Original Article
Response surface analysis for pharmacodynamic interaction between sufentanil and flurbiprofen axetil in postoperative analgesia

Lei Guan[1], Tianzuo Li[1], Wentao Liu[1], Shaoheng Wang[1], Pengfei Liu[1], Wei Lu[2], Rong Chen[2], Shuangmin Ji[2]

[1]Department of Anesthesiology, Beijing Shijitan Hospital, Affiliated to Capital Medical University, Beijing, China;
[2]College of Pharmacy, Peking University Health Science Centre, Beijing, China

Abstract: Objective: Sufentanil and flurbiprofen axetil are widely used for postoperative analgesia. However, the specific pharmacodynamic interactions have not been elucidated thus far. Two new response surface models were developed to clarify the manner and strength of interaction between sufentanil and flurbiprofen axetil. Methods: Eighty adult patients (40 men and 34 women, aged 20-60 years) were enrolled in this study. All the subjects underwent surgeries and received continuous infusions of sufentanil and flurbiprofen axetil in various concentration pairs. Initially, 80 subjects were randomly assigned to nine groups of sufentanil (from 0 to 1.2 µg/ml). In each group, sufentanil concentration was fixed, while the concentration of flurbiprofen axetil was increased in a stepwise fashion from 0 mg/mL to 2.0 mg/ml at 0.25 mg/ml intervals. The infusion rates in every concentration pair were 5 ml/h with an infusion time of 15 min. At each interval, pain was assessed with a visual analogue scale (VAS); SpO_2 was evaluated as well. The pharmacodynamic interactions between sufentanil and flurbiprofen were analyzed via a response surface methodology. Model parameters were estimated by NONMEN software. Results: The response surface analysis showed that sufentanil-flurbiprofen had synergistic analgesic effects. The results suggest that the VAS score decreased in sufentanil or flurbiprofen axetil dose-dependent manner. We also found that flurbiprofen axetil could reduce the amount of sufentanil required to achieve satisfactory analgesic effects, and vice versa. While SpO_2 was inversely related to the concentration of sufentanil, there was no correlation between SpO_2 and the concentration of flurbiprofen axetil. Moreover, the concentration pair with both satisfactory efficacy and security in our study was 0.6 µg/ml sufentanil and 2 mg/ml flurbiprofen axetil. Conclusion: Response surface methods can effectively characterize the interactions between two analgesic drugs and successfully determine the optimized concentration pair. Flurbiprofen axetil reduced the amount of sufentanil required to achieve satisfactory analgesic effects, and vice versa. The interactions had synergistic analgesic effects.

Keywords: Sufentanil, flurbiprofen, visual analogue scale, response surface model, pharmacodynamic interaction

Introduction

Different drugs producing similar effects on certain aspects of analgesia are commonly used together, leading to pharmacodynamic interactions between them. The pharmacodynamic interactions may be synergistic, additive, or infra-additive. These interactions are defined by the chemical heterogeneity and action receptors of the drugs [1]. Synergistic interaction is highly useful in postoperative analgesia for reducing applied doses and side effects of each drug [2]. Thus, it is important to explore the interactions between different analgesics.

Currently, many studies have reported the effects of different analgesia drugs and their combination in postoperative analgesia [3, 4]. Sufentanil plus flurbiprofen axetil are the most common clinically used combination [5, 6]. Sufentanil is an opioid agonist that exerts its analgesic effects through µ receptors in the central nervous system [7]. Flurbiprofen axetil, a non-steroidal anti-inflammatory drug (NSAID), accumulates in targeted areas to reduce prostaglandin expression and peripheral pain stimulation [8]. However, the specific doses for the drug combination have not been elucidated thus far.

Thus, this study examined the pharmacodynamic interactions between sufentanil and flurbiprofen axetil at various dose combinations.
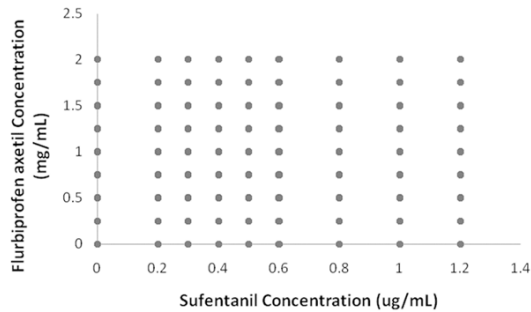
Figure 1. Study design.

Materials and methods

Subjects

Eighty adult patients (44 men and 36 women, aged 20-60 years) were enrolled in this study. All subjects were classified according to the American Society of Anesthesiologists physical status as either class I or II. The inclusion criteria were as follows: non-smokers, non-drinkers, a BMI (body mass index) in the range of 18-30 kg/m², and without serious diseases of the respiratory, circulatory, digestive, coagulation, or central nervous system. The exclusion criteria were as follows: patients with long-term surgery, drug hypersensitivity, long-term use of sedative and/or analgesic drugs (except with peptic ulcer), and serious hepatic, gastrointestinal, or coagulation system diseases [9].

Study design and drug administration

None of the subjects received premedication. The venous pathway was established, and ECG (electrocardiogram), IABP (invasive artery blood pressure), and CVP (central venous pressure) were monitored in each patient in the operating room. Anesthesia was induced by intravenous administration of midazolam, sufentanil, etomidate, and atracurium. Anesthesia was maintained with sevoflurane, remifentanil, and atracurium under bispectral index (BIS) monitoring. Administration of all drugs was stopped 10 min before the end of surgery, and endotracheal tubes were pulled out when the patients awakened.

After the operation mentioned above, postoperative analgesia was initiated. Different concentration groups of sufentanil and flurbiprofen axetil were set according to the common concentrations of analgesic drugs used clinically.

