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Randomized Trial of Midazolam Plus Meperidine Versus Midazolam Plus Fentanyl Versus Placebo for Colonoscopic Sedation

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Abstract

Objective: A combination of midazolam and opioid is usually used to achieve conscious sedation and analgesia during colonoscopy, but many patients may tolerate the procedure well without any sedation. This randomized trial aimed to compare the efficacy and recovery time of 3 different regimens consisting of (a) midazolam plus meperidine (b) midazolam plus fentanyl and (c) placebo. The endoscopists' and patients' satisfaction was assessed by an appropriate questionnaire. **Methods**: A total 248 consecutive, unselected patients attending outpatient colonoscopy at a University Hospital were enrolled with informed consent and were randomized to receive (a) midazolam with meperidine [group A] (b) midazolam with fentanyl [group B] or (c) placebo [group C]. Data for procedure times, perceived patient's discomfort (using a relative patient questionnaire) and physician's satisfaction from the procedure were collected. Patients and all endoscopy staff directly involved with the procedure except the research nurse were blinded to the regimens used. **Results:** The mean age of the patients was 58 ± 15 years (range 19–85 years) and 130 were males. The completion rate and time to reach cecum did not differ among the three groups. The recovery time was significantly shorter in group C (placebo, 10.4 ± 2.9 min) compared to the other groups ($p < 0.000$), but it was also shorter in group B (midazolam plus fentanyl, 43.0 ± 9.3 min) compared to group A (midazolam plus pethidine, 50.1 ± 9.0 min) ($p = 0.001$). Patients of group B (midazolam plus fentanyl) experienced less pain and discomfort than patients of group A (midazolam plus meperidine) ($p = 0.02$) and patients of group A experienced less pain than patients of group C (placebo). Many more patients in group B were extremely or very satisfied by the procedure(86.7%) compared to group A (59.7%) and group C (44.5%) ($p = 0.001$). Adverse events were mild in all groups and slightly less in group B. **Conclusions:** Sedation with midazolam and fentanyl was more effective, better tolerated and led to slightly faster recovery time than sedation with midazolam and meperidine. According to our findings and the literature, the most appropriate regimen for conscious sedation during colonoscopy is the combination of midazolam and fentanyl. However, both sedation regimens were proven to be effective and safe and even a significant proportion of unsedated patients could tolerate the procedure fairly well.

Keywords: midazolam; analgesia; colonoscopy; opioid; sedation

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1. Introduction

Colonoscopy has traditionally been perceived as an uncomfortable procedure by patients. While some endoscopy units provide deep sedation using propofol under the

supervision of an anesthesiologist or a physician trained in anesthesia, this practice is not yet widely implemented in many countries [1]. More commonly, conscious sedation involving a combination of midazolam and an opioid is administered to achieve both sedation and pain relief during the procedure [2]. Guidelines from both the American Society for Gastrointestinal Endoscopy and the British Society of Gastroenterology support the concurrent use of sedatives and analgesics. In Greece, the typical practice involves administering midazolam in variable doses alongside meperidine, although fentanyl is also utilized [3]. Nevertheless, many patients still undergo colonoscopy without sedation, depending on factors such as the endoscopist's approach, patient preference, and the setting of the procedure—whether it is conducted in private practice or within a hospital-based endoscopy unit [4]. Meperidine is a synthetic opioid analgesic that is primarily metabolized in the liver. Its onset of action occurs within 10 to 15 min, with effects lasting approximately 2 h, and a plasma half-life ranging from 3 to 4 h. It is quickly converted into nor-meperidine, a metabolite that is excreted by the kidneys and has a significantly longer elimination half-life of 17 h. Notably, nor-meperidine possesses greater neurotoxic potential than meperidine itself, with an increased risk of causing hallucinations and seizures [5].

Fentanyl is another synthetic opioid, known for being 50 to 100 times more potent than morphine, and is widely used for its powerful analgesic effects. In addition to its analgesic applications, fentanyl is frequently utilized as an adjunct in anesthesia [6]. However, there is limited research directly comparing fentanyl to meperidine for sedation in adult colonoscopy patients.

Recent trends in endoscopic sedation favor reducing midazolam doses to lower the risk of severe adverse events. Although evidence supports this approach, there are ongoing concerns regarding its potential impact on patient comfort during procedures. Opioids enhance the sedative effect of midazolam through a synergistic mechanism, enabling lower doses of midazolam to be used safely while still maintaining sufficient comfort for the patient [7].

