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A previously published propofol–remifentanil response surface model does not predict patient response well in video-assisted thoracic surgery

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Abstract

Modern anesthesia usually employs a hypnotic and an analgesic to produce synergistic sedation and analgesia. Two remifentanil–propofol interaction response surface models were used to predict sedation using Observer's Assessment of Alertness/Sedation (OAA/S) scores; one predicts an OAA/S <2 and the other <4. We hypothesized that both models would predict regained responsiveness (RR) after video-assisted thoracic surgery (VATS) to reduce total anesthesia time and make early extubation clinically relevant. We included 30 patients undergoing VATS received total intravenous anesthesia (TIVA) combined with thoracic epidural anesthesia (TEA). Pharmacokinetic profiles were calculated using Tivatrainer. Model predictions were compared with observations to evaluate the accuracy and precision of emergence model predictions. The mean (standard deviation) differences between when a patient responded to their name and the time when the model predicted a 50% probability of patient response were 30.80 ± 17.77 and 13.71 ± 11.35 minutes for the OAA/S <2 model and <4 model, respectively. Both models had a limited ability to predict patient response in our patients. Both models identified target concentration pairs predicting time of RR in volunteers and some elective surgeries, but another model of epidural and intravenous anesthetic combinations may be needed to predict time of RR after VATS under TIVA with TEA.

Abbreviations: ASA = American Society of Anaesthesiologists, CeP = effect-site concentration, DLT = double-lumen tube, ETT = endotracheal tube, LOR = loss of responsiveness, OAA/S = Observer's Assessment of Alertness/Sedation, OR = operating room, PACU = postanesthetic recovery unit, PCEA = patient-controlled epidural analgesia, RR = regained responsiveness, TCI = target-controlled infusion, TEA = thoracic epidural anesthesia, TIVA = total intravenous anesthesia, VAS = visual analogue scale, VATS = video-assisted thoracic surgery.

Keywords: response surface model, thoracic epidural anesthesia, total intravenous anesthesia, video-assisted thoracic surgery

1. Introduction

Use of video-assisted thoracoscopic surgery (VATS) has increased markedly in recent years.[1] General anesthesia with 1-lung ventilation is routine and used in VATS worldwide. General anesthesia with a double-lumen tube (DLT) provides good surgical exposure, a motionless surgical field, and a secure airway.[1] Usually, the DLT is removed and a conventional endotracheal tube (ETT) is inserted before the patient is transferred from the operating room (OR) if postoperative mechanical ventilation is indicated.[2] Tracheal injury due to orotracheal intubation is a rare but potentially fatal complication. The estimated incidence of tracheobronchial rupture ranges from 0.05% to 0.19% when a larger diameter double-lumen ETT is used.[3–9] Rapid emergence can decrease the likelihood of a second tracheal intubation after VATS, thus reducing the incidence of tracheal injury. Moreover, shortening the extubation time and postanesthetic recovery unit (PACU) stay would result in reasonable economic benefits and rapid OR workflows.[10,11] There are still no practical guidelines available regarding which anesthetic combinations are better to facilitate rapid emergence and early extubation after VATS.

It is common to combine opioids and anesthetics to attain adequate anesthesia with lower dose requirements than those needed for the individual drugs because of synergistic interactions, which could reduce unwanted side effects and improve recovery.[12] A response surface is a mathematical equation that relates a dependent variable, such as a drug effect, to inputs, such as 2 drug concentrations, to provide knowledge about drug interactions, evaluate clinical effects, and optimize anesthetic practice.[13] Recently, there has been increasing interest in response surface interaction models for opioid and propofol interactions; they have been used to predict anesthetic drug effects

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such as analgesia, sedation, and loss of responsiveness (LOR).[14–16] This technique allows observation of concentration–effect relationships for infinite combinations of remifentanil and propofol over a surface area in 3-dimensional space.[12,14–18] However, most models have focused on LOR; few were ever validated with anesthesia emergence. The aims of this study were to determine if these models could accurately predict emergence time in patients undergoing VATS under total intravenous anesthesia (TIVA) combined with thoracic epidural anesthesia (TEA). We hypothesized that some response models would help to find the best anesthetic combinations. The implications of this study would be useful for anesthesiologists, especially for early extubation after VATS.

