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Predictive Model for Monitor-Independent TCI Propofol Induction Based on Loss-of-Consciousness Concentration: A Prospective Observational Study

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Abstract

Background

The use of bispectral index (BIS)-guided target-controlled infusion (TCI) enables tailored propofol administration during the induction of anaesthesia; however, in the absence of depth-of-anaesthesia monitoring, the concentration required for intubation remains uncertain. We aimed to determine whether the propofol effect-site concentration at loss of consciousness (LOC-P) can predict the concentration required to achieve a BIS value of 50 for intubation (INT-P), and to derive a practical dosing formula.

Methods

This prospective observational study was conducted in operating theatres at a single university hospital (June 2021–April 2022). A total of 128 adults (American Society of Anesthesiologists (ASA) physical status I–II, aged 18–65 years) scheduled for elective non-cardiac surgery were included. Propofol was administered via TCI (Schnider model) combined with remifentanil TCI (Minto model) at a fixed effect-site concentration of 2 ng mL^{-1}. LOC-P was defined as the propofol effect-site concentration at loss of verbal response; INT-P was recorded when BIS reached 50 and remained stable for ≥ 30 s. The primary analysis used Pearson correlation and linear regression.

Results

LOC-P strongly predicted INT-P ($r = 0.90$, 95% confidence interval (CI) 0.86–0.93; $P < 0.001$). Linear regression yielded INT-P = 0.67 + 0.974 × LOC-P ($R^2 = 0.81$; $\beta = 0.974$, 95% CI 0.89–1.06; $P < 0.001$). Mean induction-to-intubation time was 9.48 ± 2.28 min. Hypotension was observed in 12/128 patients (9.4%), mainly between LOC and intubation. A haemodynamic response to intubation was observed in 69/128 patients (53.9%).

Conclusions

LOC-P was a strong predictor of INT-P, allowing derivation of a practical dosing formula for TCI induction. This formula may help individualise induction in settings without depth-of-anaesthesia monitoring. However, the frequency of haemodynamic responses suggests that deeper anaesthetic targets may be required.

Trial registration:

Not applicable. This prospective observational study was not registered in a clinical trial registry.

Background

Achieving adequate anaesthetic depth for induction and intubation is essential for patient safety and haemodynamic stability. Bispectral index (BIS) monitoring is commonly used to guide anaesthetic titration.[1,2] A Cochrane review showed that BIS-guided anaesthesia can lead to decreased medication usage and reduced recovery times.[3]

While inhalational anaesthesia uses Minimum Alveolar Concentration (MAC) as a population-based reference, total intravenous anaesthesia (TIVA) and target-controlled infusion (TCI) lack universally accepted depth parameters. Recent reviews suggest that TIVA has safety and recovery profiles comparable to inhalational anaesthesia, although individualised titration remains critical.[4]

TCI systems allow targeting of plasma or effect-site concentrations, enabling more stable titration.[5] However, substantial interindividual pharmacokinetic/pharmacodynamic (PK/PD) variability limits the usefulness of fixed effect-site targets.[6–8] We hypothesised that the propofol effect-site concentration at loss of consciousness (LOC-P) would correlate strongly with the concentration required for intubation (INT-P). LOC-based titration could reduce reliance on depth-of-anaesthesia monitoring.

BIS values between 40 and 60 are commonly used during tracheal intubation[9–11], with lower values associated with greater suppression of the stress response but an increased risk of hypotension.[12] We selected a BIS target of 50 to evaluate haemodynamic responses at this widely used threshold and to explore whether deeper levels of anaesthesia might offer additional benefit. The primary aim was to evaluate the relationship between LOC-P and INT-P and to develop a practical, individualised dosing formula. Secondary outcomes included induction timing, haemodynamic stability, and adverse events during TCI induction using this protocol.