The concentration groups were 0, 0.2, 0.3, 0.4, 0.5, 0.6, 0.8, 1.0, and 1.2 μg/ml for sufentanil, and 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, and 2.0 mg/mL for flurbiprofen axetil. This study consisted of two steps: first, 80 subjects were randomly assigned to the nine groups of sufentanil (from 0 to 1.2 μg/ml). Then, while the sufentanil concentration in each group remained fixed, infusion concentrations of flurbiprofen axetil were increased in a stepwise fashion from 0 mg/mL to 2.0 mg/ml in 0.25 mg/ml intervals. All infusion rates in every concentration pair were 5 mL/h with an infusion time of 15 min. Vital signs (including electrocardiogram, respiration, non-invasive blood pressure, heart rate, and SpO_2) of all patients were closely monitored with an ECG monitor (Philips MP50) for the duration of the study. Assisted respiration and vasoactive drugs were applied to maintain physiological homeostasis if serious side effects (such as confusion or respiratory and circulative depression) occurred. Moreover, the one study on this situation was ceased (**Figure 1**).

This was a single-blinded study. Approval was obtained from the Beijing Shijitan Hospital and the Capital Medical University Medical Ethics Committee.

Measurement of effects

The infusion duration of each concentration pair was 15 min. At the end of every combination infusion, VAS, SpO_2, and relative complications (postoperative chills, agitation, and delirium) were all recorded.

The analgesic effect was measured on a visual analogue scale (VAS) ranging from 0 to 10 points ("0" indicating painless, "10" indicating the most severe and unbearable pain). All the patients were asked to select one number from 0-10 to represent the degree of pain experienced. Zero points indicated painlessness, ≤ 3 points indicated mild and acceptable pain, 4-6 points indicated moderate yet tolerable pain that affected sleep, and 7-10 points indicated severe and intolerable pain. A VAS score lower than 4 points indicated a good analgesic effect.

Respiratory depression was one of the main side effects and safety concerns, the degree of which was reflected by SpO_2. SpO_2 less than 90% implied the occurrence of serious side effects such as hypoxemia.

Response surface models

VAS model

The Greco model was selected as the response surface model for VAS scores, which were treated as continuous endpoints in the model [10]. The formula was as follows:

$$VAS = VAS_0 - (VAS_0 - REST) \times \left(\frac{U^r}{1+U^r}\right)$$

$$U = \frac{C_{SU}}{C50_{SU}} + \frac{C_{FU}}{C50_{FU}} + ax \frac{C_{SU}}{C50_{SU}} \times \frac{C_{FU}}{C50_{FU}}$$

VAS_0 represents the VAS score at baseline in the absence of the drug. REST is the VAS score with an infinite drug concentration. In this model, REST was assumed to be 0, indicating no pain at the highest drug concentration. γ is the surface steepness factor. C_{SU} and C_{FU} represented infusion concentrations of sufentanil and flurbiprofen axetil, respectively. $C50_{SU}$ and $C50_{FU}$ are defined as the infusion concentrations of sufentanil and flurbiprofen axetil that have 50% of the maximum analgesic effect, respectively. α is the interaction factor of the two drugs. A > 0 indicates a synergistic effect, α = 0 indicates an additive effect, and α < 0 indicates antagonism.

SpO₂ (oxyhemoglobin saturation) model

SpO₂ data were converted to dummy variables. SpO₂ < 90% implies the occurrence of hypoxemia and respiratory depression and was denoted by "1". SpO₂ ≥ 90% was denoted by "0". The relationship between sufentanil concentration and the probability of hypoxemia can be described by the Emax model [11], as follows:

$$P = E_0 + E_{max} X \frac{C_s^r}{EC_{50}^r + C_s^r}$$

E_0 and E_{max} represented the probability of respiratory depression occurrence with no drug and with infinite drug concentration, respectively, and were assumed as "0" and "1", respectively. represented the corresponding concentration EC_{50} when the probability of respiratory depression occurrence was 50%. γ was the slope factor. C_S was the infusion concentration of sufentanil.

Parameter estimation

Inter-individual variability (IIV) was introduced into the VAS model in exponential form [12]:

$$PAR_i = TVPAR \times e^{\eta i}$$

TVPAR represents the typical population value of a parameter. η_i is a symmetrically distributed random variable with a mean of zero and variance ω^2.

In addition, residual variability was introduced into the VAS model in additive form:

$$Y = F + \varepsilon$$

Where Y represents dependent-variable observation and F represents the corresponding individual-specific model prediction.

All the parameters in the VAS and SpO₂ models were estimated using NONMEM (version 7.3, ICON, Development Solutions, Ellicott City, MD, USA). NONMEM's first-order conditional estimation with interaction (FOCE-I) was used in the development of the VAS model, and Laplacian estimation with interaction was used in the development of the E_{max} model.

Diagnostic graphs for the models were plotted using the persp and xyplot function of R software (version 3.1.3 for Windows, https://www.r-project.org/) and with the help of RStudio Version 0.98.1091 (2009-2014 RStudio, Inc).

Results

Of the 80 subjects, 74 completed the study while the other 6 patients were excluded for the reason of noncompliance. Using response surface models, 738 paired pharmacodynamic responses were obtained for VAS scores, Ramsay scores, and SpO₂. No obvious side effects (e.g. postoperative agitation, delirium, and conscious disturbance) were observed. Additionally, no other adverse events caused by the two drugs (such as emesis, nausea, bradycardia, urinary retention, and anaphylaxis) occurred during the week of postoperative follow-up.

Response Surface for analgesic effects (VAS model)

The Greco model gave a good fit of the data. Parameter estimates are shown in **Table 1**.