2. Methods

A prospective, observational, nonrandomized study was conducted in 30 patients with American Society of Anaesthesiologists (ASA) physical status I to III who underwent general anesthesia in 2014 at the Taipei Veterans General Hospital, Taipei, Taiwan. The study was approved by the Institutional Review Board, Taipei Veterans General Hospital (No. 2014-02-001B) and was conducted in accordance with the approved guidelines. Informed consent was obtained from all study participants. The subjects were selected from patients scheduled for elective pulmonary or mediastinal surgery and VATS under TIVA with TEA. Their ages ranged from 20 to 80 years. Seventeen participants were men and 13 were women. Patients undergoing emergency surgery, those with neurological disorders, coagulopathy, local sepsis, allergy to amide local anesthetics, hearing impairment, opioid consumption, recent use of psychoactive medication, more than 20 g of daily alcohol consumption, and taking anticoagulant or antiplatelet drugs that could not be suspended in the perioperative period were excluded. Age, weight, and height were recorded for each patient, and are presented in Table 1.

No participant received premedication. Electrocardiography and noninvasive monitoring of blood pressure and hemoglobin oxygen saturation were performed continuously and recorded. The bispectral index was monitored to observe anesthesia depth.

Before induction of anesthesia, an epidural needle was inserted between the T7 and T8 interspaces to achieve somatosensory and motor block at the T4 to T8 level with a paramedian approach.[19] The epidural space was identified by the loss of resistance technique using a 10 mL glass syringe filled with air. After catheter placement, a test dose of 2 mL of xylocaine 2% was administered to exclude intrathecal positioning and confirm the somatosensory block level. A cold discrimination test was used to demarcate blockade levels.

General anesthesia was induced with a bolus dose of fentanyl (3–5 μg/kg) and propofol, which was administered using a target-controlled infusion (TCI) device, with effect-site concentration (CeP) setting of 4 to 10 μg/mL. Pharmacokinetic propofol parameters published by Schnider et al[20] were used. After LOR, patients were administered rocuronium (0.6–1 mg/kg) as a neuromuscular blocking agent to facilitate intubation. A left DLT was inserted. The correct tube position was determined by auscultation and confirmed by fiber optic bronchoscopy before and after the patient was placed in the lateral decubitus position. TEA was performed with a loading dose of 1.5% xylocaine combined with fentanyl 50 μg or morphine 3 mg in a total volume of 10 mL. Intraoperatively, TEA was maintained with a continuous 0.25% bupivacaine infusion of 3 to 10 mL/h. General anesthesia was maintained with propofol throughout through dose adjustments to achieve an adequate anesthetic plane with a bispectral index value of 40 to 60; rocuronium was intermittently administered as an intravenous bolus to maintain 1 twitch after a train-of-4 stimulus. Ventilation was controlled artificially to maintain an end-tidal CO_2 between 35 mm Hg and 40 mm Hg; body temperature was maintained at 35.5°C and 37.0°C. Vital signs, surgical events, patient responses, anesthetic target concentrations, and drug administration details were recorded continuously.

At the end of surgery after skin closure, neuromuscular blockade was antagonized with intravenous neostigmine 1 to 2 mg and intravenous atropine 0.5 to 1 mg, and the propofol TCI pump was discontinued. One anesthetic nurse assessed and recorded the patient's level of consciousness every 20 seconds using the OAA/S scores, as presented in Table 2.[21] Assessments started after the propofol TCI pump was discontinued and ended 10 minutes after the patient showed RR. RR was defined as the first of 2 consecutive OAA/S scores ≥4. Once adequate spontaneous ventilation was established and there was RR, the DLT was removed. After extubation, patients were transported to the PACU for monitoring of vital signs, nausea/vomiting, and bleeding every 30 minutes for 2 hours. Amnesia scores were recorded (1. remembers everything about the surgery, 2. forgot a few things about it, 3. forgot most of what went on, 4. does not remember anything) in the PACU. Patient-controlled epidural analgesia (PCEA) was applied for postoperative pain control; pain levels were measured using a visual analogue scale (VAS) where 0 indicates no pain and 10 indicates severe pain at 6, 12, 24, 48, and 72 hours postoperatively.

