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Original Article

Predicting the best fit based on the synergistic interaction of remifentanil and propofol at the corrected dose in elderly patients undergoing painless gastroscopy

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Abstract: Objective: To validate a response surface model for the inhibition of somatic motor response at corrected body weight (CBW) doses of remifentanil plus propofol in elderly patients and to analyze the dose-effect relationship and optimal dosing range for total intravenous anesthesia (TIVA) induction in painless gastroscopy. Methods: We designed a prospective, open-ended, randomized, parallel group study. A total of 300 elderly patients undergoing painless gastroscopy were randomized to receive remifentanil (0-0.5 μg/kg) and propofol (0.8-2.2 mg/kg) dosing based on CBW. Gastroscopy was performed at the drug's peak effect time. The somatic motor response to gastroscopic stimulation and the adverse reactions at different points were recorded. The somatic motor response was used as the basic element in the subsequent RSM analysis. Model parameters and 95% confidence intervals were fitted by MATLAB software. Results: The CBW doses of remifentanil and propofol showed synergistic inhibitory effects on motor response to noxious stimulation and attenuated adverse reactions. The 50% effective doses of remifentanil and propofol for inhibiting the motor response were 1.754 μg/kg and 2.048 mg/kg, respectively. Conclusion: Remifentanil or propofol alone could not inhibit the somatic motor response at weight-adjusted doses among elderly patients. A combination of remifentanil and propofol showed a synergistic interaction in suppressing the motor response and adverse reactions in elderly patients. Preinjection of remifentanil could reduce the needed dose of propofol.

Keywords: Elderly patients, painless gastroscopy, corrected body weight, remifentanil, propofol, somatic motor response, adverse reactions

Introduction

Propofol-based total intravenous anesthesia (TIVA) is the main protocol at the painless clinic owing to its rapid onset and rapid recovery. While it lacks analgesic properties alone, propofol is often combined with remifentanil to obtain satisfactory anesthetic effect. This combination approach requires less dose for each drug and shows mild adverse reactions [1]. Since synergistic and additive effects from drug combinations can increase the risk of excessive sedation [2], it is crucial to determine the pharmacological interaction and identify the risk, especially for elderly patients undergoing painless gastroenteroscopy.

Previous studies have confirmed the additive or synergistic interaction between remifentanil and propofol in muscle tonic, apnea, and loss of consciousness by RSM analysis [3, 4]. However, there is no report on the interaction between these two drugs in elderly patients during anesthesia induction. Currently, the response surface methodology (RSM) is an optimal design for drug-drug interactions. Combined with other pharmacokinetic and pharmacoeconomic methods, RSM can identify the appropriate balance power and achieve the desired outcome at the most appropriate concentration of compatible drugs [3, 4].

Endoscopy usually consists of 3 distinct phases: esophagogastroduodenoscopy, colonosco-

py, and the time interval in between. Normally, at the beginning of the procedure, when the tip stimulates the throat, it causes a transient noxious reaction lasting for 3-5 seconds. Then, the stimulation intensity is significantly reduced, which requires timely adjustment of the anesthetic dosage and injection speed to avoid excessive sedation, respiratory depression, and other adverse reactions.

Although a target-controlled infusion (TCI) system is often used to study the synergistic effects of propofol and remifentanil [3, 4], it still has some limitations. First, it is too expensive to those clinics that are seeking for safe, efficient, and cost-effective system. Second, the infusion types of TCI system cannot adapt to the rapid changes in stimulus intensity, which often leads to either too deep or too shallow anesthesia [5]. Therefore, the bolus injection of remifentanil/propofol is a classic TIVA induction protocol in painless gastroscopy [1].

