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Xianhong Jiang

Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Third Hospital of Shanxi Medical University

Jiaqi Tan

Shanxi Medical University

Mengyun Shen

Chang Zhi People's Hospital

Yan Li

Second Affiliated Hospital of Shanxi Medical University

Gaoxiang Shi

Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Third Hospital of Shanxi Medical University

Ping Zhuang

zhuangping@sx bqeh.com.cn

Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Third Hospital of Shanxi Medical University

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The Optimal Dosage of Alfentanil and Propofol in Oocyte Retrieval: A Randomized Clinical Trial

Xianhong Jiang^{1,#}, Jiaqi Tan^{2,3,#}, Yan Li⁴, Mengyun Shen⁵, Gaoxiang Shi¹, Ping Zhuang^{1*}

¹Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Third Hospital of Shanxi Medical University, Tongji Shanxi Hospital, Taiyuan, 030032, China

²Department of Anesthesiology, Shanxi Medical University, 56 Xinjiannan Road, Taiyuan 030032, Shanxi, China

³Department of Pain Management, Xiongan Xuanwu Hospital, No.1 Xili Road, Start-up Area, Xiongan New Area, Hebei, China

⁴Department of Anesthesiology, Second Affiliated Hospital of Shanxi Medical University, 382 Wuyi Road, Taiyuan 030032, Shanxi, China

⁵Department of Anesthesiology, Chang Zhi People's Hospital, 502 Chang Xing Middle Road, Chang Zhi 046000, Shanxi, China

#These authors contributed equally to this work

*Corresponding author: Ping Zhuang
Department of Anesthesiology, Shanxi Bethune Hospital
99 Longcheng Street, Taiyuan 030032, Shanxi, China
Tel: +86 13700503507

Email: zhuangping@sxbqeh.com.cn

Abstract:

At present, ultrasound-guided oocyte retrieval is commonly used in clinics; nonetheless, this process can cause pain and fear in patients. Thus, an anesthetic plan is needed. The aim of this study is to determine the optimal doses of alfentanil and propofol for safe, effective, and painless oocyte retrieval. Fifty patients undergoing oocyte retrieval received a target-controlled infusion of alfentanil (0–100 ng/mL) and propofol (0–7 µg/mL) at various target concentration pairs. After reaching pseudo-steady state drug levels, the Modified Observer's Assessment of Alertness/sedation score and response to painful stimulation during oocyte retrieval were evaluated for each target concentration pair. Response surface models of pharmacodynamic interaction were constructed using sedation and analgesia endpoint data. Computer simulations were used to combine pharmacodynamic interaction models with previously reported pharmacokinetic models to identify the drug combination that yielded the smallest hemodynamic fluctuations and the fastest recovery (Modified Observer's Assessment of Alertness/Sedation score > 3) for oocyte retrieval. Computer simulations showed that hemodynamic fluctuations were lowest using 42 ng/mL of alfentanil and 2.6 µg/mL of propofol, and post-anesthesia recovery was fastest using 56 ng/mL of alfentanil and 2.4 µg/mL of propofol. In conclusion, the response surface model demonstrated a synergistic analgesic and sedative effect between alfentanil and propofol. The optimal plasma EC₅₀ combinations of alfentanil and propofol for safe and effective painless oocyte retrieval were 42–56 ng/mL and 2.4–2.6 µg/mL, respectively.

