Effective dose of remimazolam combined with different doses butorphanol inhibiting response to cervical dilation during artificial abortion: A randomized dose-finding clinical study

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Article

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Abstract

The purpose was to determine the effective dose of remimazolam (RMZ) combined with different doses butorphanol inhibiting response to cervical dilation during artificial abortion. This is a prospective, randomized, and double-blind study. Sixty-one female patients were randomly assigned to Group B10 (31 patients) and Group B15 (30 patients). All patients were given RMZ 5 min after an intravenous (IV) administration of butorphanol 10 μg/kg (Group B10) and 15 μg/kg (Group B15). According to the pre-experiment, the first dose of RMZ in the first patient was 0.35 mg/kg, and the adjacent geometric dose ratio was 0.9. The centered isotonic regression was performed to determine the ED50 and ED90 of RMZ and their corresponding 90% confidence interval (CI). The total RMZ dose administered, recovery time, and anesthesia-related adverse events were all recorded. The recovery time in Group B10 was significantly shorter than in Group B15. The incidence of post-operative nausea and vomiting (PONV) in the B10 and B15 groups was 3.2% and 16.7%, respectively. Therefore, to enhance the sedative effect of RMZ, the recommended dose of butorphanol is 10 μg/kg, and the ED50 and ED90 of the RMZ during painless artificial abortion were 0.263 and 0.331 mg/kg, respectively.

Introduction

Artificial abortion is one of the most widely accepted methods of contraceptive failure among all early abortions [1]. Artificial abortion is usually a relatively short operation, which can be completed within 3–5 min. However, pulling and dilating the cervical canal and sucking and scraping the uterine wall will cause severe pain. Many patients will experience involuntary limb movements that significantly increase the risk of surgical abortion[2]. Therefore, painless abortion frequently necessitates general anesthesia to alleviate the patient's physical discomfort during the procedure.

Butorphanol is a mixture of opioid receptor agonists and antagonists that can produce analgesic effects through kappa receptors, making it particularly suitable for treating visceral pain. Butorphanol has recently been widely used in outpatient surgery due to its good sedative and analgesic effects with a lower degree of respiratory depression compared to traditional potent opioid drugs (sufentanil or fentanyl)[3]. In addition, it can also effectively alleviate remifentanil-induced hyperalgesia [4, 5]. However, the sedative effect of butorphanol can result in side effects such as post-operative drowsiness and dizziness[6].

Remimazolam (RMZ) is an ultra-short acting benzodiazepine with the rapid induction of sedation, fast recovery, and no injection-site pain[7]. These characteristics make RMZ especially suitable for procedures such as gastroenteroscopy and hysteroscopy [8, 9]. Furthermore, a recent study revealed that RMZ pre-trials reduced the frequency and intensity of injection pain caused by propofol in abortion [10]. However, it is recommended to be used in combination with opioids for optimal effectiveness during procedural sedation [11].

We will use RMZ in combination with different doses of butorphanol in painless artificial abortion to determine the efficacy of the RMZ. The optimal dose of RMZ plus butorphanol for sedation during a painless abortion is unknown. There is no relevant research exists. Therefore, the effects of different doses of butorphanol on the median effective dose (ED_{50}) and 90% effective dose (ED_{90}) of the RMZ in inhibiting the response of cervical dilatation were investigated to provide a reference for the safety and rational use of the drug in painless artificial abortion.

Subjects and methods

Study design and participants. The present study is a prospective, randomized, and double-blind study.

Ethics Committee of of the Affiliated Shunde Hospital of Jinan University approved the study (number: JDSY-LL-2022004, 10/04/2022). The trial was registered at the Chinese Clinical Trial Registry (number: ChiCTR2200059793, 11/05/2022).

This study followed the CONSORT 2010 guidelines and included the CONSORT 2010 checklist. All trial procedures were performed in accordance with the relevant guidelines and regulations set by the Affiliated Shunde Hospital of Jinan University.