Moreover, several studies have highlighted that colonoscopy may be well tolerated without any sedation in a subset of patients, particularly when performed carefully by skilled endoscopists. Techniques such as minimizing air insufflation, using water instillation, and avoiding the formation of loops can help achieve near-painless insertion of the colonoscope [8].

This randomized clinical trial was designed to compare the efficacy and recovery profiles of three sedation strategies for colonoscopy: (a) midazolam combined with meperidine, (b) midazolam combined with fentanyl, and (c) placebo. Both patient and endoscopist satisfaction were evaluated using a structured questionnaire.

2. Results

A total of 248 patients were included in the study, of whom 130 were male, accounting for 52.4% of the cohort. The mean age was 58 $\pm$ 15 years, with ages ranging from 19 to 85 years. The American Society of Anesthesiology (ASA) physical status classification was distributed as follows: 56.4% were classified as ASA I, 35.8% as ASA II, and 6.8% as ASA III. Regarding Body Mass Index (BMI), 2.7% of patients were underweight (BMI < 18 kg/m^2), 51.3% had a normal BMI (18–25 kg/m^2), 40.3% were overweight (BMI 25–30 kg/m^2), and 6.1% were obese (BMI > 30 kg/m^2). A discrepancy in smoking status was noted, as 28.2% of patients were identified as smokers, although another value (24.5%) was also cited; the accurate figure should be clarified.

The most frequent indications for colonoscopy were scheduled polypectomy (n = 53), evaluation of abdominal pain (n = 51), investigation of anemia (n = 45), and surveillance following prior polypectomy or surgical intervention (n = 27). Less common indications

included evaluation of chronic constipation or diarrhea and screening examinations. Diagnostic procedures comprised 70% of colonoscopies, while the remaining 30% were therapeutic, including interventions such as polypectomy. Biopsies were performed in 58.6% of cases. Patients reporting abdominal pain or those with a history of irritable bowel syndrome were evenly allocated among the three study arms.

As summarized in Table 1, there were no significant differences in completion rates among the groups. Similarly, the time required to reach the cecum did not differ across groups. However, recovery time was significantly shorter in the placebo group (Group C), with an average duration of 10.4 ± 2.9 min, compared to the sedated groups ($p < 0.001$). Among the sedated patients, those in Group B (midazolam plus fentanyl) recovered more quickly (43.0 ± 9.3 min) than those in Group A (midazolam plus meperidine), who had a mean recovery time of 50.1 ± 9.0 min ($p = 0.01$).

Table 1. Demographics and patients' characteristics.

	Group A Midazolam/ Meperidine	**Group B Midazolam/ Fentanyl**	**Group C Placebo**	***p* Value**
No	82	83	83	0.77
Male/female	43/39	45/38	42/41	0.48
Mean (SD) age (y)	59 (14)	58 (15)	61 (14)	0.32
BMI (kg/m^2)	27	28	27	0.76
Smokers [n (%)]	21/61	25/58	24/59	0.51
ASA status [n (%)]				
I	46	51	43	0.51
II	30	28	31	0.54
III	6	4	7	0.45
Previous colonoscopy (n)	41	43	44	0.74
Therapeutic procedure (n)	26	27	26	0.78

Adverse Events

Oxygen desaturation below 90% occurred temporarily in 11 patients (13.4%) in Group A, 4 patients (4.8%) in Group B, and 3 patients (3.6%) in Group C. A statistically significant difference was noted between Groups A and B ($p = 0.04$), while no difference was found between Groups B and C. Supplemental oxygen was required in 31.7% of patients in Group A, 24.7% in Group B, and 4.4% in Group C. Table 2.

In terms of mild adverse events, 13 out of 82 patients (15.8%) in Group A (midazolam plus meperidine) experienced symptoms, including 10 cases of nausea and 3 cases of transient hypotension (systolic blood pressure < 100 mm Hg). In Group B (midazolam plus fentanyl), 6 out of 83 patients (7.2%) reported mild reactions—4 cases of nausea and 2 cases of temporary hypotension. Group C (placebo) had 13 adverse events among 83 patients (15.6%), including 11 cases of nausea, 1 episode of mild bradycardia, and 1 case of mild hypotension. The lowest incidence of adverse reactions occurred in Group B ($p = 0.01$). All reported adverse events were self-limiting, mild, and did not require administration of reversal agents.

