Target-controlled infusion: A comparative, prospective, observational study of the conventional TCI pump and the novel smartphone-based application iTIVA

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Abstract

Background and Aims: Empirically adjusted, standard drug doses fail to address interindividual pharmacokinetic and pharmacodynamics variability. Target-controlled infusion (TCI) delivers drugs in calibrated boluses to achieve and maintain a selected target plateau drug level (plasma or effect site). Interactive total intravenous anesthesia (iTIVA™) smartphone software simulates TCI and employs 31 established pharmacokinetic models for 11 different intravenous agents and is coupled with standard volumetric infusion pumps for administering TCI.

Material and Methods: This prospective, observational, study investigates the degree of agreement between iTIVA and a conventional TCI pump (CTP) for the volume of propofol infused using the Schnider pharmacokinetic model in adult patients of either sex undergoing oncosurgery lasting 1–3 h under total intravenous anesthesia. Bland–Altman analysis of 124 data pairs from 30 patients provided bias, precision, and limits of agreement between the volumes infused by CTP and iTIVA (V-CTP and V-iTIVA) during specific identical time periods. Spearman's rho and Kendall's tau rank correlation coefficients provided the degree of association between V-CTP and V-iTIVA.

Results: Spearman's rho and Kendall's tau were 0.996 and 0.964, respectively. Bias or the mean of differences was -0.02, while the limits of agreement were 0.58 and -0.63, respectively (Bland–Altman plot). The maximum allowed difference of 2 ml was much larger than the 95% confidence intervals for the limits of agreement. The Mountain plot was short tailed (-1.28 to 1.55) and centred over zero (0.01).

Conclusion: The volume of propofol infused using TCI pump was similar to that calculated by iTIVA in identical time periods, confirming the clinical applicability of iTIVA.

Keywords: Propofol, Schnider model, smartphone, target-controlled infusion, total intravenous anesthesia

Introduction

Intravenous (IV) drug administration using standard doses, fine-tuned as per the anesthesiologist's clinical experience, is empirical and subjective. It neglects the interindividual pharmacokinetic/pharmacodynamic variability in dose–plasma concentration (approximated at 30%) with potential adverse events.[1,2] Microprocessor chip–enabled implementation of hypothetical mathematical models, simulating the pharmacokinetics of anesthetic drugs, constitutes target control infusion (TCI). TCI allows rapid and rational titration of infusion rates, delivering calibrated boluses to achieve therapeutic effect-site and plasma target concentrations of the inputted drug. TCI enhances the quality of anesthesia and hemodynamic stability and predicts awakening.[1-4]

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Interactive total intravenous anesthesia (iTIVA™) is a smartphone-based (Android™/iOS™) software simulating TCI. We administered TCI using a dedicated commercial TCI pump (CTP; Perfusor® Space; B-Braun, Melsungen AG, Germany) under American Society of Anesthesiologists (ASA) monitoring standards, clinical vigilance, and processed electroencephalographic monitoring in all patients. Our primary objective was to study the agreement and interchangeability between iTIVA calculations and CTP regarding the volume of propofol infused per unit time, using the Schnider pharmacokinetic model, in adult patients undergoing oncosurgery under total intravenous anesthesia (TIVA).

Material and Methods

This single-blind, prospective, observational, single-centric study was carried out after obtaining written informed consent from all patients, approval from the scientific committee and institutional review board, and Clinical Trial Registry of India registration. It was conducted from December 2019 to March 2021 in the major operation theater (OT) of a tertiary care oncology center in accordance with the Helsinki protocol and included 30 adult patients.

All ASA I–III patients of either sex, aged 18–70 years and weighing 40–80 kg, scheduled to undergo oncosurgery lasting 1–3 h under propofol-based TIVA were included in the study. Prolonged QT-interval, propofol allergy, and preexisting hypotension constituted the exclusion criteria.

