The Appropriate Dose of Remimazolam Combined with Remifentanil in Anesthesia for Gastroscopy

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Research Article

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Abstract

Background: The appropriate doses of remimazolam combined with remifentanil were investigated in anesthesia gastroscopy by observing the effect of two methods of administration in fixed doses and dosed by ideal weight on success rate and recover effect in painless gastroscopy.

Methods: A total of 400 patients underwent the anesthesia of gastroscopy were randomized to divide into five groups (W1, W2, F1, F2 and C Group) in endoscopy center, with 80 cases in each group. All patients were given 0.25ug/kg of remifentanil before gastroscopy. The success rate, the quality of anesthesia resuscitation, heart rate, blood pressure, Pulse oxygen saturation, perioperative adverse events and Modified observer' s assessment of alert/sedation (MOAA/S) diachronic changes were recorded.

Results: In terms of anesthetic effects of the first dose of the drug(P<0.05), the patients in F1 group showed be lack of sedation obviously. The success rate of induction in F2 group was higher than that in F1 group. The success rate of sedation in W2 groups was highest (96%). The control group was second to W2 Group. Blood pressure in W2 Group was lower than W1 Group after first administration(P<0.05). There was no significant difference in next several minutes. There was no difference in blood pressure between W2 Group and C Group at T1(P>0.05). There was no difference in the changes of heart rate, recovery time and discharge time(P>0.05). The incidence of cough in F1 and W1 is high(P<0.05).

Conclusions: Remimazolam combined with remifentanil used were safe, and 0.3mg/kg of remimazolam combined with 0.25ug/kg of remifentanil by ideal body weight is better in painless gastroscopy.

Trial registration: The trial was registered on ClinicalTrials.gov: ChiCTR2100041759, registered 4 January 2021.

Background

Upper gastrointestinal (GI) endoscopy has been regarded as the gold standard for the diagnosis of upper GI tract diseases[1]. In recent years, endoscopies have exhibited an increasing trend. However, this is an invasive and unpleasant procedure[2]. Procedural sedation has been considered to be necessary, in order to improve the discomfort, anxiety, or pain experience[3]. The main narcotic drugs used in painless gastroscopy are propofol, midazolam and adjuvant opioids. However, each drug has its advantages and disadvantages [4, 5]. Among them, propofol has been the most preferred drug for general sedation due to its excellent sedative properties and a short terminal half-life. But propofol has the potential to cause cardiovascular and respiratory depression, and hypoxia [6-9]. Midazolam has been the most commonly used drug among benzodiazepines with rapid onset of action and potent amnestic properties [10]. Nevertheless, the rather long half-life possibly results in a comparatively long sedative effect of midazolam [11, 12]. Remimazolam is a new benzodiazepines, which is a super-short-acting sedative/anesthetic medicine[13]. This was developed to exploit in a benzodiazepine the esterase pharmacology successfully deployed in the opioid remifentanil[14]. Furthermore, this can be rapidly

hydrolyzed by unspecific cholinesterase, and its effect and metabolism are faster[15]. Remimazolam is degraded to CNS7054, which appears to have negligible hypnotic activity[16]. This has advantages in safety and efficacy [3]. Hence, this new drug can provide rapid onset sedation with prompt recovery, as well as minimized respiratory depression, airway obstruction and blood pressure perturbation[17]. Remifentanil has a rapid onset and short maintenance time and has little effect on hemodynamics[18] . There was no clear relationship between the clearance rate of remimazolam and body weight. Therefore, administering fixed dose medicine might have an advantage[19] . However, clinical practice is not consistent with that totally. In the present study, in order to optimize the effect of remimazolam combined with remifentanil in painless gastroscopy, the relationship between dose and body weight of remimazolam in painless gastroscopy was investigated.

