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ORIGINAL ARTICLE

Opioid and propofol pharmacodynamics modeling during brain mapping in awake craniotomy

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Abstract

Background: Awake craniotomy (AC) is performed to identify cerebral language center. The challenge of anesthesia is to maintain a calm, comfortable, and cooperative patient during the mapping phase. Response surface models (RSMs) are multidrug modeling algorithms. In this pharmacodynamic study, we investigate the first use of RSM with bispectral index (BIS) to predict patient's response to name calling (RNC) and wakefulness (complete neurological tests) during AC.

Methods: The study is performed in two phases. We prospectively enrolled 40 patients who received video-assisted thoracoscopic surgery (VATS) using propofol and fentanyl as the modeling group. Effect-site concentrations (Ce) and BIS values were recorded and a RSM is built from the data set. We verified the RSM retrospectively in AC patients, designated as the validation group. Corresponding BIS values were analyzed for RNC and wakefulness.

Results: A total of 155 data sets of propofol Ce, fentanyl Ce, and BIS pairs were available for modeling. The range of propofol and fentanyl Ce were 0 to 9.95 μg/mL and 0 to 3.69 ng/mL, respectively. Observed BIS ranged from 21 to 98. The model identified an additive interaction between propofol and an opioid. RNC at BIS 64 is predicted by the model and 70 is required for wakefulness.

Conclusion: RSM built from VATS patients is verified with a separate group of AC patient. The BIS target advised for RSM-predicted wakefulness is 70. The model illustrates the timeline to wakefulness during AC under propofol and an opioid. It has implications in guiding, dosing, and estimation of time to wakefulness with propofol and an opioid.

Keywords: Awake craniotomy; Opioid; Pharmacodynamics; Propofol; Response surface

1. INTRODUCTION

Awake craniotomy (AC) facilitates resection of tumors that reside in or within the vicinity of the eloquent or sensorimotor regions. Anesthesia is commonly delivered via the asleep-awake-asleep technique,[1,2] where anesthesiologists must balance the arousal state of the patient while maintaining comfort, airway safety, and good surgical conditions. Rapid return of consciousness and full orientation is critical to the mapping phase and success of the surgery. To achieve this, propofol-based target-controlled infusion (TCI) is commonly used,[3,4] usually coadministered with an opioid. Patients respond differently to an anesthetic drug, and it can be even more unpredictable with multiple drugs. Dosing, therefore, relies on the experience of the anesthesiologist in charge and often large inter-physician variability exists.

Pharmacodynamics variability is commonly analyzed with pharmacodynamics models, traditionally isobolograms and concentration-effect curves. TCI targets the plasma or effect-site drug concentration (pharmacokinetics), but usually a response end measure (pharmacodynamics) is still required to monitor the state of anesthesia. The pharmacodynamics models predict patient responses and take drug interactions into account. Among these models, response surface models (RSMs)[5,6] are a new generation of versatile mathematical algorithms that predict pharmacodynamics endpoints such as loss of response (LOR),[7–10] bispectral index (BIS),[9,11–13] or even respiratory compromise.[14] These models can identify the magnitude of interaction across all concentration spectrum for single, dual, or triple drugs.[15] RSMs to date primarily focus on building volunteer models, and only few studies applied the models to clinical scenarios.[16–18] In this study, we hypothesize that a RSM constructed from a separate patient group can be implemented into AC for navigating state of consciousness during brain mapping. This is achieved in two phases: first, a RSM that can account for the interaction of propofol and an opioid is constructed from the modeling group; second, the model is applied to a validation group of AC patients. BIS is commonly used as an indicator for anesthetic depth during various procedures including craniotomies and is considered the measure of effect for our RSM.

2. METHODS

2.1. Patient selection for modeling group

A prospective, nonrandomized study aimed at recruiting 30 American Society of Anesthesiologists (ASA) physical status I-III adult patients, between 20- and 80-years-old, who received general anesthesia in 2014 at the Taipei Veterans General Hospital. Approval by the Institutional Review Board (IRB 2014-02-001B)

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and patients' written informed consent was obtained. The subjects received video-assisted thoracoscopic surgery (VATS) under total intravenous general anesthesia (TIVA). Exclusion criteria included emergent surgery, neurological conditions that interfere with accurate BIS readings (dementia, cerebral palsy, ischemic stroke within 6 months), hearing impairment, chronic opioid or habitual alcohol consumption, recent use of psychoactive medication, and use of premedications for anxiolysis or pain before surgery.