Trial registration: ChiCTR2400083913 (7/5/2024)

Keywords oocyte retrieval, total intravenous anesthesia, alfentanil, propofol, response surface

Introduction

The incidence of infertility has increased over the past years. In vitro fertilization-embryo transfer is an assisted reproductive technology commonly used to treat infertility.^{1,2} Ultrasound-guided oocyte retrieval is an essential step in in vitro fertilization. This method is less invasive and faster than laparoscopic oocyte retrieval but is stressful and painful and thus requires anesthesia and sedation.^{3,4} According to the total intravenous anesthesia (TIVA) safe practice guidelines, the ideal anesthetic drug concentration for this surgery should provide

adequate analgesia and sedation, minimizing the impact on the cardiovascular and respiratory systems without causing serious adverse reactions.⁵

Propofol has sedative effects, a rapid onset of action, and a short duration of action and is the primary anesthetic drug used for oocyte retrieval.⁶ However, this drug has inhibitory effects on the respiratory and circulatory systems.⁷ Alfentanil is a short-acting opioid analgesic with rapid onset and metabolism, with minimal effects on the cardiovascular and respiratory systems, which makes it particularly advantageous in outpatient and minor surgery.^{8,9} Alfentanil combined with propofol significantly reduces the incidence of adverse reactions and the required dose of propofol.¹⁰ Despite these benefits, little is known about the efficacy of the combined use of these drugs for oocyte retrieval. In addition, alfentanil has been on the market in China for a relatively short time, and this trial may be the first to assess the safety and appropriate dosing of alfentanil in oocyte retrieval procedures in the Asian population.

The response surface methodology (RSM) allows for the qualitative and quantitative analysis of drug interactions and the relationship between drug dosages and the desired effects.¹¹ RSM provides a framework for evaluating the interaction between opioids and hypnotics and is superior to isobolographic, fractional, and parallel line analyses. This study used RSM to characterize the interactions between alfentanil and propofol and establish optimal doses for safe and effective oocyte retrieval without compromising follicle quality.

Materials and methods

Study design and setting

This study was a randomized, controlled, single-center trial, which was approved by the Ethics Committee of Shanxi Bethune Hospital (YXLL-2024-010) and registered with the Chinese Clinical Trial Registry (Protocol ID Number: ChiCTR2400083913). All patients provided written informed consent, and all procedures complied with the Declaration of Helsinki.

Participants

The study included 50 patients who underwent painless oocyte retrieval at Shanxi Bethune Hospital between May 20, 2024 and July 31, 2024. The inclusion criteria were patients aged 20–40 years, with a body mass index (BMI) of 18.8–28 kg/m² and American Society of Anesthesiologists (ASA) grade I or II. The exclusion criteria were ASA grade III or higher;

hypersensitivity to propofol or opioid drugs; pre-operative liver or kidney dysfunction or other systemic complications; central nervous system, respiratory, or cardiovascular diseases; mental disorders; and a recent history of acute infection.

Treatment procedures

The patients were randomly assigned to one of five groups (Groups 1, 2, 3, 4, or 5) using a random number table. Allocation concealment was performed by a third party using opaque, sealed, sequentially numbered envelopes. The envelopes were opened when the patients arrived in the operating room. An independent researcher blinded to treatment allocation prepared the drugs and evaluated outcomes.

All randomized patients were asked to fast for 8 h from solid food and 2 h from clear liquids before the procedure. Upon admission, patients were positioned in the lithotomy position, and intravenous access was established. Oxygen was administered via a face mask (5 L/min). Continuous cardiac monitoring included non-invasive blood pressure (NIBP), mean arterial pressure (MAP), electrocardiogram, heart rate (HR), and blood oxygen saturation (SpO₂).

Alfentanil (Yichang Renfu Pharmaceutical Co., Ltd., Batch number: 33S010213) was administered by target-controlled infusion (TCI) to achieve a plasma concentration of 0 ng/mL (Group 1), 25 ng/mL (Group 2), 50 ng/mL (Group 3), 75 ng/mL (Group 4), and 100 ng/mL (Group 5). After the plasma concentration of alfentanil equilibrated with the effect compartment, sedation was assessed using the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale (Supplementary Table S1). Patients with MOAA/S scores <1 were considered sedated, and the surgery commenced immediately. Evident frowning or body movement during needle puncture into the vaginal fornix was monitored to determine whether adequate analgesia had been achieved. If the MOAA/S score was >1 or adequate analgesia was not achieved, propofol (Guangdong Jiabo Pharmaceutical Co., Ltd., Batch number: 2A240518) TCI was initiated at a starting plasma concentration of 1 µg/mL. MOAA/S scores and analgesic effects were assessed when the plasma propofol concentration reached equilibrium with the effect compartment. Propofol concentration was increased gradually if sedation or analgesia was not achieved, and further assessments of sedation and analgesia were made. The above steps were repeated until sedation and analgesia were achieved, and then the effective plasma concentration of propofol was recorded. Anesthesia was performed by the same senior