Methods

Patients eligibility

The patients who received painless gastroscopy in the Endoscopic Center of Yangzhou University Affiliated Hospital were included for the present study in January 2021. These patients were approved by the Ethics Committee of Yangzhou University Affiliated Hospital(2020-YKL10-25), and provided a written informed-consent. The trial was registered at ClinicalTrials.gov with registration number ChiCTR2100041759(01/04/2021). This was a double-blind, randomized, parallel-group study. A total of 400 patients, 18-65 years old and scheduled to undergo diagnostic gastroscopy, were eligible for the present study. In addition, these patients with ASA physical status score of I or II had a body mass index (BMI) of 18-30 kg/m^2. Patients were excluded if they were pregnant or lactating, had obvious cardiopulmonary liver and kidney dysfunction before the operation, had severe neuropsychiatric diseases, or Benzodiazepine and opioids treatment history.

Procedures

These patients were randomly divided into five groups: ideal body weight of 0.2 mg/kg remimazolam group (W1 group), ideal body weight of 0.3 mg/kg remimazolam group (W2 group), fixed dose of 10 mg remimazolam group (F1 group), fixed dose of 12 mg remimazolam group (F2 group), and 1.5 mg/kg propofol control group (C group). Male: IBW (kg) = [height (cm) - 100]. Female: IBW (kg) = [height (cm) - 105]. All patients were given 0.25 ug/kg of remifentanil before receiving the study medication.

Patients received routine fasting and drinking in that morning, and the nurse opened the venous vessels for them. Then, they orally received 10 ml of dyclonine glue before the examination for surface anesthesia. Their heart rate (HR), blood pressure (BP), and blood oxygen saturation (SpO_2) were continuously monitored. Before the operation, these patients were given oxygen by nasal catheter (4L/min). All patients were intravenously given low-dose remifentanil for analgesic pretreatment. Then, according to the random arrangement, different doses of remimazolam benzenesulfonic acid were intravenously administered (Hengrui Pharmaceutical Co., Ltd., batch number: 2019S00728). Patients in

the propofol group were given a 1.5mg/kg propofol injection (AstraZeneca Pharmaceutical Co., Ltd., batch number: X19134A). The gastroscopy operation began when the MOAA/S score was ≤3. When the MOAA/S score was ≥4 at three minutes after the administration, sedation failure was recorded, and propofol was used to complete the examination. The sedation was maintained by giving 1/4 of the initial dose each time when patients made any body movement, and it was ensured that the MOAA/S score was ≤3. Within 15 minutes, no more than three additions were given. If these three additional doses within the 15-minute time window were not sufficient to maintain the sedation, sedation failure was recorded. When the heart rate was less than 50 bpm, 0.5 mg of atropine was given, and when the blood pressure decreased by more than 30% of the baseline, vasoactive drugs were given. If the SpO_2 was less than 90%, oxygen was given under pressure by mandible treatment or mask. The MOAA/S scores were recorded before the examination (T0), after the first administration (T1) per two minutes (T2, T3 and T4), until the check was finished (T5), and when the patient was awake. Then, recording was performed every five minutes, until the patient matched the standard for discharge. Vital signs, including HR, systolic (SBP)/diastolic (DBP), SpO_2, MOAA/S score, recovery time (from the time of last dose to recovery time), time to release from hospital, and adverse reactions, were all recorded from pre-administration to post-administration.

Scoring criteria

Sedation Assessment Scores[20] in Table 1 :

Table 1. Sedation Assessment Scores

Modified Observer's Assessment of Alertness/Sedation	
Response	Score level
Responds readily to name spoken in normal tone	5(alert)
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1
Does not respond to noxious stimulation	0

Separation criteria[21]:10 minutes after the end of the operation for the first time to determination of eligibility for separation, and subsequently every five minutes, until the subjects met the following conditions before leaving the hospital accompanied by their relatives; the range for blood pressure and heart rate fluctuation was within ±20% of the preoperative basic value, and stable for more than 10 minutes; no or only mild pain; no or only slight nausea and vomiting; no dizziness in the sitting position and during movement; stable gait.