2.2. Anesthetic management for VATS

Patients were monitored with the following standard noninvasive equipment: electrocardiography, pulse oximetry, and noninvasive blood pressure. Preoxygenation was performed for 5 minutes before induction under 100% oxygen. BIS sensor (Version XP, Covidien plc, Dublin, Ireland) was secured on the patient's forehead when a solid reading is obtained. Schnider effect-site concentration (Ce) model was used for propofol TCI with the Injectomat TIVA Agilia infusion pump (Fresenius Kabi, Bad Homburg v.d.H, Germany). Induction started with a 3 μg/kg bolus of fentanyl. Fentanyl Ce was calculated with a pharmacokinetic simulation software (TIVA trainer, Version 9, build 6, Euro SIVA). Propofol target Ce of 4 to 10 μg/mL began 3 minutes later through a proximal intravenous port. Concomitant Ce and BIS recording was obtained every minute. Rocuronium (0.6-1 mg/kg) was given after confirming loss of consciousness to facilitate intubation, which was performed when BIS has fallen below 60 for at least one minute after full muscle relaxation. If the BIS value remained above 60 after a steady Ce has reached, an increment of 0.5 μg/mL target Ce is readjusted. If BIS falls below 40, a decrement of 0.5 μg/mL Ce is adjusted to maintain the optimal depth of anesthesia. Only tactile stimuli from mask ventilation and name calling were present during the induction phase. Further recordings beyond intubation were not analyzed in this study because the endpoint we used for validation was only verbal. Noxious stimuli were not suitable in this part of the analysis.

2.3. Patient selection and anesthetic management for AC

The patients were retrospectively chart-reviewed after approval from IRB (Number 2013-06-017A) at Taipei Veterans General Hospital. All patients with complete chart documentations were included due to scarcity of the patients. We use the awake-sleep-awake sequence for AC without the routine use of supraglottic airways or endotracheal tubes. Patients were monitored using standard noninvasive equipment, such as electrocardiography, pulse oximetry, and noninvasive blood pressure. Oxygen 3 L/min was supplied by a nasal cannula. Additional monitors included a right internal jugular vein catheter for central venous pressure and end-tidal carbon dioxide via the left nostril. All patients received glycopyrrolate 0.2 mg before the start of induction. TCI was used for both propofol and alfentanil Schnider models. We started the first stage of the awake-sleep-awake sequence by setting the propofol Ce target at 2.0 μg/mL and alfentanil Ce at 20 ng/mL. BIS was maintained between 40 and 70 and concomitant BIS values and propofol/alfentanil concentration pairs were recorded whenever dose was adjusted. Scalp block was performed by the neurosurgeon with 1% lidocaine with 1:200 000 epinephrine in the supraorbital, supratrochlear, zygomaticotemporal, auriculotemporal, greater occipital and lesser occipital nerve region.

All medications were stopped 15 minutes before attempted brain mapping. Response to name calling (RNC) and wakefulness (oriented and completed tests for brain mapping) were considered as different endpoints. Following command and test completion required a higher state of wakefulness and, theoretically, a higher BIS level.

2.4. Response surface modeling

The model we chose was the physiology-based hierarchy model developed by Bouillon et al.[9] The main concept behind the model was that the results and parameters changed according to the sequence of drugs administered. It integrated the notion of multiple sites of action for different drugs. The original form of the model was complex and the final derivation to fit our BIS model was shown:

$$E = E_0 - (E_0 - E_{max}) \times \frac{\left(\frac{C_{prop}}{C_{50prop}} \times \left(1 + \left(\frac{C_{fen}}{C_{50fen}}\right)^{\gamma_{fen}}\right)\right)^{\gamma}}{1 + \left(\frac{C_{prop}}{C_{50prop}} \times \left(1 + \left(\frac{C_{fen}}{C_{50fen}}\right)^{\gamma_{fen}}\right)\right)^{\gamma}}$$

The model was a negative-effect model. E_0 was the BIS value under no drug effect. This is not necessarily equal to 100 but represented a regional maximum for computational purpose only. E_{max} was the BIS value at maximal drug effect and it was assumed to be 0 for model simplification. E was the model-predicted BIS value. C_{prop} and C_{fen} were the Ce for propofol and fentanyl. C_{50fen} is the Ce required to reduce the stimulus by 50%, whereas C_{50prop} is defined as the concentration needed to produce hypnosis in 50% of the patients following fentanyl administration. Both γ and γ_{fen} were the steepness parameter of the response surface.