Outcome assessor blinding, data analyst blinding, and application of appropriate statistical methods were performed to overcome any detection bias. Our primary outcome measure was the volume of propofol infused in identical time periods by the two devices in accordance with the Schnider pharmacokinetic model. The anesthesiologist who noted the amount of propofol infused by CTP in each time period was provided a sheet of paper with two columns. The first column comprised the time periods obtained from iTIVA by entering the age, weight, height, and sex of the patient. In the second column, this anesthesiologist (blinded to the amount of propofol calculated by iTIVA for each of these time periods) entered the amount of propofol infused by CTP against each corresponding time period.

The updated version of iTIVA includes a library of 56 established pharmacokinetic models (Minto, Marsh, Schnider, Rigby-Jones, Gepts, Shafer, Cortinez, and Paedfusor) for 25 different IV agents. Developed as a possible alternative to TCI pumps, it is coupled with basic volumetric infusion pumps to enable target-controlled delivery of not just propofol

and remifentanil (available in traditional TCI pumps), but also a battery of additional drugs like fentanyl, ketamine, dexmedetomidine, lignocaine, midazolam, tranexamic acid, magnesium sulfate, atracurium, cisatracurium, rocuronium, and thiopentone. "iTIVA anesthesia" is offered free and unrestricted for 10 uses, after which, although still free, a wait time of 1 s is added for each subsequent use. Upon purchasing the app ($9.99/₹899 annual fee), the user has full access to the version without time restrictions, can simultaneously simulate up to seven drugs, and export the case data to an Excel file.[5-8] A separate section that lists physiological variables, drugs, airway equipment, and IV fluids calculated on basis of patient age is exclusive to the TCI mode. Owing to their beneficial effects on postoperative nausea vomiting, environment-friendliness, compatibility with intraoperative neurophysiological monitoring, and so on, increased use of propofol-based TIVA and TCI is projected,[9,10] which made us choose propofol as the study drug.

Sample size calculation

Sample size calculation was done based on Table 1 of a manuscript by Lu *et al.*[11] with the following assumptions: Type-I error (α-error; significance) 0.05, power 80%, standardized difference limit (μ/σ) =0.3, standardized agreement limit (δ/σ) =2.7. A sample size of 123 was arrived at. Keeping the expected mean of differences (μ/σ) =0.3, the expected standard deviation of differences = 0.7, and the maximum allowed difference between methods = 2 (since 2 = 2 ml or 20 mg propofol) and feeding these assumptions into MedCalc statistical software (version 18.9.1; released 2018; MedCalc Software bvba, Ostend, Belgium), the minimum required number of pairs came out to be 109. Allowing for dropouts, we compared 124 paired readings in 30 patients.

Anesthetic technique

After application of standard monitors including the Bispectral Index (BIS) monitor, the age, sex, weight, and height of the patient were inputted into the smartphone. The TCI mode was selected and the target effect-site concentration (3 μg/ml for induction and 2.4 μg/ml for maintenance) was entered, followed by selection of the Schnider model. Under the hypnotic section, propofol 10 mg/ml was entered. The time periods in minutes (e.g., 3, 11, 12, 17, 51, etc.) and the expected volume in milliliters of propofol infused during the corresponding time period (e.g., 4.9, 8.1, 7.9, 10.5, 29, etc.) were displayed by iTIVA in response. The CTP was also programmed at identical effect-site concentrations for propofol after selecting the Schnider pharmacokinetic model. A dedicated 20G IV cannula was secured for infusing propofol. Propofol was infused by the CTP, and the graph and readings for the volume of propofol infused per given

time period obtained in iTIVA were compared with the actual volume delivered by the CTP during the same time period. "Real Time Tool" was utilized to run a stopwatch with audio-visual alarms at the same time as the start of infusion in the volumetric pump [Figure 1]. A peripheral nerve stimulator-guided atracurium infusion was utilized for neuromuscular blockade using a separate IV cannula and was reversed at the end of surgery using neostigmine and glycopyrrolate in standard doses. Hypotension was defined as a 20% fall in mean arterial pressure (MAP) from baseline and was treated with ephedrine boluses (6 μg every 2 min for three consecutive boluses, following which a noradrenaline infusion was started). Hypertension constituted a 20% rise in MAP above baseline values and was corrected using diltiazem boluses (5 mg each). Tachycardia/bradycardia, defined as a 20% rise/fall in heart rate, was treated with esmolol/atropine boluses, respectively.

