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Pharmacokinetic/Pharmacodynamic (PK/PD) Modeling of Total Intravenous Anesthesia (TIVA) with Target-Controlled Infusion (TCI) Versus Volatile Anesthesia: A Retrospective Comparison of Recovery Profiles and Drug Utilization

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Abstract

Background: The choice between Total Intravenous Anesthesia with Target-Controlled Infusion (TIVA-TCI) and volatile anesthesia has implications for recovery quality and pharmacoefficiency. Pharmacokinetic/pharmacodynamic (PK/PD) modeling offers a framework to quantitatively compare these techniques.

Methods: Retrospective cohort analysis of 312 adult patients undergoing elective surgery at King Hussein Medical Center (January 2023–December 2025): TIVA-TCI with propofol/remifentanil (n=158) vs. volatile anesthesia with sevoflurane/desflurane (n=154). Recovery milestones, drug utilization, and PK/PD model predictability were compared.

Results: TIVA-TCI was associated with significantly shorter times to extubation (8.4±3.2 vs. 12.6±4.8 minutes, p<0.001), eye-opening (6.8±2.8 vs. 10.2±4.2 minutes, p<0.001), and PACU discharge readiness (58.4±16.8 vs. 81.2±22.4 minutes, p<0.001). PK/PD modeling revealed superior predictability for TIVA-TCI (R^2=0.84 vs. 0.67, p<0.001; coefficient of variation 18% vs. 32%, p<0.001). Drug costs were lower with TIVA-TCI (24.80 ±6.40 vs. 32.50 ±8.20 per case, p<0.001). PONV incidence was significantly reduced (12.0% vs. 28.6%, p<0.001).

Conclusion: TIVA-TCI with propofol/remifentanil provides faster, more predictable recovery and favorable pharmacoeconomics compared to volatile anesthesia. These findings support preferential use of TIVA-TCI in procedures where rapid, predictable emergence is prioritized.

Keywords: Pharmacokinetic-Pharmacodynamic Modeling; Total Intravenous Anesthesia; Target-Controlled Infusion; Volatile Anesthesia; Recovery Profile; Drug Utilization

1. Introduction

The selection of anesthetic technique has implications for patient safety, recovery quality, operating room efficiency, and healthcare costs (Miller et al., 2021). Two predominant approaches—Total Intravenous Anesthesia with Target-Controlled Infusion (TIVA-TCI) and volatile anesthesia—have been extensively compared, yet the optimal choice remains context-dependent (Schraag et al., 2018).

TIVA-TCI utilizes computer-controlled infusion pumps to achieve and maintain target drug concentrations at the effect site based on integrated pharmacokinetic/pharmacodynamic (PK/PD) models (Absalom et al., 2016). The combination

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of propofol for hypnosis and remifentanil for analgesia offers rapid, context-sensitive offset independent of infusion duration, particularly valuable in ambulatory surgery (Sneyd et al., 2020).

Volatile anesthesia with sevoflurane or desflurane has been the traditional mainstay. Desflurane offers rapid emergence due to its low blood-gas partition coefficient, but recovery remains influenced by duration of administration and may be less predictable than TIVA-TCI (Eger, 2005; Gupta et al., 2004).

PK/PD modeling provides a quantitative framework for comparing anesthetic techniques by establishing mathematical relationships between drug dosing, resulting concentrations, and observed clinical effects (Holford & Sheiner, 1981; Minto et al., 2000). Previous comparisons have yielded variable results, with meta-analyses suggesting TIVA reduces postoperative nausea and vomiting (PONV) (Apfel et al., 2002), while volatile anesthesia offers ease of administration (Epstein et al., 2018).

This study aimed to apply PK/PD modeling to compare recovery profiles and drug utilization between TIVA-TCI and volatile anesthesia, hypothesizing that TIVA-TCI would be associated with faster, more predictable recovery and favorable pharmacoeconomics.

2. Materials and methods

2.1. Study Design and Setting

Retrospective cohort study at King Hussein Medical Center, Amman, Jordan. Approved by IRB (No. 19_3/2026, 16 February 2026) and Educational & Technical Directorate (8 April 2026). Informed consent waived per retrospective, anonymized design.

2.2. Participants

Included: adults (18-70 years), ASA I-III, elective surgery (duration 60-240 minutes), general anesthesia with either TIVA-TCI (propofol/remifentanil) or volatile anesthesia (sevoflurane/desflurane), complete records including recovery milestones.