The dose of propofol used in Han people is different from the ASA recommended dose due to different physical conditions, especially in elderly patients. Most recommended doses by the ASA guidelines are based on the total body weight (TBW). However, the weight composition ratio, cardiac output, organ function, and changes in regional blood flow in the elderly population should be considered. The TBW dose tends to be high and causes circulatory and respiratory depression in senile patients [6]. Hence, the concept of lean body weight (LBW) is proposed based on the lean constitution. However, the LBW dose of propofol often results in shallow anesthesia. To circumvent this issue, CBW dose is proposed by increasing in an equal proportion to LBW, which is between the doses based on TBW and LBW. It has been confirmed that the CBW dose rarely results in respiratory and circulatory depression and shallow anesthesia [7]; however, there has not been an RSM analysis of remifentanil/propofol in TIVA induction based on CBW doses among elderly patients.

Therefore, in this study, we explored the interaction and adverse effects of propofol plus remifentanil in TIVA induction based on CBW doses among elderly patients by utilizing the RSM. Furthermore, we verified the optimal compatibility concentration and provided a preliminary anesthesia strategy for elderly patients in painless gastroscopy.

Materials and methods

Study design and participants

This study was approved by the Medical Ethics Committee of our hospitals and registered in the China Clinical Trials Registry (ChiCTR-2100052985). All subjects signed an informed consent form before surgery. Demographic information and clinical characteristics were also recorded.

Inclusion criteria and exclusion criteria

The following inclusion criteria were used for patient selection: (1) 60-75 years old; (2) ASA grade I-II; (3) BMI 18.5-25 kg/m^2; (4) no history of drug or alcohol abuse; (5) no history of any known adverse effects from the study drug; (6) no psychiatric or neurological disorders or dysfunction; (7) no history of sedative or analgesic medication use within 48 h; (8) under fasting with restricted water intake and without preoperative drugs.

Exclusion criteria: (1) an abnormal BMI < 18 kg/m^2 or > 25 kg/m^2; (2) abnormal liver and renal function (ALT) or AST > 1.5 times, creatinine > 1.5 times or on dialysis within 1 month before surgery; (3) severe cardiovascular disease, severe arrhythmia, unstable angina, a difficult airway, asthma, acute respiratory infections, severe pulmonary dysfunction; (4) related drug or dissolution allergies; (5) alcohol or drug intake preoperatively within 24 h; (6) significant dehydration, electrolyte disorders; (7) dementia; (8) hearing impairment and cognitive dysfunction; (9) intraoperative bleeding > 10 ml/kg or a duration lasting more than 10 minutes; (10) pregnant and lactating women.

Removal criteria

Patients with allergic reactions, gastroscopy failure and other abnormal conditions during induction were also excluded.

Study protocol

This study had a prospective, open, randomized, and parallel group design. Each patient

Table 1. Grouping Scheme

Patient number	Remifentanil (ug/kg)	Propofol (mg/kg)
50	0	1.4, 1.6, 1.8, 2.0, 2.2
50	0.1	1.2, 1.4, 1.6, 1.8, 2.0
50	0.2	1.2, 1.4, 1.6, 1.8, 2.0
50	0.3	1.0, 1.2, 1.4, 1.6, 1.8
50	0.4	1.0, 1.2, 1.4, 1.6, 1.8
50	0.5	0.8, 1.0, 1.2, 1.4, 1.6

was randomized to receive different doses of remifentanil and propofol [8], and the dose was calculated at CBW (CBW=IBW+0.4) [7]. The administered drug combinations are shown in **Table 1**.

Randomization

Randomization was performed through a computer-generated random number table from SPSS 16.0 software (SPSS Inc., Chicago, IL).

The assigned numbers were sealed in opaque envelopes and kept by the supervisor. The envelope was opened to determine the specific investigational drug after authorization. Random sequence generation and preparation of drugs were performed by the person who was not involved in the subsequent procedures. Propofol (Yangzijiang Pharmaceutical Co., Ltd., China), as drug A, and remifentanil (Yichang Renfu Co., Ltd., China), as drug B, were diluted with normal saline.

Blinding

The medication was given by the second person who was blinded to the grouping. The data were recorded by the third person who was unaware of the study design. All data were analyzed by statistical experts who did not participate in the study. Patients were blinded to the grouping throughout the trial.