anesthesiologist, and the surgeries were performed by the same experienced team of gynecologists.

Ephedrine (3–6 mg) was administered intravenously if hypotension (MAP < 60 mmHg) occurred. Bradycardia (HR < 50 bpm) was treated using 0.2–0.5 mg intravenous atropine sulfate. In cases of intraoperative RD ($\text{SpO}_2 \leq 92\%$ or respiratory rate < 10 breaths/min), positive pressure ventilation and mechanical ventilation were performed to clear the airways.

Outcome measures

The primary outcome was the plasma concentration of alfentanil and propofol when the analgesic effect was achieved in the oocyte retrieval operating room. Secondary outcomes included waking time, follicle quality (the metaphase II (MII) oocytes rate and fertilization rate), hemodynamic fluctuations, and the frequency of intraoperative respiratory depression (RD).

The above data were collected by unassigned personnel in the operating room or the reproductive medicine department. The MII oocytes rate was defined the ratio of the number of MII oocytes to the number of punctured follicles. Fertilization rate was defined the ratio of fertilized eggs to MII oocytes.

Sample size calculation

Following the recommendations of Short et al, this study used a parallel design based on the feasibility of clinical implementation, which requires 40 samples.¹² The sample size was set at 50 to facilitate the comparison of pharmacodynamic indicators.

Statistical analysis

Statistical analysis was performed using SPSS for Windows, version 27.0 (IBM, Armonk, NY). Descriptive statistics included continuous data presented as means and SDs or median and interquartile range (IQR), and categorical data were presented as frequencies and proportions. For continuous variables, one-way ANOVA (or Kruskal–Wallis if assumptions violated) would be used. For categorical variables, the chi-square test (or Fisher's exact) would be used. If the overall test was significant ($p < 0.05$), pairwise comparisons across all five groups (10 comparisons) would be performed using Bonferroni correction. The adjusted significance level will be $0.05/10 = 0.005$. For continuous variables, Bonferroni-corrected t-tests (or Dunn's test) would be applied. For categorical variables, the chi-square partition method with Bonferroni correction will be used.

1 A response surface model of pharmacological responses was constructed using the logit
2 model, as shown below:

3 $\ln \frac{P}{1-P} = -\beta_0 + \beta_1 C_A + \beta_2 C_P + \beta_3 C_A C_P$, where P is the probability of the desired effect, C_A
4 and C_P are the plasma concentrations of alfentanil (ng/mL) and propofol (µg/mL), respectively,
5 and β_i is the estimated coefficient of the linear function. For assessing pharmacodynamic
6 responses, the data were combined and used to fit the three-dimensional response surface
7 using the surface fitting method. The model coefficients were estimated, and the
8 three-dimensional surface was displayed using Python (a popular engineering application
9 software). The model was built using an iterative procedure to maximize the log-likelihood
10 between the observations and model predictions. The contribution of β_3 was evaluated by
11 excluding it from the model and using a likelihood ratio test to determine whether the model
12 deteriorated significantly. The significance level for the likelihood ratio test was a 6.84
13 difference in the -2 log-likelihood (-2LL), adding one parameter for nested models.¹⁴ β_3 indicates
14 the nature of the pharmacodynamic interaction between alfentanil and propofol. $\beta_3 = 0$ (simple
15 model) indicates the absence of interaction between the two drugs; $\beta_3 \neq 0$ (complex model)
16 indicates a synergistic ($\beta_3 > 0$) or antagonistic ($\beta_3 < 0$) interaction between the two drugs.¹⁵