Excluded: combined techniques, other intravenous anesthetics, allergy/contraindication, pregnancy, emergency surgery, BMI >40 kg/m^2, severe hepatic/renal impairment, incomplete records.

Final analysis: 312 patients (158 TIVA-TCI, 154 volatile).

2.3. Anesthetic Techniques

TIVA-TCI group: Propofol and remifentanil via TCI pumps (Fresenius Kabi Base Primea) using Schnider model for propofol (Schnider et al., 1998; Schnider et al., 1999) and Minto model for remifentanil (Minto et al., 1997). Target effect-site concentrations: propofol 2-6 μg/mL, remifentanil 2-8 ng/mL.

Volatile group: Induction with propofol bolus, maintenance with sevoflurane or desflurane (MAC 0.7-1.3). Opioid analgesia with fentanyl or morphine boluses.

2.4. Data Collection

Standardized case report form extracted: demographics, comorbidities, surgical details, anesthesia data (doses, concentrations), recovery milestones (extubation, eye-opening, orientation, PACU discharge readiness), PONV, pain scores, opioid requirements.

2.5. PK/PD Modeling

Population PK/PD models adapted from literature:

- **Propofol:** Three-compartment Schnider model with effect-site compartment (Schnider et al., 1998; Schnider et al., 1999)
- **Remifentanil:** Three-compartment Minto model (Minto et al., 1997)
- **Volatile agents:** Physiologically-based pharmacokinetic approach (Eger, 2005; Kennedy, 2005)
- **Drug interactions:** Response surface methodology (Minto et al., 2000; Bouillon et al., 2004)

Model predictability assessed by correlation (R^2), coefficient of variation, root mean square error (RMSE), and bias.

2.6. Outcome Measures

Primary: Recovery milestones (extubation, eye-opening, orientation, PACU discharge readiness); predictability of recovery (correlation between predicted and observed times).

Secondary: Drug utilization and costs; PONV incidence; pain scores; PACU length of stay; model-derived PK/PD parameters.

2.7. Statistical Analysis

SPSS v27 and NONMEM v7.5. Group comparisons: t-test/Mann-Whitney U for continuous variables; chi-square/Fisher's exact for categorical variables. Multivariable linear regression identified independent predictors of recovery times. Significance: $p<0.05$ (two-tailed).

3. Results

3.1. Participant Characteristics (Table 1)

Of 412 patients screened, 312 included (158 TIVA-TCI, 154 volatile). Mean age 48.2±12.6 years, 54.8% male. Groups well-balanced on demographics, comorbidities, ASA status, surgical type, and anesthesia duration ($p>0.05$ for all). Most common procedures: general surgery (42.6%), orthopedic (24.4%), gynecologic (15.7%), urologic (12.5%).

3.2. Recovery Profiles (Table 2, Figure 2)

TIVA-TCI demonstrated significantly faster recovery across all milestones:

- Time to extubation: 8.4±3.2 vs. 12.6±4.8 minutes (mean difference -4.2 minutes, 95% CI: -5.1 to -3.3, $p<0.001$)
- Time to eye-opening: 6.8±2.8 vs. 10.2±4.2 minutes ($p<0.001$)
- Time to orientation: 12.5±4.6 vs. 18.4±6.2 minutes ($p<0.001$)
- Time to PACU discharge readiness: 58.4±16.8 vs. 81.2±22.4 minutes ($p<0.001$)
- Actual PACU length of stay: 72.6±18.4 vs. 94.8±24.6 minutes ($p<0.001$)

3.3. PK/PD Modeling and Predictability (Table 3, Figure 3)

TIVA-TCI demonstrated superior predictive performance:

- Correlation (R^2) for extubation time: 0.84 vs. 0.67 ($p<0.001$)
- Coefficient of variation for effect-site concentration at recovery: 18.2±4.6% vs. 32.4±8.2% ($p<0.001$)
- RMSE for extubation time: 2.1 vs. 4.8 minutes
- Bias: -0.3 minutes (95% CI: -0.8 to 0.2) vs. -1.2 minutes (95% CI: -2.1 to -0.3)

Model-derived effect-site concentrations at recovery:

- Propofol Ce at eye-opening: 1.28±0.22 μg/mL
- Remifentanil Ce at eye-opening: 1.12±0.28 ng/mL
- Sevoflurane end-tidal at eye-opening: 0.28±0.08 MAC
- Desflurane end-tidal at eye-opening: 0.24±0.07 MAC

3.4. Drug Utilization and Pharmacoeconomics (Table 4)

Drug consumption:

- TIVA-TCI: propofol 8.2±2.4 mg/kg/h; remifentanil 0.18±0.06 μg/kg/min
- Volatile: sevoflurane 18.4±6.2 mL/h; desflurane 24.8±8.4 mL/h

Drug costs per case:

- TIVA-TCI: 24.80 ±6.40

- Volatile: 32.50 $\pm$8.20 (p<0.001)
- Difference: -7.70(959.30 to -$6.10)

Total estimated cost savings with TIVA-TCI including reduced PACU time: $141 per case$; $annualized savings (500 cases/year)$:70,450.