Test procedure

All subjects were fasting for 8 h and were prohibited from taking preoperative medication and from drinking for 2 h. The nurse opened venous access as the patient was ready. The patients were usually lying on left side with a dental pad in the mouth. The heart rate (HR), blood oxygen saturation (SPO_2), and mean arterial pressure (MAP) were recorded. Patients received 100% oxygen.

As planned, the same anesthesiologist injected remifentanil first (30 seconds) and then propofol until the modified observer's assessment of alertness/sedation score (MOAA/S) reached 0. That anesthetic status was maintained during the examination. When the patient exhibited purposeful movement and spontaneous and regular breathing after the examination, he was transferred to the post-anesthesia care unit (PACU) and discharged after satisfactory recovery (a modified Aldrete score ≥ 9).

Outcomes

General outcomes: SBP, DBP, HR and SpO_2 were recorded at different time points [before induction ($T_{baseline}$), before entry (T0), 1 min (T1), 3 min (T2) and 5 min (T3)], and MOAA/S and BIS values were also evaluated [9]. The anesthesiologist determined whether adding more propofol affected the occurrence of swallowing, coughing, and body movement.

Somatic motor response to gastroscopic stimulation: During gastroscopy, the nurse recorded physical activities, including frowning, swallowing, choking, body distortion, and the motor response. When the gastroscope enters through the throat or ileocecal region, patients may cough and move, which indicates the need for more propofol. The sleep time, inspection duration, and drug consumption were also recorded. The anesthesiologist determined whether additional propofol should be injected according to the patient's reaction and anesthesia depth. The doctor provided oxygen through a mask when the SpO_2 was below 90%. Respiratory support was stopped when SpO_2 was higher than 90% and the patient was awake and alert. The data of the patients who required supplementary oxygen were recorded in the follow-up procedures.

Adverse reactions: Hypotension (20% before anesthesia or below 90 mmHg), hypertension (20% above base value or above 160/95 mmHg), and the requirement for vasoactive drugs within 24 h after the surgery (due to headache, nausea, vomiting, etc.) were considered adverse reactions and recorded.

Table 2. Demographic Data

	Median (Range)
Age, yr	68.5 (66, 74)
BMI, kg/m^2	22.3 (18.7, 24.3)
Gender, female/male	139/161

Table 3. Response Surface Model Parameters

Parameter	Estimates form final model	95% CI
β_0	3.717	1.8935.542
β_1	1.815	0.77812.851
β_2	2.119	-2.97, 7.207
β_3	2.863	-0.6492, 6.375
$ED_{50,prop}$ (mg/kg)	2.048	-
$ED_{50,remi}$ (ug/kg)	1.754	-

$ED_{50,prop}$: 50% effective dose of propofol; $ED_{50,remi}$: 50% effective dose of remifentanil; interaction index: $ED_{prop}=\beta_0/\beta_1$; $ED_{remi}=\beta_0/\beta_2$; β_3 was the interaction index.

Atropine (0.2-0.5 mg) was injected in patients with a HR below 45 times/min. Ephedrine (5-10 mg) was used for a MAP less than 20% of baseline or below 60 mmHg. The data of the patient's hypotension or bradycardia were also recorded.

Statistical analysis and the response surface model

Statistical analysis

MATLAB (R2019a, The MathWorks, Inc., Natick, MA) and SPSS20.0 (SSPS Inc., Chicago, IL, USA) were used for statistical analysis. Nonlinear regression (least squares) was selected to fit the model parameters, and the coefficient of determination of the surface (R^2) was selected to evaluate the quality of the regression model and experimental data (the standard is $R^2 > 0.7$). The fitted parameters were considered significantly different from 0 ($P < 0.05$) if the 95% confidence interval did not contain 0. If the model could not be fitted, the response surface analysis in SPSS would be used to fit the curve. The incidence of respiratory and circulatory side effects was tested by chi-square test. In addition, the prediction accuracy was arbitrarily defined by calculating the percentage of predictions that agreed with the observations. The prediction and observation were considered to agree with each other if the difference between the prediction and observation values was < 0.5 [2].

