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Research Article

Median Effective Dose of an Etomidate-Propofol Mixture with Dezocine in Inhibiting the Response to Gastroscope Insertion: Gender Differences in a Randomized Controlled Study Using Dixon's Up-and-Down Method

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What Is Known and Objective. Appropriate doses of sedatives are crucial for a successful, painless upper gastrointestinal endoscopy. Hence, we conducted a randomized controlled study to explore the effects of dezocine on the median effective dose (ED_{50}) of the etomidate-propofol (E-P) mixture in prohibiting response to gastroscope insertion in patients of different genders. *Methods*. Patients aged 18–65 years enrolled in the study of the American Society of Anesthesiologists (ASA) with physical status I or II undergoing elective gastroscopy were included. Patients were randomly assigned to the male normal saline group (MS group), male dezocine group (MD group), female normal saline group (FS group), and female dezocine group (FD group). All patients were anesthetized with an E-P mixture of 1 : 1. The FD and MD groups were intravenously injected (i.v.) 50 μg/kg dezocine 5 min before anesthesia, while the FS and MS groups were injected with an equal volume of normal saline 5 min before anesthesia. According to the preexperiment, the initial dose of the E-P mixture for the FD and MD groups was 0.4 and 0.3 mL/kg for the FS and MS groups. The variation proportion was set as 0.9 between dosages. Dixon's up-and-down method was adopted to confirm the dose of the E-P mixture for the next patient, which was reduced if the insertion was performed successfully; otherwise, the dose was increased. Centered isotonic regression was employed to determine the ED_{50} and 90% confidence interval (CI) values of the E-P mixture in the four groups. The total amount of E-P mixture consumed was recorded as well as the adverse events of patients. *Results*. The ED_{50} and 90% CI of the MS, MD, FS, and FD groups were 0.315 (0.285–0.349), 0.206 (0.175–0.237), 0.329 (0.305–0.355), and 0.207 (0.188–0.227) mL/kg, respectively. The MD group was <MS group ($P \leq 0.001$), and the FD group was <FS group ($P \leq 0.001$); no statistical difference was observed between the MS and FS groups and MD and FD groups. Dezocine reduced the total amount of E-P mixture consumed and the overall incidence of adverse events. *What Is New and Conclusion*. Dezocine significantly decreased the ED_{50} of the E-P mixture in inhibiting the response of patients to gastroscope insertion and the occurrence rate of adverse events. Further, gender had no impact on the ED_{50} of the E-P mixture.

1. What Is Known and Objective

Due to the highly sensitive pharynx, patients receiving an endoscopic probe into the esophagus during upper gastrointestinal endoscopy often experience nausea and vomiting, body movement, and even laryngospasm, which can be considerably reduced with an adequate painless procedure. Appropriate drugs, such as the commonly used propofol and etomidate combined with opioids, are crucial for a successful upper gastrointestinal endoscopy [1]. Although each drug offers benefits, these come with certain limitations. The disadvantage of propofol is that it causes injection-site pain, has a narrow therapeutic window, and induces strong circulatory and respiratory inhibition [2–4], especially in senior

patients [5]. Etomidate induction alone usually leads to muscle tremors, stiffness, and aggravation of postoperative nausea and vomiting [6, 7]. Propofol pretreatment can suppress muscle tremor and stiffness induced by etomidate [8]. The etomidate-propofol (E-P) mixture is safer and more effective because it reduces the incidence rate of adverse events and stabilizes the hemodynamics during gastroscopy as compared to propofol alone [9].

As an analgesic drug with kappa receptor agonism and partial μ receptor antagonism, dezocine causes fewer adverse events in patients and more significant sedative effects on visceral pain than a pure μ receptor agonist [10]. Dezocine can distinctly decrease the total amount of propofol used during gastroscopy and shorten the recovery time of patients [11]. Gender differences in opioid analgesia were also reported, showing more pronounced analgesic effects on females than males, which was presumably associated with hormone levels, pharmacokinetics, pharmacodynamics, and genetic and psychological factors [12]. Since there is no relevant research, the implications of dezocine on the median effective dose (ED_{50}) of the E-P mixture in inhibiting the response to gastroscope insertion and the difference in ED_{50} between genders were explored to provide a safer and more effective anesthetic for clinical practice.