Pain and discomfort levels were measured using a five-point visual analog scale (VAS). Patients in Group B (midazolam plus fentanyl) reported significantly less pain and discomfort than those in Group A (midazolam plus meperidine) ($p = 0.02$). Group A patients also reported less pain than those in Group C (placebo) ($p = 0.05$). Severe pain

during the procedure was experienced by 18.3% in Group A, 3.4% in Group B, and 11.1% in Group C. These findings indicate that although meperidine has analgesic effects, a portion of patients may still experience considerable pain at standard doses.

Table 2. Study parameters in the different groups of patients who underwent colonoscopy.

	Group A Midazolam/ Meperidine	Group B Midazolam/ Fentanyl	Group C Placebo	*p* Value
Completion rate [n (%)]	74 (90%)	78 (94%)	73 (88%)	0.45
Intubation time (min)	14.9 ± 5.5	13.9 ± 5.7	15.8 ± 5.8	0.68
Recovery time (min)	50.1 ± 9.0	43.0 ± 9.3	10.4 ± 2.9	0.001
Relative amnesia of the procedure [n (%)]	35 (42%)	32 (39%)	83 (100%)	0.001
VAS of pain (0–5)	2.60 ± 1.25	2.13 ± 0.95	3.11 ± 1.06	0.024
VAS of discomfort (0–5)	2.39 ± 0.89	1.91 ± 0.68	2.42 ± 0,86	0.031
Satisfaction from the procedure [n (%)]	49 (60%)	72 (87%)	37 (44%)	0.001
Willingness to repeat the procedure [n (%)]	54 (66%)	71 (85%)	26 (31%)	0.001
Better than previous colonoscopy [n (%)]	28/41 (68%)	37/43 (86%)	5/44 (11%)	0.001
Good recommendation to relatives/friends [n (%)]	52 (63%)	75 (90%)	48 (58%)	0.001

Patients were asked to rate their overall satisfaction with the procedure. A significantly higher proportion of patients in Group B (86.7%) reported being extremely or very satisfied, compared to 59.7% in Group A and 44.5% in Group C ($p = 0.0000$). Very low satisfaction ("very dissatisfied") was reported by 2.4% of patients in Group A, none in Group B, and 12.2% in Group C.

When asked about their willingness to undergo the procedure again, 85% of patients in Group B responded affirmatively without hesitation, compared to 66% in Group A and 31% in Group C ($p < 0.001$). Additionally, 30% in Group A, 14% in Group B, and 65% in Group C were willing to repeat the procedure only if necessary. The proportion of patients unwilling to repeat the procedure was low: 4% in Groups A and C, and 1% in Group B.

Partial amnesia related to the procedure was reported by 42% and 39% of patients in Groups A and B, respectively ($p > 0.05$). As expected, 100% of patients in Group C (placebo) retained full recall of the procedure, given that no sedatives were administered. Amnesia levels were similar between Groups A and B, reflecting the effect of midazolam rather than the opioid component.

A notable number of participants had previously undergone colonoscopy: 41 in Group A, 43 in Group B, and 44 in Group C. Among these, 68% of Group A, 86% of Group B, and only 11% of Group C patients considered the current procedure more comfortable than their past experience ($p = 0.001$).

Willingness to recommend the procedure to others was high. Among patients in Group B, 90% said they would recommend it without hesitation, compared to 63% in Group A and 58% in Group C. A smaller percentage of patients expressed hesitation before recommending it: 36% in Group A, 9% in Group B, and 40% in Group C. These findings suggest that despite occasional discomfort, most patients recognized the clinical value of the procedure and were likely to endorse it.

Patient responses to the follow-up questionnaire administered via phone 48 h after the procedures were consistent with the initial assessments. No serious adverse events were reported during follow-up. However, six patients in Group A reported persistent mild nausea lasting more than 8 h post-procedure, likely related to the use of meperidine.

A subgroup analysis was conducted to assess whether the type of intervention (diagnostic vs. therapeutic colonoscopy) influenced recovery time and patient-reported outcomes. No statistically significant differences were observed in recovery time ($p = 0.187$) or discomfort scores ($p = 0.243$) between the two groups. Table 2.