All patients who had an artificial abortion from May to September 2022 were included in the study. Each patient was asked to sign an informed consent.

Inclusion and exclusion criteria. Inclusion criteria: Perform elective artificial abortion; American Society of Anesthesiologists (ASA) I or II; clinically confirmed early-pregnancy by color doppler ultrasound (< 12 weeks); between 18 and 49 years of age; and body mass index (BMI) between 18 to 30 kg/m^2. Exclusion criteria: Refuse to participate; ASA class III or higher; allergy to RMZ or butorphanol; severe liver/kidney/cardiopulmonary/central nervous system dysfunction; a procedure time > 10 min; and long-term use of sedative or analgesic medications.

Grouping and anesthesia management. In the present study, 61 patients were randomly assigned into one of the two groups: Group B10 (31 patients) and Group B15 (30 patients). All patients were given RMZ after 5 min of an intravenous (IV) administration of butorphanol 10 μg/kg (Group B10) or 15 μg/kg (Group B15).

Patients have fasted for more than 8 h, and drinking was prohibited for at least 2 h. After entering the operating room, venous access was obtained at the dorsum of the left hand using an IV infusion needle with a diameter of 0.6 mm, and oxygen was given through nasal straw at the flow rate of 3 L/min. Electrocardiogram (ECG), blood pressure (BP), and blood oxygen saturation (SpO_2) were measured. The same experienced gynecologist and anesthesiologist performed all surgical procedures and anesthesia. The patient received IV butorphanol (Jiangsu Hengrui Medicine Co., China, diluted to 10 mL with normal saline, lot number: 220129BP), 10 μg/kg (Group B10) or 15 μg/kg (Group B15) at least 5 min before IV

administration of RMZ (Jiangsu Hengrui Medicine Co., China, diluted to 1 mg/mL with normal saline, lot number: 220326AK) for sedation. The maximal consumption of butorphanol was 1 mg in both groups.

The most painful part of the procedure was reported to be cervical dilation [12]. Cervical dilatation at the time of using a cervical dilating rod, if the patient has body movement and affects the gynecologist's operation, we define it as "Ineffective". Therefore, the next patient received an increased RMZ dose. Otherwise, it was defined as "Effective", and the RMZ dose was reduced in the next patient. According to the pre-experiment, the first RMZ dose in the first patient was 0.35 mg/kg, and the adjacent geometric dose ratio was 0.9. Therefore, the doses for the A and B groups were as follows: 0.35, 0.315, 0.283, 0.255, 0.229, 0.206, 0.186, and 0.167 mg/kg.

All patients were transported to the Post Anesthesia Care Unit (PACU) after the surgery until they awoke. The ECG, BP, and SpO_2 were also continuously monitored every 5 min for at least 30 min. Ability to walk independently, stable vital signs and no obvious adverse reactions were the criteria for transferring out of the PACAU.

Outcome assessments. The primary outcome measure The dose of RMZ for each patient was measured using the up-and-down method.

The secondary outcome: SBP/DBP, heart rate (HR), and SpO_2 were recorded at 5 min after entering the operating room (T1) and immediately after IV injection of RMZ (T2). Respiratory depression (SpO_2 < 90%), hypotension, bradycardia, injection-site pain, uterine contraction pain, dizziness, and post-operative nausea and vomiting (PONV) were also measured. In addition, the initial RMZ dose, the total RMZ dose, the total duration of the surgical procedure, and the recovery time were all recorded.

It was defined as injection-site pain when the patient frowned or complained of pain in the back of the hand or the ipsilateral arm escape reflex. The recovery time was the duration between the last RMZ injection and the eye-opening on command. Adverse events were managed as follows: hypotension (20% reduction in MAP compared to baseline) IV ephedrine 6–12 mg; bradycardia (HR < 50 beats/min) IV atropine 0.25–1 mg; respiratory depression (SpO_2 < 90%) maintain ventilation with a mask or laryngeal mask; PONV IV tropisetron 2 mg; and uterine contraction pain (VAS score ≥ 4) IV sufentanil 3–5 μg.

