Drug Design, Development and Therapy

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CLINICAL TRIAL REPORT

Clinical Study of Flumazenil Antagonizing Remimazolam on Nausea and Vomiting After Gynecologic Day Surgery

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Purpose: To evaluate the effect of flumazenil antagonizing remimazolam on postoperative nausea and vomiting (PONV) after gynecologic day surgery.

Patients and Methods: 141 cases of gynaecological daycase surgery patients in Weifang People's Hospital were selected, randomized into group F (flumazenil group, 71 cases) and group C (control group, 70 cases). Dexamethasone 5 mg, flurbiprofen axetil 50 mg, and droperidol 1 mg were given intravenously before induction of anesthesia in both groups. Anesthesia induction: Remimazolam 0.25mg / kg was injected within 1 minute. After the patient fell asleep, mivacurium chloride 0.2mg / kg was injected for 30 seconds and alfentanil 20ug / kg was injected for 30 seconds. Anesthesia maintenance: Remimazolam 1mg/kg/h and alfentanil 40ug/kg/h were continuously pumped by micro pump. Stopping the injection of remimazolam and alfentanil at the end of the operation. Flumazenil 0.2 mg was given to antagonize remimazolam in group F after 1 minute. Group C was given an equal volume of saline. The incidence of PONV in the postoperative PACU and over a 24-hour period, patient awakening time, and general patient information were recorded.

Results: The incidence of PONV in both groups within 24 hours was 50.70% in group F was significantly higher than 32.86% in group C. The difference was statistically significant ($P < 0.05$). The incidence of PONV in the PACU was 5.6% in group F and 8.6% in group C. The difference was not statistically significant ($p > 0.05$).

Conclusion: Flumazenil antagonism of remimazolam increases the incidence of PONV within 24 hours in gynecologic day surgery patients and has no significant effect on the incidence of PONV in the PACU.

Keywords: flumazenil, remimazolam, gynecologic day surgery, postoperative PONV

Introduction

With the improvement of medical technology, gynecological day surgery has developed into a mature mode of surgical management, which can significantly shorten the patient's hospitalization time, reduce the patient's hospitalization cost, accelerate the turnover of beds, and improve the utilization rate of medical resources.[1] As a short-acting opioid, alfentanil has the characteristics of mild respiratory depression and low incidence of PONV.[2] As a new type of benzodiazepine, remimazolam has a rapid onset of action, no accumulation, and little effect on respiration and circulation.[3] Flumazenil as a specific antagonist of remimazolam accelerates patient awakening and improves turnover in day surgery.[4] The expert consensus on anesthesia for hysteroscopic practice recommends that remimazolam combined with alfentanil may be used for general anesthesia.[5] However, according to the literature in general anesthesia surgery, the incidence of PONV with remimazolam is significantly higher than that with propofol.[6,7] Prophylactic combination of different antiemetics reduces the incidence of PONV with remimazolam.[8] There is a lack of research on whether flumazenil antagonizing remimazolam affects the incidence of PONV. By studying whether flumazenil can increase the incidence of postoperative nausea and vomiting, the experimental results obtained are used to guide future clinical work, explore and avoid the risk factors

Received: 11 October 2023
Accepted: 13 February 2024
Published: 4 March 2024

of postoperative nausea and vomiting, which is conducive to rapid postoperative recovery and optimize the patient ‘s medical experience.

Information and Methodology

Methodology and Design

This was a randomized, controlled study that, to observe the effect of flumazenil antagonizing remimazolam on PONV in gynecologic day surgery patients. One hundred and forty-one patients who underwent gynecological day surgery at Weifang People’s Hospital from August 2023 to September 2023 were selected as study subjects. The study was approved by the Medical Ethics Committee of Weifang People’s Hospital and China Clinical Trials Registry [ChiCTR2300074137], and informed consent was obtained from the patients. The present study was performed according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients before the procedures.