Response surface model

In this study, the response surface model generated by utilizing MATLAB software was applied to investigate the interaction between propofol and remifentanil during TIVA induction [10]. The selected model formula used was:

$$P = \frac{1}{1 + e^{(\beta_0 - \beta_1 \times D_{prop} - \beta_2 \times D_{remi} - \beta_3 \times D_{prop} \times D_{remi})}}$$

Where $ED_{prop}=\beta_0/\beta_1$ and $ED_{remi}=\beta_0/\beta_2$. Specifically, P represented the probability of inhibiting the motor response. ED_{prop} and ED_{remi} represented the dosages of propofol and remifentanil, respectively. $ED_{prop,50}$ and $ED_{remi,50}$ represented the 50% effective doses of propofol and remifentanil for inhibiting the motor response, respectively. β_3 was the interaction index; if $\beta_3 > 0$, the drug interaction was synergistic; if $\beta_3=0$, it was additive; if $\beta_3 < 0$, it was antagonistic. The five values in the correlation model were β_0, β_1, β_2, β_3 and R. The correlation coefficient R^2 of the regression parameter was used to assess the extent to which the nonlinear regression model was applied.

Results

General data

A total of 300 patients were included in the follow-up analysis. Their detailed clinical data are shown in **Tables 1** and **2**. Three patients developed hypotension, and five completed the study after brief bradycardia during induction.

RSM verified the synergistic effects between these two drugs

Pharmacodynamic data were fitted by an RSM model. The combination of propofol and remifentanil showed synergistic effects in inhibiting the motor response to noxious stimulation. The $ED_{50,prop}$ and $ED_{50,remi}$ values were 2.048 mg/kg and 1.754 μg/kg, respectively. The parameters of the RSM model are presented in **Table 3**.

Table 4. Effects of different dosages of propofol on $ED_{50,remi}$ and $ED_{95,remi}$

D_{remi} (ug/kg)	$ED_{50,prop}$ (mg/kg)	$ED_{95,prop}$ (mg/kg)
0	2.05	3.67
0.1	1.67	3.07
0.2	1.38	2.61
0.3	1.158	2.25
0.4	0.97	1.96
0.5	0.82	1.73

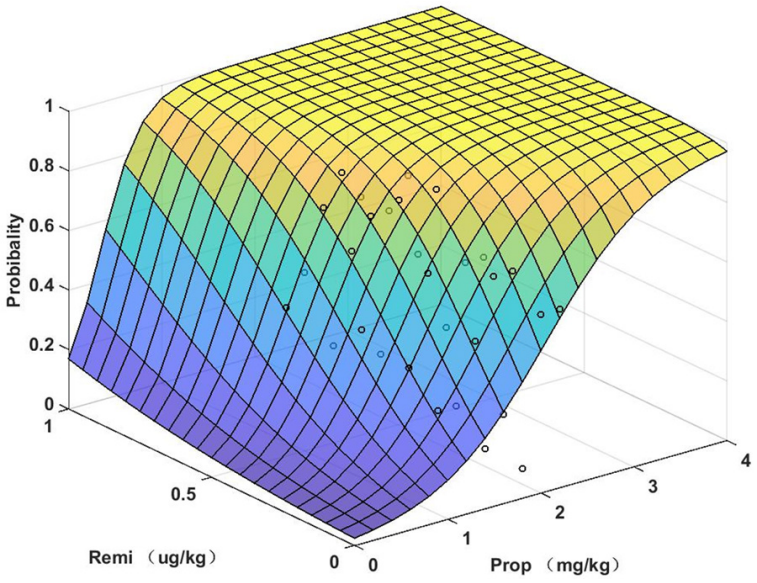

Figure 1. Response surface for probability of inhibiting the motor response.