Blinding method. The randomization assignments were computer generated and then group information was sealed in an opaque envelope. All surgical procedures and anesthesia were performed by the same experienced gynecologist and anesthesiologist. An independent observer who was also blinded to group assignment and recorded the patients' vital signs and any anesthesia-related adverse events. The butorphanol was diluted with normal saline to 10 ml which appeared colorless and odorless, the 10ml transparent syringe without any label was placed in a tray together with propofol for the recruited patient, an independent researcher was responsible for drug distribution. Both the anesthesiologist and data recorder were blinded to the drug being injected.

Statistical Analysis. The sample size calculation was determined using Dixon's up-and-down method [13]. For statistical analysis, seven crossovers (Effective to Ineffective) are required. We performed statistical analyses using SPSS version 20.0 (Inc., Chicago, IL, USA). Data were presented as means ± standard deviations (SD), median [range], or n (%), depending on the distribution of the data. Normally distributed continuous variables were compared using t-test, while the Mann-Whitney U test was used for non-normally distributed continuous variables. Categorical variables were compared using the Chi-square or Fisher exact probability test in two groups. The centered isotonic regression of R Language was performed to determine the ED_{50} and ED_{90} of RMZ and their respective 90% CI[14]. $P < 0.05$ was indicated to represent statistically significantly difference.

Results

A total of 64 female participants were enrolled in the present study. Three participants were excluded, and 61participants completed the study successfully. The flow diagram of the study is shown in Fig. 1. Table 1 demonstrates patients' characteristic data for all patients. There were no statistically significant differences ($P > 0.05$) between the 2 groups in terms of ASA, age, height, weight, BMI, gestational week, number of times pregnant, number of cesarean sections, number of vaginal deliveries, and number of abortions.

Table 1
Patients' characteristics.

Characteristics	Group B10, n = 31	Group B15, n = 30	*P* value
ASA (I/II)	30/1	29/1	-
Age (yrs)	29.8 ± 7.5	30.0 ± 6.3	0.870
Height (cm)	158.6 ± 1.2	159.3 ± 1.0	0.597
Weight (kg)	55.3 ± 7.1	54.6 ± 6.7	0.712
BMI (kg/m^2)	22.0 ± 2.4	21.5 ± 2.2	0.410
Gestational week	6.1 ± 0.9	6.3 ± 0.9	0.758
Number of times pregnant	3[2–4]	3[3–4]	0.133
Number of cesarean sections	0[0–0]	0[0–0]	0.754
Number of vaginal deliveries	1[0–2]	2[1–2]	0.222
Number of abortions	0[0–1]	0[0–1]	0.513
Note: Data are expressed as means ± standard deviations (SD) or median [range]. Group B10 received butorphanol 10 μg/kg. Group B15 received butorphanol 15 μg/kg.			

The sample size was achieved after seven effective/ineffective crossovers using the up-and-down method (Fig. 2). There were 31 and 30 patients in Groups B10 and B15, respectively. Furthermore, 14 patients were ineffective and given RMZ as rescue therapy in both groups. The ED_{50} (90% CI) and ED_{90} (90% CI) of the RMZ were 0.263 (0.215–0.310) mg/kg and 0.331 (0.299–0.436) mg/kg in Group B10, and 0.224 (0.191–0.261) mg/kg and 0.275 (0.253–0.374) mg/kg in Group B15, respectively (Table 2).

Table 2
ED_{50} and ED_{90} of RMZ for two groups.

Group	ED_{50}(90% CI), mg/kg	ED_{90}(90% CI), mg/kg
Group B10	0.263 (0.215–0.310)	0.331 (0.299–0.436)
Group B15	0.224 (0.191–0.261)	0.275 (0.253–0.374)
Note: The centered isotonic regression was used to determine ED_{50} and ED_{90} of RMZ and their respective 90% CI.		