Patient Inclusion Criteria

141 patients who underwent elective gynecologic day surgery; ASA classification I–II; BMI 18~30 kg/m2; Ages 18~60. Exclusion Criteria: Patients who were allergic to benzodiazepines, opioids, mivacurium and other drugs;Patients hospitalized for more than 24 hours; Postoperative deconditioned patients; those who were operated for more than 1 hour.

Methods of Anesthesia

The patients were routinely forbidden to eat, and no drugs were used before entering the operating room. Preoperative Apfel score was used to evaluate the risk factors of PONV in each patient, as detailed in Table 1. After admission, the upper limb forearm venous access was opened, and 500 mL of sodium lactate Ringer ‘s solution was routinely infused. Connected to monitor ECG, HR, spO2, NIBP, BIS, measured every 5 minutes. Both groups were prophylactically administered dexamethasone 5 mg, flurbiprofen axetil 50 mg, and droperidol 1 mg before induction; Anesthesia induction: Patients in both groups were given remimazolam 0.25 mg/kg IV pumping,[9] limited to 1 minute. After the patients lost consciousness, mivacurium chloride 0.2 mg/kg was given intravenously over 30 seconds in both groups. Alfentanil 20ug/kg was administered intravenously over 30 seconds and a laryngeal mask was placed 3 minutes later. Anesthesia maintenance:

Table 1 General Information of Patients

Index	Group F (n = 71)	Group C (n = 70)	P
Age (years, $\bar{x} \pm S$)	41.14±8.52	42.41±9.17	0.40
Weight [kg, M(Q1~Q3)]	62 (50.6,67)	61.5 (56.75,70)	0.78
BMI [kg/ m^2, M(Q1~Q3)]	23.63 (21.61,25.56)	23.95 (22.67,26.06)	0.17
ASA grade			0.21
I	44 (61.97)	38 (54.29)	
II	27 (38.03)	32 (45.71)	
Apfel Score			0.48
2	50 (70.42)	53 (75.7)	
3	21 (29.58)	17 (24.3)	
Operative category			0.29
Hysteroscopy	56 (78.87)	60 (85.71)	
Cone cutting	15 (21.13)	10 (14.29)	

Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists.

Both groups were given remimazolam 1mg/kg/h compounded with alfentanil 40ug/kg/h pumped for maintenance. The parameters were set as follows: tidal volume 6~8 mL/kg, respiratory rate 10~12 times/min, I / E.

1:2, and end-expiratory CO2 maintained at 35~45 mmHg. Anesthesia awakening: One minute after stopping the drug, group F was given flumazenil 0.2 mg intravenously.[10] Group C was given an equal volume of saline. After the patient called to open his eyes, the laryngeal mask was removed and he was transferred to the PACU for observation. Aldrete scores ≥ 9 were sent back to the ward and discharged after meeting the criteria for discharge. Follow-up was performed the day after surgery by means of an electronic questionnaire. In the presence of intraoperative somatic movements that interfere with surgery, a single additional dose of remimazolam 0.05 mg/kg was added and repeated as necessary. Atropine 0.3 mg was given to treat bradycardia (HR < 50 beats/min); Hypotension (SBP below <90 mmHg or ≥30% lower than preoperative or mean arterial pressure <60 mmHg) was elevated with ephedrine 6 mg.

Observation Indicators

Main indicators:Incidence of PONV in patients within 24 hours.

Secondary indicators: (1) Incidence of PACU (2) Time to wakefulness, defined as the time from cessation of sedative medication to removal of the laryngeal mask (the first of 3 consecutive MOAA/S scores of 5); (3) Induction and maintenance doses of anesthetic drugs; (4) Duration of anesthesia, defined as the time from the start of anesthesia induction to the end of surgery when the drug was discontinued; (5) Time to achieve adequate sedation, defined as the time to obtain adequate sedation from the initial dose (first item of the MOAA/S score ≤ 3); (6) Incidence of treatment-associated hypotension (defined as hypotension occurring during sedation and requiring at least one administration of antihypertensive medication); (7) Apfel scores were recorded; (8) Vital signs (heart rate, respiration, blood pressure, oxygen saturation [SpO2]) and routine clinical laboratory tests were monitored at various times during the trial to assess safety; (9) Monitor for any adverse events (AEs) associated with flumazenil, including hypotension, sinus bradycardia.