Methods

Study Design and Oversight

This prospective observational study was approved by the Ankara University Faculty of Medicine Human Research Ethics Committee, Ankara, Türkiye (decision no. İ6-416-21; Chairperson Prof. Nuray Yazıhan) on 17 June 2021. All participants provided written informed consent. Sample size was calculated for Pearson correlation analysis based on a pilot study of 31 patients conducted in May 2021, which demonstrated a strong correlation between LOC-P and INT-P ($r = 0.881$, $R^2 = 0.776$). Based on this effect size, 128 patients would provide > 99% power to detect a correlation coefficient of $r \geq 0.80$ at $\alpha = 0.05$ (two-tailed). The study was conducted in the operating theatres of Ankara University İbni Sina Hospital between June 2021 and April 2022, in accordance with the Declaration of Helsinki. Reporting follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.13

Setting and Participants

Adults scheduled for elective non-cardiac surgery under general anaesthesia were assessed for eligibility. Inclusion criteria were American Society of Anesthesiologists (ASA) physical status I–II and age 18–65 years. Between June 2021 and April 2022, 135 patients were enrolled. Seven patients with a train-of-four (TOF) count > 0 at the time intubation criteria were met were excluded, leaving 128 patients for the final analysis. Patient characteristics, including age, sex, body mass index (BMI), and ASA physical status, were recorded. Baseline comorbidities were documented for descriptive purposes.

Exclusion Criteria

Patients were excluded if they met any of the following criteria: emergency surgery; ASA physical status ≥ III; age < 18 or > 65 year; cognitive impairment or hearing loss that would interfere with assessment of loss of consciousness; known allergy to propofol, remifentanil, rocuronium, or fentanyl; TOF count > 0 at the time intubation criteria were reached; or lack of informed consent.

Monitoring and Anaesthesia

Standard ASA monitoring (electrocardiography, pulse oximetry, and non-invasive blood pressure), bispectral index (BIS) monitoring (BIS VISTA; Medtronic, Dublin, Ireland), and neuromuscular monitoring using acceleromyography (ToFscan; IDMED, Marseille, France) were applied. After peripheral intravenous access and fentanyl premedication (1 μg kg^{-1} i.v.), anaesthetic induction was performed using target-controlled infusion (TCI) of propofol (Schnider model) and remifentanil (Minto model). Remifentanil effect-site concentration (Ce) was fixed at 2 ng mL^{-1}. Propofol Ce was initiated at 2 μg mL^{-1} and increased by 0.2 μg mL^{-1} every 20 s. Loss of consciousness was assessed every 5 s by verbal command from the primary investigator (calling the patient's name), and the propofol Ce at loss of response was recorded as LOC-P. Rocuronium 1 mg kg^{-1} i.v. was administered immediately after LOC-P determination. Propofol titration continued at the same rate (0.2 μg mL^{-1} every 20 s) until BIS reached 50 and was maintained for ≥ 30 s;[20,21] this propofol Ce at BIS of 50 was recorded as the intubation concentration (INT-P). Tracheal intubation was performed only in patients with a TOF count of zero. Haemodynamic variables (mean arterial pressure and heart rate) and BIS values were recorded at baseline, at loss of consciousness, at intubation readiness, immediately after tracheal intubation, and at 1, 3, 5, and 10 minutes after intubation. Recordings affected by artefact or motion interference were excluded a priori. No missing data were observed for the primary variables.

Outcomes

The primary outcome was the relationship between LOC-P and INT-P assessed using Pearson correlation and linear regression. Secondary outcomes included:

1. time from induction to intubation,
2. peri-intubation haemodynamics (mean arterial pressure (MAP) and heart rate (HR)) and BIS values from pre-induction to 10 min after intubation,
3. incidence of hypotension and bradycardia,
4. haemodynamic response to intubation,
5. total induction doses of propofol and remifentanil.

Outcomes were pre-specified. Hypotension was defined as a ≥ 20% decrease in MAP from baseline and treated with 10 mg i.v. ephedrine boluses if required. Bradycardia was defined as HR < 50 beats min^{-1} and treated with 0.5 mg i.v. atropine if persistent or symptomatic. Haemodynamic response to intubation was defined as a ≥ 20% increase in MAP and/or HR compared with pre-intubation baseline values.