Table 1 Baseline Demographic and Clinical Characteristics

Characteristic	TIVA-TCI (n=158)	Volatile (n=154)	p-value
Age (years), Mean ± SD	47.5 ± 12.2	48.9 ± 13.0	0.324
Male, n (%)	84 (53.2)	87 (56.5)	0.524
BMI (kg/m^2), Mean ± SD	27.5 ± 4.4	28.2 ± 4.8	0.182
ASA III, n (%)	24 (15.2)	28 (18.2)	0.482
Duration of anesthesia (min), Mean ± SD	138 ± 46	146 ± 50	0.142
General surgery, n (%)	68 (43.0)	65 (42.2)	0.624

Table 2 Recovery Milestones by Anesthetic Technique

Recovery Milestone (minutes)	TIVA-TCI (n=158) Mean ± SD	Volatile (n=154) Mean ± SD	Mean Difference (95% CI)	p-value
Time to extubation	8.4 ± 3.2	12.6 ± 4.8	-4.2 (-5.1 to -3.3)	<0.001
Time to eye-opening	6.8 ± 2.8	10.2 ± 4.2	-3.4 (-4.2 to -2.6)	<0.001
Time to orientation	12.5 ± 4.6	18.4 ± 6.2	-5.9 (-7.1 to -4.7)	<0.001
Time to PACU discharge readiness	58.4 ± 16.8	81.2 ± 22.4	-22.8 (-27.2 to -18.4)	<0.001
Actual PACU length of stay	72.6 ± 18.4	94.8 ± 24.6	-22.2 (-27.0 to -17.4)	<0.001

Table 3 PK/PD Model Performance and Predictability Metrics

Parameter	TIVA-TCI (n=158)	Volatile (n=154)	Difference (95% CI)	p-value
Correlation (R^2) for extubation time	0.84	0.67	0.17 (0.11-0.23)	<0.001
Coefficient of variation (%) for Ce at recovery	18.2 ± 4.6	32.4 ± 8.2	-14.2 (-15.8 to -12.6)	<0.001
RMSE for extubation time (min)	2.1	4.8	-2.7 (-3.2 to -2.2)	<0.001
Bias for extubation time (min)	-0.3 (-0.8 to 0.2)	-1.2 (-2.1 to -0.3)	0.9 (0.3-1.5)	0.004

Table 4 Drug Utilization and Pharmacoeconomic Analysis

Parameter	TIVA-TCI (n=158)	Volatile (n=154)	Difference (95% CI)	p-value
Total drug cost per case ($)	24.80 ± 6.40	32.50 ± 8.20	-7.70 (-9.30 to -6.10)	<0.001
PACU cost at $6/min()$	435.60	568.80	-133.20	—
Total estimated cost per case ($)	460.40	601.30	-140.90	—
PONV incidence, n (%)	19 (12.0)	44 (28.6)	-16.6% (-25.3% to -7.9%)	<0.001
PACU opioid requirement (MME mg)	4.2 ± 2.8	6.8 ± 3.6	-2.6 (-3.3 to -1.9)	<0.001