To satisfy the condition of a VAS score lower than 4 in 50% of patients, the corresponding infusion concentrations of sufentanil and flurbiprofen axetil were 1.15 µg/ml and 3.21 mg/ml, respectively. Both were much higher clini-

Table 1. Parameter estimates of VAS model

Parameter	Estimate	RSE	95% CI
$C50_{SU}$ (μg/ml)	1.15	7.90%	0.911-1.334
$C50_{FU}$ (mg/ml)	3.21	7.10%	2.604-3.675
α	1.76	30.60%	0.623-2.903
VAS_0	9.13	1.40%	8.860-9.391
γ	1.55	8.60%	1.281-1.810
Inter-individual Variability (IIV) (%CV)			
IIV on $C50_{SU}$	55.8	10.00%	43.3-65.9
IIV on γ	33.5	19.00%	17.4-44.1
Residual Variability (standard deviation)			
Additive Variability	0.363	15.20%	0.308-0.417
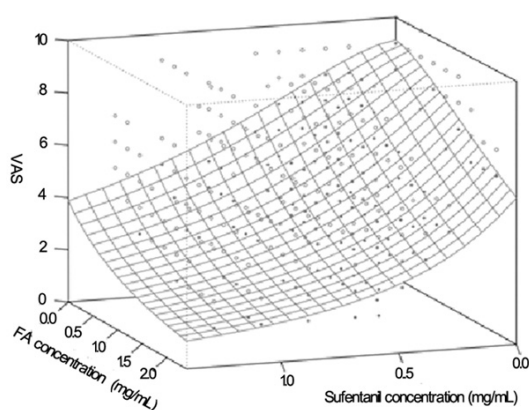
Figure 2. Response surface for VAS scores of interaction between sufentanil and flurbiprofen axetil. Raw data are shown above the surface as open circles and below the surface as filled circles.

cally used concentrations. The RSEs of most parameters were lower than 20%, implying that these estimates were reliable. Moreover, α = 1.76 > 0 suggested a synergistic analgesic effect between the two drugs.

The three-dimensional response surface for the VAS scores of various sufentanil-flurbiprofen axetil combinations is shown in **Figure 2**. The raw data circles are distributed evenly above and below the surface, suggesting a good fit of the raw data.

Figure 3 shows scatter diagrams of VAS scores vs. drug concentration. The results showed a relationship between VAS scores and the concentration of sufentanil or flurbiprofen axetil. VAS scores showed a downward trend along with the concentration of either sufentanil or flurbiprofen axetil. However, this trend slowed

down in high concentration pairs, implying that Hill's equation-based Greco model may be appropriate here.

Graphic diagnosis

Figure 4 shows the diagnostic plots of the response surface model on VAS score. All points were distributed in a relatively narrow scope on both sides of the unit line, as shown in the graph. The Loess regression curve of these points nearly coincided with the unit line with no obvious deviation, implying that this model was a good fit.

Visual predictive checks

The results of the visual predictive checks for the model on VAS score are shown in (**Figure 5A** and **5B**). All the dots represent the actual observed values. The red lines represent the median line of observed values, while the two blue lines indicate the 2.5% and 97.5% lines of observed data. The shaded areas represent the 95% confidence interval of 2.5%, 50%, and 97.5% of the predicted value. The three aforementioned lines overlapped substantially with the shaded areas, suggesting that this response surface model is a good predictor.
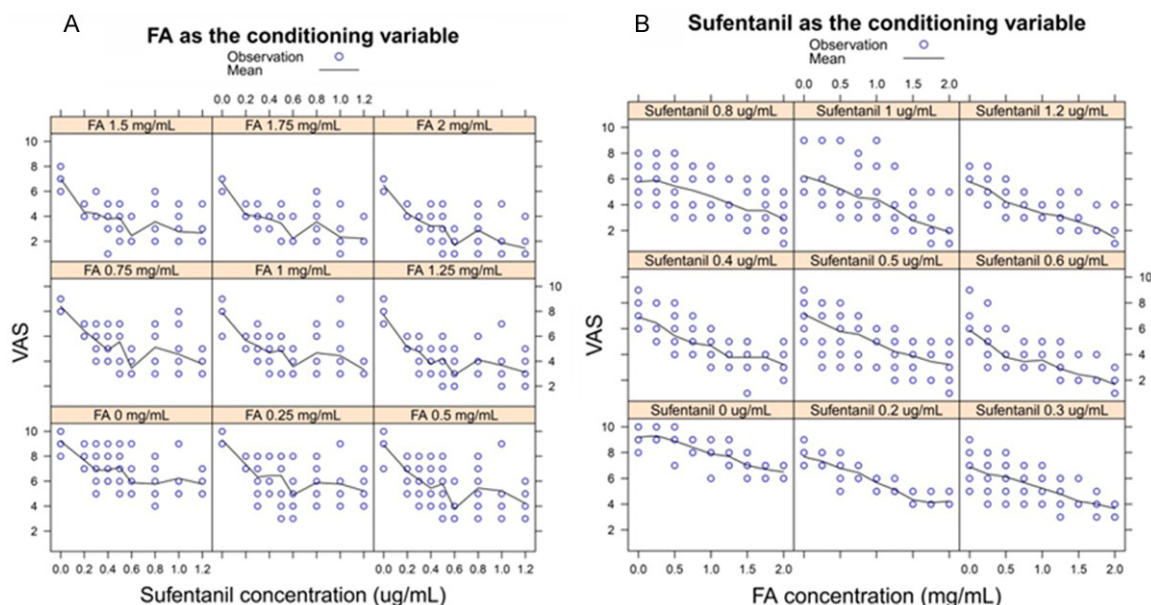
Response surface for side effect (respiratory depression) (SpO_2 model)

Figure 6 shows the correlation between SpO_2 and the concentration of sufentanil or flurbiprofen axetil. The results show that while SpO_2 was inversely related to the sufentanil concentration, it had no relationship with the concentration of flurbiprofen axetil. Moreover, exploratory data analysis showed that SpO_2 data was highly scattered. The group average does not reflect the changes in the incidence rate of respiratory depression with increasing drug concentration. A number of patients may be in great danger while the average value of SpO_2 remains normal.

Thus, the SpO_2 index was transformed to a dummy variable to be dealt with. $SpO_2 < 90\%$ or hypoxemia, indicated that the side effect of respiratory depression had occurred; this was denoted by "1", otherwise denoted by "0". The

Figure 3. The correlation between VAS scores and concentration of sufentanil or flurbiprofen axetil. A. Concentration-response relativity with FA (flurbiprofen axetil) as the conditioning variable. B. Concentration-response relativity with sufentanil as the conditioning variable.

relationship between the probability of SpO_2 < 90% and the drug concentration was shown in (**Figure 7A** and **7B**).