Statistical analysis

Normally distributed, continuous/quantitative variables were expressed as mean ± standard deviation (SD), whereas categorical/qualitative variables were expressed as numbers and percentage. Descriptive statistical data employed Microsoft Excel 2010 (Microsoft Corp., Redmond, WA, USA).

MedCalc Statistical Software was utilized for Bland–Altman analysis. $P < 0.05$ was considered statistically significant. The degree of association between the volumes infused by CTP and iTIVA (V-CTP and V-iTIVA, respectively) was calculated using Spearman's rho (ρ) and Kendall's tau (τ) rank correlation coefficients.[12]

Bias, precision, and limits of agreement (LoA) between V-CTP and V-iTIVA during specific identical time periods were calculated using Bland–Altman analysis, in which bias was summarized as the mean of differences between CTP and iTIVA values and precision the SD of this difference. The mean of differences between two measurements ±1.96 times their SD provided the LoA. The maximum allowed difference (Δ) was predefined as 2 ml or 20 mg of propofol. The two methods of target-controlled infusion were considered to be in agreement when Δ and −Δ were larger than the upper 95% confidence interval (CI) limit of higher limit and lower than the lower 95% CI limit of LoA, respectively.

The Mountain plot (folded empirical cumulative distribution plot) provided a graphical representation of the distribution of differences between V-CTP and V-iTIVA for 124 observations taken together.

Table 1: Demographic and surgical profile of patients

	Min.	Max.	Arithmetic mean	95% CI for mean	SD
Age	30	76	50.4	46–54.9	12
Weight	43	90	61.7	57.7–65.8	10.8
Height	136	177	157.1	154.2–159.9	7.7
Sex			6/30 (20%) Male: 24/30 (80%) Female		
Surgery (type)			22/30 (73%) Breast surgery: 8/30 (27%) others		
Surgery duration (minutes)	60	175	120.2	108.1–132.2	32.05
Duration of comparison	29	152	72.1	60.4–83.9	31.4

CI=Confidence interval, SD=Standard deviation
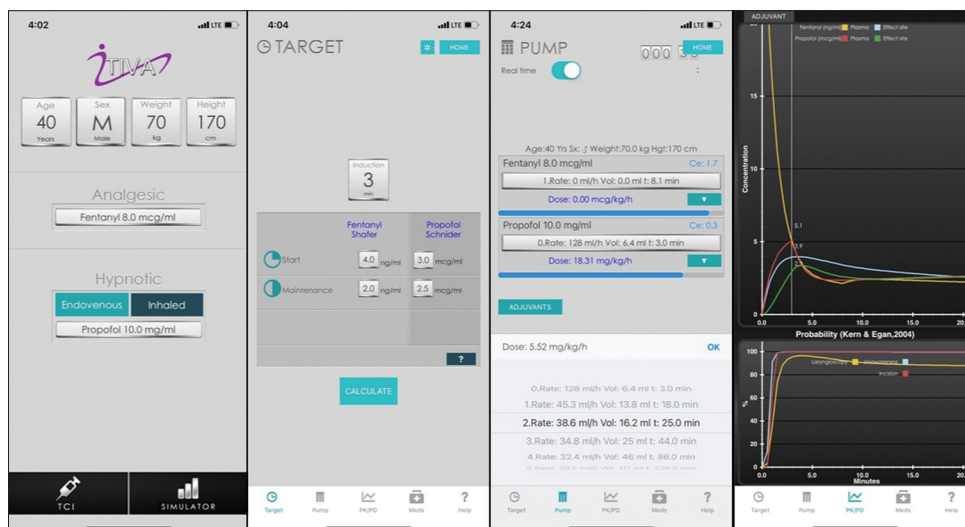
Figure 1: iTIVA smartphone app. iTIVA = interactive total intravenous anesthesia