Table 3 displays the perioperative outcomes. The initial and total dosage of RMZ consumed in Group B10 was significantly higher than that in Group B15 (14.9 ± 2.5 *vs.* 12.7 ± 2.7 mg, 17.9 ± 3.3 *vs.* 16.0 ± 3.7 mg, $P < 0.05$, respectively). The procedure duration (3.7 ± 1.0 *vs.* 3.5 ± 0.8 min, P = 0.365) was not significantly different between the two groups. The recovery time in Group B10 was faster than in Group B15 (9.8 ± 2.3 *vs.* 12.5 ± 3.6 min, $P < 0.001$).

Table 3
Comparison of perioperative outcomes between the 2 groups.

Items	Group B10	Group B15	*P* value
Initial dose of RMZ (mg)	14.9 ± 2.5	12.7 ± 2.7	0.002
Total dose of RMZ (mg)	17.9 ± 3.3	16.0 ± 3.7	0.037
Duration of procedure (min)	3.7 ± 1.0	3.5 ± 0.8	0.365
Recovery time (min)	9.8 ± 2.3	12.5 ± 3.6	0.001
Note: Data are expressed as mean ± SD. The total dose of RMZ: initial dose plus additional dose. Students t-test was used to assess differences.			

The results that the reduction of MAP in both groups was about only 11%. HR, MAP, and SpO_2 levels in the two groups at different time points have no statistical difference ($P > 0.05$) (Table 4). The incidence of PONV in the B10 and B15 groups was 3.2% and 16.7%, respectively. But there were no statistically differences between the 2 groups in the rate of all anesthesia-related adverse events ($P > 0.05$) (Table 5).

Table 4
Comparison of HR, MAP, and SpO_2 of the two groups at different time points.

Parameters	Group	Time point		*P* value
		T1	T2	
HR (beats/min)	Group B10	80.1 ± 14.7	83.1 ± 11.3	0.602
	Group B15	79.0 ± 12.6	81.1 ± 12.0	0.507
MAP (mmHg)	Group B10	87.8 ± 8.4	77.9 ± 9.4	0.196
	Group B15	86.4 ± 7.5	77.0 ± 6.4	0.660
SpO_2 (%)	Group B10	99.5 ± 0.6	98.9 ± 1.2	0.596
	Group B15	99.5 ± 0.6	99.0 ± 0.9	0.720

Note: Date are expressed as mean ± SD. T1: 5 min after entering the operating room; T2: Immediately after IV injection of RMZ. Students t-test was used to assess differences.

Table 5
Anesthesia-related adverse events.

Adverse events	**Group B10** n = 31	**Group B15** n = 30	***P* value**
SpO_2 < 90%	0(0)	0(0)	-
Hypotension	2(6.4)	2(6.6)	-
Bradycardia	0(0)	0(0)	-
Injection-site pain	1(3.2)	0(0)	-
Injection-site pain VAS score	1[0–0]]	0 [0–0]	-
Uterine contraction pain	4(12.9)	5(16.7)	0.731
Uterine contraction pain VAS score	0 [0–0]	0 [0–0]	-
Dizziness	2(6.5)	2(6.7)	-
PONV	1(3.2)	5(16.7)	0.104

Note: Data are expressed as n [%] or median [range]. A Chi-square or Fisher exact probability test was used to assess differences of adverse events.

Discussion

Cervical dilatation during a painless artificial abortion can result in intense stimulation [12]. Light or deep anesthesia can cause severe adverse events, posing many challenges for anesthesiologists regarding

actual drug selection. The most common drug combination for painless artificial abortion is sedative and analgesic drugs. Due to the short duration of abortion surgery, anesthesiologists required rapid induction while also ensuring the safety and quality of the anesthesia. The minimum effective dose can achieve adequate anesthesia while reducing drug dosage and the incidence of adverse events.