Statistical Analysis

Normality was assessed using the Shapiro–Wilk test. Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range [IQR]), as appropriate, and categorical variables as n (%). The association between LOC-P and INT-P was assessed using Pearson correlation and linear regression. Linear regression assumptions (linearity, normality of residuals, and homoscedasticity) were evaluated by visual inspection of residual plots. Influential observations were assessed using Cook's distance (threshold > 1); no influential outliers were identified. Correlation and regression coefficients are reported with 95% confidence intervals.

Changes in haemodynamic variables over time were analysed using repeated-measures ANOVA. Sphericity was assessed using Mauchly's test, and Greenhouse–Geisser correction was applied when violated. Bonferroni correction was used for pairwise comparisons. Statistical significance was set at $P < 0.05$ (two-tailed). Effect sizes are reported as partial eta-squared (η^2p) for ANOVA. Analyses were performed using IBM SPSS Statistics v25 (IBM Corp., Armonk, NY, USA). No missing data were present for the primary variables; analyses were conducted as complete-case.

This manuscript adheres to the STROBE statement for observational studies; see Additional file 1 (STROBE checklist).13

Results

Patient Characteristics

A total of 135 patients were enrolled; 7 patients with TOF count > 0 at the time intubation criteria were met were excluded, leaving 128 patients for analysis. Baseline patient characteristics are summarized in Table 1. Mean age was 47.3 ± 12.1 year; 68 (53.1%) were female. Mean BMI was 25.9 ± 3.6 kg m^{-2}. Most patients were ASA I (92, 71.9%), with 36 (28.1%) ASA II. Hypertension was present in 24 (18.7%) patients.

Table 1
Baseline patient characteristics

Characteristic	Mean ± SD or n (%)	Median (min–max)
Age (yr)	47.30 ± 12.11	48 (18–65)
Sex		
Female	68 (53.1)	
Male	60 (46.9)	
BMI (kg m^{-2})	25.90 ± 3.55	26 (17–35)
ASA physical status		
I	92 (71.9)	
II	36 (28.1)	
Hypertension		
Yes	24 (18.7)	
No	104 (81.3)	

n = 128. Values are presented as mean ± SD, median (min–max), or n (%), as appropriate. BMI, body mass index; SD, standard deviation. Hypertension was defined as physician-diagnosed hypertension.

Primary Outcome: Relationship between LOC-P and INT-P

Mean propofol effect-site concentration (Ce) at LOC was 2.66 ± 0.35 μg mL^{-1} (range 2.0–3.8 μg mL^{-1}). Mean propofol Ce at intubation was 3.26 ± 0.37 μg mL^{-1} (range 2.4–4.4 μg mL^{-1}). LOC-P and INT-P were strongly correlated (r = 0.900, 95% confidence interval (CI) 0.861–0.929; P < 0.001; Fig. 1). Linear regression analysis yielded INT-P = 0.670 + 0.974 × LOC-P (R^2 = 0.810, adjusted R^2 = 0.808; standard error of estimate = 0.164 μg mL^{-1}; P < 0.001). The regression slope (β = 0.974, 95% CI 0.890–1.057) indicated that for each 1 μg mL^{-1} increase in LOC-P, INT-P increased by 0.974 μg mL^{-1}, demonstrating an approximately 1:1 relationship. Regression assumptions were met, with residual plots confirming linearity and homoscedasticity, and no influential outliers detected (maximum Cook's distance = 0.11).

Induction Time and Drug Doses

Mean time from induction start to intubation was 9.48 ± 2.28 min (range 3.0–16.0 min). The mean total induction doses were 137.27 ± 30.66 mg for propofol and 106.33 ± 30.79 μg for remifentanil.