2. Methods

2.1. Study Design. A single-center randomized double-blinded control study was conducted using Dixon's up-and-down method, authorized by the Ethics Committee of the Shunde Hospital of Southern Medical University (No. 20190576) and registered at https://www.chictr.org.cn/ (registration number: ChiCTR1900023875).

2.2. Inclusion and Exclusion Criteria. Inclusion criteria: patients who underwent elective gastroscopy; who were aged 18–65 years; who underwent diagnostic gastroscopy; with American Society of Anesthesiologists (ASA) class I or II; with a body mass index (BMI) of 17.5–27 kg/m^2.

Exclusion criteria: refusal to participate; serious hepatic or renal dysfunction; chronic pain; mental-related diseases; symptomatic cardiovascular or pulmonary diseases; related drug allergies; obstructive sleep apnea-hypopnea syndrome; hemostasis, polypectomy, or other treatment before/during the examination; history of alcoholism or psychotropic medication before gastroscopy; analgesic medication intake within 24 h before the procedure.

2.3. Randomization and Blinding. Based on gender, patients were randomly assigned to the male normal saline group (MS group), male dezocine group (MD group), female normal saline group (FS group), and female dezocine group (FD group). Allocations were sealed in sequentially numbered opaque envelopes. None of the participants, their family members, anesthetists, endoscopists, or procedure and recovery room nurses were informed of the grouping. A single researcher was unblinded in an emergent event during the procedure.

2.4. Anesthesia Procedure. All participants received a standardized anesthesia protocol. Thirty minutes before the examination, patients were given local oral anesthetics (gastroscope gel, containing 2% lidocaine hydrochloride, 7 mL/bottle, Xinyu Boyuan Biochemical Medical Products Co., Ltd., China). Their dorsal-hand veins were opened before entering the operation room. After entering the operation room, they were positioned in the lateral recumbent position and given oxygen at a rate of 4 L/min via a nasal straw connected to a multifunction device to monitor the vital signs. An E-P mixture (20 mL composed of 10 mL etomidate and 10 mL propofol) was used for anesthesia at 3 mL/s (etomidate was purchased from Jiangsu Enhua Pharmaceutical Co., Ltd., 2 mg/mL, 10 mL each, batch number: YT201026; propofol was purchased from Fresenius Kabi, 20 mg/mL, 20 mL each, batch number: 16NM6293). Patients from the MD and FD groups were intravenously injected (i.v.) with dezocine at 50 μg/kg 5 min before the anesthesia (Yangtze River Pharmaceutical Group, 5 mg/mL, 1 mL each, batch number: 20052521), and the MS and FS groups were administered equal volumes of normal saline 5 min i.v. before the anesthesia. Dezocine was diluted to 5 mL with normal saline via a 5 mL syringe, and 5 mL of normal saline was also prepared.

According to the preexperiment, the initial doses of the E-P mixture with and without dezocine administration were 0.3 and 0.4 mL/kg, respectively, so that 95% of participants could successfully complete gastroscopy. The variation proportion was set as 0.9 between dosages; thus, the MD and FD groups were divided into the following doses: 0.3, 0.27, 0.243, 0.219, 0.197, and 0.177 mL/kg. The MS and FS groups were divided into the following doses: 0.4, 0.36, 0.324, 0.292, and 0.262 mL/kg. All medications were prepared by an unblinded researcher and given to an anesthesiologist. The target sedation level was achieved when the eyelash reflex of the patient disappeared, followed by a pain-free gastroscopy performed by an endoscopist. Gastroscopy for all patients was performed by the same endoscopist, and anesthesia was conducted by the same anesthesiologist, each with five years of working experience. Following gastroscopy, patients were transferred to the postanesthesia care unit (PACU) for observation, and they could leave when their vital signs were stabilized without pronounced adverse events.