Among the many methods for determining ED_{50} and ED_{90}, up-and-down method is quick and simple, and it can yield solid conclusions with a relatively small sample size [13]. The experiment in the present study was terminated when seven crossover points (effective to ineffective) were achieved with 31 and 30 samples, respectively. Using the probit regression analysis, the ED_{50} of RMZ was 0.263 mg/kg in Group B10 (10 μg/kg butorphanol) and 0.224 mg/kg in Group B15 (15 μg/kg butorphanol). In contrast, the ED_{90} of RMZ was 0.331 mg/kg in Group B10 and 0.275 mg/kg in Group B15.

As a classic sedative in anesthesia for outpatient surgery, propofol has the strengths of fast onset time, profound sedative effect, and short duration. However, it produces significant respiratory and circulatory depression, increasing the risk for adverse events like hypoxemia and hypotension [15, 16]. When used for procedural sedation, the sedative efficiency of RMZ was less than that of propofol as a novel IV sedative drug [17, 18]. However, RMZ may be a safer sedative during anesthetic induction than propofol [9, 19]. Many studies demonstrated that RMZ may reduce the incidence of hypotension, hypoxemia and injection-site pain compared to propofol, which is its most pronounced feature and advantage [7, 18, 20]. Our findings revealed that the reduction of MAP in both groups was about 11%. This finding is consistent with Oka [21]. Only one patient in both groups had a maximum decrease in MAP (26.1%). However, no vasoactive medication is required, and the patient can recover relatively quickly. In either group, no patient experienced respiratory depression. The results indicate that RMZ has a little respiratory depressant effect. Therefore, our findings reveal that RMZ combined with butorphanol provided a good efficacy and safety profile in the sedation of painless artificial abortion.

When administered intravenously, butorphanol has strong analgesic and sedative effects. Various studies have demonstrated that the incidence of adverse events of butorphanol is dose-dependent [22]. Butorphanol is widely used in outpatient surgical anesthesia. However, there were differing views on the appropriate dose of butorphanol [3, 6], particularly for painless abortion. In the present study, patients were given two doses of butorphanol: 10 μg/kg (Group B10) and 15 μg/kg (Group B15). Butorphanol has a 3 to 5 min onset time, and RMZ should be administered 5 min after an IV bolus of butorphanol to maximize analgesic and sedative effects during a painless artificial abortion.

Butorphanol caused itching, somnolence, dizziness, nausea and vomiting among its adverse events [23]. Our findings revealed that the recovery time of Group B10 was faster than Group B15 (9.8 ± 2.3 *vs.* 12.5 ± 3.6 min, $P < 0.05$), which could be due to an increased incidence of somnolence and dizziness with an increase of butorphanol dosage, which significantly affects patient recovery time [22]. However, the incidence of PONV was lower in Group B10 (3.2% *vs.* 16.7%) than in Group B15, but not statistically different ($P = 0.104$). This result could be attributed to a small sample size.

The present study has several limitations. First, we found that patients without a history of vaginal delivery had relatively stronger stimulation of cervical dilation than those with a history of vaginal delivery. Because the dose of the next patient depended on the response of the previous patient, thus individual differences may affect the accuracy of the final result. Second, our pre-trials demonstrated that consumption for RMZ use alone was very high in terms of inhibiting stimulus-to-response of cervical dilatation and was prone to hemodynamic instability. Therefore, the study design did not include the blank control group (RMZ use alone). Third, as the dosage is increased, the likelihood of adverse drug reactions increases. However, the two groups have no statistical difference in adverse events. We believe that the small sample size is the main reason, and if the sample size was larger, the ED value would be more accurate, and the 90% CI would be narrower [14].

Conclusion

In summary, to enhance the sedative effect of RMZ, the recommended dose of butorphanol is 10 μg/kg. The ED_{50} and ED_{90} of the RMZ during artificial abortion were 0.263 and 0.331 mg/kg, respectively.