Propofol Concentrations Over Time

The time course of propofol effect-site concentrations from LOC through 10 min post-intubation is shown in Fig. 2. Mean propofol Ce values were LOC 2.66 ± 0.35, intubation readiness 3.26 ± 0.37, 1 min

3.27 ± 0.38, 3 min 3.27 ± 0.37, 5 min 3.25 ± 0.37, and 10 min 3.24 ± 0.39 μg mL^{-1}. After reaching the intubation target concentration, propofol levels remained stable throughout the post-intubation monitoring period.

Haemodynamics and BIS

Haemodynamic variables and BIS values from pre-induction baseline through 10 min post-intubation are presented in Table 2. Mean arterial pressure (MAP) decreased significantly from baseline at all post-LOC time points (all $P < 0.001$). Heart rate (HR) decreased at LOC and at intubation readiness (both $P < 0.001$), returned to near-baseline values immediately after intubation through 5 min post-intubation ($P = 1.000$ at intubation and 1–3 min, $P = 0.080$ at 5 min), and decreased again by 10 min ($P < 0.001$). BIS decreased significantly from baseline at all post-LOC time points (all $P < 0.001$). Hypotension (≥ 20% decrease in MAP from baseline) occurred in 12/128 patients (9.4%), predominantly between LOC and intubation, and was treated with ephedrine 10 mg i.v. boluses (8 patients received one bolus, 3 patients two boluses, 1 patient three boluses). Bradycardia (HR < 50 beats min^{-1}) occurred in 1/128 patients (0.8%) and was treated with atropine 0.5 mg i.v. A haemodynamic response to intubation (≥ 20% increase in MAP and/or HR) occurred in 69/128 patients (53.9%). No patient experienced oxygen desaturation (SpO_2 <90%).

Table 2
Haemodynamic parameters and bispectral index values during TCI induction

Time point	MAP (mmHg)	P value	HR (beats min^{-1})	P value	BIS	P value
Pre-induction (baseline)	106.08 ± 13.15	—	82.44 ± 15.53	—	97.52 ± 1.29	—
LOC	89.20 ± 12.51	< 0.001	69.80 ± 12.15	< 0.001	76.44 ± 10.79	< 0.001
Intubation readiness	74.18 ± 13.97	< 0.001	70.45 ± 12.00	< 0.001	48.06 ± 5.27	< 0.001
Intubation (0 min)	86.84 ± 16.80	< 0.001	80.91 ± 14.38	1.000	47.92 ± 5.18	< 0.001
1 min	83.42 ± 16.97	< 0.001	81.53 ± 13.47	1.000	48.02 ± 4.80	< 0.001
3 min	77.71 ± 14.84	< 0.001	79.76 ± 13.68	1.000	45.94 ± 4.06	< 0.001
5 min	74.01 ± 14.01	< 0.001	78.09 ± 13.22	0.080	45.48 ± 3.29	< 0.001
10 min	70.15 ± 13.74	< 0.001	75.57 ± 12.89	< 0.001	44.91 ± 3.58	< 0.001

n = 128. Values are presented as mean ± SD. P values are from repeated-measures ANOVA with Bonferroni correction versus pre-induction baseline. MAP, mean arterial pressure; HR, heart rate; BIS, bispectral index; LOC, loss of consciousness; TCI, target-controlled infusion; SD, standard deviation.

Discussion

Principal Findings

This study demonstrates that the individually titrated propofol effect-site concentration at loss of consciousness (LOC-P) strongly predicts the concentration required to achieve a predefined intubation target during TCI induction. The derived formula (INT-P = 0.67 + 0.974 × LOC-P; R^2 = 0.81) enables clinicians to estimate the propofol concentration needed for intubation immediately after observing LOC, potentially improving the precision and safety of TCI induction. The regression slope of 0.974 indicates an approximately 1:1 relationship between LOC-P and INT-P. This finding supports LOC as a reliable clinical anchor for individualised anaesthetic titration, particularly in settings without depth-of-anaesthesia monitoring.