17 The correlation coefficient of the regression equation was used to evaluate how well the
18 nonlinear regression model described the observed data. Correlation coefficients >0.7
19 indicated that the predicted surface response was in good agreement with the measured
20 data.¹⁶

21 A quadratic function model was used to fit the EC50 curves of the two drugs for achieving
22 analgesic effect against the absolute value of patients' blood pressure fluctuation and recovery
23 time, and the corresponding curves were plotted to determine the optimal plasma EC50
24 combination of propofol and alfentanil under analgesic effect.

25 Results

26 Fifty patients were fulfilled the research criteria and randomly assigned, and there was no loss
27 to follow-up or withdrawals during the trial. Finally, 50 patients were included in the
28 analysis. The CONSORT Flow-diagram (Fig. 1) describes the flow of patients through the trial.

1 There were no significant differences in demographic characteristics, baseline
2 hemodynamic, surgical time, the MII oocyte rate and fertilization rate among the five groups.
3 However, the awake times were different among the five groups, and the group 1 was the
4 longest (Table 1).

5 All parameters of the RSM were identifiable. The logit model parameters estimated by
6 nonlinear regression are shown in Table 2. The -2LL of the nested model with one additional
7 parameter was 25.41, indicating a significant difference between the two models. In the
8 complex model, $\beta_3 = 37.31$, indicating that the analgesic effect of the two drugs was synergistic.
9 The correlation coefficient between the actual points and the validity of the model was 0.9449,
10 indicating good fit of the model. A three-dimensional response surface plot was constructed
11 using the synergistic model (Fig. 2A). The median effective concentration (EC₅₀) of the
12 response surface of the analgesic effect of the drug combination is shown in Fig. 2B.

13 The quadratic function model was used to fit the EC₅₀ curves of the two drugs for
14 achieving analgesic effect against the absolute value of patients' blood pressure fluctuation and
15 recovery time. The coefficients of determination (R^2) for the two curves were 0.775 (for blood
16 pressure fluctuation) and 0.917 (for recovery time), indicating a good fit. The lowest point on the
17 curve (P_{BP}) represents the combined effect concentration (EC₅₀) of propofol and alfentanil at
18 which blood pressure fluctuation was minimized, corresponding to 2.6 $\mu\text{g/ml}$ of propofol and 42
19 ng/ml of alfentanil, and the point of post-anesthesia recovery fastest (P_{WK}) on the curve
20 corresponds to a plasma EC₅₀ of 2.4 $\mu\text{g/ml}$ of propofol and 56 ng/ml of alfentanil (Fig. 3).

21 A horizontal line was drawn at a mean MAP fluctuation of 20%, and the compatibility
22 measure of the area between the line and the curve could be considered hemodynamically
23 stable (Fig. 4).

24 The study found that the frequencies of intraoperative respiratory depression and
25 hemodynamic fluctuations-common adverse events during TIVA-were affected differently by
26 alfentanil target concentrations. Specifically, target concentrations of 25 ng/mL and 50 ng/mL
27 had little effect on respiration, whereas concentrations of 0 ng/mL and 100 ng/mL had the
28 greatest impact on blood pressure (Table 3).

Discussion

This study utilized various concentrations of alfentanil and propofol by TCI, covering the dosage range commonly used in clinical practice. The analgesic effect, hemodynamic fluctuations, waking time, and the frequency of intraoperative RD and body movement were evaluated to determine the most effective dose.