3. Discussion

This randomized clinical trial found that combining midazolam with fentanyl provided superior sedation compared to the combination of midazolam with meperidine, with the added benefit of a faster recovery period. Both opioid-containing regimens were better tolerated than placebo, and all sedation protocols demonstrated only mild, self-limiting adverse effects.

The increasing demand for endoscopic procedures—driven by the need for screening and surveillance of diseases like colorectal cancer and Barrett's esophagus—has heightened the focus on improving procedural efficiency. Strategies such as using sedatives with shorter half-lives or performing colonoscopies without sedation altogether are gaining traction as ways to reduce recovery time and improve throughput [9,10].

Fentanyl is a synthetic opioid that not only provides potent analgesia—being 80 to 100 times stronger than morphine—but also has a rapid onset of action (approximately 1.5 min) and a relatively short duration (1–2 h) [11]. Meperidine, another opioid analgesic, has a slower onset (around 5 min) and a slightly longer duration (2–4 h). Multiple studies have confirmed fentanyl's safety and effectiveness in gastrointestinal endoscopic sedation [10,12].

Head-to-head comparisons between fentanyl and meperidine are limited. In one randomized trial involving 24 children (mean age 10.4 years), no significant difference was found in discomfort or recovery time between the two agents [13]. However, this study assessed cognitive function rather than discharge time, using the Trieger test at 30 and 60 min. Although children receiving fentanyl performed marginally better, the study was likely underpowered to detect significant differences. Another single-center randomized trial involving 111 patients undergoing colonoscopy or upper endoscopy found that fentanyl reduced total procedure time compared to meperidine, primarily due to shorter recovery times. The advantage was consistent across both types of endoscopy [10]. Interestingly, meperidine appeared to cause less pain than fentanyl in that study, which may be attributed to its slower onset and the possibility of additional dosing before the full sedative effect was achieved.

A randomized study conducted in the UK involving 287 patients found that using fentanyl with low-dose midazolam significantly shortened recovery time compared to meperidine, without compromising analgesic effect [12]. Adverse events were rare (<1%) and comparable between groups. Additionally, observational and comparative studies, including those in obstetric and anesthetic settings, have generally favored fentanyl for its safety profile. The faster recovery seen with fentanyl may thus be linked to fewer complications. Interestingly, healthcare staff—both endoscopists and nurses—tended to rate discomfort higher than patients, likely due to midazolam's amnesic effects.

Another study compared tramadol and fentanyl (both combined with midazolam) for analgesia during outpatient colonoscopy [14]. Tramadol, which has weaker affinity for opioid receptors, was associated with higher pain scores and a greater incidence of adverse events, both during and after the procedure, compared to fentanyl. These results emphasize the critical role of opioids in achieving effective sedation during colonoscopy. In another double-blind, placebo-controlled trial, Tu et al. demonstrated that administering diphenhydramine prior to standard sedation with midazolam and meperidine enhanced the overall effectiveness of conscious sedation [15].

Mui et al. reported that premedication with ketorolac, a potent NSAID, reduced pain during colonoscopy without causing serious complications, although it did not lessen the need for patient-controlled sedation using a propofol and alfentanil mixture [16]. Similarly, a study evaluating the addition of meperidine to propofol found improved patient tolerance and recovery, with lower propofol requirements compared to propofol alone [17].

Our trial also included a placebo group that received no sedation. These patients had not specifically requested unsedated colonoscopy but agreed to participate with full knowledge of their possible assignment. While they generally tolerated the procedure well, their experience was understandably less comfortable than that of sedated patients. They were also less inclined to repeat the procedure, though they benefited from the shortest recovery times. Several studies from Europe and Asia—and more recently from the U.S.—have shown that unsedated colonoscopy can be feasible and well tolerated [18,19]. Park et al. demonstrated that using smaller-caliber or upper endoscopes in patients with low body mass index can make sedation-free colonoscopy both tolerable and effective [20].

Adverse events in our study were infrequent but did occur. A small number of patients—particularly those in the meperidine group—experienced transient oxygen desaturation below 90%, which was effectively managed with supplemental oxygen. Mild nausea and hypotension were also reported. Overall, adverse reactions were least frequent in the midazolam-fentanyl group (Group B, $p = 0.01$). Importantly, all adverse events were mild, resolved without intervention, and required no administration of reversal agents.