Accuracy was defined as difference < 10 between observed and model-predicted BIS. Matlab (R2015a, The MathWorks, Inc., Natick, MA) was used to perform the optimization process. Bootstrap technique was adopted with 1000 iterations to improve model stability. Coefficient of variance (CV) was calculated by:

$$CV = \frac{\sigma}{\mu}$$

where σ stands for SD and μ stands for mean.

2.5. Validation in AC

The constructed model was examined in AC patients. Opioid potency was interchangeable.[5,16] Fentanyl Ce in the model was converted to alfentanil Ce in the AC group by using a fixed potency ratio (fentanyl:alfentanil = 1:0.0625).[19,20] BIS values were recorded during key events RNC and wakefulness for brain mapping. The BIS value for RNC and wakefulness were used as surrogates to predict these two events. The model was constructed from the timeframe that covered the transition from complete awake to loss of consciousness. It is therefore suitable to predict events that involved the transition between return and loss of consciousness. Temporal changes in the model predicted BIS was compared with observed BIS and clinical events.

3. RESULTS

3.1. Patient demographics and pharmacokinetics

Thirty patients in the VATS group were available for modeling, and five patients in the AC group for model validation. Patient demographics were listed in Table 1. In the VATS group, 16 were men and the average age was 60 years. Mean induction time and surgical time was 6.1 (1.6) and 198.3 (45.3) minutes, respectively. The mean estimated blood loss was < 100 mL in the VATS group. In the AC group, two patients were men and the average age was 31.8 years. Mean surgical time was 267.2 (28.9) minutes. The average blood loss was limited and did not require fluid boluses or blood transfusion.

In the VATS group, a total of 155 data sets were available for pooling. The propofol Ce and fentanyl Ce ranged from 0 to 9.95 μg/mL and 0 to 3.69 ng/mL, respectively. In the AC group, the propofol Ce and alfentanil Ce ranged from 0 to 8.28 μg/mL and 0 to 45 ng/mL (equivalent to fentanyl 2.8 ng/mL),[20] respectively.

Table 1

Patient demographics of the VATS and AC group

	VATS group (n = 30)	AC group (n = 5)
Age	60.0 (9.8)	31.8 (3.7)
No. of male, %	16 (53.3%)	2 (40%)
Body mass index, kg/m^2	23.7 (2.8)	24.0 (4.9)
Average surgical time, min	198.27 (45.3)	267.2 (28.9)
Mean time to intubation, min	4.97 (1.88)	…

Intubation was not performed in the AC group.

AC = awake craniotomy; VATS = video-assisted thoracoscopic surgery.

Concentrations used for model construction covered the entire Ce distribution in the AC group, indicating that the predictions were not extrapolated. The range of BIS recorded was 21 to 98.

3.2. Pharmacodynamic profiles and RSM

The response surface parameters were summarized in Table 2. E_{max} is 91.5, which was the maximum BIS value used by the model. C_{50prop} was 4.7 μg/mL and C_{50fen} is 13.1 ng/mL. The high C_{50fen} value indicated that the hypnotic property of opioids was unreliable and agreed with previous reports.[7,21] The successful prediction rate in the VATS group was 92.8% with a BIS error margin of 10.

The response surface was illustrated in Fig. 1. The BIS value reliably decreased as propofol concentration increased but this phenomenon was not seen with fentanyl. Black solid lines on the response surface were the isoboles that represented BIS at 40, 60, or 70. The filled circles were the observed concentration sets. The blue circles were accurate and the red ones were not. Data clustering was seen in two regions. First cluster was at the higher BIS region. This was because fentanyl was given first and only caused very little decrease in BIS, if at all. The second region was clustered near the BIS 40 isobole, which represented the values immediately before intubation took place.

Fig. 2 showed how model-predicted BIS value of each AC patient changed relative to propofol Ce. Time zero marked the beginning of the wake-up process. The examinations took 6 to 35 minutes according to lesion site. RNC occurred at BIS > 64 but wakefulness did not take place until predicted BIS was > 70.

The concentration at which the patient was asleep and RNC were mapped on the superimposed isobologram is shown in Fig. 3. A total of 19 recordings were available. BIS 64 isobole separated the two groups. The isoboles slightly concaved toward the origin, indicating some synergy was observed between propofol and fentanyl under tactile stimuli.