Declarations

Data availability statement

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

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Author contributions

Zhongqi Zhang conceived and designed the study. Jinming Chen wrote the manuscript. Xiaoling Li contributed to data collection. Zilan Hu performed the surgery. Yuling Zheng performed data analysis and interpretation. Ying Mai performed intravenous anesthesia. All authors read and approved the final manuscript.

Conflict of interest statement

The authors declare no conflict interests in this work.

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Figures

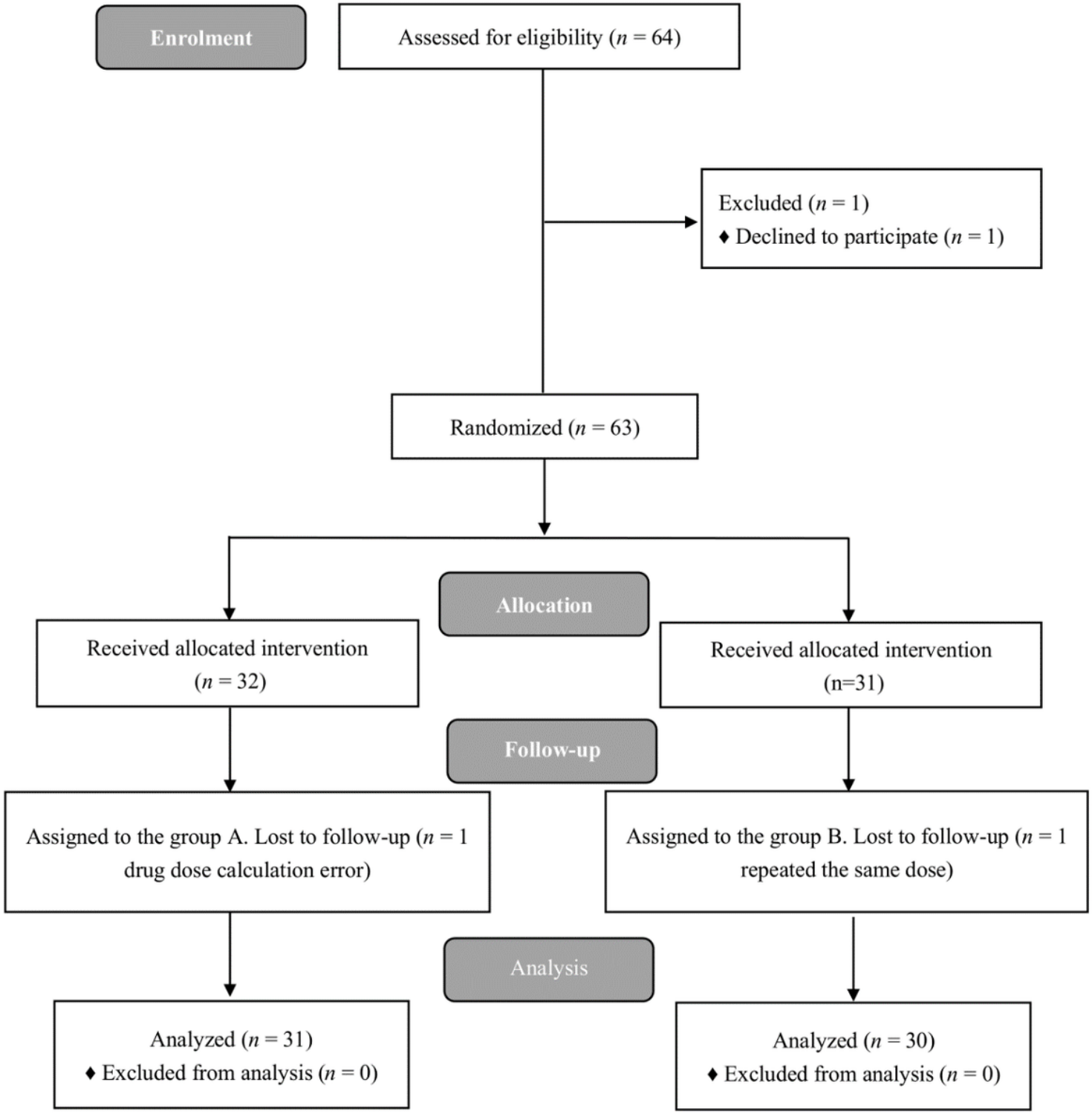
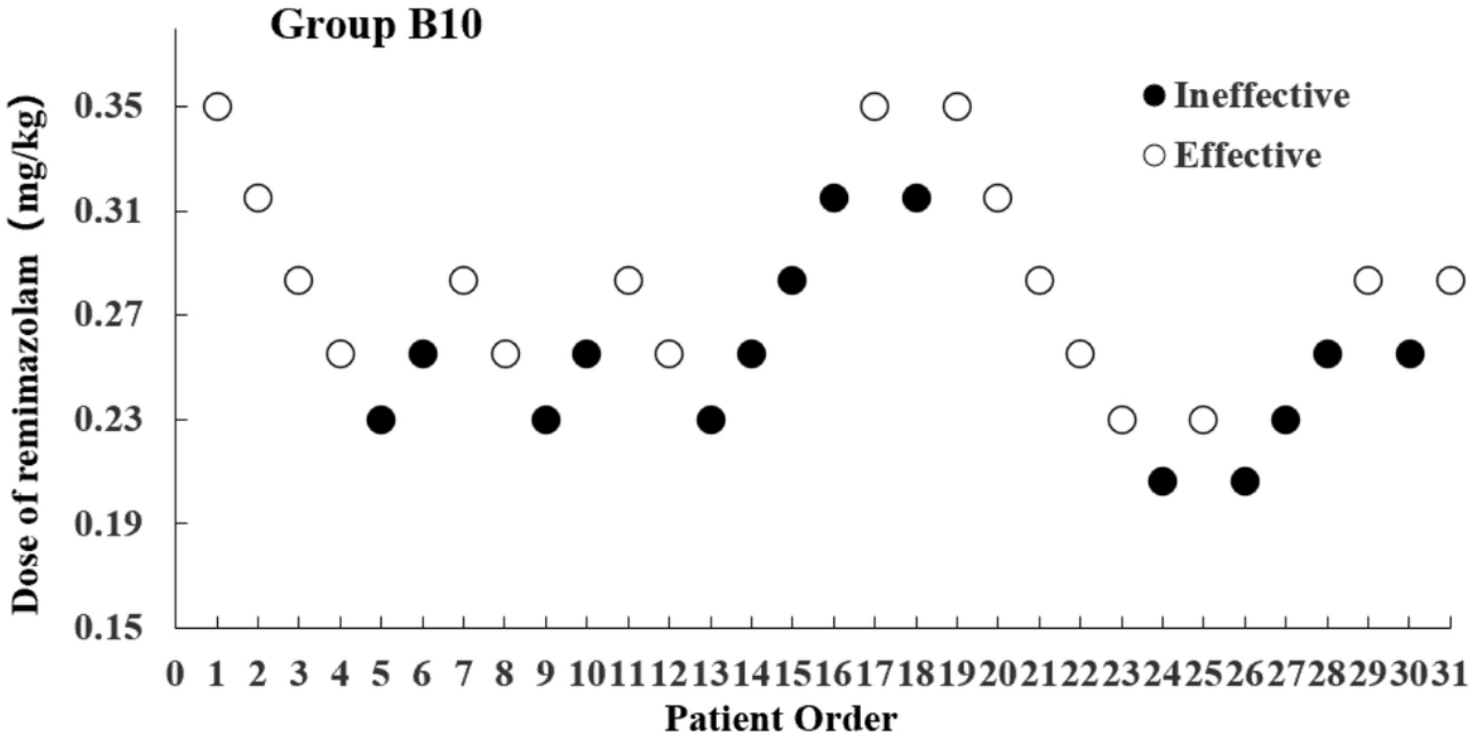


Figure 1

Flow diagram of the study.