Statistical Analysis

By pretest, the incidence of PONV within 24 hours after surgery was 60% in group F and 33.3% in group C, respectively. According to $\alpha = 0.05$, $1\text{-}\beta = 0.9$, the proportion of the experimental group and the control group was 1: 1. The sample size was calculated by PASS software 2021, and 69 patients were needed in group F and group C respectively.

Statistical analysis was performed using SPSS 25.0 software. Shapiro–Wilk test was used to test the normality of the data. Measurement data with normal distribution were expressed as mean ± standard deviation ($\overline{x} \pm S$) and analyzed by independent sample *T*-test; The continuous variables with non-normal distribution were expressed as median (inter-quartile range) [M (Q1 ~ Q3)], and the rank sum test was used; Count data were analysed using the chi-square test, with results expressed as percentages. Hemodynamics was analyzed using repeated measures analysis of variance for hemodynamics, and the line chart was generated by GraghPad Prism mapping software. $P < 0.05$ was considered statistically significant.

Results

Patient Condition

From August 5, 2023 to September 20, 2023, a total of 163 patients were included, 14 patients were excluded, of which 9 patients were excluded due to incomplete recording of key data, 5 patients were excluded due to intraoperative change of anesthesia method (2 patients), and operation time more than 1 hour (3 patients), and a total of 149 patients were collected, and 8 were lost to postoperative visits, and a total of 141 patients were finally included in this study. See Figure 1.

Comparison of Patients' General Information

There was no significant difference in age, weight, BMI, ASA classification, Apfel score, and type of surgery between the two groups (P>0.05), and they were comparable. See Table 1.