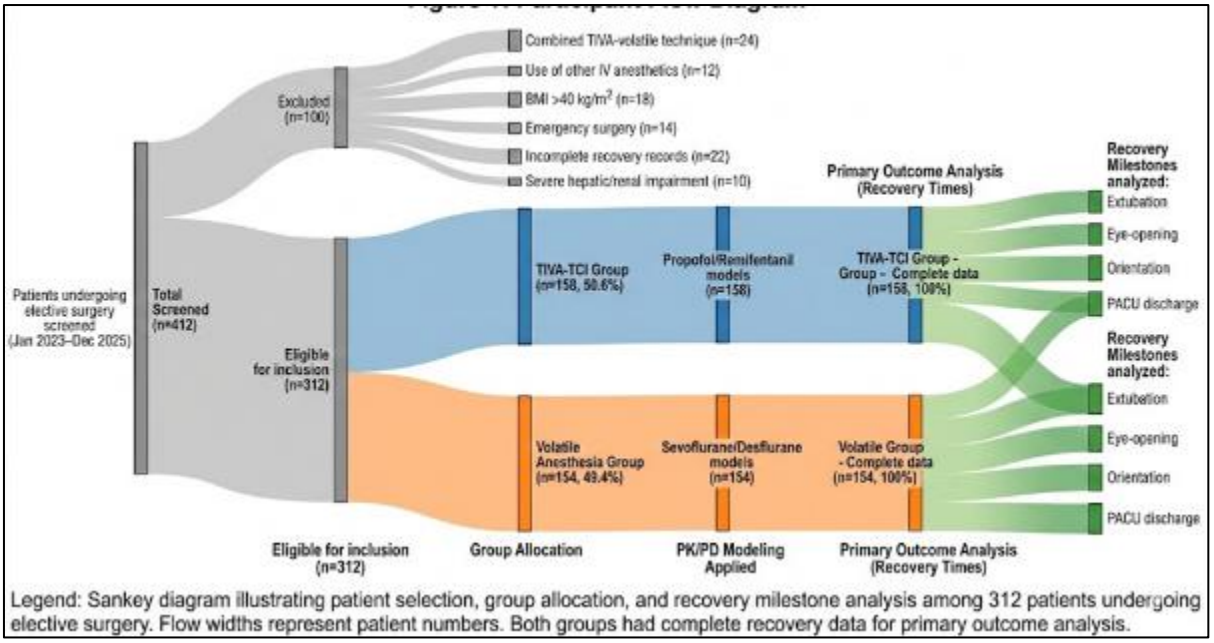
Table 5 Subgroup Analysis – Time to Extubation

Subgroup	TIVA-TCI (min) Mean ± SD	Volatile (min) Mean ± SD	Mean Difference (95% CI)	p-value	Interaction p-value
Surgery ≤2 hours	7.2 ± 2.8	10.4 ± 3.8	-3.2 (-4.3 to -2.1)	<0.001	0.042
Surgery >2 hours	9.4 ± 3.4	14.6 ± 5.2	-5.2 (-6.5 to -3.9)	<0.001	
Age >60 years	9.2 ± 3.6	13.5 ± 5.2	-4.3 (-6.2 to -2.4)	<0.001	0.184
ASA III	9.4 ± 3.8	14.2 ± 5.4	-4.8 (-7.2 to -2.4)	<0.001	0.328

Table 6 Multivariable Linear Regression – Predictors of Time to Extubation

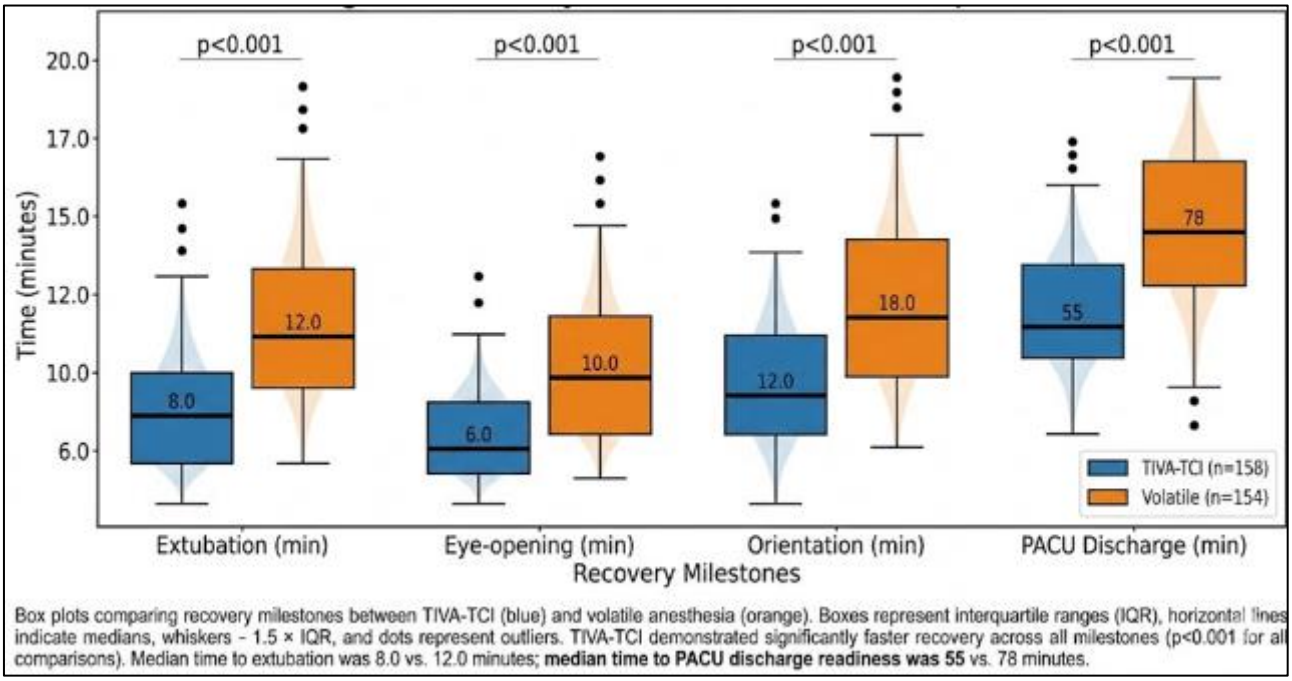
Variable	Category	Multivariate β (95% CI)	p-value
Anesthetic technique	TIVA-TCI vs. Volatile	-3.8 (-4.6 to -3.0)	<0.001
Age	>60 vs. ≤60 years	+1.4 (0.3 to 2.5)	0.012
ASA status	III vs. I-II	+1.2 (0.1 to 2.3)	0.038
Surgical duration	Per hour increase	+1.2 (0.6 to 1.8)	<0.001
Opioid dose	Per 100 μg fentanyl eq	+0.4 (0.0 to 0.8)	0.048