Statistical methods

The SPSS 25.0 statistical software was used for data processing. The measurement data were expressed as ($\bar{x}$ ± SD). Continuous variables should be normality checked first, expressed as ($\bar{x}$ ± SD) if the normal distribution is met. The between-group comparisons of were analyzed by ANOVA test. And each group within the comparison was analyzed by paired sample test. The counting data was expressed in rate, and χ^2 test was used. P<0.05 was considered statistically significant.

Results

2.1 *General situation of patients*

The gender, mean age, weight, height, body mass index, examination operation time, and vital signs of all patients are presented in Table 2. There was no significant difference in basic parameters among the groups (P>0.05). The heart rate, mean arterial pressure and pulsive oxygen saturation were not significantly different between groups (P>0.05).

Table 2 Baseline characteristics of the patients (n=80)

Characteristic	W1 group	W2 group	F1 group	F2 group	C group
Gender (M/F)	42/38	41/39	43/37	49/31	44/36
Age (years)	49.9 11.9	47.5 13.1	11.0	49.2 10.5	50.3 10.7
Weight (kg)	67.5 6.8	67.5 10.5	66.7 9.7	69.7 12.5	67.1 8.5
Height (cm)	168.7 7.7	168.2 6.9	167.3 7.5	167.0 8.6	167.7 7.7
BMI (kg/m^2)	23.7 2.0	23.8 2.8	23.8 2.7	24. 8 2.8	23.8 2.5
Duration of gastroscope (min)	5.3 2.7	5.6 3.6	6.8 2.2	6.5 3.5	6.8
HR (times/minute)	81.8 15.0	76.9 11.8	81.9 13.8	76.8 14.7	14
MAP (mmHg)	102 12	101 12	107 13	107 15	105 14
SPO_2 (%)	99.4 1.0	99.2 1.1	98.9 1.0	99.2 1.1	99.4 0.8

2.2 *HR and MAP changes of the patients during the perioperation*

During the course of sedation, the heart rate diachronic analysis (Fig. 1) revealed that the heart rate in these five groups tended to be stable, and no significant changes were observed during the examination and after the anesthesia (P>0.05). Furthermore, none of the patients suffered from sinus tachycardia or bradycardia. The analysis of diachronic changes in blood pressure (Fig. 2) revealed that the blood pressure of patients in the W2 group significantly decreased (P<0.05), when compared to the W1 group, after the initial administration. But there was no significant difference between after administration at two minutes and later (P<0.05). All five groups had lower blood pressure at T1, but these were within the normal range. There was no difference in blood pressure between the W2 Group and C Group at T1 (P>0.05).

2.3 *Effects, recovery and adverse reactions of anesthesia*

The MOAA/S scores in each group (Fig. 3) began to decrease after administration, The MOAA/S decreased more in the W2 group than in the W1 group (P<0.05). The MOAA/S decreased more in the F2 group than that in the F1 group (P<0.05). For the sedative effects of the first dose (Table 3, P<0.05), patients in the F1 group presented with lack of sedation. The success rate was clearly higher in the F2 group, when compared to the F1 group. The W2 group had the highest success rate, while the C group had a success rate second to the W2 group (P<0.05).

Both recovery times in each group, and the time from last administration to discharge are presented in Table 3 The difference among groups was not statistically significant (P>0.05). The common adverse reactions were mild respiratory inhibition and hiccups, but there was no significant difference among these five groups (P>0.05). The incidence of cough was the highest in the F1 group, and the incidence of injection pain in the whole experimental group was 4%. However, the incidence of injection pain was 60% in the propofol control group (P<0.05).