The RSM showed that alfentanil and propofol had synergistic analgesic effects during oocyte retrieval, consistent with the results of previous studies.^{17,18} The optimal plasma EC₅₀ doses of alfentanil and propofol to achieve safe and effective painless oocyte retrieval were 42–56 ng/mL and 2.4–2.6 µg/mL. Observations of multiple curves in the response surface model indicated that the curves were relatively flat at lower values on the axes, suggesting that the low concentration of either drug did not effectively inhibit the noxious stimuli caused by needle insertion during oocyte retrieval. Notably, 2 µg/mL of propofol can lead to sleep disturbances, suggesting that propofol concentrations lower than 2 µg/mL may lead to wakefulness.

Therefore, when administering anesthesia using lower propofol concentrations, the blood levels of opioids may play a decisive role in the state of consciousness. Shafer et al found that 480 ng/mL of alfentanil inhibited electroencephalographic activity.¹⁹ Additionally, in the presence of propofol, increasing the dose of alfentanil has no significant effect on the bispectral index.²⁰ This result indicates that alfentanil alone does not produce reliable hypnotic effects.

There was no significant difference in MII oocyte rate and fertilization rate among the all groups, indicating that the drug combination did not significantly affect follicle quality in our cohort. However, our study showed plasma concentrations of alfentanil at 25 and 50 ng/mL had minimal impact on respiration, the higher frequency of intraoperative RD when the plasma concentrations of alfentanil were more than 50 ng/mL. These were consistent with the findings by Glass et al, who found that the median effective concentration of alfentanil for inhibiting minute ventilation in healthy volunteers was 49.4 ng/mL.²¹

Our study showed some patients with plasma alfentanil concentrations of 0 ng/mL and 25 ng/mL exhibited body movement after sedation when the needle used in oocyte retrieval punctured the vaginal fornix. Thus, propofol concentration was increased to complete the procedure. This finding indicates that alfentanil concentrations lower than 25 ng/mL do not

1 effectively suppress pain stimuli. Intraoperative body movements can affect surgical success
2 and increase the risk of uterine injury. Inadequate analgesia can increase propofol
3 requirements and prolong recovery times.²² In our study, post-anesthesia recovery was fastest
4 using plasma concentration 56 ng/mL of alfentanil and 2.4 µg/mL of propofol. Vuyk et al found
5 that the optimal blood concentrations of alfentanil and propofol to induce recovery from lower
6 abdominal surgery in women were 85 ng/mL and 3.5 µg/mL, respectively.²³ A possible
7 explanation is that the pain stimulus of lower abdominal surgery is greater than that of oocyte
8 retrieval. What's more, higher doses of propofol and alfentanil caused extended recovery time
9 and hemodynamic instability. Therefore, combined medication maybe a preferable option
10 during the oocyte retrieval procedure.

11 According to TIVA guidelines, plasma concentrations of alfentanil and propofol of 42–56
12 ng/mL and 2.4–2.6 µg/mL, respectively, can effectively induce loss of consciousness and
13 suppress pain stimuli, with minimal impact on hemodynamics and respiration, allowing for rapid
14 recovery without affecting follicle quality. These results maybe also apply to short surgical
15 procedures performed under TIVA, such as hysteroscopy and fiberoptic bronchoscopy.
16 Nevertheless, prospective research may be necessary.

17 This study have some limitations. First, this study was a single-center study, further
18 multi-center, prospective research may be necessary. The surgical operators in this study were
19 relatively consistent, which to some extent reduced data bias caused by variations in technical
20 skill levels. However, this also limits the generalizability of the study findings. Second, our study
21 is that the results apply only to good physical condition women of childbearing age. Further
22 studies are needed to determine the optimal dose for other age groups and patients with
23 comorbidities.

24 **Conclusion**

25 The RSM demonstrated that the analgesic effect of alfentanil combined with propofol was
26 synergistic. The optimal plasma EC₅₀ combinations of alfentanil and propofol for safe and
27 effective painless oocyte retrieval were 42–56 ng/mL and 2.4–2.6 µg/mL, respectively. What's
28 more, the combination regimen significantly lowers the dose of each single drug and reduces
29 the risk of drug-related adverse reactions.