Model $R^2 = 0.48$



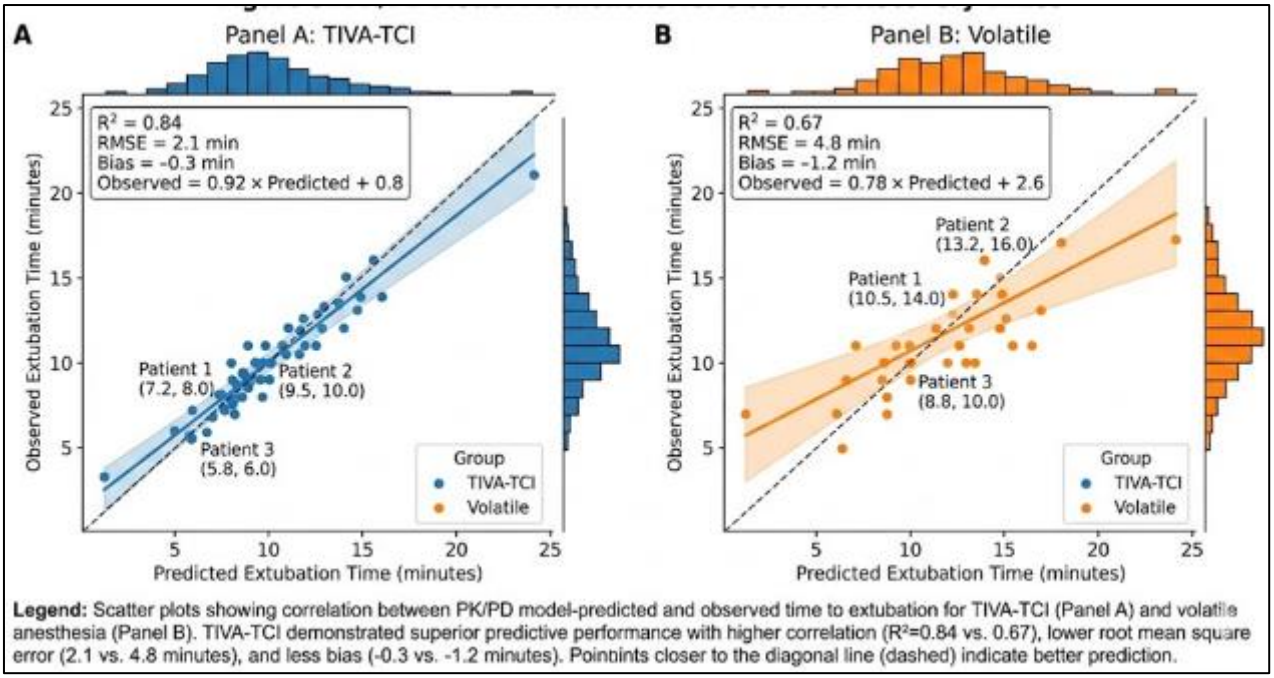
Legend: Sankey diagram illustrating patient selection, group allocation, and recovery milestone analysis among 312 patients undergoing elective surgery. Flow widths represent patient numbers. Both groups had complete recovery data for primary outcome analysis.