Table 3 Anaesthesia effects, recovery and complications in each group (X±s, n=80)					
	C group	W1 group	W2 group	F1 group	F2 group
success rate no. (%)	65（81）	57（71）$^{\Delta}$	77（96）	16（20）▲	53(66)
Awakening time (minute)	11.2	9.3 2.9	10.1 3.3	9.0 3.1	9.7 .5
Discharge time (minute)	30.0	31.3 8.2	35.6 9.8	29.2 9.1	30.9 9.5
hiccup no. (%)	6（7.5）	13（16）	3（4）	3（4）	10（12.5）
Respiratory inhibition no. (%)	13（16）	10（12.5）	10（12.5）	0（0）	10（12.5）
Cough no. (%)	13（16）	3（4）	0（0）	48（60）	3（4）
Injection pain no. (%)	48（60）	3（4）*	0（0）*	0（0）*	0（0）*
Note: Compared with W2 group, $^{\Delta}P$<0.05; compared with F2 group, ▲P<0.05; compared with C group, *P<0.05					

Discussion

In recent years, patients have very high requirements for comfort in gastroscopy with the development of painless gastroscopy. Propofol were widely used to perform the anesthesia sedatives in painless gastroscopy with lots of advantages. However, there is always the unavoidable problem of inhibiting the respiratory and circulatory system[8] . The new benzodiazepine, remimazolam, acts on $GABA_A$ receptor[22]. This induces the hyperpolarization of the nerve cell membrane by increasing the opening of the chloride channel , thereby inhibiting neuronal activity[23]. Its elimination half-life is short, and this does not depend on the P450 enzyme metabolism. Remimazolam takes effect rapidly, the clearance is fast, and the metabolite is inactive, and has little effect on heart rate and blood pressure[14]. Remifentanil is an agonist of a μ receptor, which rapidly reaches the blood-brain balance in one minute, and can be rapidly hydrolyzed by nonspecific esterases[24]. Furthermore, the effect does not depend on liver and kidney function. Studies have shown that the combination of remifentanil and sedatives in painless gastroscopy can reduce the amount of sedatives and maintain stable vital sign[25]. In addition, remimazolam and remifentanil have similar rapid onset and elimination effects, and they have strong synergistic effects [26]. Fentanyl combined with remimazolam could obtain better sedative and analgesic effect in gastroscopy anesthesia[6] . However, both fentanyl and sulfentanyl have the characteristics of slow onset and long duration of action, while duration of gastroscopy examination is short, and no additional analgesia is required after the examination. Thus, remimazolam combined with remifentanil with a short duration may be a better choice[27].

In the instructions, remimazolam is recommended for painless gastroscopy at a dose of 5 mg. However, a proper anesthetic level is often not achieved in clinical practice. According to the study conducted by Rex

D etc [28], a dosage of 10mg was selected for the F1 group, and the results revealed that the sedation success rate of remimazolam was only 20% in first dose 10mg (F1 group), while the success rate of 12mg (F2 group) was significantly higher, when compared to that in the F1 group. In addition, clinical practice has revealed that there are significant individual differences in the anesthetic effect of remimazolam, according to the actual body weight, especially for obese patients and emaciated patients, who are prone to sedation deficiency or significant recovery delay. Therefore, the present study also used ideal body weight to calculate the dosage of anesthetics. The results revealed that the success rate of first-dose anesthesia in the W1 and W2 groups significantly improved. Furthermore, the success rate of first-dose anesthesia in the high-dose W2 group was the highest, and there was no obvious delay, when compared to the W1 group, in terms of recovery time and discharge time. Moreover, there was no significant difference in anesthetic effect, when compared with traditional propofol. The sedation level and onset time were better in the W2 group, and the maintenance time was the most suitable for gastroscopy. The recovery time in the five groups ranged within 9-10 minutes, indicating that there was no significant difference in the recovery time of remimazolam and propofol on systema nervorum centrale inhibition. This could satisfy the sedation level and maintenance time required for the operation.