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3 **Acknowledgments**

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5 Department of Shanxi Bethune Hospital for their contributions to this work.

6 **Author contributions**

7 Xianhong Jiang: Writing original draft, Data curation, Conceptualization. Jiaqi Tan: Writing
8 original draft, Investigation, Conceptualization. Mengyun Shen: Supervision, Software, Formal
9 analysis. Yan Li: Validation, Software; Gaoxiang Shi: Software, Formal analysis. Ping Zhuang:
10 Conceptualization, Methodology, Supervision.

11 **Data availability statement**

12 The datasets analysed during the current study available from the corresponding author on
13 reasonable request.

14 **Funding statements**

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16 Fundamental Research Program of Shanxi Province: 202403021222405.

17

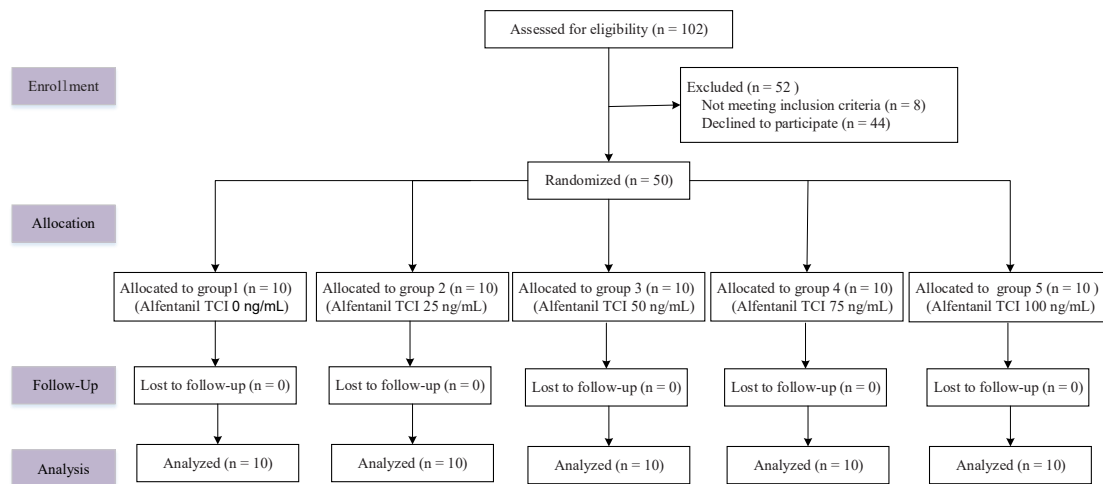
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21

22 **Fig.1.** CONSORT flow diagram.



TCI: target-controlled infusion

Fig.2a. Alfentanil-propofol interaction for analgesic effect

Fig.2b. Equivalent lines of 5%, 50%, and 95% effect probabilities for analgesic effect

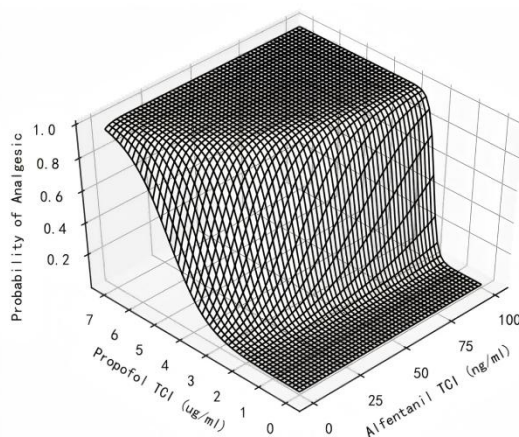
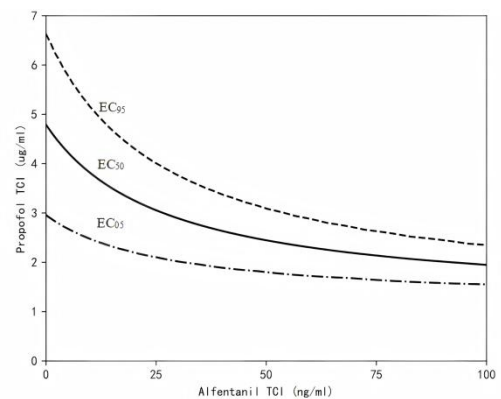