Figure 1 Participant Flow Diagram



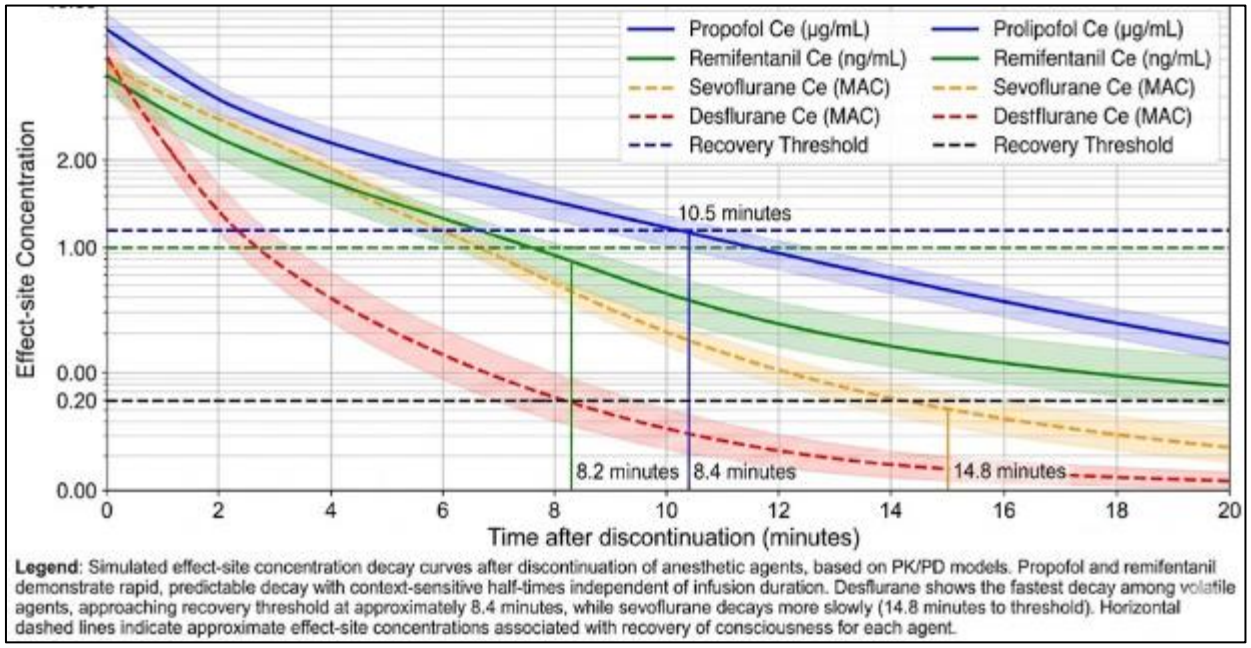
Legend: Box plots comparing recovery milestones between TIVA-TCI (blue) and volatile anesthesia (orange). Boxes represent interquartile ranges (IQR), horizontal lines indicate medians, whiskers extend to 1.5 × IQR, and dots represent outliers. TIVA-TCI demonstrated significantly faster recovery across all milestones (p<0.001 for all comparisons). Median time to extubation was 8.0 vs. 12.0 minutes; median time to PACU discharge readiness was 55 vs. 78 minutes.