Comparison with Prior Work

Compared with conventional TIVA, using effect-site concentration (Ce) in TCI improves the precision of titration.[14,15,16] Reported propofol concentrations at LOC vary widely, highlighting interindividual PK/PD variability and the limitations of fixed Ce targets—hence the rationale for individualised titration.[12,17,18] Our mean LOC-P (2.66 μg mL^{-1}) and INT-P (3.26 μg mL^{-1}) closely align with Mu et al. (about 2.7 and 3.0 μg mL^{-1}, respectively).[18] Previous studies have demonstrated that individual effect-site concentrations at LOC are related to those at intubation,[17,19] supporting our hypothesis. Studies examining predictive performance of TCI models have shown acceptable accuracy in diverse populations, though performance varies with patient characteristics.[8]

Co-administration of remifentanil reduces the propofol requirement to suppress responses to painful stimuli such as intubation.[20] This is consistent with LOC around 2.6 μg mL^{-1} in our cohort at remifentanil Ce 2 ng mL^{-1}. The synergistic interaction between propofol and remifentanil has been extensively characterised, demonstrating that opioids significantly reduce hypnotic requirements for both LOC and suppression of response to noxious stimuli.[20–24]

Clinical Application

The derived formula enables real-time prediction of the propofol concentration needed for intubation immediately after observing LOC. For example, if LOC occurs at a propofol Ce of 2.6 μg mL^{-1}, the predicted INT-P is 3.20 μg mL^{-1} according to our formula. Given the incremental titration rate of 0.2 μg mL^{-1} every 20 s used in this study, achieving this target would require approximately 2 min after LOC. This LOC-anchored approach may be particularly valuable in centres without depth-of-anaesthesia monitoring,[25] enabling clinicians to anticipate intubation readiness based solely on the initial clinical observation of LOC. The formula could also guide pump programming and help predict the timing of intubation when transitioning from induction to maintenance anaesthesia.

Haemodynamics and Practical Implications

Haemodynamic variability around induction and laryngoscopy is well documented[26,27] and clinically relevant. In our cohort, 69/128 (53.9%) demonstrated a haemodynamic response to intubation (≥ 20% increase in MAP and/or HR), despite achieving a BIS of 50 with remifentanil 2 ng mL^{-1}.[28,29] This notably high incidence suggests that BIS of 50 may not provide sufficient anaesthetic depth for laryngoscopy in a substantial proportion of patients with this opioid regimen. Within the commonly recommended range of 40–60, a target nearer BIS of 40 may better attenuate the stress response to intubation.

Several strategies merit consideration: (i) targeting deeper anaesthetic levels (BIS of 40–45) before laryngoscopy,[10,11] though this must be balanced against increased risks of hypotension[26,27] and delayed recovery; (ii) increasing remifentanil concentration to 3–4 ng mL^{-1},[20,21] which may better attenuate the stress response; or (iii) using adjunctive pharmacological agents (lidocaine, esmolol, or dexmedetomidine) when appropriate.[30–33] BIS values of 40–50 have been reported during intubation,[9–11] and given the 20–30 s BIS processing delay,[34,35] our protocol's ≥ 30 s stabilisation period after reaching the target appears prudent. Future studies should explore whether deeper BIS targets or higher opioid doses reduce the incidence of haemodynamic responses while maintaining an acceptable safety profile.

Limitations

This single-centre study included ASA I–II adults (18–65 year) and used a single drug combination (propofol–remifentanil) with an intubation target of BIS of 50; therefore, generalisability to older patients, higher-risk populations (ASA ≥ III), emergency surgery, other opioid regimens, and settings that use different BIS targets may be limited. Haemodynamic parameters were measured non-invasively. The design was observational without external validation, and we did not adjust analyses for individual cardiovascular comorbidities; residual confounding cannot be excluded. Additionally, LOC determination was subjective and performed by a single investigator; while this ensured consistency within our study, inter-rater reliability was not assessed, and observer bias cannot be excluded. The use of a fixed remifentanil concentration (2 ng mL^{-1}) may not reflect routine clinical practice where opioid dosing is often individualised. These findings should be interpreted as hypothesis-generating and warrant validation in larger, multicentre trials.