2.5. Sample Size Estimation. Patients who had positive responses (e.g., choking, coughing, or body movement) during the gastroscope insertion and could not continue the examination were labeled as "Effective." In this case, the next patient would receive a higher dosage of the E-P mixture. Otherwise, the patients were labeled as "Ineffective," and a lower dosage of the E-P mixture would be administered to the next patient. The total number of participants was determined by the up-and-down method of Dixon [13]. This method requires at least six crossover points (effective to ineffective) for statistical analysis. The experiment was terminated when seven crossover points were achieved with the sample size obtained. For the "Ineffective" patients, 3–5 mL of E-P mixture was administered i.v. to enhance the anesthetic effect, which could be repeated until the end of the examination.

2.6. Outcomes

(1) Primary outcomes: The dose of E-P mixture for each patient using the up-and-down method of Dixon was recorded in order.

(2) Secondary outcomes: Mean arterial pressure (MAP), heart rate (HR), and peripheral capillary oxygen saturation (SpO_2) before anesthesia (T0) and after E-P mixture administration (T1) were determined. The disappearance time of the eyelash reflex (from E-P mixture administration to eyelash reflex disappearance), gastroscopy time, waking time, and total amount of E-P mixture used were recorded. In addition, postoperative nausea and vomiting (PONV), myoclonus, injection pain, respiratory depression, bradycardia, hypotension, and dizziness were recorded. Waking time was defined as from the last administration of the E-P mixture to when the assessment alert/sedation (OAA/S) score was 5 (OAA/S ~ 5 represents a free response to calling their name). Respiratory depression was defined as SpO_2 lower than 90% during the examination, and the patient would be given jaw support, airway opening, and mask-assisted oxygen administration. Bradycardia was defined as HR <50 beats/min, and patients were administered 0.3–0.5 mg of atropine. Hypotension was defined as two consecutive MAP declines greater than 30% of the base value, and 5–10 mg of ephedrine would be administered i.v. to the patient.

2.7. Statistical Analysis. The statistical analysis was performed using SPSS (version 22.0, SPSS Inc., Chicago, Illinois, USA) and R Language. Data were presented as means ± standard deviations (SD), median (range), or no. of patients (n), depending on the distribution of the data. Comparisons between groups were performed with one-way ANOVA or the rank-sum test if the variance was not homogeneous. Categorical variables data were analyzed with the chi-square test or Fisher's exact test. Normally distributed continuous variables were compared using the least significant difference t-test (LSD-t) or Mann–Whitney U test for nonnormally distributed continuous variables. ED_{50} (90% CI) of each group and differences between groups were calculated with the centered isotonic regression R Language package [14]. A $P < 0.05$ was considered statistically significant.

3. Results

Gastroscopy screening was performed on 114 patients between July 2019 and December 2021, of which 103 were finally included in this study, recruited based on gender, and randomly assigned to four groups (Figure 1).

No significant difference was observed in the general information and gastroscopy-related factors between the four groups (Table 1).

The orders in Dixon's up-and-down method of the four groups are exhibited in Figure 2.

The ED_{50} and 90% CI of the MS, MD, FS, and FD groups were 0.315 (0.285–0.349), 0.206 (0.175–0.237), 0.329 (0.305–0.355), and 0.207 (0.188–0.227) mL/kg, respectively. The MD group < MS group ($P \leq 0.001$) and the FD group- < FS group ($P \leq 0.001$). No significant difference in ED_{50} was observed between the MS and FS groups and MD and FD groups (Table 2).

The total amounts of E-P mixture used (initial dose plus additional dose) for the MS, MD, FS, and FD groups were 0.381, 0.279, 0.385, and 0.265 mL/kg, respectively; MD group < MS group ($P \leq 0.001$), and FD group < FS group ($P \leq 0.001$) (Table 3).

A significant decline in MAP was observed at T1 in the MS and FS groups versus T0 ($P < 0.05$). The SpO_2 of the four groups exhibited a certain reduction after the E-P mixture administration, i.v. ($P < 0.05$) (Table 4).

As for adverse events, a significant difference was observed in myoclonus, injection pain, and incidence rate of overall adverse events ($P < 0.05$). The FD group had a lower occurrence rate of injection pain than the FS group ($P < 0.05$). The incidence rate of overall adverse events of the MD and FD groups was lower than that of the MS and FS groups ($P < 0.05$) (Table 5).