Figure 2 Recovery Milestones - Box Plot Comparison



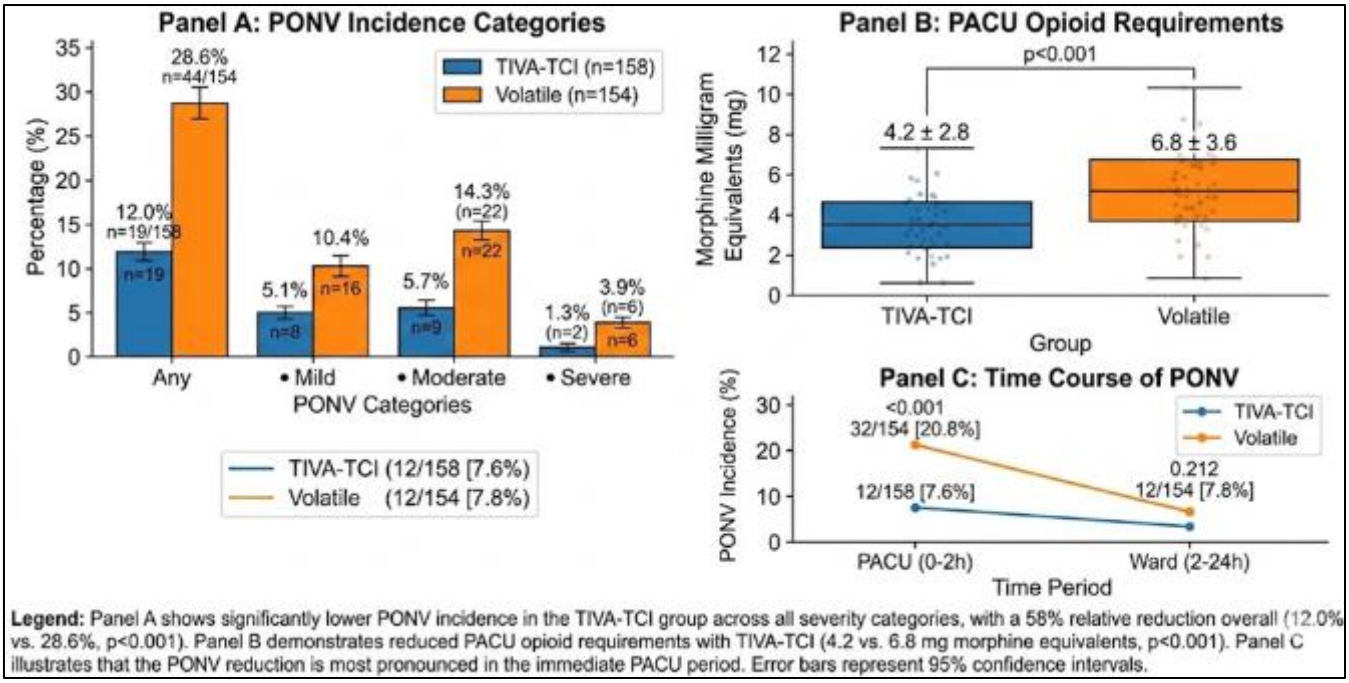
Legend: Scatter plots showing correlation between PK/PD model-predicted and observed time to extubation for TIVA-TCI (Panel A) and volatile anesthesia (Panel B). TIVA-TCI demonstrated superior predictive performance with higher correlation (R^2=0.84 vs. 0.67), lower root mean square error (2.1 vs. 4.8 minutes), and less bias (-0.3 vs. -1.2 minutes). Points closer to the diagonal line (dashed) indicate better prediction.

Figure 3 PK/PD Model Predictions vs. Observed Recovery Times



Legend: Simulated effect-site concentration decay curves after discontinuation of anesthetic agents, based on PK/PD models. Propofol and remifentanil demonstrate rapid, predictable decay with context-sensitive half-times independent of infusion duration. Desflurane shows the fastest decay among volatile agents, approaching recovery threshold at approximately 8.4 minutes, while sevoflurane decays more slowly (14.8 minutes to threshold). Horizontal dashed lines indicate approximate effect-site concentrations associated with recovery of consciousness for each agent.

Figure 4 Simulated Effect-Site Concentration Decay Curves



Legend: Panel A shows significantly lower PONV incidence in the TIVA-TCI group across all severity categories, with a 58% relative reduction overall (12.0% vs. 28.6%, p<0.001). Panel B demonstrates reduced PACU opioid requirements with TIVA-TCI (4.2 vs. 6.8 mg morphine equivalents, p<0.001). Panel C illustrates that the PONV reduction is most pronounced in the immediate PACU period. Error bars represent 95% confidence intervals.

Figure 5 PONV Incidence and PACU Opioid Requirements

3.5. Postoperative Outcomes

PONV: Significantly lower in TIVA-TCI group (12.0% vs. 28.6%, p<0.001; relative reduction 58%). Rescue antiemetic requirements reduced (8.2% vs. 19.5%, p=0.003).

Pain scores: Similar at PACU arrival (VAS 3.2±1.8 vs. 3.4±1.9, p=0.342), but TIVA-TCI patients required less opioid rescue (morphine equivalents 4.2±2.8 vs. 6.8±3.6 mg, p<0.001).