No correlation was observed between SpO_2 and the concentration of flurbiprofen axetil. Therefore, only the effect of sufentanil was considered in the model for respiratory depression. The Emax model was used; relative parameter estimates are listed in **Table 2**. The RSEs of all the parameters were lower than 30%, indicating high precision of this model.

The response surface for SpO_2 and the raw data are shown in **Figure 8**. The raw data is distributed evenly above and beneath the surface with no deviation trend, implying that the model fit the data well.

The probability of SpO_2 < 90% predicted by the model and the raw data were plotted in the same graph. The measured data (blue lines) fluctuated around the model predictive data (purple lines), also indicating that a good fit was achieved (**Figure 9**).

Optimization of concentration pairs between sufentanil and flurbiprofen axetil

According to the response surface model of analgesic effects and respiratory depression

effects, expected standards (including VAS score < 4 and probability of respiratory depression (SpO_2 < 90%) < 0.1) were set and a contour map was made (**Figure 10**).

In **Figure 10**, gray dots represent the sampling points of the study. The pink area is the scope interpolated by these actual sampling points, while the white part is the extrapolated area. The orange curve was the contour line of a VAS score of 3. The upper right area of the orange curve is the ideal efficacy area (VAS score < 3), and the bottom left area is the non-ideal efficacy area (VAS score > 3). Similarly, the blue curve was the contour line of a probability (incidence rate of SpO_2 < 90%) of 0.1. The left area of the blue curve was the safe area (probability < 0.1), while the right part was the danger zone (probability > 0.1).

Therefore, both the yellow and green areas represent the effective and safe concentration combinations of sufentanil and flurbiprofen axetil. The yellow area is the extrapolated region and the green area is the interpolated region. Theoretically, the interpolated conclusion is more reliable than the extrapolated one. Consequently, the concentration combinations within the green area are optimal. One sample in this study fell within that area, with infusion

Goodness of fit plots
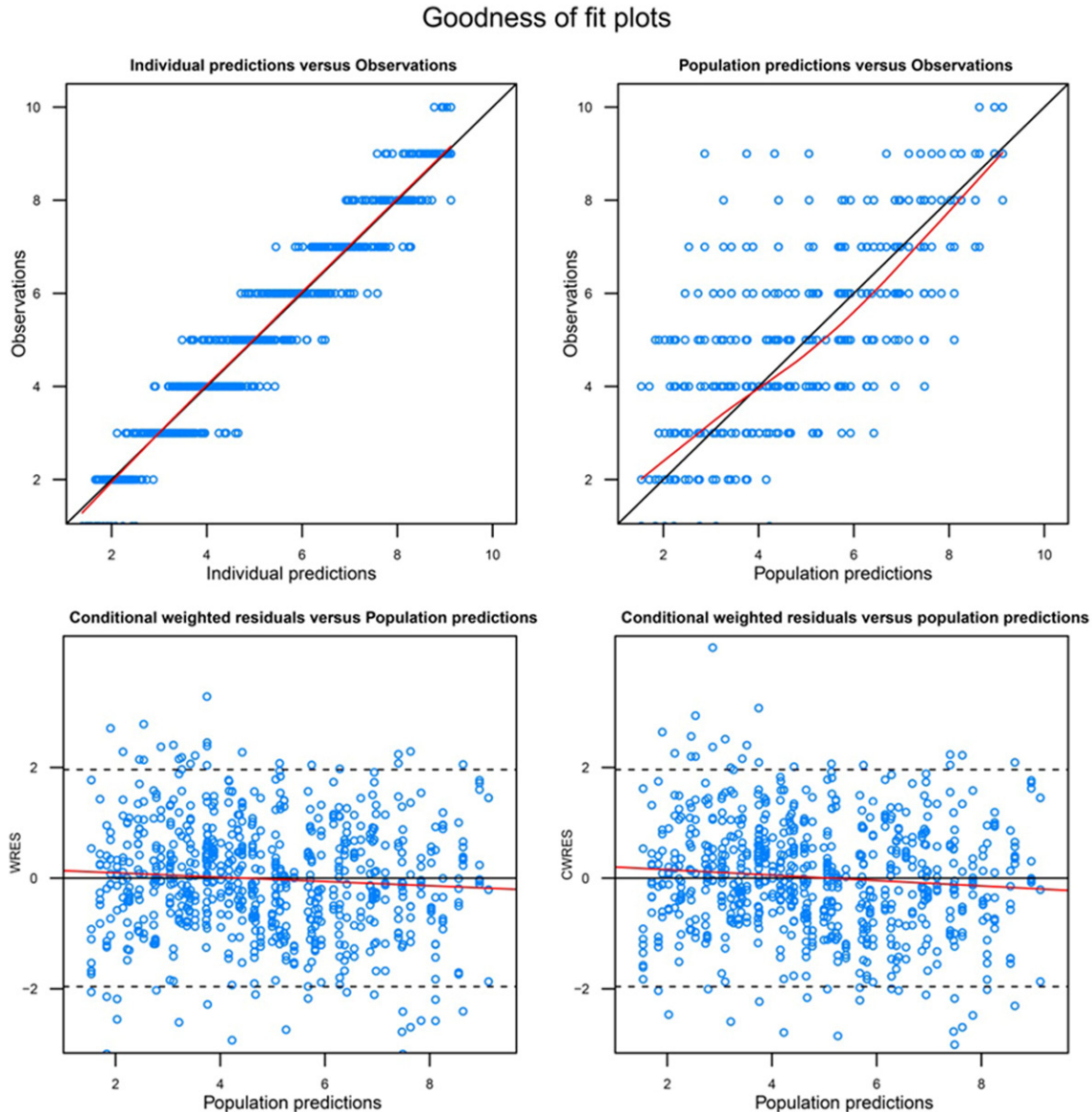
**Figure 4.** Goodness of fit plots for the response surface model on VAS score.

concentrations of 0.6 μg/ml and 2 mg/ml of sufentanil and flurbiprofen axetil, respectively.