4. DISCUSSION

We constructed a clinical RSM that estimated time to RNC and wakefulness during awake craniotomies. The accuracy of the model-predicted BIS was 92.8% with an error margin < 10. Model BIS target value for RNC was at least 64 but a value > 70 was advised for wakefulness.

The RSMs were known to predict patient responses with multiple drugs in various clinical scenarios[8,10,14,17,22] but this was the first time a RSM was validated with AC. The hierarchy model had a physiological basis that accounted for the sequential interaction of opioid and propofol,[9] which was ideal for our study. Specifically, this model assumed that opioids reduced stimulus intensity and propofol produced hypnosis at this reduced level of stimulus. A similar surface was illustrated by Lobo et al.,[3] who investigated the remifentanil–propofol interaction during AC using multiple regression. They found an inverse relationship between remifentanil and BIS. This finding conflicted with ours, in which opioids minimally influenced BIS. Our high C_{50fen} finding was supported by other studies.[23,24] We suggest this discrepancy is a result of difference in anesthetic techniques. Laryngeal mask was used by Lobo et al.,[3] which can affect the pharmacodynamics response of opioids. Opioids are generally considered ineffective for BIS endpoint but they can attenuate the magnitude of BIS changes when combined with propofol under painful stimuli.[25]

C_{50prop} was the propofol concentration required to reduce the E_{max} by half. C_{50prop} was 4.7 μg/mL in our study and at this value it would yield a BIS value of 46. For BIS to reach 60, 64, and 70, the model-derived propofol concentration would be 2.75, 2.33, and 1.76 μg/mL, respectively, without concomitant opioids. Other studies had reported similar C_{50prop}, C_{prop}, or BIS value for return of consciousness.[3,9,23,26,27] BIS between 40 and 60 were advised for surgical anesthesia and 70 or above was associated with wakefulness.[28] This coincided with our findings where RNC occurred at BIS 64 and wakefulness at BIS > 70. However, variable BIS targets for wakefulness had been reported.[3,26,29] Regaining consciousness was not enough to complete the neurological tests. Our model gave a time estimate to RNC and wakefulness when linked with concomitant pharmacokinetic parameters. This differed from isolated propofol concentration calculations because our RSM took opioid concentrations and drug interaction into account.

The calculated interaction index was 0.97, suggesting an additive interaction between propofol and fentanyl for the BIS endpoint. This had been observed in current literatures.[9] Reducing BIS was not opioid's primary pharmacodynamics target. The type and degree of stimulus may be another factor. We had observed additive interaction between a hypnotic and an opioid under light stimuli and synergism increased as the intensity of the stimulus increased.[7] We built the model based on the induction phase of anesthesia where noxious stimuli were absent. The lack of noxious stimuli could be insufficient to unmask synergism between opioids and propofol for the BIS endpoint. Opioids were known to decrease BIS changes when a strong stimulus was applied.[30]

The validity of the hierarchy RSM was verified externally. This differed from RSM studies that were validated internally with the same group of patients. One prerequisite was that similar stimuli intensity must exist in the two groups. A RSM was required for each endpoint, for example LOR to verbal stimuli or to intubation. In this study, we constructed a BIS model at the beginning of an anesthesia induction process before intubation. Only tactile stimuli existed. This was similar to the degree of stimuli in the wake-up process during AC. We suggest that a model can be generalized to different patient groups that share similar stimuli intensities.

There were several limitations in our study. We only explored the effects of the clinical doses of propofol and opioids. Concentrations in the more extreme ranges were absent. It

Table 2

Response surface model parameters and performance

E_{max}	CV, %	C_{50prop}	CV, %	C_{50fen}	CV, %	γ	CV, %	γ_{fen}	CV, %
91.5	0.8	4.7	6.2	13.1	10.6	1.2	5.4	1.2	32.7
Pearson coefficient			***p***			**Successful prediction**		**OFV**	
0.98			< 0.05			92.8%		142.3	

Successful prediction is defined by BIS difference < 10 between model prediction and observed value.

CV = coefficient of variance; C_{50prop} = effect-site concentrations for propofol; C_{50fen} = effect-site concentrations for fentanyl; E_{max} = maximal BIS value used by the model; OFV = objective function value; $\gamma = \gamma_{fen}$ = the steepness parameter of the response surface.