This study has several notable strengths. It provides clear evidence that sedation with midazolam and fentanyl is not only better tolerated but also associated with fewer side effects compared to midazolam with meperidine. Participants in Group B expressed higher satisfaction, were more willing to repeat the procedure, and more frequently recommended it to others. Still, nearly half of the patients in the unsedated group (44.5%) reported being satisfied with the experience. Only 12.2% were very dissatisfied, suggesting that, under the right conditions, a significant portion of patients—potentially up to half—can successfully undergo colonoscopy without sedation, thereby benefiting from quicker recovery. Additionally, the average recovery time for Group B was approximately seven minutes shorter than that of Group A.

However, our study is not without limitations. Although randomization was blinded, the absence of sedation likely revealed the placebo group due to the lack of relaxation typically seen with sedation. Nonetheless, this recognition did not appear to affect patient attitudes or responses, likely owing to trust in the medical team and institutional setting. Furthermore, responses from sedated patients in Groups A and B may have been influenced by midazolam's amnesic effects, potentially affecting the reliability of questionnaire data.

In summary, this randomized trial showed that the combination of midazolam and fentanyl offers more effective and better-tolerated sedation than midazolam with meperidine, with the added benefit of a slightly shorter recovery time. Based on our findings and the current literature, midazolam combined with fentanyl appears to be the most suitable option for conscious sedation during colonoscopy. Nonetheless, both sedation regimens were proven to be safe and effective, and a significant proportion of patients in the unsedated group also tolerated the procedure reasonably well.

Although some studies suggest that therapeutic interventions may be associated with greater procedural discomfort, our data did not demonstrate a significant difference in patient-reported discomfort or satisfaction based on procedure type. This may reflect the effectiveness of procedural techniques and sedation strategies in minimizing discomfort across different intervention types.

4. Methods

4.1. Patient Selection and Study Design

Adult outpatients aged 18 years and older who were scheduled for colonoscopy were consecutively invited to participate in the study. Informed consent was obtained prior to randomization. Exclusion criteria included American Society of Anesthesiologists (ASA) physical status classification IV or V, known allergies to opioids or benzodiazepines, pregnancy, and a history of severe respiratory disease. The primary endpoint was patient comfort, assessed using a dedicated questionnaire. Secondary endpoints included intubation time, recovery time, and the endoscopist's overall evaluation of the procedure. Patients were randomized using a computer-generated randomization schedule to one of three groups: Group A received midazolam plus meperidine, Group B received midazolam plus fentanyl, and Group C received placebo. Sample size calculation to detect a 5% difference indicated the need for 80 patients per group. Thus, the goal was to enroll at least 80 participants in each group. This study was approved by the Institutional Ethics Committee of University Hospital of Ioanina, Greece under approval number AN 29-06-2022/202, and was conducted in accordance with the Declaration of Helsinki.

Sample size was calculated using an expected 20% difference in patient-reported discomfort between sedation groups, with a power of 80% and a two-sided alpha level of 0.05. Based on this calculation, a minimum of 30 patients per group (90 total) was required. To account for potential dropouts or protocol deviations, we aimed to enroll 100 patients. Patients were randomly assigned to one of the three study arms (Group A: midazolam + meperidine, Group B: midazolam + fentanyl, Group C: placebo) using a computer-generated random sequence with block randomization in blocks of six to ensure balanced group sizes. Allocation was concealed using sequentially numbered, opaque, sealed envelopes prepared by an independent statistician not involved in patient recruitment or data collection.

4.2. Endoscopists

All procedures were performed by experienced, consultant-level endoscopists with documented proficiency in colonoscopy. The number of participating endoscopists was selected to enhance recruitment while minimizing variability in technique. All endoscopists followed a standardized methodology, including torque steering, loop resolution, patient repositioning, and the application of abdominal pressure, to ensure consistency across procedures.

4.3. Sedation Regimen and Monitoring

The sedation assignment was blinded for patients, endoscopists, and nurses, except for the research nurse administering the sedation. In our institution, nurse-administered sedation under physician supervision is standard practice and follows established national and international guidelines. In this study, all sedative agents were administered by a trained research nurse in accordance with institutional protocols and under the direct supervision of the endoscopist. While full blinding was attempted, the absence of sedation in the placebo group (Group C) may have been noticeable. The research nurse, who played no role in performing the colonoscopy or in analyzing the data, administered all sedative agents. Continuous monitoring during the procedure included pulse oximetry for desaturation, automated sphygmomanometry for blood pressure, and pulse rate monitoring. Supplemental oxygen was administered if oxygen saturation dropped below 92%.