2.1. Pharmacokinetic simulation

Pharmacokinetic profiles, including plasma and effect-site concentrations, were estimated using the Tivatrainer simulation program (version 8). A previously published pharmacokinetic model for fentanyl by Shafer et al[22] was applied to calculate fentanyl effect-site concentrations. The calculated effect-site concentrations for fentanyl during the whole course of anesthesia

Table 1

Patient demographic profiles (mean ± SD).

Age, (yr)	60.2±9.8
No. male	17
No. female	13
Weight, kg	63.5±9.7
Height, cm	162.6±8.4
Body mass index, kg/m^2	24.0±2.8
No. ASA physical status I	2
No. ASA physical status II	21
No. ASA physical status III	7

ASA = American Society of Anaesthesiologists, SD = standard deviation.

Table 2

The observers assessment of alertness/sedation (OAA/S) scores.

Value	Description
5	Responds readily to name spoken in normal tone.
4	Lethargic response to name spoken in normal tone.
3	Responds only after name is called loudly and/or repeatedly for the individual to open their eyes.
2	Responds only after moderate prodding or shaking.
1	Does not respond to moderate prodding or shaking
0	Does not respond to deep stimulus

An OAA/S score more than 4 was considered surrogate the condition of extubation.

Table 3

Propofol–remifentanil interaction model parameters to responses recorded in volunteers for OAA/S<2 and OAA/S<4.

Model parameters	C50p (μg/mL)	C50r (ng/mL)	N	Alpha
OAA/S<2	2.2	33.1	5	3.6
OAA/S<4	1.8	12.5	3.76	5.1

Alpha = interaction between propofol and remifentanil for a given drug effect, C50p and C50r = propofol and remifentanil predicted effect-site concentrations associated with a 50% probability of the maximal effect, n = model parameters representing the steepness, OAA/S = observer's assessment of alertness/sedation.

were converted to equivalent remifentanil concentrations using a relative remifentanil-to-fentanyl potency of 1:1.2.[23] Schneider pharmacokinetic model[20] was used to calculate propofol effect-site concentrations throughout the procedure by entering the times when TCIs of propofol were administered.

2.2. Response surface models

The response surface models were constructed using a Greco model structure (equation 1). Two published Greco intravenous propofol–remifentanil interaction models established at numerous concentration pairs were used to calculate sedation probabilities of an OAA/S <2,[15] and an OAA/S <4.[16] The model parameters for both Greco models are presented in Table 3.[13]

$$\text{Effect} = \frac{E_{\max} \times \left[\frac{C_e r}{C_{50r}} + \frac{C_e p}{C_{50p}} + a \times \left(\frac{C_e r}{C_{50r}} \times \frac{C_e p}{C_{50p}}\right)\right]^n}{\left[\frac{C_e r}{C_{50r}} + \frac{C_e p}{C_{50p}} + a \times \left(\frac{C_e r}{C_{50r}} \times \frac{C_e p}{C_{50p}}\right)\right]^n + 1} \quad (1)$$

Effects ranged from 0 to 1 (0%–100% probabilities of no response, respectively), where E is the predicted effect at a measured steady-state plasma concentration, E0 is the effect at baseline, Emax is the maximal effect of propofol and remifentanil for a given effect measure (i.e., 100% probability of an OAA/S <2), EC50 is the steady-state plasma concentration that produces 50% of the maximal effect, and C50p is the effect-site concentration that produces 50% of the maximal effect for propofol administered alone (i.e., 50% probability of an OAA/S <2), n is the pharmacodynamics response curve slope, and α is the propofol–remifentanil interaction parameter.

Calculated remifentanil and propofol effect-site concentrations were used as model inputs; predicted LOR probabilities (from 0% to 100%) for each patient were converted to RR probabilities by the arithmetical operation of 1—the probability of LOR.

