Review Article

Target-controlled infusion – Past, present, and future

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Abstract

Target-controlled infusion (TCI) is a novel drug delivery system wherein a microprocessor calculates the rate of drug to be infused based upon the target plasma or effect site concentration set by the operator. It has found its place in the operation theaters and intensive care units (ICUs) for safe administration of intravenous anesthesia and analgosedation using drugs like propofol, dexmedetomidine, opioids, and so on. Operating a TCI device requires the user to have a primitive understanding of drug pharmacokinetics and pharmacodynamics and an awareness of the practical problems that can arise during its administration. Ongoing research supports their usage in other clinical settings and for various other drugs such as antibiotics, vasopressors, and so on. In this article, we review the underlying principles and commonly used drugs for TCI, the practical aspects of its implementation, and the scope of this technology in future. TCI technology is increasingly being used in the field of anesthesiology and critical care due to the myriad advantages it offers when compared to manual infusions. It is, therefore, essential for the reader to understand the relevant principles and practical aspects related to TCI technology, as well as to be aware of the commonly used TCI models.

Keywords: Compartment model, pharmacodynamics, pharmacokinetics, propofol, target-controlled infusion

Introduction

Target-controlled infusion (TCI) is a novel drug delivery system involving computer-controlled infusion of the drug according to a computerized model. Over the past two decades, this technology has been variously referred to as computer-assisted total IV anesthesia (CATIA),[1] titration of IV agents by computer (TIAC),[2] computer-assisted continuous infusion (CACI),[3] and computer-controlled infusion pump.[4] The term TCI was initially used by White and Kenny in their publication in 1992,[5] following which a consensus was reached in 1997 that the term TCI be adopted as the generic description of the technology.[6] Since then, around 60,000 TCI pumps have been sold in more than 90 countries around the world and are being used to provide intravenous anesthesia to millions of patients per year.[7]

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Material and Methods

For this review, reference articles were obtained through searches in PubMed, Medline, Ovid, and Google Scholar using search items "target-controlled infusion," "propofol TCI," "TCI for opioids," "dexmedetomidine TCI," "three compartment model of target-controlled infusions," "recent advances in target-controlled infusion." Articles were also identified from the reference list of searched articles. Only papers that were published in the English language were reviewed.

How TCI works

At the outset, one must understand the fundamental difference between TCI and total intravenous anesthesia (TIVA).

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TIVA, as the name suggests, involves the use of anesthetic agents solely by the intravenous route.[8] TCI is a technique of administering TIVA using pharmacokinetic (PK) models to maintain a steady plasma or effect site concentration of the anesthetic agents using an infusion device.[9]

The first TCI model was based on a bolus–elimination–transfer (BET) approach. In the BET model, a bolus is administered, which is calculated as the product of the target plasma concentration and the volume of distribution. This is followed by a maintenance infusion, which is equal to the drug's elimination rate and is calculated as the target plasma concentration times the systemic clearance. However, the BET model fails to maintain a steady drug concentration in plasma because it does not consider the transfer of drug from plasma to peripheral compartments over time, as is the case with most intravenous anesthetic agents. Hence, a three-compartment PK model was described, in which the drug distributes between the central compartment or plasma (V1) and two other compartments, namely, the rapidly equilibrating, well-perfused compartment or muscle group (V2) and slowly equilibrating, poorly perfused compartment or fatty tissue (V3). After a drug bolus is injected into the central compartment (V1), the plasma concentration of a typical drug follows an exponential decline in three distinct phases due to three events, which are illustrated in Figures 1 and 2.[10] Initially, during the first phase, the whole of the drug appears in V1. The drug concentration falls quickly because the drug distributes to V2 and also gets cleared. With transition to the second phase, the drug concentration in V1 falls below the drug concentration in V2. Since the drug flows down the concentration gradient, when the concentration in V1 is less than that in the small peripheral V2, the flow of the drug reverses. This reversal of flow accounts for the gradual slowing of the rate of fall in drug concentration during the second phase. Subsequently, the drug concentration in V1 falls below the drug concentration in both peripheral compartments. The drug returns to V1 from both V2 and V3 at this stage, slowing the rate of drug decrease further until equilibrium is reached. The attainment of equilibrium is dependent on the rate constants between the three compartments (k12- rate constant between V1 and V2, k21- rate constant between V2 and V1, k13- rate constant between V1 and V3, k31- rate constant between V3 and V1, k10- rate constant for drug elimination from the central compartment). V3 is usually larger than V1 because most anesthetic drugs are readily soluble in fat and tend to move out of the central compartment.

