only after mild to moderate physical prodding or shaking; 1 = responds only after trapezius muscle squeeze²⁰.

The procedure was performed by a specialist endoscopist. The rectosigmoid junction was selected as the primary assessment point because it represents an early and clinically relevant phase of colonoscope insertion²¹, during which patient discomfort is commonly encountered, while limiting the potential confounding effects of anatomical variations, progressive loop formation, and operator-dependent factors during further advancement. Procedural success was defined as the absence of patient movement, pain, or verbalization during passage of the colonoscope through the rectosigmoid junction and a MOAA/S score ≤ 2 at the second minute after induction. If these criteria were not met (i.e., movement, pain, verbalization, or MOAA/S ≥ 3 occurred), the case was considered a failure and a rescue dose of propofol (0.25–0.5 mg/kg) was titrated and administered. For the subsequent patient, the initial propofol dose was adjusted by 0.1 mg/kg, increased after failure and decreased after success.

Colonoscopy insertion conditions were assessed only until passage through the rectosigmoid junction. After the start of the procedure, if the patient experienced pain, exhibited movement, verbalized, or had a MOAA/S score ≥ 3 at any point, an additional titrated dose of propofol (0.25–0.5 mg/kg) was administered. Throughout the procedure, the target was to maintain a MOAA/S score of ≤ 2 for all patients, and these scores were systematically assessed at 2-minute intervals. Patients' vital signs, procedure durations, and administered drug doses were recorded. At the end of the procedure, patients were awakened using verbal and tactile stimulation. Following completion of the endoscopic procedure, all patients were transferred to the post-anesthesia care unit (PACU) until they achieved a Modified Aldrete score of 10, after which they were discharged.

2.5. Primary and Secondary Outcomes

The primary outcome of the study was to determine the ED₅₀ of propofol required for advancing the colonoscope to the rectosigmoid junction.

Secondary outcomes included estimation of the ED₉₅ of propofol for the same endpoint; the additional and total propofol doses administered; the occurrence of pain during injection; and hemodynamic parameters, including heart rate (HR), mean arterial pressure (MAP), and peripheral oxygen saturation (SpO₂), recorded at four time points: before sedation (T0), during colonoscope passage through the rectosigmoid junction (T1), two minutes after insertion (T2), and at the end of the procedure (T3). Haemodynamic parameters were also continuously monitored throughout the procedure, and the incidences of hypotension, hypertension, bradycardia, and tachycardia were recorded. Hypotension was defined as any single MAP measurement showing a $\geq 20\%$ decrease from baseline, whereas hypertension was defined as any single MAP measurement showing a $\geq 20\%$ increase from baseline. Bradycardia was defined as any single HR measurement below 60 beats/min, and tachycardia was defined as any single HR measurement exceeding 100 beats/min. In addition, the incidence of hypoxemia (SpO₂ <90% lasting more than 10 seconds), the minimum SpO₂ observed during the procedure, and any procedural interruptions due to airway interventions (chin lift, jaw thrust, or mask ventilation) were assessed as secondary outcome measures.

2.6. Sample Size

In a Dixon up-and-down sequential design, the non-independence of data and the unknown underlying distribution preclude the establishment of theoretically strict rules for sample size calculation²². Therefore, sample size is determined according to the predefined stop rule²². Because at least six ineffective responses must be followed by effective ones, patient enrollment continues until this criterion is met²². Simulation studies have indicated that enrolling 20–40 patients is generally sufficient to obtain stable estimates of the target dose across most scenarios²². Consistently, previous anesthesia studies employing this method have typically included 20–40 participants¹⁷. In the present study, eight crossover points were deemed sufficient for this purpose, and enrollment was terminated once this number was reached.