2.3. Evaluation of response surface model predictions

Model predictions of OAA/S ≥2 and OAA/S ≥4 ranging from 0% to 100% were calculated every 20 seconds from termination of the propofol TCI pump until 10 minutes after each patient's RR. To assess the accuracy of each model's RR prediction, predictions were compared with observations using the following analyses.

2.3.1. Graphical analysis. Model predictions were compared graphically on 2 plots: model prediction over time, and remifentanil-equivalent effect-site concentrations and CeP values at emergence superimposed on a topographical representation of model predictions for OAA/S ≥4 and ≥2. The topographical plot included 5%, 50%, and 95% isoboles. Isoboles were remifentanil–propofol concentration pairs producing the same probability of effect. In general, a good model fit resulted in an equal distribution of LOR model predictions above and below the 50% isobole.

2.3.2. Temporal analysis. We calculated differences between the times each response surface model predicted a 50% probability of response (OAA/S ≥2 and ≥4) and when patients with lethargy responded to their name during emergence. A negative, zero, or positive time difference indicated that the observed RR occurred prior to, exactly at, or after the 50% probability from the model predictions. Time differences are reported as the mean ± standard deviation.

2.3.3. Empirical cumulative distribution. The empirical cumulative distribution was plotted as the population percentage versus sorted model predictions. The models' predicted probabilities for OAA/S ≥2 and ≥4 were calculated at the time of RR. Model predictions at RR were sorted according to increasing probability. A percentage value was assigned to each patient as a fraction of all patients according to the observed probability at the transition. The patient population percentage was plotted versus sorted model predictions. A consistent distribution of model predictions across patient percentage values from 0% to 100% was considered a good fit.

3. Results

Thirty patients (17 men; 13 women) were enrolled; all subjects completed the study. ASA physical status classifications ranged from I to III. Height, weight, body mass index, and age were 162.6 ± 8.4 cm, 63.5 ± 9.7 kg, 24.0 ± 2.8 kg/m^2, and 60.2 ± 9.8 years, respectively. Demographic profiles are presented in Table 1. Estimated blood loss was <100 mL for all patients. The mean propofol CeP was 0.97 ± 0.26 μg/mL, and the mean remifentanil equivalent concentration was 0.36 ± 0.1 ng/mL at the time the patient responded to voice commands. Figure 1 shows model predictions for OAA/S ≥2 and OAA/S ≥4 over time during emergence from anesthesia for each patient. Figure 2 shows the empirical cumulative distribution, which is a prediction of the probability of response for both models at the time of RR versus the percentage of patients.

Figure 3 shows the time difference between when each of the 2 OAA/S models predicted a 50% probability of patient response and the time when each patient showed RR. The averages and standard deviations of the differences were 30.32 ± 16.9 minutes for the OAA/S ≥2 model and 14.02 ± 10.9 minutes for the OAA/S ≥4 model. After recovery, no patient recalled the procedure or required reintubation.

The OAA/S ≥2 model predicted a mean probability of 96.20% ± 4.3% at the time the patient would have responded to their name spoken in a normal tone during emergence. Figure 4 shows the 5%, 50%, and 95% probability isoboles for the OAA/S ≥2 model and predicted concentration pairs at RR. Data points are distributed around the 95% isobole.

The OAA/S ≥4 model predicted a mean probability of 80.49% ± 13.15% at the time the patient would have lethargically responded to their name spoken in a normal tone during emergence. Figure 5 shows predicted propofol–remifentanil concentration pairs at the time of emergence superimposed on a topographical representation of the model predicting an OAA/S ≥4. Data points were mainly distributed between the 95% and 50% isoboles.