Discussion

Pain after surgery increases circulating load followed by drastic systemic stress responses; moreover, it markedly influences disease prognosis and life quality of patients. Thus, reducing pain after surgery is a widely discussed topic in anesthesiology. Nowadays, multimodal analgesia proposed by previous studies successfully solves this problem [13]. Multimodal analgesia refers to the utilization of two or more different mechanisms of analgesics or analgesia methods, to achieve optimal analgesic effect. This helps avoid side effects caused by excessive use of a single drug [14, 15].

Combination use of opioids and NSAIDs is a universally employed analgesic solution [16, 17]. In domestic, sufentanil and flurbiprofen axetil are commonly used in combination in clinical setting. However, the pharmacodynamic interactions between these two drugs require further research. This study discusses the specific interactions of these two drugs in postoperative analgesia by using a response surface model.
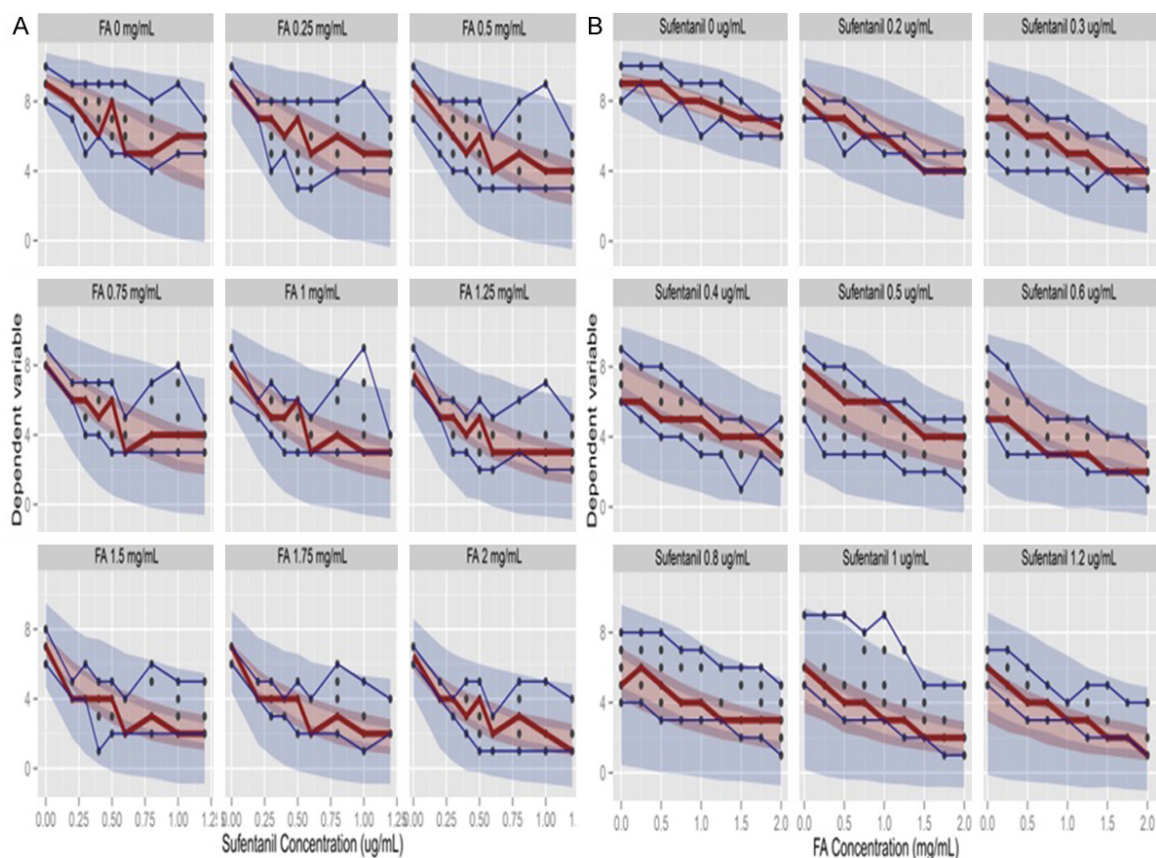
Figure 5. A. Visual predictive checks for response surface model with respect to VAS scores, with flurbiprofen axetil as the conditioning variable. B. Visual predictive checks for response surface model with respect to VAS scores, with flurbiprofen axetil as the conditioning variable.
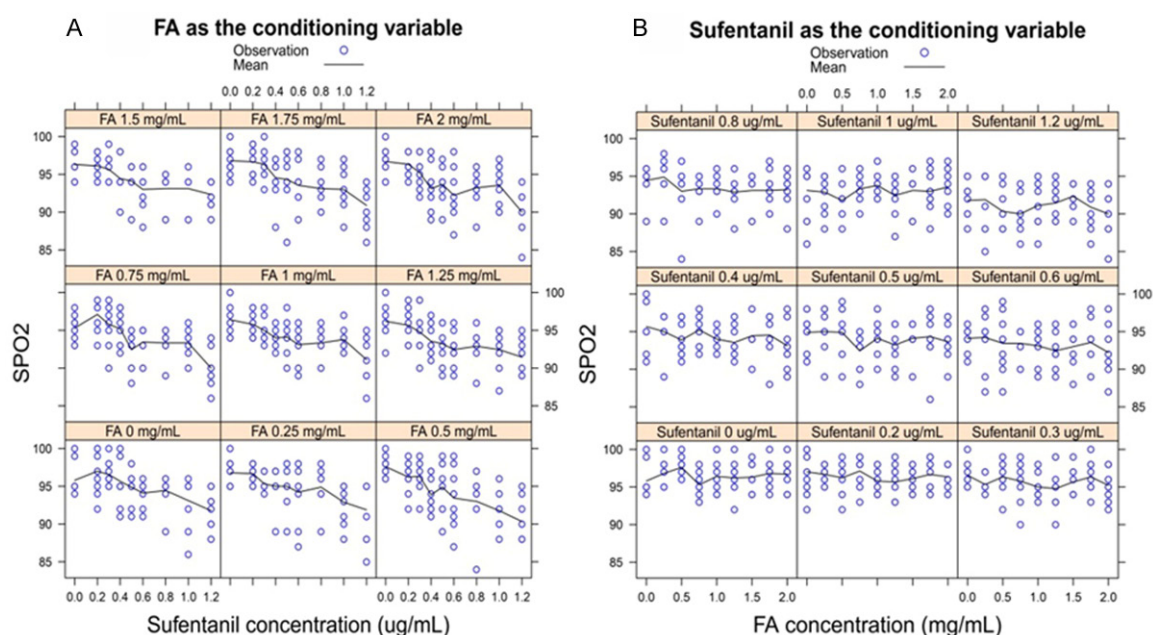
Figure 6. Exploratory data analysis for response surface model on SpO$_2$. A. Concentration-response relativity with FA (flurbiprofen axetil) as the conditioning variable. B. Concentration-response relativity with sufentanil as the conditioning variable.
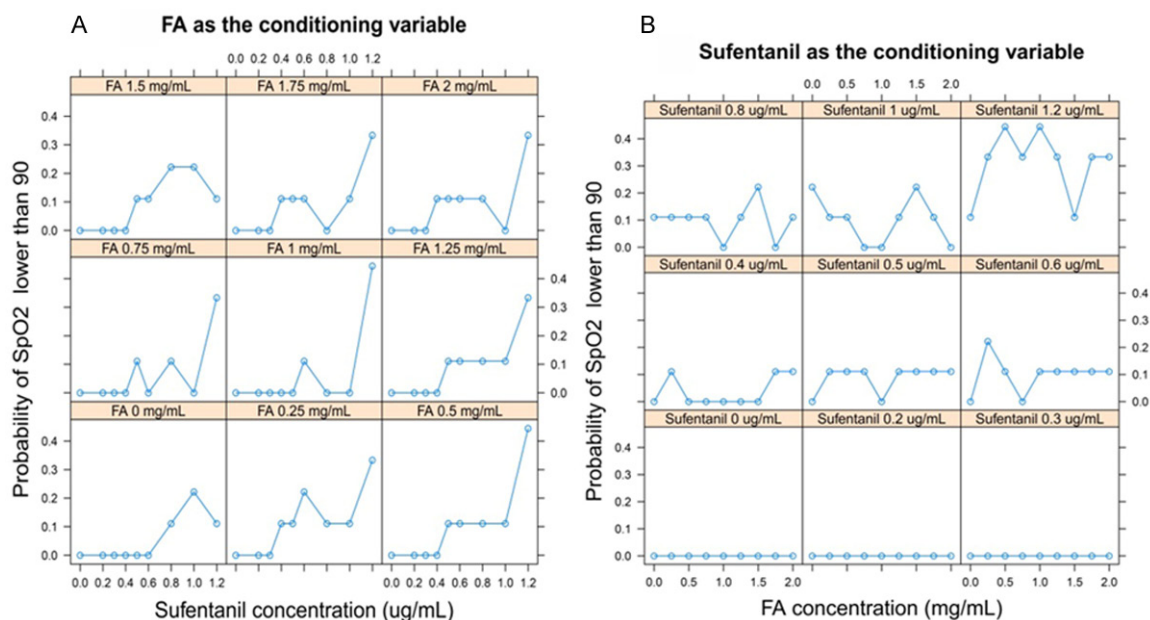
Figure 7. Quantal dose-response curve of SpO_2. A. Concentration-response relativity with FA (flurbiprofen axetil) as the conditioning variable. B. Concentration-response relativity with sufentanil as the conditioning variable.
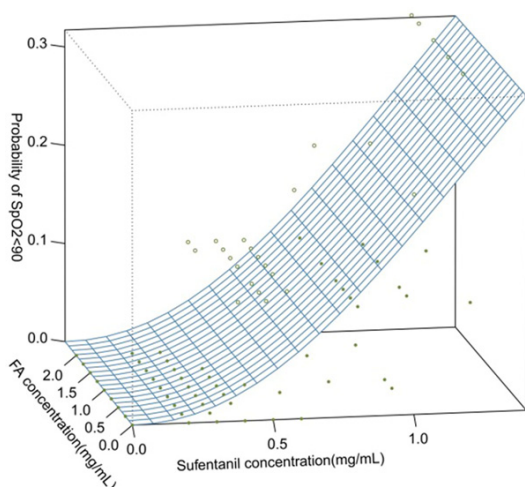
Table 2. Parameter estimates of SpO_2 model