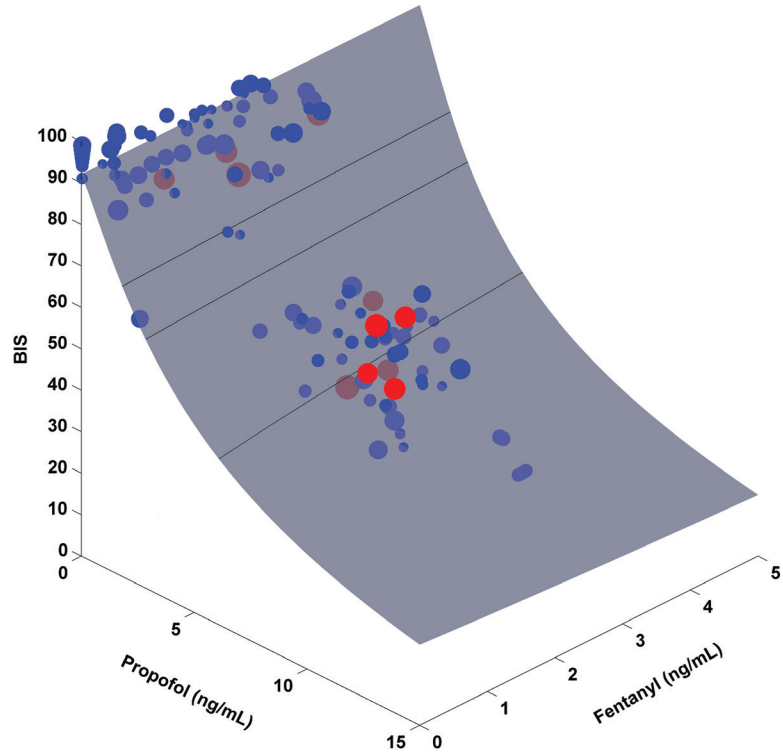

Fig. 1 Response surface and scattered plot for BIS. Black solid lines on the surface are the BIS 40, 60, and 70 isoboles. Blue circles are accurate data sets and the red ones are not. Accuracy is defined as a difference between observed and model-predicted BIS < 10.

may be suboptimal to build a pharmacodynamics model but we believed it adequately covered the drug concentrations required for AC without laryngeal masks.

The fluctuations in drug concentrations during anesthesia induction are common. The $t_{1/2}$ keo of the Schnider propofol model was 1.5 minutes.[31] The average induction time in our VATS patient group was 6.1 minutes. Studies using propofol TCIs usually allowed 5 to 15 minutes interval before effective measures.[9,14] Steady-state Ce was unlikely but our average induction time was within the reported time frame.

Schnider model derived keo from processed raw electroencephalogram rather than BIS.[31,32] The possibility of inadequate correlation with BIS was dismissed by Billard et al.,[33] who estimated similar keo for spectral edge frequency and BIS.

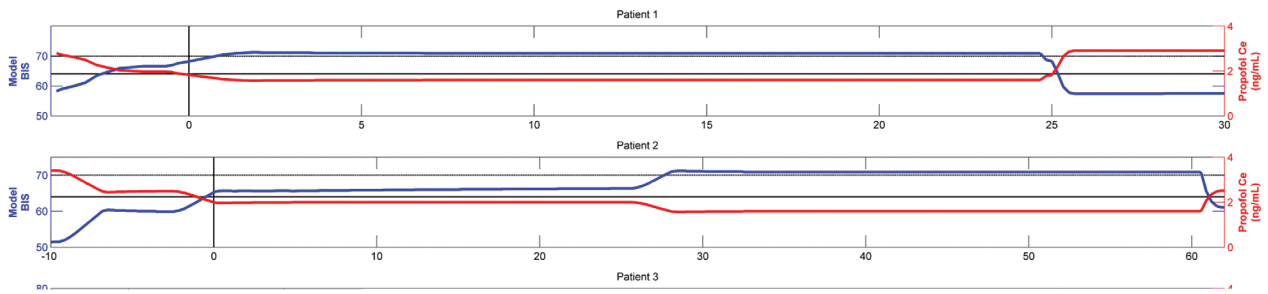

Fig. 2 Time course with the relevant BIS and propofol Ce during the wake-up process in awake craniotomy. The black solid and dotted lines are the BIS 64 and 70 lines. Blue lines are the model-predicted BIS values with axes on the left. Red lines are the propofol Ce with axes on the right. Time zero is the start of the waking-up process. The patients responded to name calling when model BIS reaches 64. Wakefulness and brain mapping were completed at model-predicted BIS > 70. BIS=bispectral index; Ce=effect-site concentration.