Fig.2a

Fig.2b

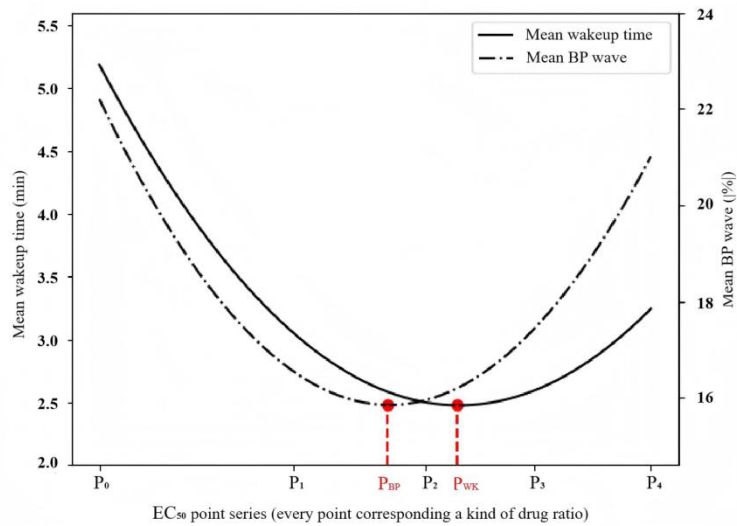
The Logit response surface model prediction for analgesia for the patient is presented in **Fig.2a**.

The surface predicted by the model is represented by the grid-lined surface. Equivalent lines of

5%, 50%, and 95% effect probabilities for analgesic effect are presented in **Fig.2b**.

EC₅₀: median effective dose

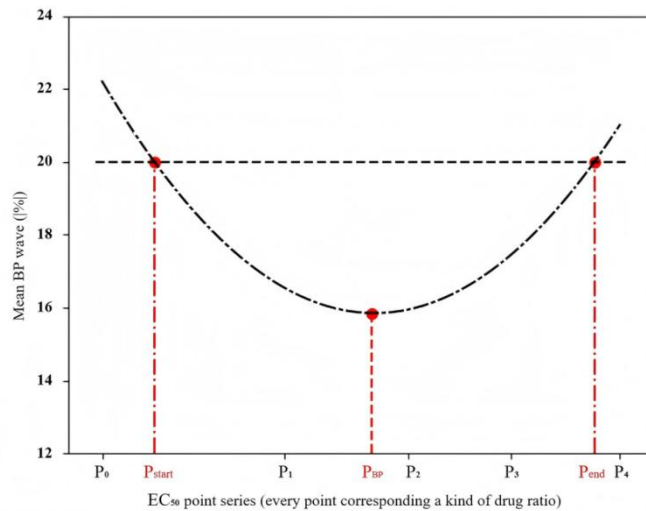
Fig.3. Quadratic function curve of MAP and awakening time.



A quadratic function was used to derive a curve using the EC₅₀ common to both drugs as the horizontal coordinate, and the fluctuation in MAP (%) and awakening time were used as the ordinate. P_{BP} indicates the optimal dosage value for hemodynamic stability; P_{WK} indicates the optimal dosage value for awakening time.

BP: Blood pressure; EC₅₀: median effective dose

Fig.4. Hemodynamic stability with plasma concentration ranges of propofol and alfentanil



A horizontal line is drawn at a 20% fluctuation in blood pressure, and the compatibility measurement of the area between the line and the curve can be considered hemodynamically stable.