2.7. Statistical Analysis

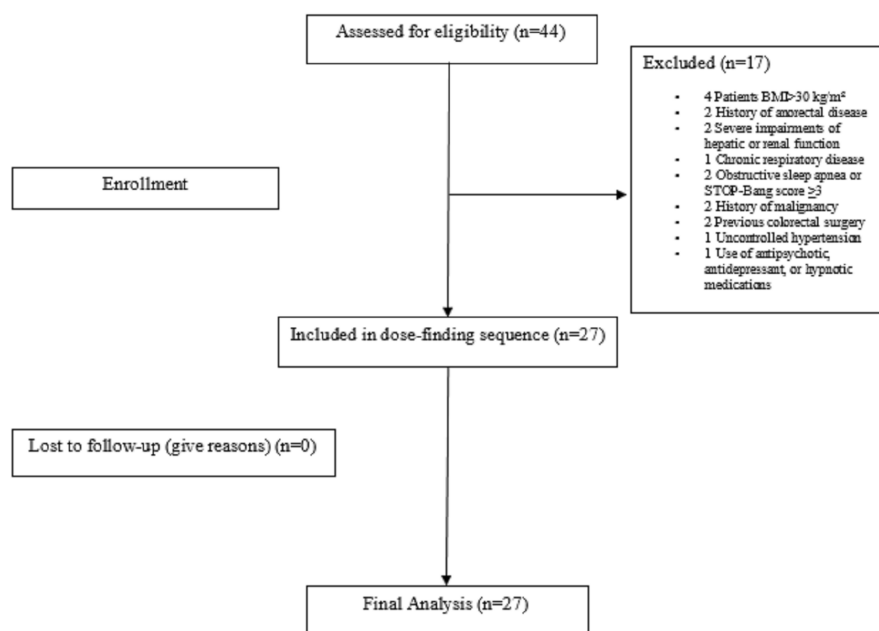
Statistical analyses were performed using IBM SPSS Statistics version 27.0. The normality of quantitative data was assessed with the Shapiro–Wilk test; variables with normal distribution were expressed as mean $\pm$ standard deviation (SD), whereas non-normally distributed continuous variables were presented as median (minimum–maximum). Categorical variables were expressed as number (n) and percentage (%). Changes in hemodynamic and respiratory variables were analyzed using the Friedman test. A p-value of <0.05 was considered statistically significant.

The ED₅₀ and ED₉₅ values were estimated using a logistic dose–response model fitted to the binary success/failure outcomes obtained from the Dixon up-and-down sequence. Propofol dose was log-transformed before model fitting, and the effective doses with their 95% confidence intervals were derived from the fitted model using the delta method. All dose–response analyses and visualizations were performed using R software.

3. Results

3.1. Participant Flow and Baseline Data

Participant enrollment began on September 12, 2025 and was completed by October 15, 2025. A total of 44 patients were screened for eligibility, of whom 17 were excluded (Figure 1). The remaining 27 patients were enrolled in the study.

**Figure 1. Flow chart**

As eight crossover events were observed during the trial, enrollment was concluded after 27 participants. No participants withdrew, and data from all enrolled patients were included in the final analysis. Although ASA III patients were eligible for inclusion, no ASA III patient was enrolled during the study period; therefore, the final analysis included only ASA I–II patients. Baseline characteristics of the study population are summarized in Table 1, and periprocedural data are presented in Table 2.

Table 1. Patient baseline characteristics

Variable	Value
Gender (Male/Female)	15 (55.6) / 12 (44.4)
Age	50 (22–60)
Height (m)	1.7 ± 0.1
Weight (kg)	80 (43–93)
BMI (kg/m ²)	25.4 ± 3.4
Smoking	9 (33.3)
Hypertension	3 (11.1)
Diabetes mellitus	1 (3.7)
Heart disease	2 (7.4)
Other diseases	0 (0)
ASA classification I/II	12 (44.4) / 15 (55.6)
Mallampati classification I/II	19 (70.4) / 8 (29.6)
Indications for Colonoscopy	
Control	22 (81.5)
Tumor	0 (0)
Diarrhea	3 (11.1)
Constipation	2 (7.4)

Data are presented as number (%), median (minimum–maximum) or mean ± standard deviation.

Table 2. Summary of perioperative variables

Variable	Value
Initial bolus dose (mg)	90.5 ± 23.4
Additional drug dose (mg)	88.2 ± 45
Total drug dose (mg)	178.6 ± 42.5
Procedure duration (min)	11.7 ± 3.4
MOAA/S at 2 min post-induction (1/2/3/4)	1 (3.7) / 20 (74.1) / 2 (7.4) / 4 (14.8)
Lowest SpO ₂ (%)	97 (91–100)
Incidence of hypotension	4 (14.8)
Incidence of hypertension	0 (0)
Incidence of bradycardia	1 (3.7)
Incidence of tachycardia	3 (11.1)
Injection pain	8 (29.6)
Airway intervention	0 (0)
Postoperative pain	3 (11.1)
Postoperative nausea	3 (11.1)
Postoperative vomiting	0 (0)

Data are presented as number (%), median (minimum–maximum) or mean ± standard deviation.

3.2. Primary Outcome

Using R software, the ED₅₀ of propofol for successful colonoscope insertion was estimated at 1.026 mg/kg (95% CI, 0.735–1.317 mg/kg). Patient responses were analyzed using the modified Dixon up-and-down method, and the corresponding dose–response curve for successful colonoscope insertion is presented in Figures 2 and 3.