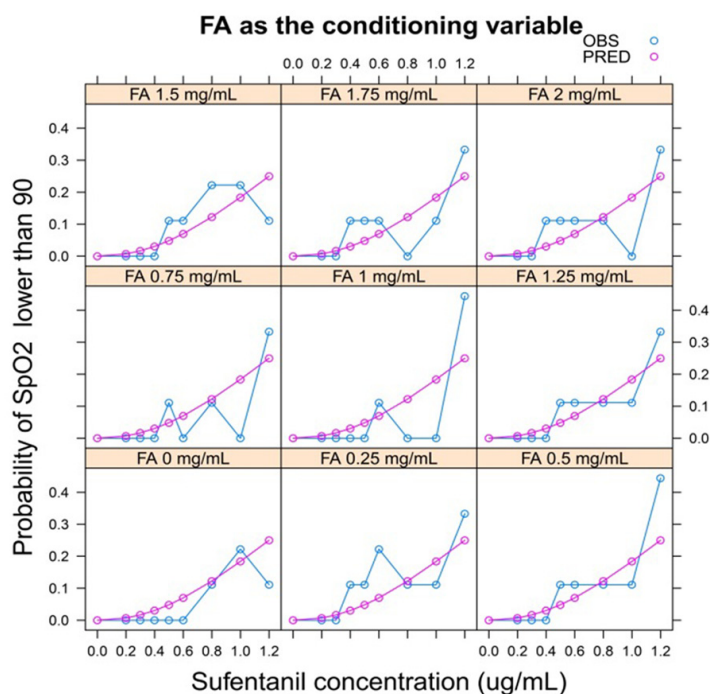| Parameter	Estimate	RSE	95% CI
EC_{50} (µg/mL)	2.00	21.9%	3.074-6.566
γ	2.15	25.6%	0.553-0.783

Figure 8. Response surface for SpO_2. Raw data above the surface are shown as open circles and below the surface as filled circles.