These results show that remimazolam has the effect of increasing heart rate slightly [29]. During cardiovascular safety studies conducted in animals, as a result of the decrease in systemic vascular resistance, remimazolam produced a dose-related modest reduction in mean arterial blood pressure and a compensatory increase in heart rate [23, 30]. The present study revealed that the fluctuation of heart rate and blood pressure slightly increased with the increase in dose. Patients in the W2 group and F2 group presented with an early increase in heart rate. Hence, remimazolam may have a unique advantage in the stabilizing heart rate for patients with sinus bradycardia. Except for the decrease in blood pressure in the C group, the heart rate and blood pressure of patients in the other groups were stable. Therefore, remimazolam has the advantage of less influence on the circulatory system, when compared to propofol. The common side effect of remifentanil is bradycardia[31]. In the study on remimazolam combined with remifentanil in painless gastroscopy, the heart rate increased slightly after first administration and then stabilized till the end of anesthesia. the anesthesia of remimazolam combined with remifentanil could stabilize the heart rate. The incidence of injection pain in the experimental group was significantly lower than that in the control group. Therefore, remimazolam effectively avoids the adverse reactions of propofol injection pain compared with propofol.

Conclusion

Briefly, remimazolam combined with remifentanil can provide the safe and effective sedation for gastroscopy, with success rates that are very encouraging. The ideal weight of 0.3 mg/kg of remimazolam combined with 0.25 ug/kg of remifentanil is more suitable for painless gastroscopy. This is a single-center, small-sample study, and also requires a lot of research to further verify our conclusions. In addition, the pharmacokinetics and pharmacodynamics of remimazolam were described by a standard three-compartment effect model[14]. It is suitable for target controlled infusion, allowing for a possible

better effect in short time sedation and general anesthesia. On the basis of these data, further studies on the potential utility of remimazolam for sedation/anesthesia are warranted. For example, the application effect of remimazolam in total anesthesia.

Abbreviations

BMI: Body mass index; HR: heart rate; BP: blood pressure; SpO_2: blood oxygen saturation; MOAA/S: Modified observer' s assessment of alert/sedation

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from all participants. The study was approved by the Yangzhou University Affiliated Hospital research ethics board(2020-YKL10-25). The trial was registered on ClinicalTrials.gov: ChiCTR2100041759, registered 4 January 2021.

http://www.chictr.org.cn/showproj.aspx?proj=119674

Consent for publication

Not applicable.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Conceptualization: MHW, STL; Methodology: YZ; Formal analysis and investigation: MG; Writing-original draft preparation: FXL, MG; Writing-review and editing: JYZ, MHW. All authors have read and approved the manuscript