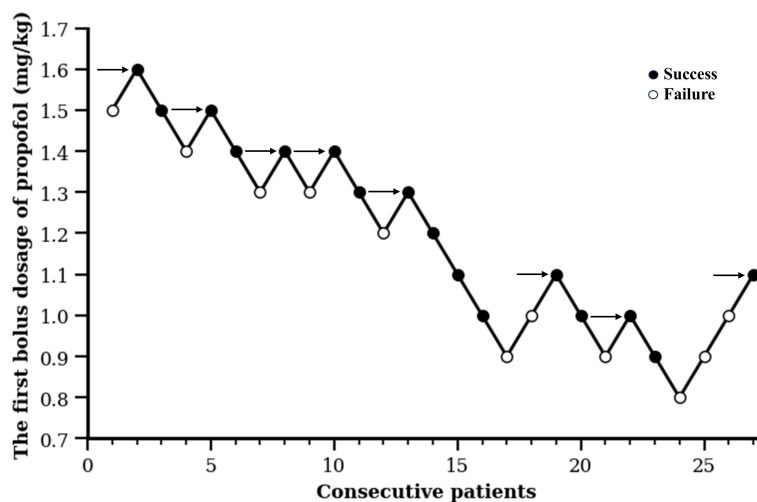


Figure 2. Responses of patients with the modified Dixon's up-and-down method.

3.3. Secondary Outcomes

Using R software, the ED₉₅ of propofol for successful colonoscope insertion was estimated at 2.538 mg/kg (95% CI, 0–5.287 mg/kg). The total propofol dose administered during colonoscopy was 178.6 ± 42.5 mg, with an additional post-induction dose of 88.2 ± 45 mg (Table 2). Hypotension occurred in 4 patients (14.8%), whereas no episodes of hypertension were observed (Table 2). Bradycardia and tachycardia occurred in 1 patient (3.7%)

and 3 patients (11.1%), respectively (Table 2). The mean procedure duration was 11.7 ± 3.4 minutes. Pain on injection following induction occurred in eight patients (29.6%). The lowest SpO₂ recorded during the procedure was 97 (91–100)%, and the incidence of airway intervention was 0 (0%). HR, SpO₂, and MAP measured at the four predefined time points showed no significant differences ($p > 0.05$) (Table 3).

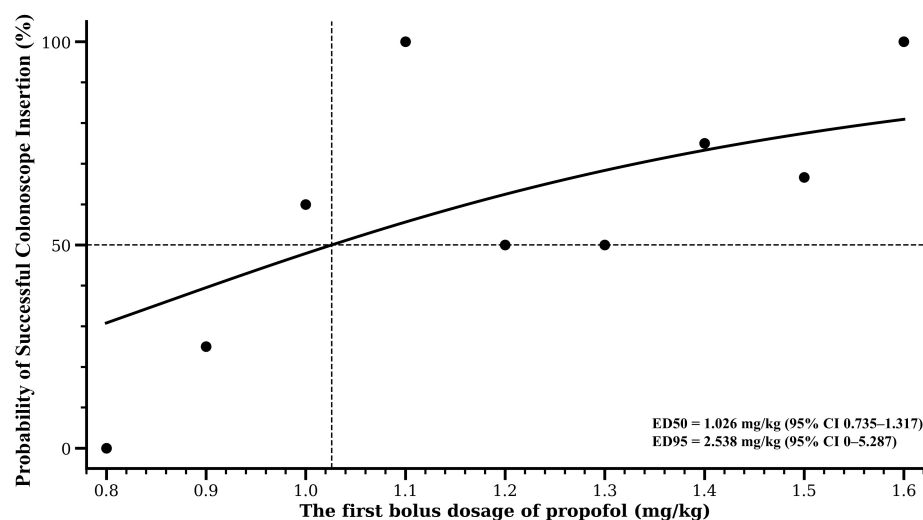


Figure 3. Dose–response curve.

Table 3. Changes in hemodynamic and oxygenation parameters during the procedure

	Before sedation	Endoscope insertion	2 min after endoscope insertion	End of procedure	p-value
HR (beats/min)	80 (62–95)	79 (68–98)	80 (61–118)	80 (59–100)	0.744
MAP (mmHg)	81 (66–110)	79 (62–97)	77 (64–107)	76 (67–99)	0.228
SpO ₂ (%)	98 (92–100)	98 (92–100)	98 (91–100)	98 (92–100)	0.266

Data are presented as median (minimum–maximum). $p < 0.05$ was considered statistically significant; Friedman Test. HR: Heart Rate (beats per minute); MAP: Mean Arterial Pressure (mmHg); SpO₂: Peripheral Oxygen Saturation (%).