4. Discussion

During painless gastroscopy, an endoscope probe stimulates the pharynx when it enters the esophagus. Either inadequate or excessive anesthesia may result in severe adverse events, thereby posing a challenge to anesthesia procedures. Sedatives and analgesics are the most common drug combination for digestive endoscopic examinations. Due to the short duration of gastroscopy, anesthesiologists need to achieve a swift induction and ensure the safety and quality of the anesthesia. The minimum effective dose can achieve adequate anesthesia, save drug usage, and reduce the occurrence of adverse events. Via Dixon's up-and-down method, the ED_{50} of the E-P mixture in the four groups was 0.315 mL/kg (MS group), 0.206 mL/kg (MD group), 0.329 mL/kg (FS group), and 0.207 mL/kg (FD group). The ED_{50}s of the MS and FS groups were significantly higher than those of the MD and FD groups, indicating that dezocine can markedly reduce the ED_{50} of the E-P mixture, preventing a response to gastroscope insertion of patients without significant distinction between males and females.

Etomidate and propofol have been commonly applied in clinical painless gastroscopy as sedative drugs [15]. Different from propofol, etomidate leads to stable hemodynamics, which is its most pronounced feature and advantage [16]. In addition, an E-P mixture can better stabilize hemodynamics with fewer complications than propofol or etomidate alone, which has more clinical merits [17]. In this study, the MAP of MS and FS groups declined by approximately 19% following E-P administration. Hypotension occurred in three patients from both groups, which was distinctly ameliorated with 5–10 mg ephedrine. The MAP of the MD and FD groups significantly decreased by approximately 14%, implying that dezocine impacted stabilizing hemodynamics. Dezocine is an opioid receptor agonist/antagonist as well as

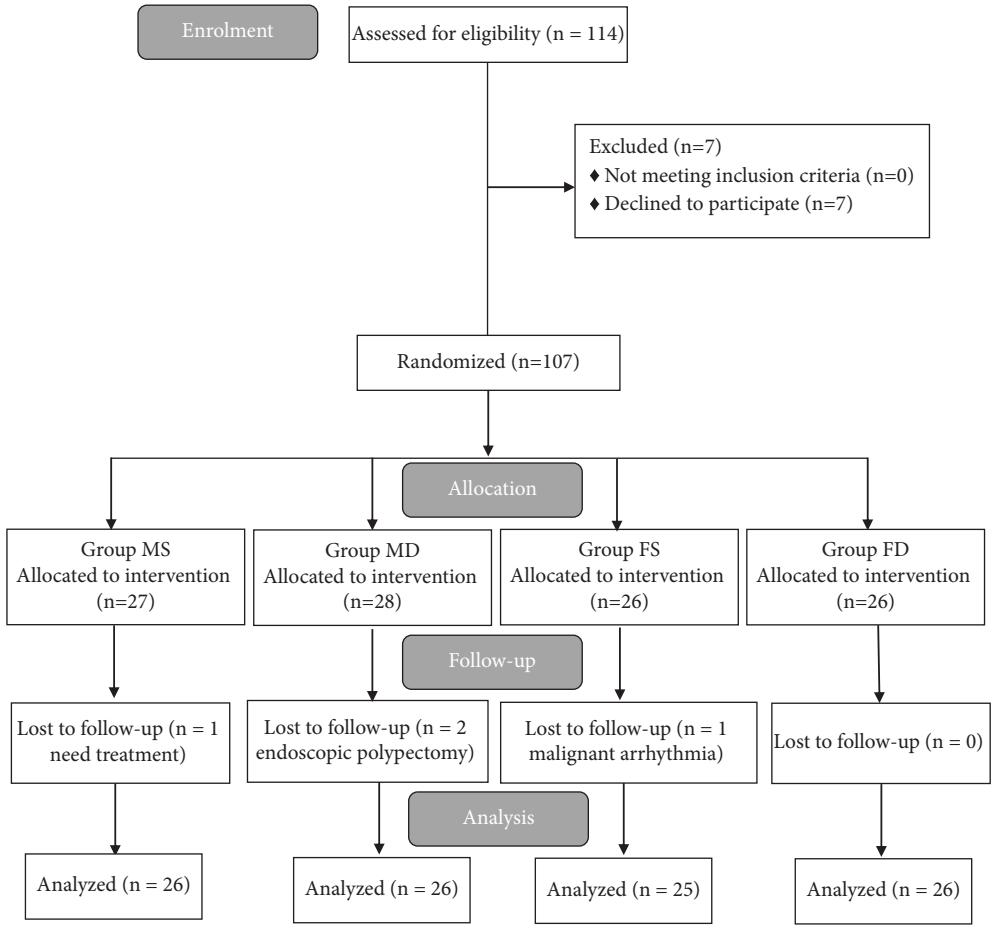

Figure 1: Flow diagram showing the inclusion of the participants.