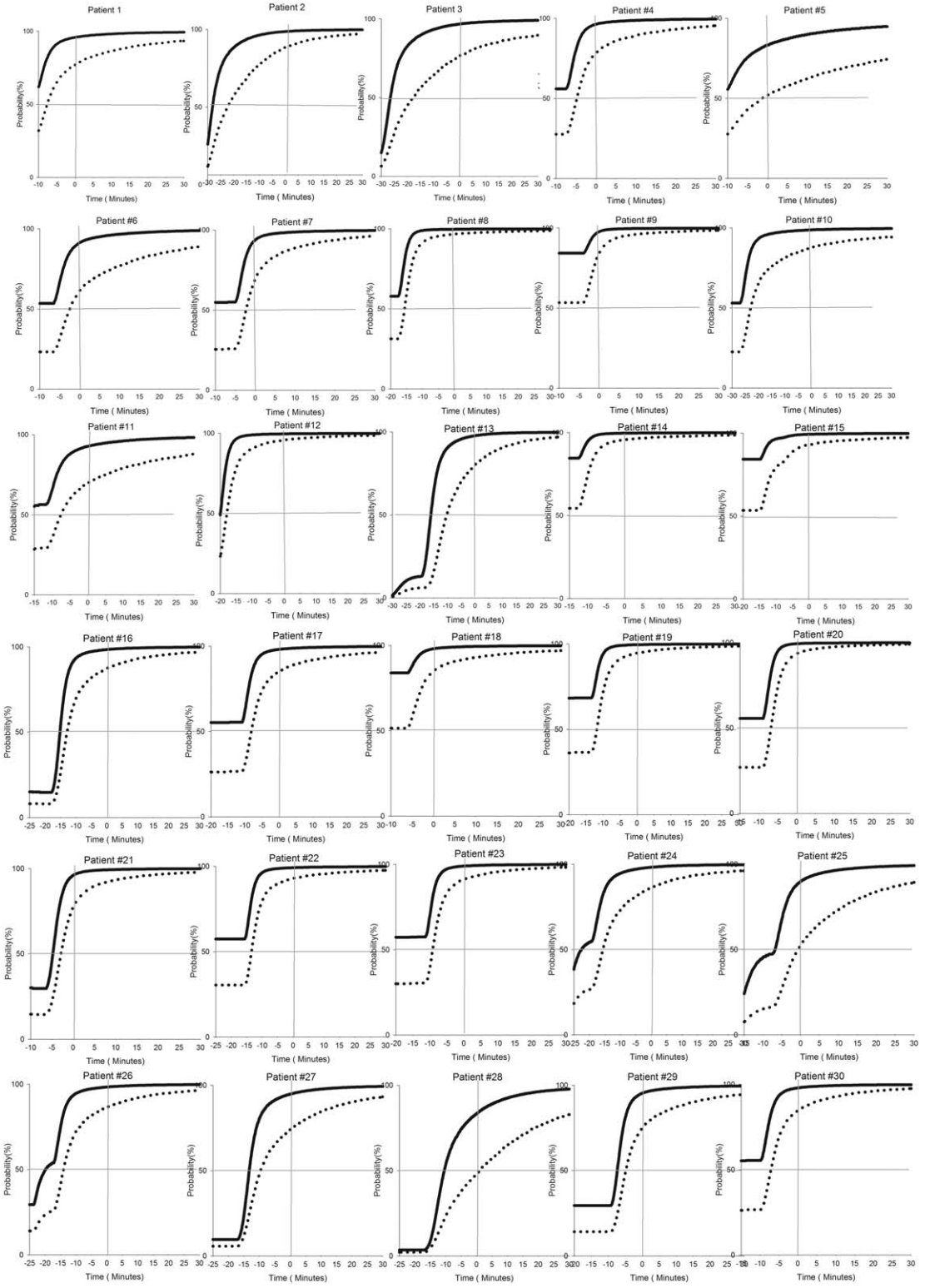

Figure 1. The gray vertical line of time 0 represents the time at which each patient became responsive (OAA/S ≥4). The gray horizontal line represents the 50% model probability. The solid line shows the probability of model prediction for OAA/S ≥2. The dashed line shows the probability of model prediction for OAA/S ≥4. OAA/S = observer's assessment of alertness/sedation.