Sedation regimens followed recommendations from major gastroenterology societies [2,3]. When sedation was used, the opioid was given first, followed by the benzodiazepine one minute later. Initial doses were 50 mg of meperidine (reduced to 25 mg for

patients under 50 kg, over 70 years of age, or with significant comorbidity) or 50 mcg of fentanyl (1 mcg/kg rounded to the nearest 25 mcg, max dose 100 mcg), followed by 2.5 mg of midazolam (0.05 mg/kg, capped at 2 mg in older or comorbid patients). For the placebo group, normal saline was injected to simulate the sedation process.

Additional sedative doses were generally avoided and permitted only at the discretion of the endoscopist after using standard measures to reduce patient discomfort (e.g., correcting loop formation, repositioning, or reducing air insufflation). If further sedation was requested in the placebo group, another placebo injection was administered. If that failed, the patient was considered a failure of the placebo arm. If adverse events required pharmacologic reversal or other intervention, the treatment allocation was unblinded. At the end of each procedure, various parameters were recorded, including whether the procedure was diagnostic or therapeutic, whether cecal intubation was achieved, insertion time to the cecum, total procedure duration, and any complications observed.

4.3.1. Recovery and Questionnaire Completion

Following the procedure, patients were transferred to a recovery area where initial vital signs—including heart rate, blood pressure, and oxygen saturation—were documented. They were continuously observed for five minutes, with re-evaluation every two minutes thereafter. Any adverse events were immediately communicated to the supervising staff. Recovery time was defined as the interval between the patient's arrival in recovery and the point at which they were fully alert, communicative, and free from hypotension (systolic BP < 100 mm Hg) or hypoxia (oxygen saturation < 95%). A recovery time of zero was assigned if the patient already met these criteria upon arrival.

Once fully recovered, patients were asked to complete a brief questionnaire regarding their experience (Appendix A). The questionnaire addressed pain, discomfort, overall procedure satisfaction, willingness to undergo the procedure again if needed, and recall of the event (amnesia). This tool was adapted from a validated questionnaire developed by Cohen et al. [11]. The form was user-friendly and designed to be completed in just a few minutes. Pain and discomfort were assessed separately using a five-point visual analog scale (VAS), where 0 indicated no pain or discomfort and 5 represented unbearable symptoms. This approach was chosen because patients may experience considerable discomfort without pain. The visual numeric scale provided a straightforward and semi-objective assessment of patient experience.

At 48 h post-procedure, patients were contacted via phone by the research nurse and asked to complete the same questionnaire again, as well as to report any delayed adverse reactions.

4.3.2. Data Collection and Analysis

The research nurse administered the post-procedure questionnaire and conducted follow-up calls at 48 h. All clinical personnel, including recovery staff, remained blinded to the patient's group allocation. Data were analyzed using SPSS version 17.0. Normality was assessed with the Shapiro-Wilk test. Depending on data distribution, comparisons were made using Student's *t*-test or the Mann- U test. Categorical variables were compared using the χ^2 test. A two-tailed *p*-value of <0.05 was considered statistically significant. Baseline demographic and clinical characteristics, including age, sex, body mass index (BMI), comorbidities, and indication for colonoscopy, were recorded for all participants. Comparability among the three study groups was assessed using one-way ANOVA for continuous variables and chi-square tests for categorical variables. No statistically significant differences were observed among groups, confirming baseline equivalence. Statistical analysis was performed using SPSS version 17.0. Continuous variables were first tested

for normality using the Shapiro-Wilk test. Normally distributed data were expressed as means ± standard deviation (SD) and compared using one-way analysis of variance (ANOVA). Non-normally distributed data were reported as medians and interquartile ranges (IQR) and compared using the Kruskal-Wallis test. Categorical variables were presented as counts and percentages and compared using the chi-square test or Fisher's exact test, as appropriate. A two-tailed p-value of <0.05 was considered statistically significant.