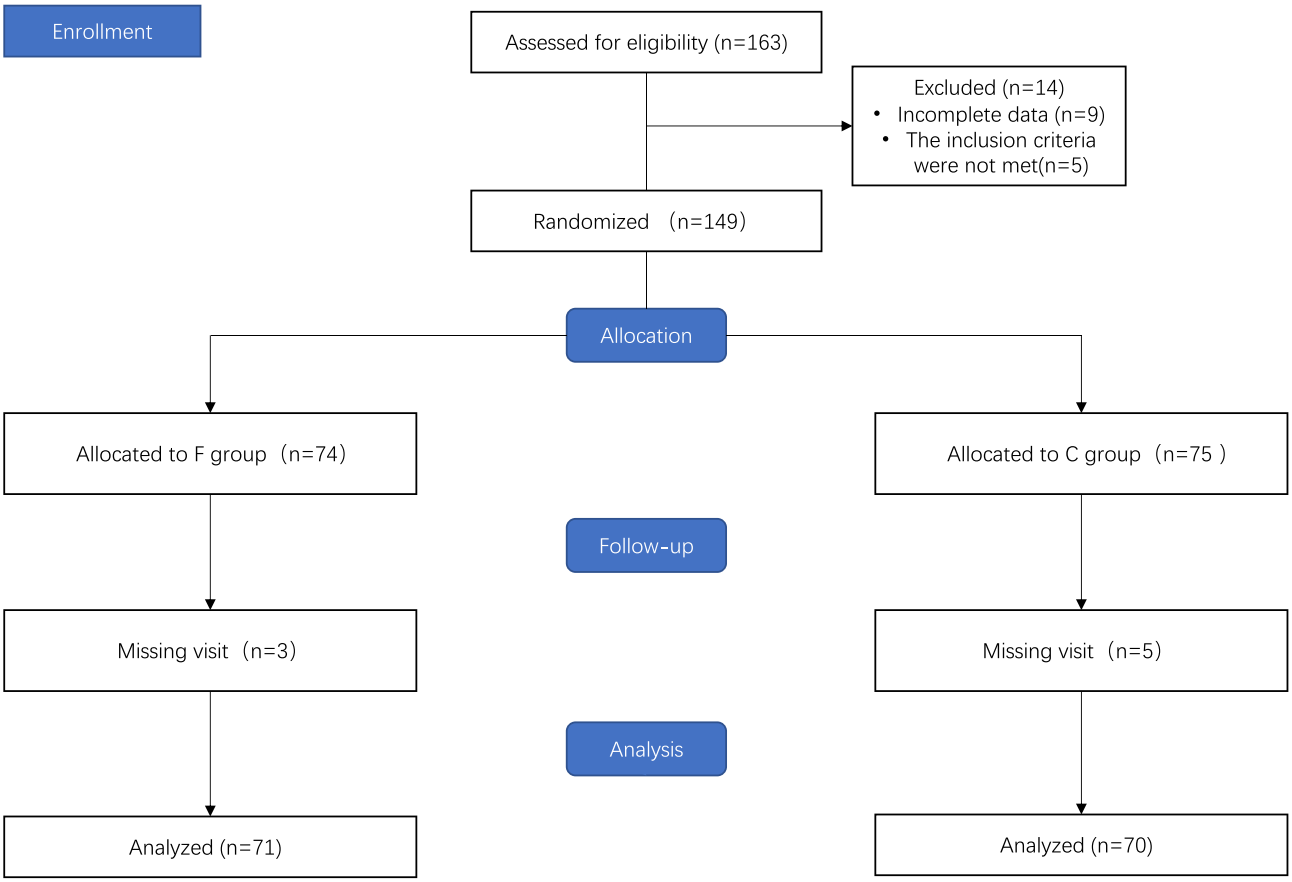

Figure 1 Research flow chart A. total of 163 patients were initially included in the study, but the data of 9 patients were missing, and the other 5 patients did not meet the inclusion criteria and were excluded. Of the 149 patients collected, 8 were lost to follow-up, and 141 patients completed the trial.

Comparison of Anesthesia Time and Dosage

There was no statistically significant difference in the duration of anesthesia maintenance, and the comparison of the dosage of remimazolam, alfentanil, and mivacurium chloride ($p > 0.05$). See Table 2.

Primary and Secondary Observational Indicators

The incidence of PONV in the two groups within 24 hours after surgery was 50.70% in group F and 32.86% in group C, which was significantly higher than that in group C. The difference was statistically significant ($P < 0.05$). The incidence of PONV in the postoperative PACU was 5.6% in group F and 8.6% in group C. The difference was not statistically

Table 2 Comparison of Anesthesia Time and Dosage of Medication

Index	Group F (n = 71)	Group C (n = 70)	P
Anesthesia induction time [Second, M(Q1~Q3)]	95 (85,106)	90 (75,110)	0.32
Anesthesia maintenance time [minute, M(Q1~Q3)]	19.7 (15,25)	18.5 (15,26.25)	0.93
Total dose of remimazolam [mg, M(Q1~Q3)]	31 (26,38)	30.1 (25.8,36.83)	0.58
Total dose of alfentanil [mg, M(Q1~Q3)]	1.79 (1.58,2.1)	1.81 (1.64,2.17)	1.00
Total dose of mivacurium chloride [mg, M(Q1~Q3)]	13 (11,13)	13 (11.75,15)	0.31

Table 3 Primary and Secondary Observational Indicators

Index	Group F (n = 71)	Group C (n = 70)	P
PACU in PONV [example (%)]	4 (5.6)	6 (8.6)	0.5
The incidence of PONV at 24 hours after operation [example (%)]	36 (50.70)	25 (32.86)	0.03
Mean arterial pressure before medication (mmHg, $\bar{x} \pm S$)	78±11.75	81.63±12.22	0.18
Mean arterial pressure after (mmHg, $\bar{x} \pm S$)	90.07±12.14	89.29±10.48	0.69
Pre-dose heart rate (Times/minute, $\bar{x} \pm S$)	62.39±9.38	65.34±9.53	0.66
Post-medication heart rate (Times/minute, $\bar{x} \pm S$)	71.03±11.6	70.82±11.99	0.92

significant (P > 0.05). Flumazenil and saline were given respectively, and there was no statistical difference in mean arterial pressure and heart rate between the two groups before and after the administration of flumazenil (P > 0.05). See Table 3. There was no significant difference in blood pressure at different time points during the operation, as shown in Figure 2.