4. Discussion

The aim of our study was to determine the effective dose of propofol required to facilitate well-tolerated and motionless passage of the colonoscope through the rectosigmoid junction in adult, non-obese patients undergoing colonoscopy with propofol monosedation. Using the modified Dixon up-and-down method, the ED₅₀ of propofol was calculated as 1.026 mg/kg (95% CI: 0.735–1.317 mg/kg), and the ED₉₅ was estimated as 2.538 mg/kg (95% CI: 0–5.287 mg/kg). The ED₉₅ value was reported because it may provide complementary clinical information regarding the dose likely to achieve successful procedural conditions in the majority of patients. However, this estimate should be interpreted with caution, because the Dixon up-and-down design primarily concentrates observations around the ED₅₀, and the limited sample size provides less information for estimating the upper tail of the dose–response curve. Therefore, the ED₉₅ value should not be regarded as a definitive dosing recommendation, but rather as a complementary estimate that requires confirmation in larger studies.

Propofol has long been widely used in gastrointestinal endoscopic procedures, and its efficacy has been confirmed in various studies². In the literature, the use of propofol as a single agent has been reported to provide clinical outcomes that are comparable to, or even superior to, those achieved with combination sedation protocols involving other sedative agents^{1,23,24}. The European Society of Gastrointestinal Endoscopy recommends propofol monotherapy for sedation during colonoscopy, except in specific situations such as advanced age, left ventricular dysfunction, or a history of propofol-related adverse effects²⁵. In addition, it has been noted that administering propofol as a single agent with careful titration may reduce the risks of toxicity, tolerance, and dependence⁴. However, the requirement for higher doses of propofol during colonoscopy has been associated with an increased risk of hypotension, which remains one of the most clinically relevant adverse effects of propofol sedation⁹. Moreover, bowel preparation with sodium phosphate prior to the procedure may further contribute to this hemodynamic effect²⁶. In this context, avoiding unnecessarily high doses of propofol may reduce the likelihood of developing hypotension. Our study was designed in line with this approach, aiming to achieve effective sedation during colonoscopy while preventing excessive propofol administration.

The modified Dixon up-and-down method was used to determine the effective dose of propofol. This staircase technique, in which the dose administered to each subsequent patient is increased or decreased based on the previous patient's response, is commonly employed in anesthesia research to estimate dose-response relationships^{6,27}. For this method to yield reliable estimates, at least six crossover points are required⁶. In a similar study conducted by Liu et al., the ED₅₀ value of propofol during upper gastrointestinal endoscopy in healthy adults aged 18–65 years was calculated as 1.90 mg/kg (95% CI: 1.78–2.10 mg/kg) using the modified Dixon up-and-down method⁶. In our study, the ED₅₀ value was found to be 1.026 mg/kg (95% CI: 0.735–1.317 mg/kg). This difference may be attributed to two possible factors. First, ethnic and pharmacogenetic variations may influence the pharmacodynamic response to propofol⁶. Second, in Liu's study, the targeted level of sedation may have required higher doses because suppression of the gag reflex is often necessary during upper gastrointestinal endoscopy. Nevertheless, further studies in different ethnic populations are needed to allow direct generalization of findings across diverse patient groups⁶.

Hayes et al. reported an ED₅₀ value of 6.1 mg/kg for propofol in children undergoing gastroduodenoscopy under deep sedation¹⁴. The substantially higher value reported in that study compared to our adult population can be attributed to the physiological differences inherent to pediatric patients^{14,28}.

Current literature indicates that the use of propofol as a sole sedative agent during colonoscopy is associated with faster recovery times and higher patient satisfaction²⁹. However, the fact that propofol administration is restricted to anesthesia professionals in many centers may limit its widespread use³⁰. In our study, propofol monosedation was administered by an experienced anesthesiologist. The use of propofol monotherapy during colonoscopy has been investigated from multiple clinical perspectives in the literature^{30,31}. One study reported that propofol sedation was associated with higher polyp detection rates, as well as increased cecal and terminal ileum intubation rates, suggesting that optimized sedation may improve procedural efficiency and diagnostic yield³⁰. Another study indicated that propofol-based sedation protocols may result in deeper levels of sedation compared to alternative regimens; therefore, careful titration is essential to minimize the risks of hypotension, aspiration, and other sedation-related complications³¹.

However, data on the optimal initial bolus dose required for well-tolerated and motionless passage of the colonoscope through the rectosigmoid junction remain limited. In our study, we specifically focused on identifying the effective initial bolus dose required to facilitate well-tolerated and motionless passage of the colonoscope through the rec-

tosigmoid junction. Although additional pain stimuli may occur at different points throughout the procedure due to the tortuous anatomy of the colon, the present study evaluated only the initial bolus dose, and intermittent titration doses administered during the procedure were not included within the scope of the investigation.