5. Conclusions

This randomized controlled trial demonstrated that the combination of midazolam and fentanyl offers superior sedation for colonoscopy compared to midazolam with meperidine or no sedation (placebo). Patients receiving midazlam-fentanyl reported significantly greater comfort, higher satisfaction, fewer adverse events, and a shorter recovery time, making it the most effective and well-tolerated regimen among those studied. While both sedation combinations were generally safe and effective, fentanyl showed advantages in terms of patient experience and safety profile. Notably, a substantial proportion of unsedated patients also tolerated the procedure well, suggesting that unsedated colonoscopy remains a viable option in selected cases. Overall, the findings support the use of midazlam-fentanyl as the preferred regimen for conscious sedation during colonoscopy, offering an optimal balance between efficacy, patient comfort, safety, and recovery.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to patient confidentiality and ethical restrictions.

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Abbreviations

NSAID	Non-Steroidal Anti-Inflammatory Drug
SD	standard deviation
ANOVA	one-way analysis of variance
IQR	interquartile ranges

Appendix A. Questionnaire

How would you grade the pain you felt during the procedure from 1 to 10 (1 no pain–5 worst possible pain, visual analog scale provided).

How would you grade the discomfort you felt during the procedure from 1 to 10 (1 no pain–5 worst possible pain, visual analogue scale provided).

How satisfied are you from the procedure? (1 extremely pleased, 2 very pleased, 3 rather pleased, 4 quite unpleased, 5 very unpleased)

Would you accept repeating the procedure in the future? (1 Certainly, 2 probably, 3 Only if it were necessary, 4 Probably not, 5 Definitely not)

How well do you remember the whole procedure? (1 I remember everything, 2 I remember some parts of the procedure, 3 I remember only few parts of the procedure, 4 I do not remember anything).

If you have undergone a colonoscopy previously, how would you grade the present procedure? (1 better, 2 same, 3 worse).

Would you recommend the procedure to relatives and friends? (1 Definitively yes, 2 Yes with hesitation, 3 Definitively no).