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Figures

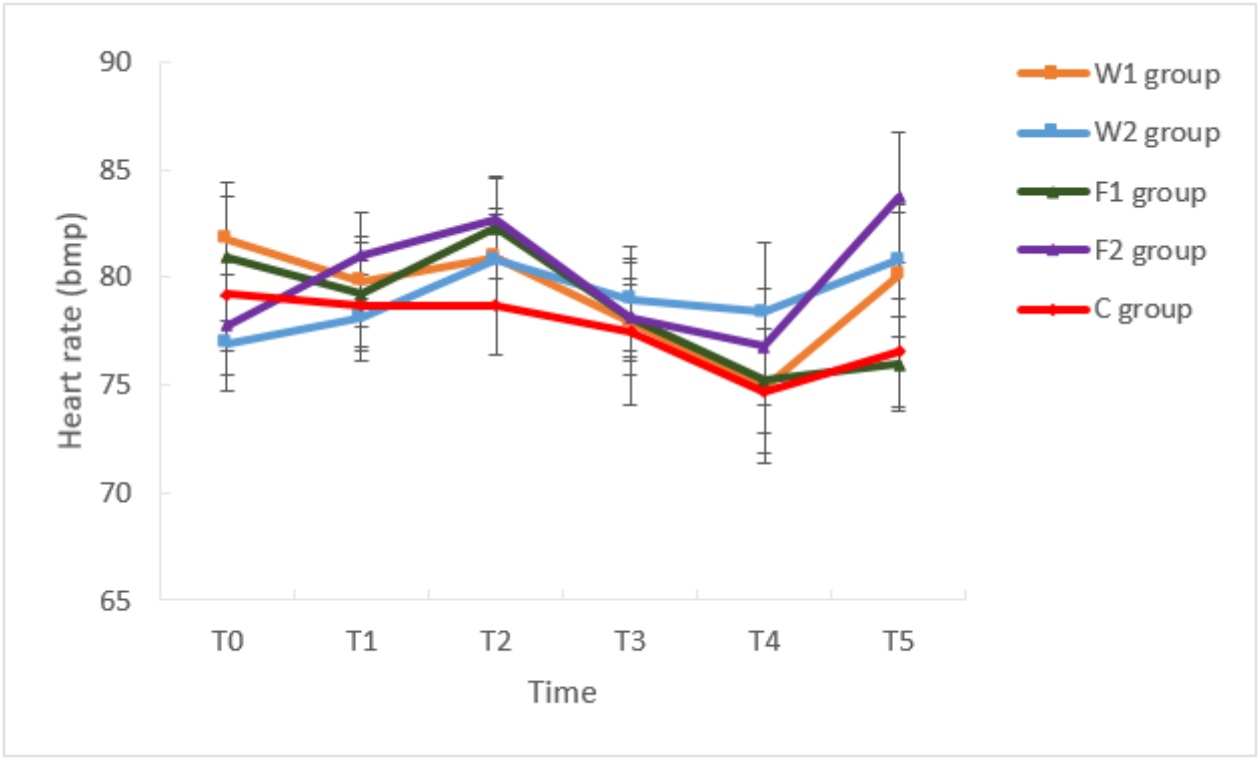

Figure 1

Changes of heart rate of patients before and after administration

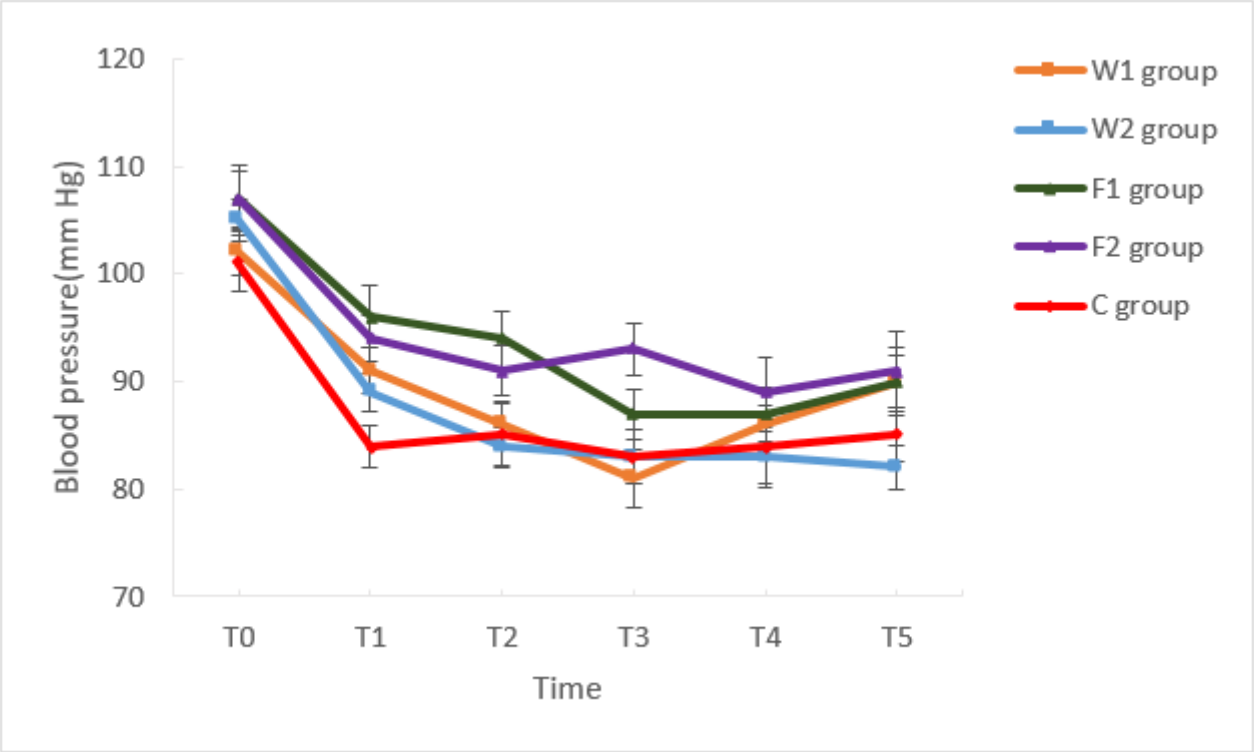

Figure 2

Changes of blood pressure of patients before and after administration