Moreover, optimizing the initial bolus dose of propofol has the potential not only to decrease the incidence of sedation-related adverse events, but also to reduce procedural costs by minimizing unnecessary drug consumption³¹. In this context, future research could focus on titration-based dosing strategies that encompass all stages of the colonoscopy procedure, rather than the initial bolus dose alone.

The primary adverse effects associated with propofol administration include respiratory depression, dose-dependent hypotension, and injection pain, all of which must be carefully monitored during sedation for colonoscopy². In our study, mean arterial pressure, heart rate, and peripheral oxygen saturation were evaluated at four time points, and no significant changes were observed in these parameters over time. The lowest SpO₂ value recorded during the procedure was 97%, and no patient experienced respiratory depression or required airway intervention. Injection pain occurred in approximately 30% of patients, which is consistent with previously reported rates in the literature (28–90%)^{32,33}. These findings suggest that the dose range identified in our study may be associated with effective sedation during passage of the colonoscope through the rectosigmoid junction in selected low-risk adult patients. However, given the relatively small sample size and low-risk study population, the safety findings should be interpreted with caution. Our results may contribute to clinical decision-making regarding the initial bolus dose of propofol and may serve as a basis for future larger studies in different patient populations.

This study has several limitations. First, the modified Dixon up-and-down method is primarily designed to estimate the ED₅₀ and provides less reliable estimates for higher quantiles such as the ED₉₅. Therefore, the ED₉₅ value reported in this study should be interpreted with caution and should not be regarded as a definitive dosing recommendation. Second, the relatively small sample size may have limited the precision and robustness of the dose estimates and may have reduced the ability to detect uncommon adverse events, particularly respiratory complications. Third, the study evaluated only the initial bolus dose of propofol required for well-tolerated and motionless passage of the colonoscope through the rectosigmoid junction; therefore, the findings should not be interpreted as reflecting propofol requirements throughout the entire colonoscopy procedure. Additional painful stimuli may occur at different stages of colonoscopy, and intermittent titration doses administered during the procedure were not included in the dose-finding analysis. Fourth, the study population was limited to patients aged 18–65 years with ASA physical status I–II; therefore, the findings may not be generalizable to patients with higher risk profiles or to older individuals. Sedation depth was assessed solely using the MOAA/S scale, and objective neuromonitoring tools such as bispectral index or electroencephalography were not utilized. In addition, plasma or effect-site concentrations of propofol were not measured, preventing the establishment of a direct pharmacokinetic–pharmacodynamic dose–response relationship. Finally, the study was conducted in a relatively homogeneous Turkish population; considering that pharmacodynamic and pharmacokinetic responses may vary according to ethnic and genetic factors, the generalizability of our results to populations with different ethnic backgrounds may be limited.

5. Conclusion

In this study, we determined the ED₅₀ value of propofol required for well-tolerated and motionless passage of the colonoscope through the rectosigmoid junction in adult patients aged 18–65 years using the modified Dixon up-and-down method. By focusing on the initial bolus dose administered at the start of the procedure, our study provides

preliminary data on propofol dose requirements for this specific clinical endpoint. However, given the limited sample size and the evaluation of only the initial bolus dose, our findings should not be interpreted as reflecting propofol requirements throughout the entire colonoscopy procedure. These results may contribute to the development of more rational and controlled dose titration strategies for the initial bolus dose of propofol in clinical practice. Further studies with larger sample sizes and more diverse patient populations are needed to validate these findings and assess their generalizability.

genAI: Artificial intelligence–assisted technology (ChatGPT, OpenAI) was used solely for language editing and clarity improvement during the preparation of this manuscript. The authors reviewed and critically evaluated all generated content and take full responsibility for the accuracy, integrity, and originality of the work.

Statement of Ethics: Ethical approval (Approval Number: KAEK/09.bI.03) was granted on May 15, 2025, by the Kocaeli University Clinical Research Ethics Committee in accordance with the Declaration of Helsinki. The clinical trial was registered with the identifier NCT07166640 on August 25, 2025. Written informed consent was obtained from all participants.

Data Availability: The data supporting the findings of this study are not publicly available but can be shared by the corresponding author upon reasonable request.

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Conflict of Interest: The authors declare that they have no conflict of interest.

Author Contributions: **Bedirhan Gunel:** Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Interpretation, Writing – original draft, Writing – review & editing, Project administration. **Ayse Sencan:** Investigation, Interpretation, Data curation, Writing – original draft, Writing – review & editing. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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