Table 1: General information about the patients from the four groups.

Item	MS group	MD group	FS group	FD group	*P* value
ASA (I/II)	20/6	21/5	20/5	21/5	0.984
Age (years)	44.4 ± 9.0	45.4 ± 9.9	46.7 ± 8.5	45.9 ± 10.1	0.828
BMI (kg/m^2)	22.7 ± 2.7	22.5 ± 2.4	22.9 ± 2.5	22.0 ± 2.4	0.588
Disappearing time of eyelash reflex (s)	55.7 ± 2.6	55.5 ± 2.2	55.1 ± 1.5	54.9 ± 1.7	0.429
Gastroscopy time (min)	5.3 ± 1.0	4.8 ± 0.7	5.1 ± 1.5	4.9 ± 0.8	0.273
Recovery time (min)	8.3 ± 1.8	7.6 ± 1.5	8.3 ± 1.5	7.9 ± 1.4	0.291

Note. Data are expressed as mean ± SD or number of patients. One-way ANOVA was used to quantitative data. Fisher's exact test was used to categorical variables data ($P < 0.05$ was considered statistically significant). BMI, body mass index; ASA, American Society of Anesthesiologists.

a norepinephrine and serotonin reuptake inhibitor [18]. It has less inhibitory effects on respiration and can improve visceral pain versus the pure opioid receptor agonist fentanyl, making it more suitable analgesia in gastrointestinal endoscopy [19]. Li et al. [11] reported that dezocine i.v. could remarkably lower the dose of propofol and alleviate its suppression of the respiratory and cardiovascular systems. Likewise, preinjection of dezocine significantly decreased the ED_{50} and overall dose of the E-P mixture with propofol replaced by an E-P mixture.

Etomidate can cause myoclonus and injection-site pain, which cannot be avoided even when combined with propofol. In this study, the incidence rate of myoclonus was approximately 30% and 20% of injection-site pain. Preinjection of dezocine can lower the occurrence rate of myoclonus induced by etomidate, dampen the severity of myoclonus, and improve injection-site pain caused by propofol [20] without bringing about dizziness, nausea, or heart rate disturbance [21]. Similar findings were demonstrated in this study, with a more significant inhibitory effect on overall adverse events. The incidence rate of adverse events in the MS and FS groups was approximately 70%, while that of the MD and FD groups was significantly lower (30%), indicating that dezocine could effectively lower the occurrence rate of anesthesia-associated adverse events during gastroscopy.

The potency of anesthetic agents is affected by multiple factors, and gender can be one of them [22]. Nevertheless, a study demonstrated that blood drug concentration depended on the volume of distribution (Vd) and clearance