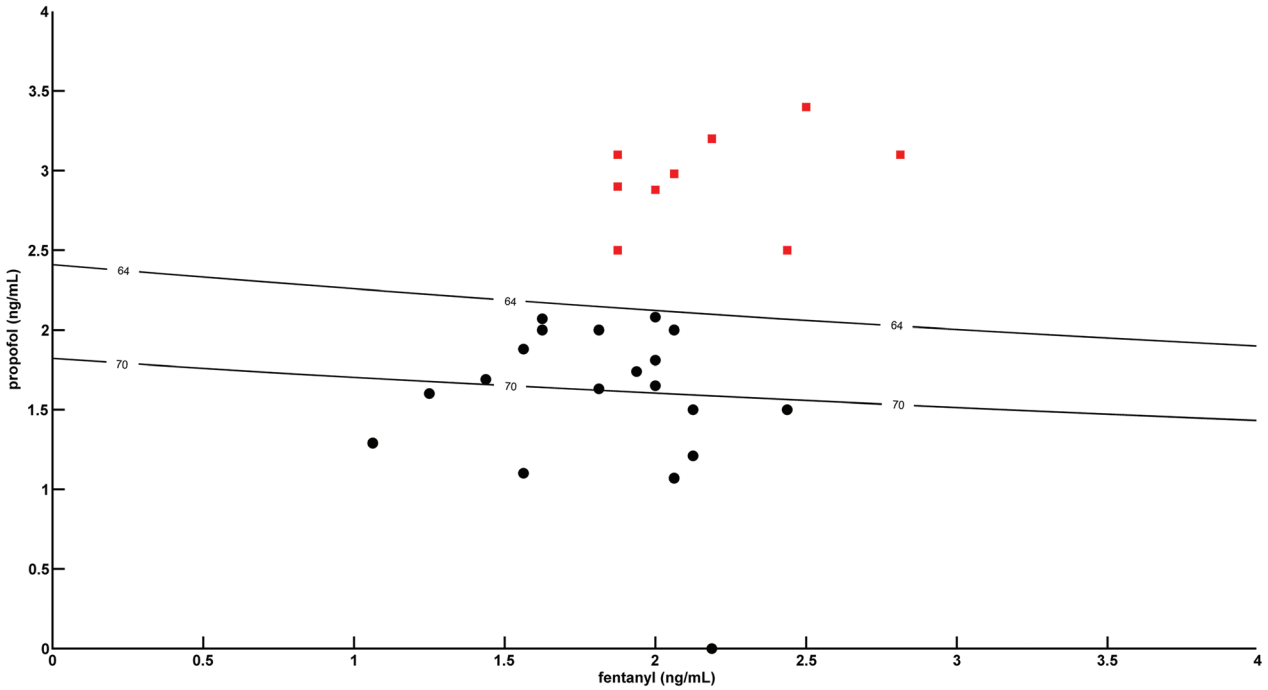

Fig. 3 Isobologram of propofol–fentanyl combination. The bispectral index (BIS) 64 and 70 isoboles are represented by the solid black lines. Data sets during the wake-up process in awake craniotomy are scattered on the isobologram. Red squares are the data sets when the patients were nonresponsive to name calling and the black circles are ones that responded. Note that the BIS 64 isobole demarcates the two groups and can be used to predict return of consciousness. Wakefulness does not occur before model-predicted BIS value of 70. Small concavity is observed from the isoboles, indicating mild degree of synergy.

The number of AC patients was small and recall was not analyzed. AC was a rare procedure that required careful patient selection. One similar study constructed a multiple regression model from eight patients.[3] Another study investigated propofol Ce and BIS during key moments during AC in 13 patients.[26] Our model was constructed from 30 patients. It was above the 20 minimum advised for building a response surface.[34] More patients would be needed to accurately describe the pharmacodynamics during the AC process in general.

Recall and wakefulness were different and memory consolidation was impaired under the influence of anesthesia.[35] As much as 27% of patients had no recollection of being awake during AC.[36] Efforts to delineate a model target to prevent awareness should be made in the future.

In conclusion, we explored the interaction between propofol and opioids under tactile stimuli with a hierarchy RSM. This model attained applicability in a separate group of AC patients and described the timeline to wakefulness during the wake-up process. The model has implications for future automated system designs and inform physicians of the time to wakefulness in AC when an opioid and propofol were administered. Prospective designs are still needed to fully validate the generalization of the model.

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