The response surface model is a powerful approach to quantitatively describe and predict pharmacodynamic interactions between two or more drugs. Response surface methodology was first reported by Minto for the interactions
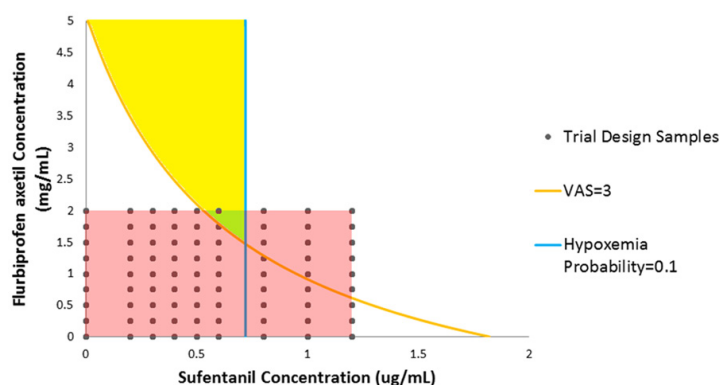
among anesthetics [18]. Short calculated corresponding samples for parallel, crisscrossed, and radial designs in this model [19]. Compared to the other two designs, the crisscrossed design required the smallest number of samples (at least 20), while others needed at least 40 [19]. Because of feasibility, the parallel design was selected for our research. Sufentanil (the primary drug) was fixed while the concentration of flurbiprofen axetil was gradually increased. Then, interactions of different combinations were successively discussed. Seventy-four patients completed this study.

Our study selected the VAS score as an effectiveness index. VAS score < 4 implied a good analgesic effect. Our results demonstrated that there existed synergistic effects on analgesia (VAS score) between sufentanil and flurbiprofen axetil (α = 1.76 > 0). To satisfy the condition of VAS score < 4 in 50% of patients in our model, the corresponding infusion concentration of sufentanil was 1.15 µg/mL (with 95% CI 0.911-1.334 µg/ml), while that of flurbiprofen axetil was 3.21 mg/ml (with 95% ci 2.604-3.675 mg/ml). Both were much higher than the clinically used concentrations. The scatter diagrams depicted the relevance between VAS scores and the concentration of sufentanil or flurbiprofen axetil. VAS scores showed a downward trend along with concentration of either sufentanil or flurbiprofen axetil, both presenting

Figure 9. Diagnostic plots for response surface model on SpO_2, flurbiprofen axetil as the conditioning variable.

Figure 10. The contour map of response surface model of analgesic effects and respiratory depression effects.

Thus, either drug can reduce the required dosage of the other.

Respiratory depression and excessive sedation are two side effects of the drugs, and were common complications in postoperative follow-up [20]. During this study, no patients exhibited excessive sedation. Consequently, SpO_2 was selected as the index of side effects. Response surface models were established to elucidate the safe range of infusion concentration pairs. A condition of $SpO_2 < 90\%$ suggested respiratory depression and hypoxemia. The results showed that SpO_2 was inversely related to the concentration of sufentanil, but showed no correlation with the concentration of flurbiprofen axetil. The concentration pairs that satisfied both effectiveness and security in our study were 0.6 μg/mL 2 mg/mL of sufentanil and flurbiprofen axetil, respectively.

Various response methodological approaches were compared to response surface models reported in previous literature. Minto et al [21] built a model flexibly characterizing the interaction of two drugs, which was developed by Dahanet et al by introducing the interaction function I (Q) [12]. Their works were well recognized for being able to quantitatively describe drug interaction that changes with the concentration combination. However, these models may over parameterize due to insufficient data and complicated structures. The Logit model, however, could not provide the pharmacodynamic parameters that the study needed [22]. Thus, the Greco model was selected to establish the response surface model for analgesic interaction between the two drugs; this could provide essential pharmacodynamic parameters. Nevertheless, because it showed no correlation with the dosage of flurbiprofen axetil, the SpO_2 index was transformed to a dummy variable to be further analyzed with the Emax model [11]. Both models could maintain their reliability and veracity.

the dose-response reactions. The data demonstrated that flurbiprofen axetil could reduce the amount of sufentanil required to achieve satisfactory analgesic effects. The result was consistent with results inferred by the analgesic mechanisms of these two drugs. Sufentanil is an opioid agonist that exerts its analgesic effect through the μ receptor in the central nervous system [7]. Flurbiprofen axetil, an NSAID in the form of lipid microsphere particles, migrates into areas affected by pain and acts by inhibiting expression of prostaglandins and weakening peripheral pain stimulation [9].

This study elucidated the pharmacodynamic interaction of various concentration pairs of sufentanil and flurbiprofen axetil, in order to find the appropriate infusion concentration pairs for postoperative intravenous analgesia. In China, intravenous analgesia pumps with sufentanil and flurbiprofen axetil were widely used after surgery. The intravenous infusion concentration, rather than blood concentration was selected for discussion, which was closer to clinical application.

However, there were limitations. The first one was the choice of cases. The objects of this study were patients with laparotomy and thoracotomy, which does not represent all the cases that received intravenous analgesia. Secondly, for the sake of feasibility and patient compatibility in our study, the VAS score and SpO_2 were selected to evaluate analgesic effects and the degree of respiratory inhibition, respectively. There were also various other methods reflecting these indicators and the other side effects. Another limitation was the problem of selecting alternative process models. All the models have advantages and disadvantages, and the most fitting model for each data set is unclear.