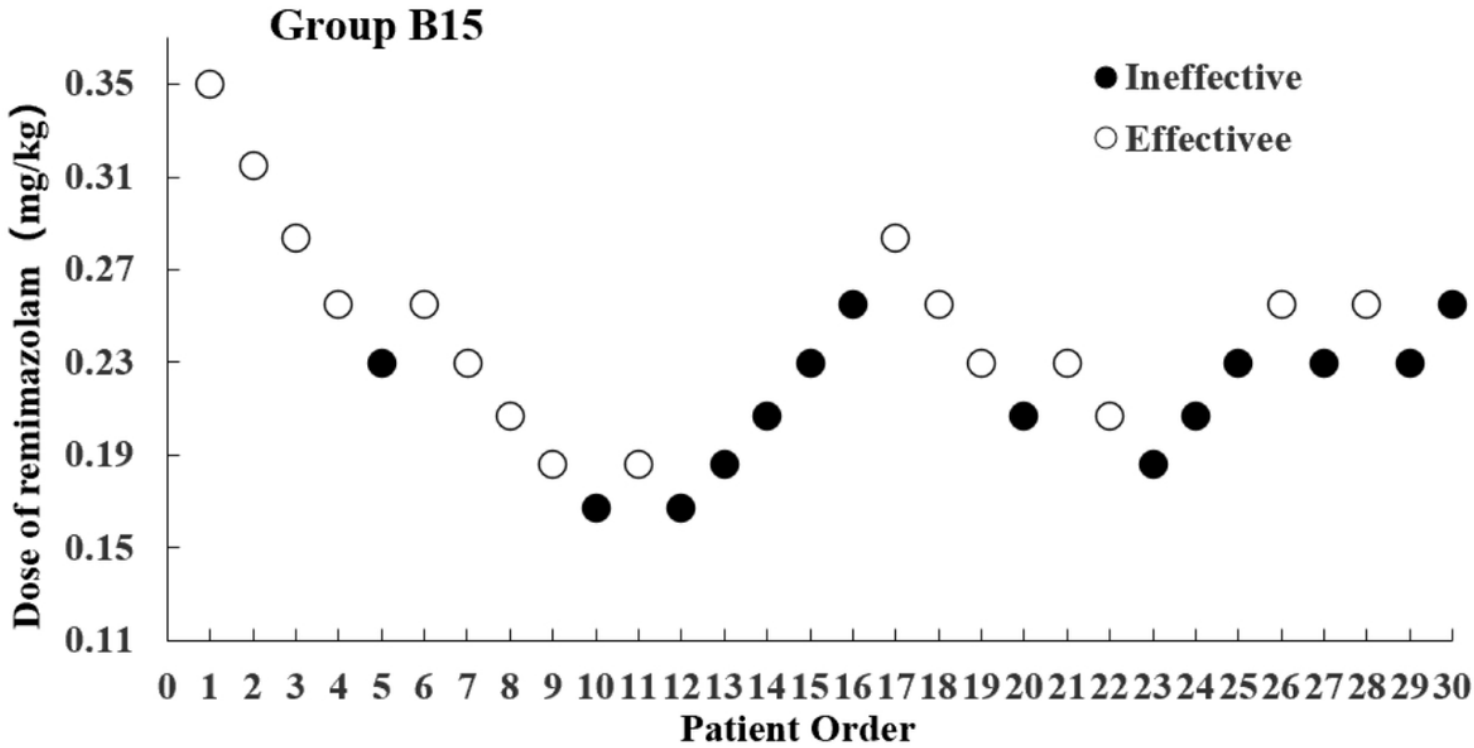


Figure 2

Dixon's up-down method plots for two groups.

Note: The white and black dots represent the "Effective" and "Ineffective" patient order, respectively.