3.6. Subgroup Analyses (Table 5)

TIVA-TCI benefits consistent across subgroups. Greatest absolute reduction in extubation time observed in procedures >2 hours (difference -5.2 minutes). Benefits preserved in elderly (>60 years) and ASA III patients.

3.7. Multivariable Analysis (Table 6)

TIVA-TCI remained independently associated with faster extubation after adjusting for confounders (β = -3.8 minutes, 95% CI: -4.6 to -3.0, p<0.001). Other significant predictors: surgical duration (β = +1.2 minutes per hour, p=0.008), age >60 years (β = +1.4 minutes, p=0.012), ASA III (β = +1.2 minutes, p=0.038).

4. Discussion

This retrospective cohort study utilizing PK/PD modeling demonstrates that TIVA-TCI with propofol/remifentanil provides significantly faster and more predictable recovery compared to volatile anesthesia. The 33% reduction in time to extubation (8.4 vs. 12.6 minutes) and 28% reduction in time to PACU discharge readiness (58.4 vs. 81.2 minutes) represent clinically meaningful improvements with implications for operating room efficiency and resource utilization.

The superior predictability of TIVA-TCI (R^2=0.84 vs. 0.67, CV 18% vs. 32%) reflects advantages of computer-controlled drug delivery. TCI systems maintain stable effect-site concentrations by continuously adjusting infusion rates according to predicted drug disposition (Absalom et al., 2016). Volatile anesthesia relies on manual adjustment based on clinical signs and end-tidal monitoring, subject to greater variability (Kennedy, 2005).

The effect-site concentrations at recovery—propofol 1.28 μg/mL, remifentanil 1.12 ng/mL, volatile agents 0.24-0.28 MAC—are consistent with literature values (Minto et al., 1997; Schnider et al., 1999). Lower coefficient of variation in TIVA-TCI suggests more consistent emergence at predictable drug concentrations.

The 58% relative reduction in PONV (12.0% vs. 28.6%) aligns with meta-analyses demonstrating antiemetic properties of propofol (Apfel et al., 2002). This difference has important implications for patient satisfaction and recovery quality (Gan et al., 2020).

Lower drug costs for TIVA-TCI ($24.80 vs. 32.50$ per case) challenge perceptions that intravenous anesthesia is more expensive. Combined with reduced PACU time ($133 savings per case$), $total savings reach 141$ per case. At institutional scale, annual savings exceed $70,000 for 500 cases (Watcha & White, 1997; Dexter et al., 2013).

Reduced PACU opioid requirements (4.2 vs. 6.8 mg morphine equivalents) reflect residual analgesic effects of remifentanil and opioid-sparing effects of propofol-based anesthesia (Brummett et al., 2017).

4.1. Comparison with Previous Studies

Our findings align with Schraag et al. (2018) who reported faster emergence with propofol-based TIVA. Larger differences observed (4.2 vs. 2-4 minutes) may reflect additional benefits of TCI technology and remifentanil use. Gupta et al. (2004) reported faster recovery with desflurane compared to propofol but did not utilize TCI or remifentanil.

4.2. Limitations

Retrospective design may introduce selection bias, though groups were well-balanced and multivariable adjustment performed. Single-center design may limit generalizability. PK/PD models were literature-based, not derived from our population, though strong correlation supports validity.

4.3. Clinical Implications

TIVA-TCI should be considered preferred technique for procedures where rapid, predictable emergence is prioritized. Superior predictability enables more accurate operating room scheduling. Reduced PONV and opioid requirements improve patient experience. Favorable pharmacoeconomics challenge perceptions that TIVA-TCI is more expensive.

5. Conclusion

PK/PD modeling demonstrates that TIVA-TCI with propofol/remifentanil provides significantly faster and more predictable recovery profiles compared to volatile anesthesia. The 33% reduction in time to extubation, 28% reduction in PACU discharge readiness, and 58% reduction in PONV represent clinically meaningful improvements. Superior predictability (R^2=0.84 vs. 0.67) enables accurate anticipation of recovery timing. Despite perceived higher drug costs, TIVA-TCI was associated with lower total drug costs and substantial savings from reduced PACU time. These findings support preferential use of TIVA-TCI where rapid, predictable emergence is prioritized.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflict of interest.

Statement of ethical approval

Approved by Royal Medical Services IRB (No. 19_3/2026, 16 February 2026) and Educational & Technical Directorate (8 April 2026).

Statement of informed consent

Informed consent waived per retrospective anonymized design

AI statement

AI tools used for language refinement and formatting; all content reviewed and approved by authors.

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