The body motion response verified by the RSM model

As shown in **Table 4**, when the dose of remifentanil was increased from 0 to 0.5 μg/kg, the $ED_{50,prop}$ decreased from 2.05 μg/kg to 0.82 μg/kg, while the $ED_{95,prop}$ decreased from 3.67 μg/kg to 1.73 μg/kg. **Figure 1** shows the effect of different doses of remifentanil on the dose-effect curve (S curve) of propofol. The propofol dose-effect curve was gradually shifting to the left along with the increasing dose of remifentanil (**Figure 2**), suggesting that remifentanil could effectively reduce the dose of propofol to be used.

The motor response induced by gastroscopy stimulation was determined by the RSM model. **Figure 3** showed the 5%, 50%, and 95% equivalent lines of drugs that inhibited the motor response, and the equivalent lines were curved which also indicated a synergistic interaction of propofol and remifentanil.

The occurrence of adverse reactions

Totally, 33 patients presented with nausea and apnea, while 15 patients completed the study after a brief bradycardia period during the induction of anesthesia in this study.

Discussion

We determined the dose-response relationship and the interaction between propofol and remifentanil based on corrected body weight (CBW) doses in total intravenous anesthesia (TIVA) induction using the response surface methodology (RSM) model. We obtained the dose-effect relationship at any dose combination of remifentanil and propofol. The results showed that the hypnotic and analgesic interactions between the two drugs were synergistic in elderly patients undergoing painless gastroscopy. Moreover, remifentanil alone could not effectively inhibit body movement in response to gastroscopy stimulation, but it could effectively reduce the dosage of propofol to within the range of CBW.

Clinical advantages of a bolus injection of remifentanil and propofol

TCI infusion is one of the ideal infusion methods in TIVA induction [11]. The higher dosage and faster pumping speed often result in more adverse reactions during TCI infusion [5]. Each gastroscopy procedure last 5-10 minutes, and skilled doctors can complete it in 3-5 minutes. When the tip of the scope passes through the throat, it often causes short and strong stimulation lasting 3-5 seconds. Then, the stimulation reduces quickly, and the anesthesia depth

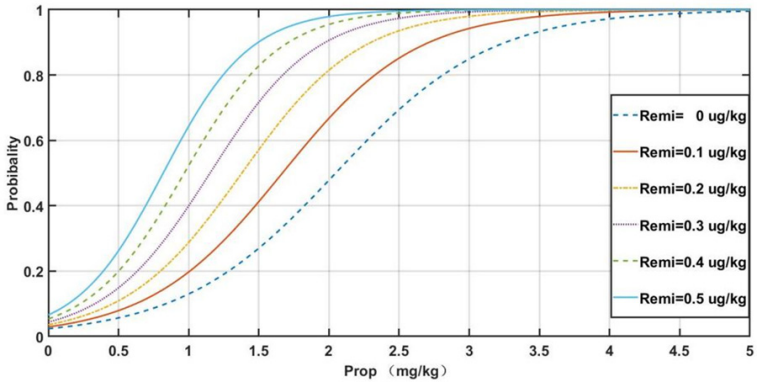

Figure 2. Dose-response curves of propofol at different doses of remifentanil.

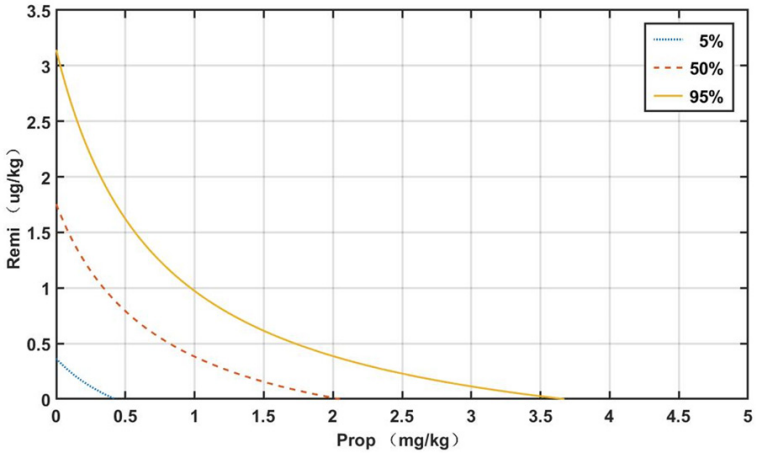

Figure 3. Equivalent lines of probability (5%, 50%, and 95%) in inhibition of somatic responses.

needs to be adjusted accordingly to avoid side effects. Obviously, TCI infusion affects safety, efficiency, and cost in this condition. Bolus injection of remifentanil/propofol is a traditional TIVA induction protocol for painless gastroscopy, which is efficient and popular in China.