Future Directions

Several avenues warrant investigation. First, external validation of this formula in diverse populations is essential, including older patients (> 65 year), higher-risk cohorts (ASA ≥ III), emergency settings, and obese patients, as PK/PD variability may differ substantially in these groups. Second, comparative studies evaluating different opioid regimens (varying remifentanil doses or alternative opioids such as sufentanil or alfentanil) and different BIS targets would clarify the generalisability and optimal application of LOC-anchored dosing. Third, prospective trials comparing LOC-guided versus conventional BIS-guided induction could assess whether this approach improves clinical outcomes such as time-to-intubation, haemodynamic stability, total drug consumption, and recovery profiles.[3] Finally, incorporation

of additional physiological signals (e.g., heart rate variability, pupillometry) alongside LOC might further refine individualised dosing algorithms for TCI anaesthesia.

Conclusions

In this prospective study of 128 ASA I–II adults, the individually titrated propofol effect-site concentration at loss of consciousness (LOC-P) strongly predicted the concentration required to achieve a BIS of 50 for intubation during TCI induction with remifentanil 2 ng mL^{-1} (R^2 = 0.81). The derived formula (INT-P = 0.67 + 0.974 × LOC-P) offers a simple, clinically applicable tool to personalise induction and anticipate intubation timing, particularly in settings without depth-of-anaesthesia monitoring. However, the high incidence of haemodynamic response to intubation (53.9%) suggests that deeper anaesthetic targets — such as BIS of 40 rather than 50 — or higher remifentanil concentrations may be preferable for attenuating the intubation stress response. External validation across different populations, opioid regimens, and BIS targets is warranted before widespread clinical adoption.

Abbreviations

ASA
American Society of Anesthesiologists
BIS
Bispectral index
BMI
Body mass index
Ce
Effect-site concentration
CI
Confidence interval
HR
Heart rate
INT-P
Propofol effect-site concentration at intubation readiness (BIS = 50)
IQR
Interquartile range
LOC
Loss of consciousness
LOC-P
Propofol effect-site concentration at loss of consciousness
MAC
Minimum alveolar concentration
MAP
Mean arterial pressure

PK/PD
Pharmacokinetic/pharmacodynamic
SD
Standard deviation
SpO_2
Peripheral oxygen saturation
STROBE
Strengthening the Reporting of Observational Studies in Epidemiology
TCI
Target-controlled infusion
TIVA
Total intravenous anaesthesia
TOF
Train-of-four

Declarations

Ethics approval and consent to participate:

This study was approved by the Ankara University Faculty of Medicine Human Research Ethics Committee, Ankara, Türkiye (decision no. İ6-416-21). All participants provided written informed consent.

Consent for publication:

Not applicable.

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Author Contribution

M.Y.B. and B.C.M. conceptualised and designed the study. M.Y.B., B.C.M., S.K.E. and V.B. were responsible for data curation and investigation. Y.Y. performed the formal statistical analysis. M.Y.B. wrote the original draft. All authors reviewed and edited the manuscript. B.C.M. and N.A. provided supervision and project administration. All authors read and approved the final manuscript.

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Not applicable.

Data Availability

De-identified data and analysis code are available from the corresponding author upon reasonable request for non-commercial research, subject to institutional ethics approval and a data-use agreement.