Results

Out of 34 potentially eligible patients undergoing oncosurgery under TIVA, 34 were examined for eligibility, and 31 were found to be eligible. Two were excluded owing to preexisting hypotension, while the third one exhibited a prolonged QT-interval on electrocardiogram (ECG). One eligible patient scheduled for right modified radical mastectomy and left lumpectomy was excluded since a dedicated 20G cannula could not be secured on either of the lower limbs (upper limbs were exempt due to surgical considerations) for propofol infusion owing to thrombophlebitis and obliteration of veins post-chemotherapy. The descriptive statistics pertaining to demographics and surgery are summarized in Table 1. Twenty-two were breast surgery patients, while eight others were posted for head and neck surgery (five underwent modified neck dissection and one each underwent thyroidectomy, lachrymal gland excision, and partial glossectomy) The duration of comparison was shorter than the duration of surgery since after the fourth reading, the time period displayed by iTIVA exponentially increased in accordance with the Schnider pharmacokinetic model.

For the volume of propofol infused in identical time periods, the mean ± SD and the lowest and highest values for V-CTP were 11.3 ± 10.9, 2.4, and 54.8 respectively, whereas those for V-iTIVA were 11.4 ± 10.9, 2.4, and 55.0, respectively, which is comparable. V-CTP was found to have a strong positive correlation with V-iTIVA. Correlation coefficients were calculated to quantify the degree of association between V-iTIVA and V-CTP in a sample size of 124 data pairs. Since the distribution of these variables was not normal, the degree of association between them was calculated using Spearman's rho and Kendall's tau rank correlation coefficients.

Spearman's coefficient of rank correlation was 0.996 ($P < 0.001$), with 95% CI for rho being 0.994–0.997. Kendall's tau was 0.964 ($P < 0.001$), with 95% CI for tau being 0.937–0.976, estimated using bias-corrected and accelerated bootstrap (500 iterations; random number seed: 978).

After charting V-iTIVA and V-CTP on the Bland–Altman plot, the bias or the mean of differences was −0.02, while the LoA (1.96 SD above and below the mean) were 0.58 and −0.63, respectively. The maximum allowed difference of 2 ml was much larger than the 95% CIs for LoA [Figure 2].

The Mountain plot was short tailed (−1.28 to 1.55) and centered over zero (0.01), indicating that the two methods are unbiased with respect to each other with very small differences between them [Figure 3].
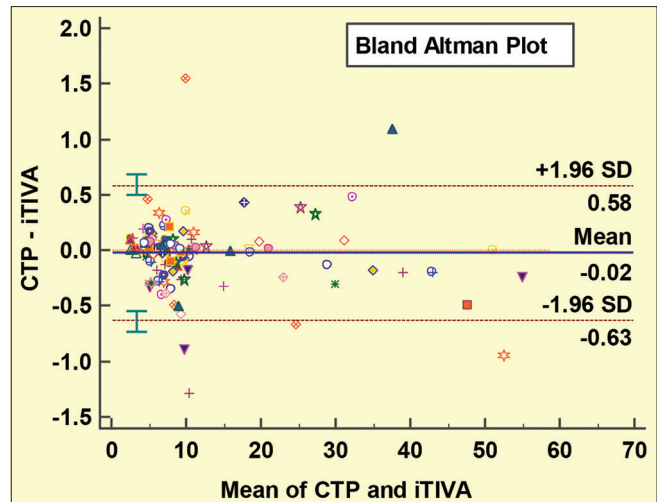
Figure 2: Bland–Altman plot (x-axis depicts the mean of conventional target-controlled infusion pump and iTIVA smartphone application values; y-axis depicts the difference between the propofol volume values calculated by CTP and iTIVA smartphone application). CTP = conventional target-controlled infusion pump, iTIVA = interactive total intravenous anesthesia, SD = standard deviation

Hypotension was observed in seven patients, which subsided with ephedrine boluses. No other hemodynamic perturbations were observed. BIS was maintained between 40 and 60 at all time points throughout surgery in all the patients.

Discussion

The range of values containing the true correlation coefficient with 95% probability was narrow, and both the correlation coefficients (rho and tau) demonstrated an excellent correlation between the volume of propofol actually infused by the CTP and that calculated by iTIVA for the same time periods.