4. Discussion

To predict the time of emergence from anesthesia in patients after VATS for early extubation, 2 previously published remifentanil–propofol interaction models of unresponsiveness developed in volunteers and in patients undergoing a variety of surgeries were applied to our patients. These models are the only 2 available response surface models for LOR from propofol–remifentanil interaction to date. Extubation times differ significantly among anesthetic drugs.[24] Propofol is often

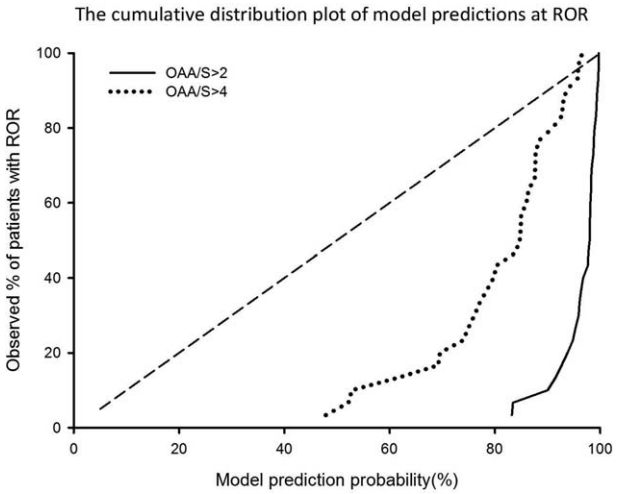

Figure 2. The models' predicted probabilities for OAA/S ≥2 and ≥4 were calculated at the time of regained responsiveness. The patient population percentage was plotted versus sorted model predictions. A consistent distribution of model predictions across patient percentage values from 0% to 100% was considered a good fit. OAA/S = observer's assessment of alertness/sedation.

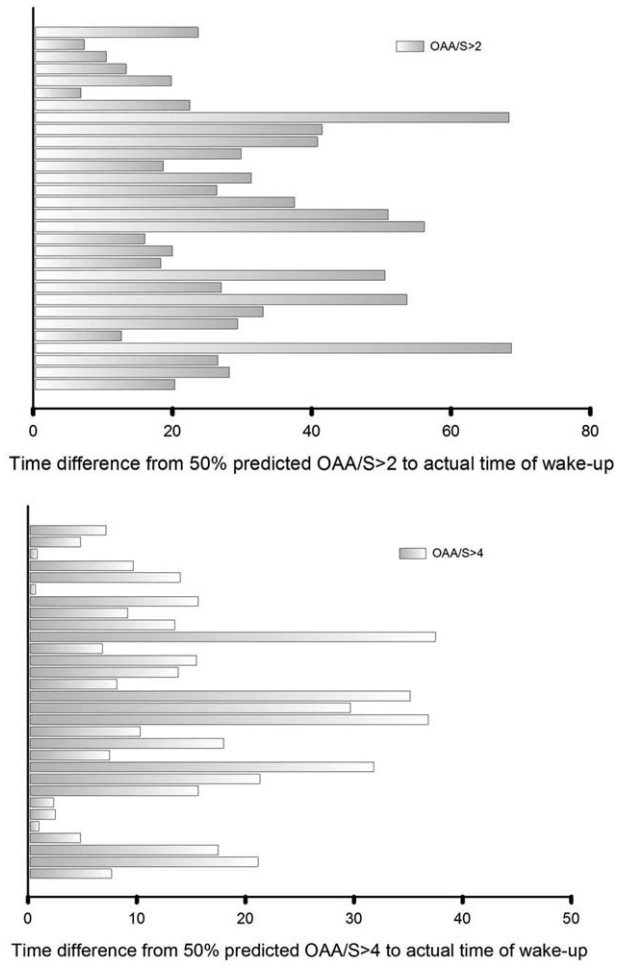

Figure 3. The averages and standard deviations of the differences were 30.32 ± 16.9 min for the OAA/S ≥2 model and 14.02 ± 10.9 min for the OAA/S ≥4 model. OAA/S = observer's assessment of alertness/sedation.