Discussion

There was no statistically significant difference in basic information such as age, weight, BMI, ASA classification, and type of surgery between the two groups; There was no statistically significant difference in the amount of intraoperative alfentanil and

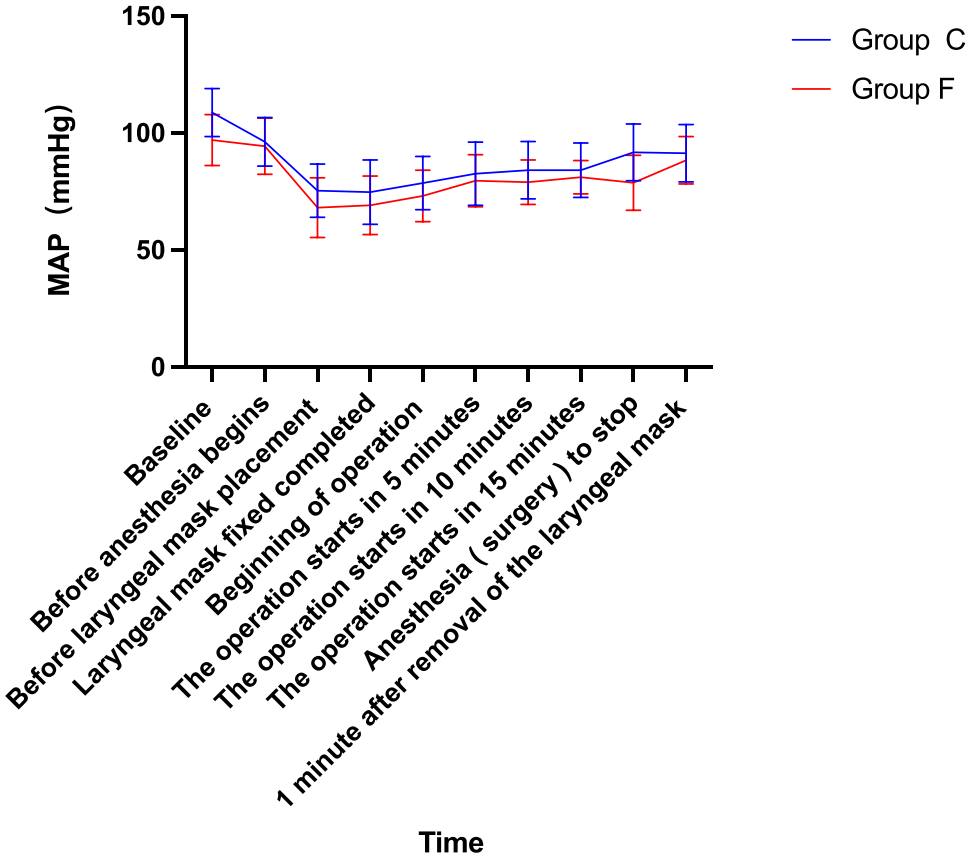

Figure 2 Comparison of MAP at different time points between the two groups of patients P=0.123>0.05.

remimazolam used, or in the duration of surgery; there was no statistically significant difference in intraoperative blood pressure. Therefore, the two groups of patients were comparable. The incidence of PONV within 24 hours after surgery was 50.70% in group F and 32.86% in group C, indicating that flumazenil can increase the incidence of PONV.

Studies have shown that the benzodiazepine drug midazolam can prevent the occurrence of PONV,[11] Lee Y 's study[12] suggested that midazolam 2mg and ondansetron 4mg had similar effects on preventing PONV. Bauer et al[13] Found that preoperative intravenous midazolam 0.04 mg/kg was an effective method to reduce the incidence of PONV and improve patient satisfaction. It is assumed that remimazolam, as a new benzodiazepine drug, also has the effect of preventing PONV. While reversing its sedative effect, flumazenil can also eliminate the effect of remimazolam in preventing PONV.