The volume of propofol infused per corresponding time period by the two devices showed good agreement (Bland–Altman plot), which will allow us to convert any ordinary volumetric infusion pump into a TCI pump using iTIVA. Ramírez and Calvache,[7] in their study spanning 240 min of propofol infusion, found that to maintain a stable plasma/effect-site concentration during induction, a single infusion rate for propofol was required. However, to maintain a stable concentration throughout the 235 min of maintenance, between two and five changes in the infusion rate for propofol (mode = 4) were required. This corresponds to a mean of (1 + 3) readings per patient obtained by us during surgery lasting 120–180 min, since each time period of ours displayed a constant infusion rate during the entire time period. The first time period in each patient corresponded to induction and the remaining three/four time periods displayed three/four different rates per patient based upon the age, weight, height, and gender of that particular patient. Different time periods had different infusion rates set as per the Schnider
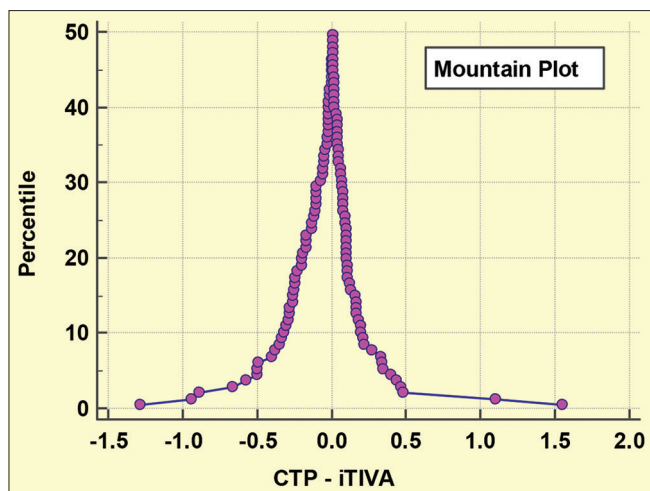
Figure 3: Mountain plot. CTP = conventional target-controlled infusion pump, iTIVA = interactive total intravenous anesthesia

pharmacokinetic model to maintain the desired effect-site concentration.

Muller *et al.*[13] compared manual versus target-controlled infusion techniques for propofol TIVA in gynecological laparoscopy patients and reported a pharmaco-economical advantage with TCI stemming from a 5 min earlier awakening. Conventional TCI pumps are technically complex, labor intensive, and expensive and require regular maintenance, storage space, and shifting to the patient site (OT/intensive care unit [ICU]) whenever required. Since technical failure accounts for majority of awareness episodes during TIVA, TCI pumps need a pre-use check-up as meticulous as the anesthesia workstation.[10,14] In contrast, an app-based TCI infusion system like iTIVA is likely to be used frequently in view of its easy accessibility, cost-effectiveness, and versatility (not equipment specific; cafeteria choice of drugs/pharmacokinetic models available), while maintaining the same standards of drug delivery and patient care, providing the best of both worlds: early awakening like TCI and accessibility, familiarity, and monetary benefits minus the tedious mathematical calculations (exponential polynomial equations) of manual infusions. In developing countries like India where financial constraints limit easy access to technology, the app-based TCI can be a cost-effective, user-friendly substitute for the conventional TCI pumps.

We selected the effect-site concentration over plasma concentration as a target because a user-defined target effect-site concentration is rapidly achieved by the TCI pump by manipulation of plasma propofol concentration around the target and existence of hysteresis between the plasma concentration and the clinical effect, affected by the temporal delay in equilibrium between plasma and effect-site (site of action in the central nervous system [CNS]).[3]

The rate of plasma/effect-site equilibration is governed by the cardiac output, cerebral blood flow, lipid solubility, and ionization of the drug. The time course of plasma/effect-site equilibration can be mathematically described by a first-order rate constant (k_{eo}), which defines the proportional change in each unit of time of the concentration gradient between the plasma and effect-site. Time to peak effect (1.0–2.4 min; median 1.6 min for propofol), a model-independent parameter, was used for k_{eo} estimation by Schnider *et al.*[4] to arrive at a value of 0.456 min^{-1}.