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Figures

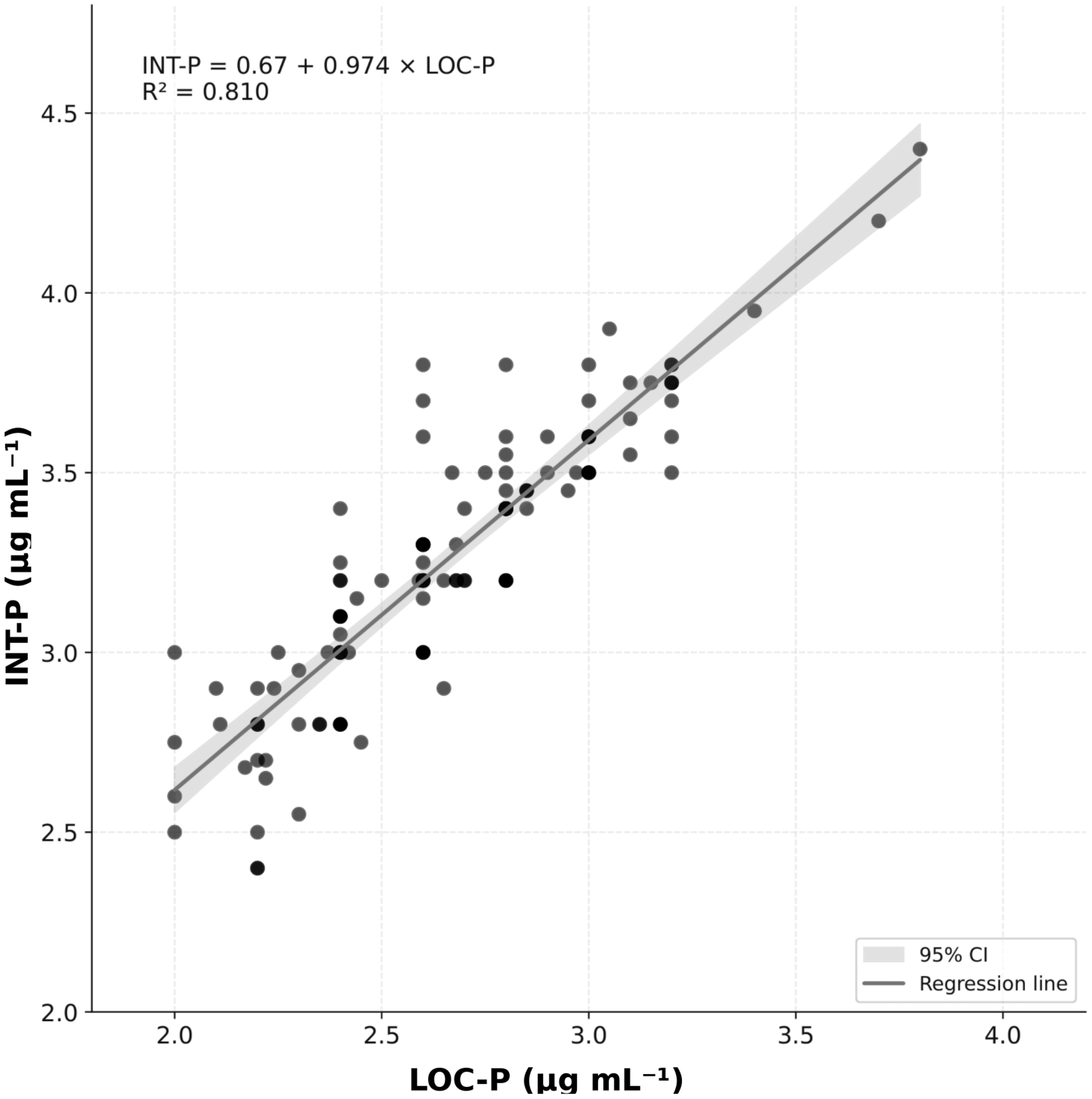

Figure 1

Scatter plot of LOC-P versus INT-P (n = 128). The solid line represents the linear regression fit; the shaded area represents the 95% confidence interval. Pearson r = 0.900 (95% CI 0.861–0.929; P < 0.001). CI, confidence interval; INT-P, propofol effect-site concentration at intubation readiness (BIS = 50); LOC-P, propofol effect-site concentration at loss of consciousness.