References

1. Viazis, N.; Vlachogiannakos, J.; Apostolopoulos, P.; Mimidis, K.; Tzouvala, M.; Tsionis, T.; Goulas, S.; Thomopoulos, K.; Paraskeva, K.; Paspatis, G.; et al. Sedation during endoscopic procedures: A Hellenic Society of Gastroenterology position statement. *Ann. Gastroenterol.* **2023**, *36*, 231–243. [CrossRef] [PubMed]
2. Early, D.S.; Lightdale, J.R.; Vargo, J.J., II; Acosta, R.D.; Chandrasekhara, V.; Chathadi, K.V.; Evans, J.A.; Fisher, D.A.; Fonkalsrud, L.; Hwang, J.H.; et al. Guidelines for sedation and anesthesia in GI endoscopy. *Gastrointest. Endosc.* **2018**, *87*, 327–337. [CrossRef] [PubMed]
3. Sidhu, R.; Turnbull, D.; Haboubi, H.; Leeds, J.S.; Healey, C.; Hebbar, S.; Collins, P.; Jones, W.; Peerally, M.F.; Brogden, S.; et al. British Society of Gastroenterology guidelines on sedation in gastrointestinal endoscopy. *Gut* **2024**, *73*, 219–245. [CrossRef] [PubMed]
4. Leung, F.W.; Aljebreen, A.M.; Brocchi, E.; Chang, E.B.; Liao, W.C.; Mizukami, T.; Schapiro, M.; Triantafyllou, K. Sedation-risk-free colonoscopy for minimizing the burden of colorectal cancer screening. *World J. Gastrointest. Endosc.* **2010**, *2*, 81–89. [CrossRef] [PubMed]
5. Rembacken, B.J.; Axon, A.T. The role of pethidine in sedation for colonoscopy. *Endoscopy* **1995**, *27*, 244–247. [CrossRef] [PubMed]
6. Ramos-Matos, C.F.; Bistas, K.G.; Lopez-Ojeda, W. Fentanyl. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2023. Available online: https://www.ncbi.nlm.nih.gov/books/NBK537175/ (accessed on 30 May 2025).
7. Thiis-Evensen, E.; Hoff, G.S.; Sauar, J.; Vatn, M.H. Patient tolerance of colonoscopy without sedation during screening examination for colorectal polyps. *Gastrointest. Endosc.* **2000**, *52*, 606–610. [CrossRef] [PubMed]
8. Takahashi, Y.; Tanaka, H.; Kinjo, M.; Sakumoto, K. Sedation-free colonoscopy. *Dis. Colon Rectum* **2005**, *48*, 855–859. [CrossRef] [PubMed]
9. Robertson, D.J.; Lawrence, L.B.; Shaheen, N.J.; Baron, J.A.; Paskett, E.; Petrelli, N.J.; Sandler, R.S. Quality of colonoscopy reporting: A process of care study. *Am. J. Gastroenterol.* **2002**, *97*, 2651–2656. [CrossRef] [PubMed]
10. Robertson, D.J.; Jacobs, D.P.; Mackenzie, T.A.; Oringer, J.A.; Rothstein, R.I. Clinical trial: A randomized study comparing meperidine (pethidine) and fentanyl in adult gastrointestinal endoscopy. *Aliment. Pharmacol. Ther.* **2009**, *29*, 817–823. [CrossRef] [PubMed]
11. Cohen, L.B.; Hightower, C.D.; Wood, D.A.; Miller, K.M.; Aisenberg, J. Moderate level sedation during endoscopy: A prospective study using low-dose propofol, meperidine/fentanyl, and midazolam. *Gastrointest. Endosc.* **2004**, *59*, 795–803. [CrossRef] [PubMed]
12. Hayee, B.; Dunn, J.; Loganayagam, A.; Wong, M.; Saxena, V.; Rowbotham, D.; McNair, A. Midazolam with meperidine or fentanyl for colonoscopy: Results of a randomized trial. *Gastrointest. Endosc.* **2009**, *69*, 681–687. [CrossRef] [PubMed]
13. Ali, S.; Davidson, D.L.; Gremse, D.A. Comparison of fentanyl versus meperidine for analgesia in pediatric gastrointestinal endoscopy. *Dig. Dis. Sci.* **2004**, *49*, 888–891. [CrossRef] [PubMed]
14. Hirsh, I.; Vaissler, A.; Chernin, J.; Segol, O.; Pizov, R. Fentanyl or tramadol, with midazolam, for outpatient colonoscopy: Analgesia, sedation, and safety. *Dig. Dis. Sci.* **2006**, *51*, 1946–1951. [CrossRef] [PubMed]
15. Tu, R.H.; Grewall, P.; Leung, J.W.; Suryaprasad, A.G.; Sheykhzadeh, P.I.; Doan, C.; Garcia, J.C.; Zhang, N.; Prindiville, T.; Mann, S.; et al. Diphenhydramine as an adjunct to sedation for colonoscopy: A double-blind randomized, placebo-controlled study. *Gastrointest. Endosc.* **2006**, *63*, 87–94. [CrossRef] [PubMed]
16. Mui, W.L.; Kwong, W.H.; Li, A.C.; Au Yeung, A.C.; Poon, C.M.; Chiu, P.W.; Chan, Y.L.; Leong, H.T.; Ng, E.K. Premedication with intravenous ketorolac trometamol (Toradol) in colonoscopy: A randomized controlled trial. *Am. J. Gastroenterol.* **2005**, *100*, 2669–2673. [CrossRef] [PubMed]
17. Hsieh, Y.H.; Chou, A.L.; Lai, Y.Y.; Chen, B.S.; Sia, S.L.; Chen, I.C.; Chang, Y.L.; Lin, H.J. Propofol alone versus propofol in combination with meperidine for sedation during colonoscopy. *J. Clin. Gastroenterol.* **2009**, *43*, 753–757. [CrossRef] [PubMed]

18. Petrini, J.L.; Egan, J.V.; Hahn, W.V. Unsedated colonoscopy: Patient characteristics and satisfaction in a community-based endoscopy unit. *Gastrointest. Endosc.* **2009**, *69*, 567–572. [CrossRef] [PubMed]
19. Leung, F.W. The case of unsedated screening colonoscopy in the United States. *Gastrointest. Endosc.* **2009**, *69*, 1354–1356. [CrossRef] [PubMed]
20. Park, C.H.; Lee, W.S.; Joo, Y.E.; Kim, H.S.; Choi, S.K.; Rew, J.S.; Kim, S.J. Sedation-free colonoscopy using an upper endoscope is tolerable and effective in patients with low body mass index: A prospective randomized study. *Am. J. Gastroenterol.* **2006**, *101*, 2504–2510. [CrossRef] [PubMed]