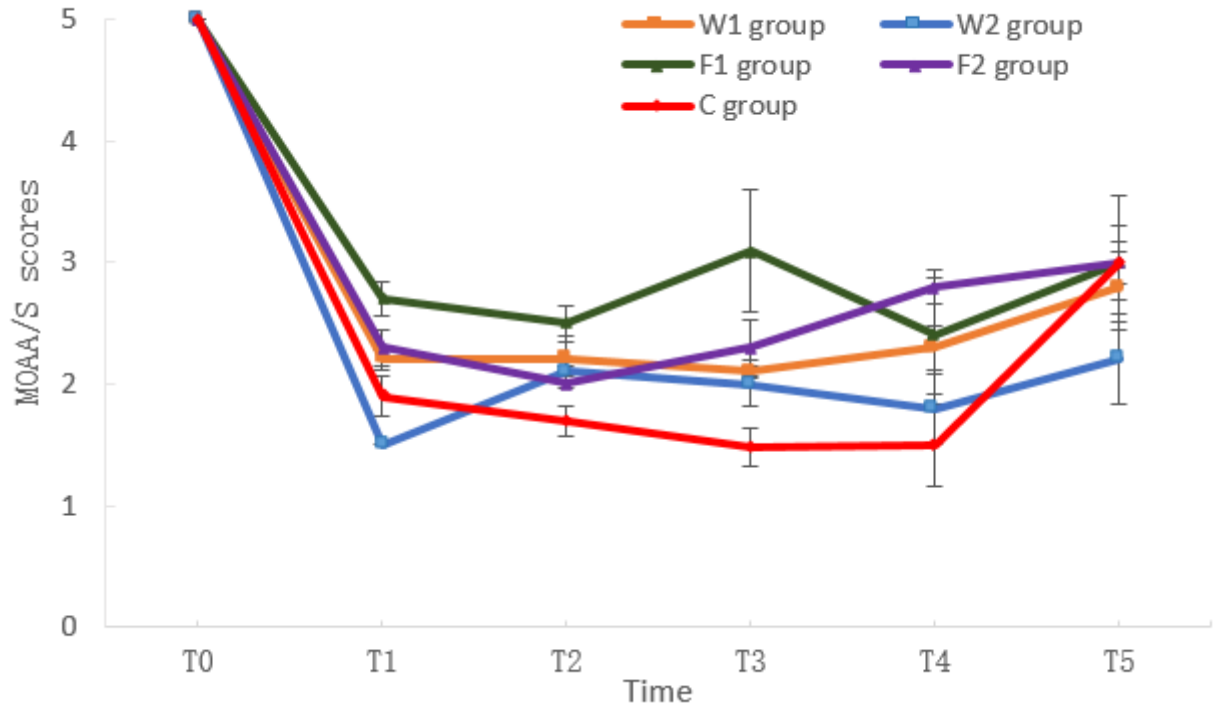

Figure 3

Changes of sedation level of patients before and after administration Note: MOAA/S=Modified observer’s assessment of alert/sedation

Supplementary Files

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