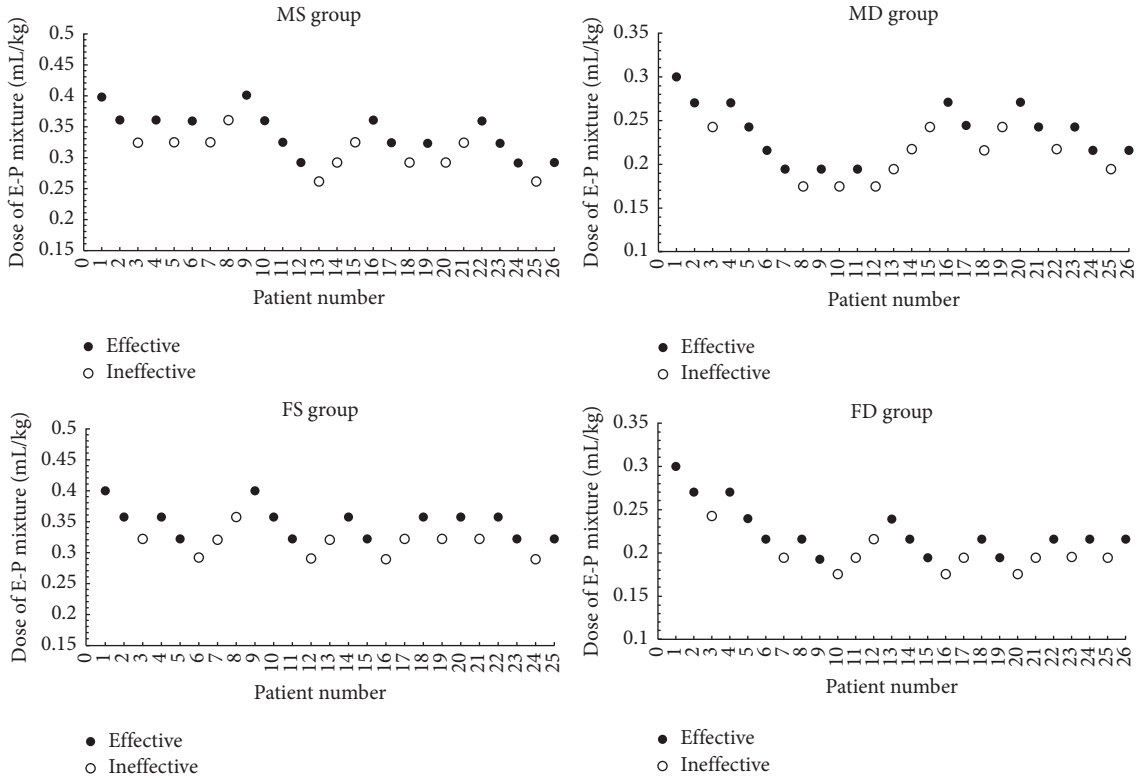

Figure 2: Dixon's up-and-down method plots for each group. Note: the black and white dots represent the "effective" and "ineffective" patients, respectively.

Table 2: ED_{50} (90% CI) of the E-P mixture between the four groups.

Group	ED_{50} (90% CI) of the E-P mixture (mL/kg)
MS group	0.315 (0.285–0.349)
MD group	0.206 (0.175–0.237)[a]
FS group	0.329 (0.305–0.355)
FD group	0.207 (0.188–0.227)[b]

Note. [a]$P \leq 0.001$ vs. MS group, [b]$P \leq 0.001$ vs. FS group, MS group vs. FS group, and MD group vs. FD group show no statistically significant differences. ED_{50} (90% CI) of the E-P mixture calculated using centered isotonic regression ($p < 0.05$ = significant difference). ED_{50} (90% CI) of each group and differences between groups were calculated with the centered isotonic regression and the Mann–Whitney U test.

Table 3: Total amount of the E-P mixture consumed (initial dose plus additional dose) during the upper gastrointestinal endoscopy.

Group	E-P mixture dose (mL/kg)
MS group	0.381 ± 0.08
MD group	$0.279 \pm 0.06^{*}$
FS group	0.385 ± 0.06
FD group	$0.265 \pm 0.06^{\#}$

Note. Data are expressed as means ± SD. $^{*}P \leq 0.001$ vs. MS group, $^{\#}P \leq 0.001$ vs. FS group according to the LSD test ($p < 0.05$ = significant difference).

(Cl) but was irrelevant to gender [23]. Furthermore, clinical data have depicted minimal gender-specific differences in pharmacodynamics and pharmacology among adults [24]. This study revealed that dezocine reduced the ED_{50} ($P < 0.05$) of the E-P mixture during gastroscopy, while no statistical difference in the ED_{50} between female and male patients was witnessed in the gender subgroup analysis ($P > 0.05$), which agreed with the results of most clinical studies.