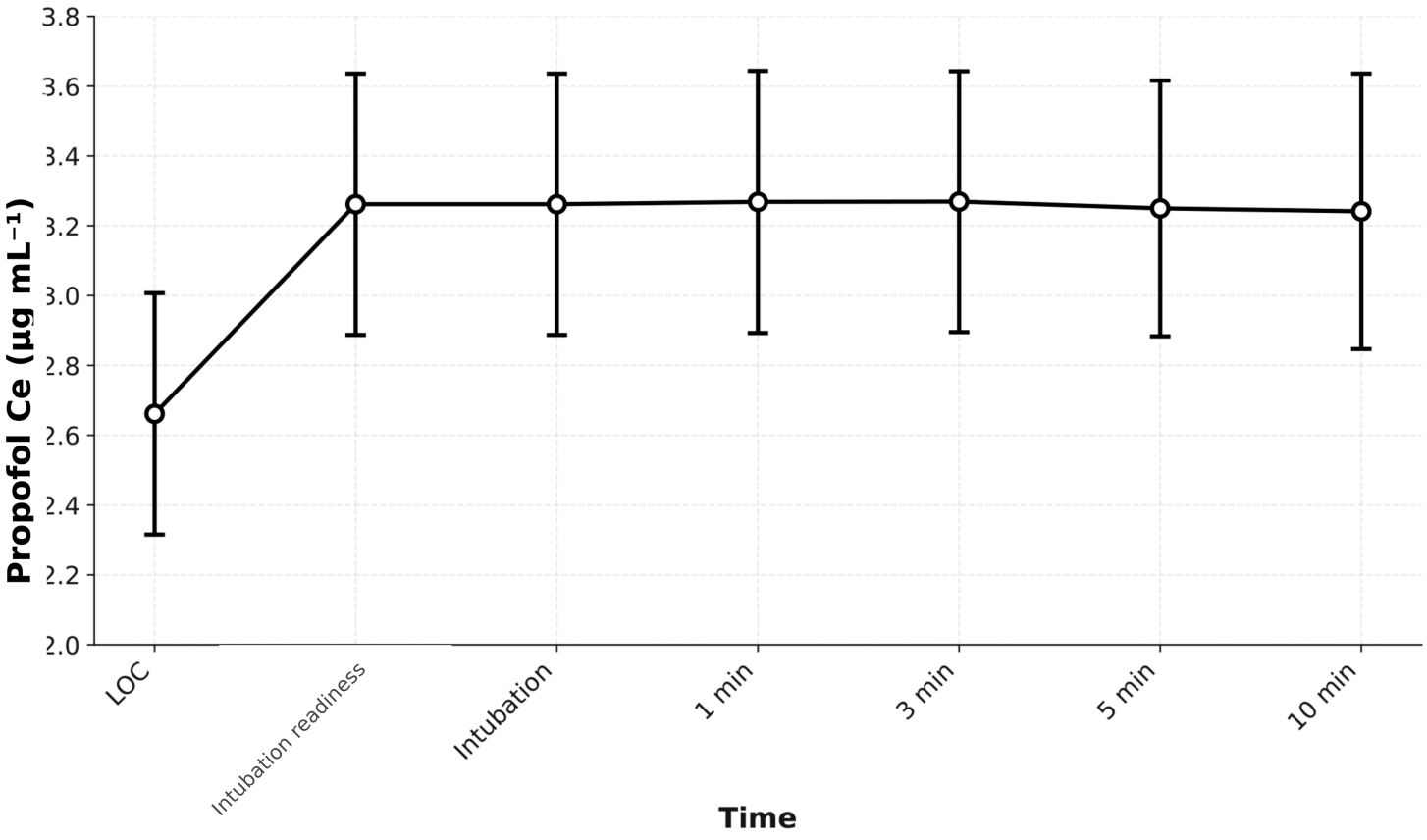

Figure 2

Mean propofol effect-site concentration (Ce; μg mL⁻¹) at seven time points (n = 128). Error bars represent ± SD. LOC, loss of consciousness; Intubation readiness, BIS = 50 sustained for ≥30 s. BIS, bispectral index; Ce, effect-site concentration; SD, standard deviation.

Supplementary Files

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