In a Meta-analysis of adverse events associated with the use of flumazenil for the treatment of benzodiazepine poisoning, it was found that the main adverse events associated with flumazenil treatment of poisoning were nausea and vomiting.[14] However, whether the increase in postoperative PONV is due to flumazenil's own side effects or due to flumazenil's reversal of remimazolam's PONV-preventing effects is unclear.

Studies suggest the most likely causes of PONV are volatile anesthetics, nitrous oxide and postoperative opioid use.[15,16] Prolonged general anesthesia and higher doses of opioids further increase the incidence of PONV.[17] SUZUKI Y[18] concluded that the risk of PONV with remimazolam anesthesia is higher than with propofol and lower than with inhalation anesthetics. Different populations and types of surgery also contribute to the increased probability of PONV. Hysteroscopic surgery pulls on the uterus during manipulation, causing vagal reflexes and hemodynamic changes, which in turn lead to PONV.[19] female patients are more likely to cause PONV than males. In this study, patients were assessed for PONV risk using a simplified Apfel score before anesthesia, and each group of patients had an Apfel score of 2~3, which means that there were 2~3 risk factors for PONV, and the risk of developing PONV was 40%~60%.[20] Intraoperative prophylactic use of antiemetic drugs reduces the incidence of postoperative PONV, and the combination of different types of antiemetic drugs can block multiple central nervous system receptors, providing a better preventive effect than single use of drugs.[21,22]

The secondary results showed that there were no differences in mean arterial pressure and heart rate before and after administration of flumazenil and saline, respectively, suggesting that flumazenil had no hemodynamic effect. There are also no relevant reports demonstrating the hemodynamic effects of flumazenil. Studies have shown[23,24] that the use of flumazenil to reverse benzodiazepines in endoscopy or pediatric anesthesia is also safe and therefore can be safely used for postoperative antagonism of remimazolam. Adverse events associated with flumazenil also include dizziness, sweating or shivering, headache, blurred vision and tinnitus.[25] However, no such adverse events were found in this study. A previous study showed that application of 1.0 to 10.0 mg of flumazenil increased the risk of AE in patients seen for benzodiazepine toxicity.[14] However, the mean dose of flumazenil used in this study was only 0.21 mg, with a maximum dose of 0.3 mg. The low dose of flumazenil is one reason why AE did not occur in this study.

Deficiencies in this study: Patients in both groups with Apfel scores of 2~3 were at intermediate to high risk of PONV and antiemetic drugs were given prophylactically in both groups for ethical reasons. In this study, we found that the incidence of PONV within 24 hours was significantly higher than the incidence of PONV in the PACU; is it related to the change in patient's position, premature discharge activities, and metabolism time of antiemetic drugs? It is uncertain in this study whether the short-acting benzodiazepine remimazolam also has a preventive effect on PONV. Therefore, further studies are needed on postoperative PONV of remimazolam and interactions with opioids.[26] The present study did not find relevant reports of adverse events of flumazenil, which may be related to the inclusion of a small sample size, low dosage of flumazenil, and patients with ASA grading of I~II. Further studies are needed to investigate the efficacy and safety of flumazenil in elderly patients and patients suffering from comorbidities.

Conclusions

Flumazenil antagonism of remimazolam increases the incidence of PONV within 24 hours in gynecologic day surgery patients and has no significant effect on the incidence of PONV in the PACU.

Abbreviations

ASA, American Society of Anesthesiologists; PONV, postoperative nausea and vomiting; PACU, Postanesthesia care unit; BMI, Body Mass Index; MOAA/S score, modified observer's assessment of alert score.

Data Sharing Statement

All data generated or analyzed during this study were included in the published article. Further inquiries about the datasets can be directed to the first author on reasonable request.

Acknowledgments

The authors would like to thank all the staff who assisted with this RCT.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

The authors have no competing interests in this work.

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