The limitations of this study reside in several aspects. First, among the multiple methods of determining ED_{50}, Dixon's up-and-down method is swift and simple, yet it has much fortuitous error caused by individual differences as the examination was performed one by one. Expanding the sample size can diminish this error. In this study, the experiment was terminated when seven crossover points (effective to ineffective) were achieved with 25–26 samples. Despite the small size, we believe the results are accurate. Nevertheless, more samples are required owing to potential individual differences, assuring a more accurate ED_{50} and a narrower 90% CI to enhance credibility. Second, this study is limited to gastroscopy, which usually lasts for 5–10 min. Longer gastroscopies or when a gastric polyp is found during the examination that needs treatment should be ruled out. Third, the cases included in this study were strictly limited to adult patients with ASA classes I or II and a BMI of 17.5–27 kg/m^2. Hence, it does not apply to patients with ASA class ≥III and BMI >27 kg/m^2, showing limitations in the applicable population.

Table 4: Hemodynamic indicators of patients from four groups.

Hemodynamic	Time point	MS group	MD group	FS group	FD group	*P*value
MAP (mmHg)	T0	90.0 ± 8.6	91.1 ± 9.6	90.9 ± 8.2	92.2 ± 10.6	0.455
	T1	73.2 ± 7.9[a]	77.1 ± 7.9	74.1 ± 8.7[a]	79.4 ± 7.6	0.216
HR (beats/min)	T0	76.9 ± 9.9	72.6 ± 9.4	75.2 ± 11.0	75.3 ± 10.7	0.455
	T1	72.7 ± 10.0	70.8 ± 10.1	70.6 ± 11.2	71.9 ± 10.1	0.851
SpO_2 (%)	T0	99.8 ± 0.6	99.7 ± 0.5	99.9 ± 0.6	99.8 ± 0.5	0.948
	T1	98.7 ± 2.0[a]	99.0 ± 1.5[a]	98.9 ± 1.7[a]	99.1 ± 1.4[a]	0.581

Note. Data are expressed as mean ± SD. Compared with T0, $^aP < 0.05$. One-way ANOVA for comparisons between the four groups. Comparison of hemodynamic between T0 and T1 was performed using the *t* test ($P < 0.05$ was considered statistically significant). MAP, mean artery pressure; HR, heart rate. SpO_2, peripheral capillary oxygen saturation.

Table 5: Comparison of adverse events between the four groups (*n* (%)).

Adverse events	MS group ($n = 26$)	MD group ($n = 26$)	FS group ($n = 25$)	FD group ($n = 26$)	*P* value
PONV	2 (7.7)	1 (3.8)	1 (4)	2 (7.7)	0.878
Myoclonus	6 (23.1)	1 (3.8)	7 (28)	1 (3.8)[b]	0.013
Injection pain	5 (19.2)	1 (3.8)	5 (20)	0 (0)[b]	0.012
Respiratory depression	1 (3.8)	1 (3.8)	1 (4)	1 (3.8)	1
Bradycardia	0 (0)	0 (0)	0 (0)	1 (3.8)	0.426
Hypotension	3 (11.5)	2 (7.7)	3 (12)	1 (3.8)	0.672
Dizziness	1 (3.8)	2 (7.7)	1(4)	3 (11.5)	0.663
Overall	18 (69.2)	8 (30.8)[ab]	18 (72)	9 (34.6)[ab]	0.002

Note. Data are expressed as *n* (%). Compared with the MS group, $^aP < 0.05$; with the FS group, $^bP < 0.05$. Analysis of adverse events was performed using the chi-square test or Fisher's exact test ($P < 0.05$ was considered statistically significant). PONV, postoperative nausea and vomiting.

5. What Is New and Conclusion

To conclude, dezocine can significantly decrease the ED_{50} of the E-P mixture by suppressing the response of patients to gastroscope insertion, during which patients had stable vital signs with minimal adverse events. Therefore, dezocine can be applied and promoted for clinical practice. Although gender had no relevance to the ED_{50} of the E-P mixture, future work should explore the ED_{50} of overweight and obese people.

Data Availability

All data generated in this study are available from the corresponding author upon reasonable request.

Ethical Approval

The study was approved by the Medical Ethics Committee of the Shunde Hospital of Southern Medical University (Number: 20200903).

Consent

The patients/family members wrote an informed consent form in this study.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

YWZ conceived and designed study. YLZ, YFX, and HBL contributed to the data collection. ZQZ performed data analysis and interpretation. SYT wrote the manuscript. YQS contributed to the blind design. All authors read and approved the final manuscript. Shuyi Tang and Zhongqi Zhang contributed equally to this study.

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