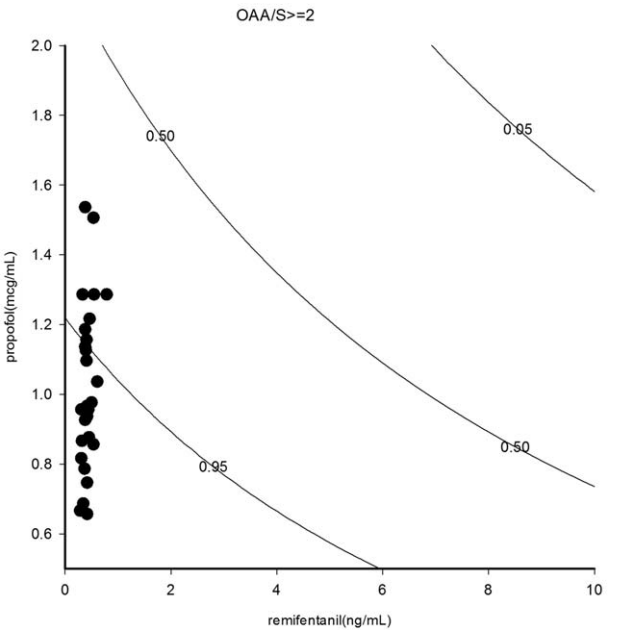

Figure 4. Data points are distributed around the 95% isobole.

used in combination with remifentanil because both drugs have been reported to enable rapid emergence and an early return to normal activities.[24] However, remifentanil has not been available in Taiwan to date. Thus, we used a previously reported fentanyl pharmacokinetic model to predict fentanyl effect-site concentrations and then converted them to equivalent remifentanil effect-site concentrations.[23] In addition, TIVA combined with TEA is beneficial in reducing pain-related morbidities, improving pulmonary function, and

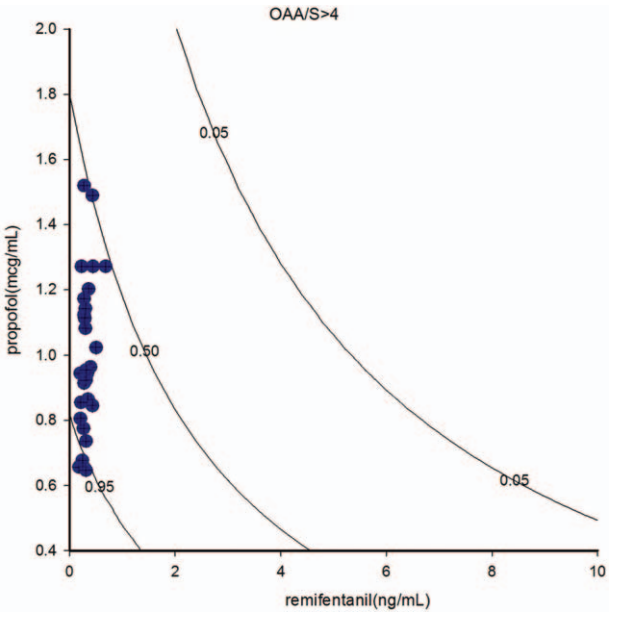

Figure 5. Data points were mainly distributed between the 95% and 50% isoboles. In general, a good model fit resulted in an equal distribution of LOR model predictions above and below the 50% isobole. LOR = loss of responsiveness.

promoting better postoperative outcomes including earlier extubation, early mobilization, and a shorter intensive care unit stay.[25] TEA has been considered the gold standard for pain relief after thoracic surgery.[26–31] The above reasons are why we focused on patients undergoing VATS using TIVA combined with TEA in this study.

Comparing the 2 models, all observed RR occurred after the model predictions of RR (Fig. 3). Significant model error with a poor data distribution was evident during emergence in predicted effect-site propofol-remifentanil concentration pairs. As illustrated in Fig. 3, the time differences between the predicted emergence from the 2 models and the observations were less (14.02 ± 10.9 minutes) in the OAA/S ≥ 4 model than in the OAA/S ≥ 2 model (30.32 ± 16.9 minutes). Ideal model predictions would be equally distributed around the 50% isobole; however, concentration pairs in our study were more equally distributed around the 95% isobole in the OAA/S ≥ 2 model and around 50% to 95% in the OAA/S ≥ 4 model. The reasons for the time differences are discussed below.