In summary, the sufentanil-flurbiprofen axetil response surfaces estimated in our research report clear and profound synergistic analgesic effects. Additionally, using the two response surface models for analgesic effects and side effects, we found the safest and most effective concentration pairs. However, the optimal concentration to achieve desired effects with minimum side effects still needs to be further explored in patients who have undergone various kinds of surgery. More indicators and analgesic drugs will be selected for discussion in the future.

Acknowledgements

Disclosure of conflict of interest

None.

Address correspondence to: Pengfei Liu, Department of Anesthesiology, Beijing Shijitan Hospital, Affiliated to Capital Medical University, 10 Tieyi Road, Haidian District, Beijing 100038, China. Tel: +86-15210626257; E-mail: pengfei437@sina.com

References

[1] Meibohm B and Derendorf H. Basic concepts of pharmacokinetic/pharmacodynamic (PK/PD) modelling. Int J Clin Pharmacol Ther 1997; 35: 401-413.

[2] Tang J, Wennerberg K and Aittokallio T. What is synergy? The Saariselka agreement revisited. Front Pharmacol 2015; 6: 181.

[3] Rosero EB and Joshi GP. Preemptive, preventive, multimodal analgesia: what do they really mean? Plast Reconstr Surg 2014; 134: 85S-93S.

[4] Tan M, Law LS and Gan TJ. Optimizing pain management to facilitate Enhanced Recovery After Surgery pathways. Can J Anaesth 2015; 62: 203-218.

[5] Lin X, Zhang R, Xing J, Gao X, Chang P and Li W. Flurbiprofen axetil reduces postoperative sufentanil consumption and enhances postoperative analgesic effects in patients with colorectal cancer surgery. Int J Clin Exp Med 2014; 7: 4887-4896.

[6] Geng W, Hong W, Wang J, Dai Q, Mo Y, Shi K, Sun J, Qin J, Li M and Tang H. Flurbiprofen Axetil Enhances Analgesic Effects of Sufentanil and Attenuates Postoperative Emergence Agitation and Systemic Proinflammation in Patients Undergoing Tangential Excision Surgery. Mediators Inflamm 2015; 2015: 601083.

[7] Minkowitz HS. A review of sufentanil and the sufentanil sublingual tablet system for acute moderate to severe pain. Pain Manag 2015; 5: 237-250.

[8] Shirasaka W, Toriyama S, Tsujikawa S, Yamashita T, Tani Y and Ikeshita K. [Use of flurbiprofen before emergence from anesthesia relieves pain during immediate postoperative period after laparoscopic inguinal hernia repair]. Masui 2015; 64: 60-64.

[9] Rahman NM, Pepperell J, Rehal S, Saba T, Tang A, Ali N, West A, Hettiarachchi G, Mukherjee D, Samuel J, Bentley A, Dowson L, Miles J, Ryan CF, Yoneda KY, Chauhan A, Corcoran JP, Psallidas I, Wrightson JM, Hallifax R, Davies HE, Lee YC, Dobson M, Hedley EL, Seaton D, Russell N, Chapman M, McFadyen BM, Shaw RA, Davies RJ, Maskell NA, Nunn AJ and Miller RF. Effect of Opioids vs NSAIDs and Larger vs Smaller Chest Tube Size on Pain Control and Pleurodesis Efficacy Among Patients With Malignant Pleural Effusion: The TIME1 Randomized Clinical Trial. JAMA 2015; 314: 2641-2653.

[10] Greco WR, Bravo G and Parsons JC. The search for synergy: a critical review from a response

surface perspective. Pharmacol Rev 1995; 47: 331-385.

[11] Magnusdottir BT. Optimal designs for a multi-response Emax model and efficient parameter estimation. Biom J 2016; 58: 518-34.

[12] Dahan A, Nieuwenhuijs D, Olofsen E, Sarton E, Romberg R and Teppema L. Response surface modeling of alfentanil-sevoflurane interaction on cardiorespiratory control and bispectral index. Anesthesiology 2001; 94: 982-991.

[13] Secrist ES, Freedman KB, Ciccotti MG, Mazur DW and Hammoud S. Pain Management After Outpatient Anterior Cruciate Ligament Reconstruction: A Systematic Review of Randomized Controlled Trials. Am J Sports Med 2016; 44: 2435-47.

[14] Devin CJ and McGirt MJ. Best evidence in multimodal pain management in spine surgery and means of assessing postoperative pain and functional outcomes. J Clin Neurosci 2015; 22: 930-938.

[15] Girard P, Chauvin M and Verleye M. Nefopam analgesia and its role in multimodal analgesia: A review of preclinical and clinical studies. Clin Exp Pharmacol Physiol 2016; 43: 3-12.

[16] Neubert A, Verhamme K, Murray ML, Picelli G, Hsia Y, Sen FE, Giaquinto C, Ceci A, Sturkenboom M and Wong IC. The prescribing of analgesics and non-steroidal anti-inflammatory drugs in paediatric primary care in the UK, Italy and the Netherlands. Pharmacol Res 2010; 62: 243-248.

[17] Akbari E. The role of cyclo-oxygenase inhibitors in attenuating opioid-induced tolerance, hyperalgesia, and dependence. Med Hypotheses 2012; 78: 102-106.

[18] Minto CF, Schnider TW, Short TG, Gregg KM, Gentilini A and Shafer SL. Response surface model for anesthetic drug interactions. Anesthesiology 2000; 92: 1603-1616.

[19] Short TG, Plummer JL and Chui PT. Hypnotic and anaesthetic interactions between midazolam, propofol and alfentanil. Br J Anaesth 1992; 69: 162-167.

[20] Wong I, St John-Green C and Walker SM. Opioid-sparing effects of perioperative paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) in children. Paediatr Anaesth 2013; 23: 475-495.

[21] Minto C and Vuyk J. Response surface modelling of drug interactions. Adv Exp Med Biol 2003; 523: 35-43.

[22] Egan TD and Minto C. Common pharmacodynamic drug interactions in anesthetic practice. In: Evers AX, Maze M, editors. Anesthetic Pharmacology: Physiologic Principles & Clinical Practice. London: Churchill Livingstone; 2004. pp. 94-97.