We selected the Schnider model over the Marsh model because as per a study by Absalom *et al.*[3] for an initial effect-site target concentration of 4 µg/ml, for a 70 kg patient, the initial propofol bolus will be 172 mg as per the Marsh model and 77 mg as per the Schnider model. Clinical ramifications of this much larger initial propofol dose include likely hemodynamic instability in most Indian patients. The Marsh model in effect-site targeting mode in CTP uses a k_{eo} of 0.26 min^{-1} (slower/smaller than the k_{eo} used with the Schnider model), resulting in much lesser degree of overshoot (~150% vs. 300% for Schnider model) of the estimated plasma concentration because the estimated rate of decline in plasma concentrations after a bolus is far slower with the Marsh model versus the Schnider model. However, the much larger V_1 value in the Marsh model results in much greater initial doses being administered in effect-site concentration mode. Another advantage of the Schnider model comprises adjusting doses and infusion rates according to patient age to circumvent hypotension in elderly and infirm cancer patients. A simulation study by Masui *et al.*[1] concluded Schnider model to be superior to Marsh, Schuttler, and Upton models for propofol.

Drug interactions have a significant influence on various anesthetic endpoints. New advisory devices incorporating these interactions, SmartPilot View (Drager Medical, Lubeck, Germany) and Navigator Suite (GE Healthcare, Helsinki, Finland), display both the kinetics of individual drugs and the combined interaction effects quantifying probabilities of consciousness and of sympathetic/motor response to noxious stimulation like laryngoscopy or skin incision.[15] iTIVA provides a similar Pharmacokinetics versus Pharmacodynamics (PK/PD) graphic display on the smartphone for complex combined interaction effects of analgesic and hypnotic drugs. Remifentanil, fentanyl, sufentanil, alfentanil, ketamine, lidocaine, and procaine are the analgesic options available. Propofol, dexmedetomidine, and midazolam fall under the endovenous hypnotic category in iTIVA.

Hsieh *et al.*[16] compared TCI and manual infusion of propofol as anesthesia for electroconvulsive therapy. For

intergroup comparisons, iTIVA Anesthesia Plus (the same smartphone-based app employed by us) was used for calculation of the predicted blood levels of propofol in the manual infusion group.

The major strength of our study is its novelty which could make TCI accessible to all institutions equipped with an ordinary volumetric infusion pump. No previous study has been reported in medical literature comparing the volume of propofol infused during identical time periods by conventional TCI pumps and smartphone-guided ordinary infusion pumps. Also, the observations were made under actual clinical conditions in oncosurgical patients Moreover, the Schnider model, currently adjudged the best pharmacokinetic model for effect-site concentration targeting, was compared. Although performed in oncosurgical patients, the study is generalizable to all patients undergoing TIVA.

A limitation is that this research project does not validate an algorithm-based pharmacological forecast versus an actual blood concentration measurement. We simply compared our mathematical forecast as estimated with the iTIVA algorithm versus that delivered by a conventional TCI pump, which makes it as good or bad as the dedicated CTP. Only the Schnider pharmacokinetic model was tested, leaving many other models like Gept and Marsh. Future prospective studies should be directed at taking a direct measurement of plasma propofol concentrations and comparing these values with the real-time forecasts of the pharmacokinetic model selected in iTIVA. In this way, other drugs like ketamine for which commercial TCI pumps do not exist can also be tested and used as target-controlled infusion.

Conclusion

The volume of propofol infused using TCI pump was similar to that calculated by iTIVA in identical time periods, confirming the clinical applicability of iTIVA in day-to-day anesthesia practice without compromising patient safety.

Acknowledgements

Key points

- The bias (-0.02) and limits of agreement (0.58 and -0.63) for the volume of propofol infused using the conventional TCI pump versus smartphone-based iTIVA find them to be in excellent agreement.
- iTIVA makes pharmacokinetic model-guided anesthetic drug delivery more economical by coupling with easily accessible volumetric pumps.

- Availability of a dedicated commercial TCI pump is no longer a prerequisite for reaping the benefits of target-controlled infusion.

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Conflicts of interest

There are no conflicts of interest.

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