The OAA/S ≥ 4 model was established from 24 ASA class I volunteers aged 18 to 45 years.[16] We applied this model to predict the time of emergence in patients whose tracheas were intubated with a DLT. The VAS scores after VATS in our patients, controlled by PCEA with a 0.1% bupivacaine infusion, were all less than 3 after VATS in the PACU. One of the limitations of this model's application is that the model was determined from unstimulated volunteers without surgical pain or ETTs. We suspected that the level of stimulation could affect the depth of sedation; it is possible that an unstimulated volunteer response surface analysis for sedation will not accurately predict the RR of patients undergoing surgical procedures, especially VATS. Under the same target concentration pairs of propofol and remifentanil, the volunteers may have experienced different levels of sedation than patients with a DLT and surgical wound pain. We assumed that the complexities of the clinical environment could not be fully emulated by this volunteer study. The differences between the volunteer study and clinical environments could possibly impact the model's performance.

The OAA/S ≥ 2 model was developed from 21 ASA class I to III patients aged 41 ± 17 years with wide variability in surgical stimulus (i.e., duration, type, or extent of surgery, use of local infiltration into the surgical site). The extensive range of surgical procedures might partially explain the time differences and variance between the OAA/S ≥ 2 model predictions and observations. In our study, we focused purely on patients undergoing VATS with a well-controlled pain status.

Another potential influencing factor is premedication with 12.5 μg/kg midazolam 10 minutes before induction in the development of the OAA/S ≥ 2 model. Midazolam has synergistic interactions with propofol and remifentanil,[32] and may thus cause prolonged emergence time predictions.

Furthermore most fentanyl drug levels in our patients were negligible (the mean remifentanil equivalent concentration was 0.36 ± 0.1 ng/mL) at the time of RR after VATS. The probability isoboles for the 2 models with predicted concentration pairs at the observed RR (Fig. 4) were deviated to the left. However, the lowest remifentanil effect site concentration in the OAA/S <4 model construction was 0.5 ng/mL, and the lowest mean remifentanil concentration in the OAA/S <2 model was 2.5 ± 0.4 ng/mL, and both were higher than in our patients. This may be one of the reasons why the 2 models had limitations in predicting RR in our patients.

Regarding the effect of epidural blockade, patient age plays an important role in determining the epidural spread of anesthetic solution. In older patients, lateral escape of the local anesthetic solution is minimal, due to the sclerotic intervertebral foramina, thus favoring a more longitudinal spread.[33] Bromage[34] found a direct inverse linear relationship between patient age and epidural anesthetic dose required to block each spinal segment in adults. Moreover, it has been demonstrated that higher spinal block was associated with sedation.[35] In our study, we wanted to find the best anesthetic combinations for early extubation in patients with TEA after VATS. The wide range of patient ages (29–78 years) may be a confounding factor in our study of regained responsiveness after VATS, due to the presence of a higher epidural blockade in older patients. In other words, 1 limitation of this study is that we included a wide range of ages to determine the accuracy of our method for predicting OAA/S arousal time.

In our patients, TEA was maintained with a continuous intraoperative 0.25% bupivacaine infusion. In essence, central nervous system activity was depressed at the level of the spinal cord, and this therefore created an entirely different system from those in the experiments that were used to determine the response surface. This would have shifted the distribution of wake up times for our patients, because they had a greater combined anesthetic state compared with either of the original conditions, which were achieved without an epidural anesthetic. Thus, the subjects used in the original model responded sooner compared with the patients in our study. Therefore, we speculated that the model predictions of RR may be affected by epidural fentanyl and local anesthetic dosing. This is the most likely explanation for the wider discrepancy between the model predictions and observations in our patients.

5. Conclusion

Our results suggest that although the 2 models were able to identify target concentration pairs predicting the time of RR in volunteers and in some elective surgeries, in patients after VATS with double-lumen intubation under TIVA with TEA, we may need another response surface model of epidural and intravenous anesthetic combinations to predict the time of RR. We found that if we could extend this concept to epidural anesthetics in drug-drug interaction models, they may have value in guiding the delivery of anesthetic combinations by predicting the time to emergence. Proposing new therapeutic approaches for early extubation is clinically relevant because a decreased incidence of pulmonary complications will have an economic impact, particularly after thoracic surgery. Further work is needed to create models of epidural and intravenous anesthetic combinations to provide good predictions for patients undergoing VATS

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