Our study showed that none of the patients had any explicit memories of painful or a terrifying intraoperative stimulation, indicating that an ideal depth of anesthesia was achieved at the current dose. Thus, the CBW dose not only achieves the purpose of induction but also considers individual differences. Moreover, 6 cases with bradycardia and 9 cases with respiratory depression during induction in this trial, respectively, indicated that the appropriate dose may reduce the side effects. Nevertheless, since this is a preliminary observation in patients of 60-75 years old (ASA grades I-II), the merits of CBW dosage in older and critically ill patients need to be further evaluated.

CBW dosage

Induction doses differ among individuals and ethnicity, which can be influenced by cardiac output, fat ratio, age, race, and body temperature [12]. The TBW dosages often result in more side effects due to the excessive dosage used in the procedure. Therefore, a more precise calculation and optimal ranges should be considered, in addition to TBW dosage.

Recently, a new CBW dose was defined by increasing proportionally the LBW dose [13]. The value of CBW is between LBW and TBW, which can not only make up for the deficiencies caused by LBW but also reduce the serious depression and side effects [7, 8]. However, there are few reports about the interactions between remifentanil and propofol at a CBW dose, especially in elderly patients. In the present trial, only 4 patients exhibited serious depression and recovered earlier, indicating that the selected dosages were relatively safe. However, the results may also indicate that the present dosage is conservative, which will be tested by using higher doses in our future studies.

Interactions between remifentanil and propofol

The interaction between remifentanil and propofol in TCI-based TIVA may induce deep or shallow anesthesia. As auxiliary drugs, opioids can reduce adverse consequences and decrease sedative requirements in maintaining stable hemodynamics and satisfied depth of anesthesia [14]. In the previous RSM models [4, 15], remifentanil reduced the dose of propo-

fol in certain dosage ranges. Furthermore, propofol and fentanyl/morphine synergistically interact and cause more side effects based on different parameters such as the BIS index, and muscle rigidity [16, 17]. However, the mechanism of the interaction between propofol and remifentanil has not been well-explained. Bouillon et al. [18] proved that the synergistic interactions of propofol and remifentanil may decrease the pain threshold to noxious stimulation, reduce the projection to the cortex, and inhibit the neural circuits of the cerebral cortex.

The RSM analysis showed that the $ED_{50,prop}$ was 2.05 mg/kg for inhibiting motor response, which is similar to the result ($ED_{50,prop}$=1.90 mg/kg) from a previous study [19]. The $ED_{50,remi}$ was 1.75 μg/kg, which suggests that remifentanil alone in the normal dose range could not provide a satisfactory effect. However, further tests from different conditions are needed to verify these findings.

Limitations

Our study had some limitations. First, we could not measure the changes in blood drug concentration compared to the TCI system. However, most of the TCI values related to blood drug concentrations are computer generated estimations, which are not the actual blood concentration. Second, the remifentanil cannot be used alone in this trial for ethical reasons, so we cannot explore the boundaries of the RSM. Third, the present ranges of dosage are relatively narrow because the high doses are not safe forelderly patients. Fourth, the current conclusions are not applicable to high-risk patients because the selected subjects are not serious. Finally, other limitations include the small sample size and the lack of cases with complex complications.

In conclusion, a combination of remifentanil and propofol at the CBW dose can reduce the dosage of each one, but achieve better efficacy than monotherapy, and reduce the side effects for the elderly patients undergoing painless gastroscopy.

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Disclosure of conflict of interest

None.

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