Table 1 Demographics, baseline hemodynamic, surgical time, awake time, follicle quality (the

1 MII oocyte rate, and fertilization rate) for all groups patients

Variable	Group 1 (n = 10)	Group 2 (n = 10)	Group 3 (n = 10)	Group4 (n = 10)	Group 5 (n = 10)	P-value
Age (year), Mean $\pm$ SD	31.4 $\pm$ 3.8	32.2 $\pm$ 5.1	32.3 $\pm$ 2.8	31.1 $\pm$ 3.5	34.0 $\pm$ 5.7	0.60
BMI (kg/m ²), Mean $\pm$ SD	22.2 $\pm$ 1.8	22.3 $\pm$ 1.5	22.9 $\pm$ 2.0	23.4 $\pm$ 1.7	22.9 $\pm$ 1.3	0.48
Heart rate (beats/min), Mean $\pm$ SD	79.49 $\pm$ 6.53	79.73 $\pm$ 6.87	79.77 $\pm$ 10.59	80.32 $\pm$ 7.73	79.38 $\pm$ 8.66	0.22
MAP (mmHg), Mean $\pm$ SD	88.80 $\pm$ 4.30	88.84 $\pm$ 6.28	88.65 $\pm$ 4.08	88.13 $\pm$ 8.22	88.49 $\pm$ 5.76	0.13
Surgical time (min), Mean $\pm$ SD	12.6 $\pm$ 4.5	12.1 $\pm$ 3.0	10.7 $\pm$ 3.1	12.9 $\pm$ 3.3	11.8 $\pm$ 3.1	0.65
Awake time (min), Mean $\pm$ SD	4.9 $\pm$ 1.4	2.8 $\pm$ 0.8	2.6 $\pm$ 0.7	3.0 $\pm$ 0.9	3.4 $\pm$ 1.0	<0.001
The MII oocyte rate (%), Mean $\pm$ SD	71.9 $\pm$ 19.3	71.9 $\pm$ 19.3	80.6 $\pm$ 15.1	78.4 $\pm$ 19.3	82.2 $\pm$ 21.9	0.75
Fertilization rate (%), Mean $\pm$ SD	66.5 $\pm$ 14.0	66.5 $\pm$ 14.0	79.0 $\pm$ 19.4	61.7 $\pm$ 21.4	68.5 $\pm$ 20.0	0.39

2 P value compares group1,2,3,4 and 5. One-way ANOVA was used to compare means across
3 the five groups, and the chi-squared test was used to compare proportions.
4 SD: Standard Deviation, BMI:Body Mass Index, MAP: Mean Arterial Pressure

5
6

7 **Table 2** Logit model parameters

Variable	Δ -2LL	β_0	β_1	β_2	β_3	Correlation Coefficient
Value	25.41	5.25	6.22	9.37	37.31	0.9449

8 LL: log-likelihood

9

10

11 **Table 3** Adverse events in each group

Adverse events	Group 1 (n = 10)	Group 2 (n = 10)	Group 3 (n = 10)	Group 4 (n = 10)	Group 5 (n = 10)	<i>P</i> -value
Respiratory depression, n (%)						<0.001
Yes	8 (80)	2 (20)	3 (30)	7 (70)	8 (80)	
No	2 (20)	8 (80)	7 (70)	3 (30)	2 (20)	
Blood pressure fluctuation rate (%)	21.1 ± 10.3	13.3 ± 6.2	14.7 ± 6.3	19.0 ± 7.3	20.9 ± 8.9	<0.001
Mean ± SD						

1 *P* value compares group1,2,3,4 and 5. One-way ANOVA was used to compare means across
2 the five groups, and the chi-squared test was used to compare proportions.

3 SD: Standard Deviation

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Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementaryfile.pdf](#)