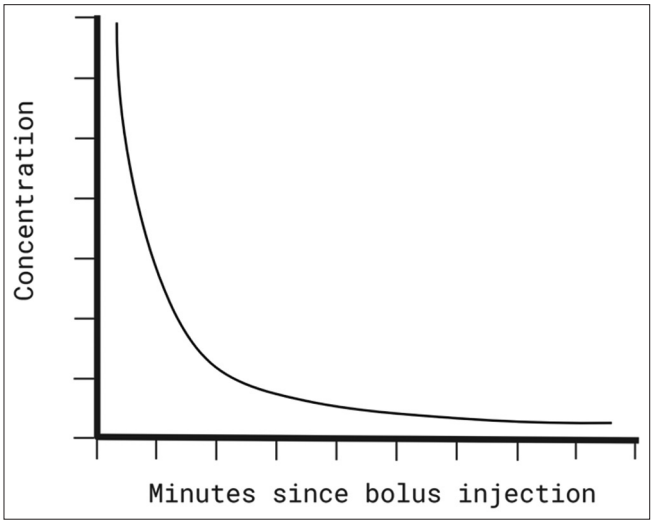

Figure 1: Plasma concentration of drug minutes after a bolus injection

The basic components of TCI are a microprocessor or a computer in which the PK/pharmacodynamic (PD) profiles of different drugs are fed into an algorithm and an infusion device [Figure 3].[11] Because real-time plasma or effect site concentration of intravenous anesthetic agents cannot be measured, the microprocessor uses these PK/PD algorithms to estimate the drug concentration. Once the clinician enters the target plasma or effect site concentration, the microprocessor calculates the amount of drug needed to achieve the target using the algorithms and patient covariates. It then directs an infusion pump to deliver the drug as bolus and maintenance infusion.

The TCI apparatus

There are three key elements of a TCI apparatus that one must be familiar with – the manufacturer, the model, and the mode. The manufacturer creates a TCI device, incorporating software for one or more of the various available drug PK (and recently, PD) models. These models can operate in either of the two modes – plasma mode or effect site mode [see Figure 4].

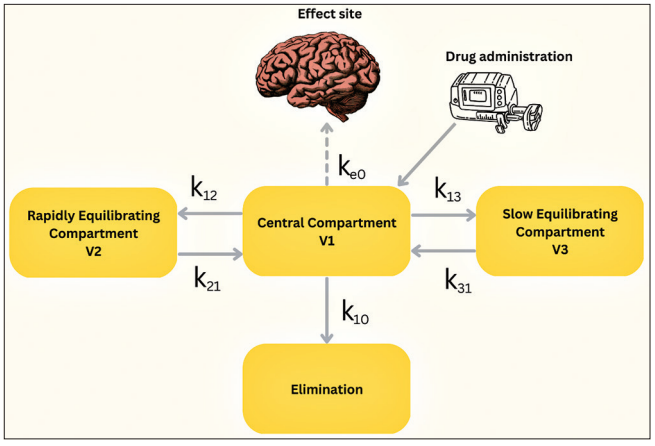

Figure 2: The three-compartment model
V1: central compartment, V2: rapidly equilibrating, well-perfused tissue group, V3: slowly equilibrating, poorly perfused tissue group, k12: rate constant between V1 and V2, k21: rate constant between V2 and V1, k13: rate constant between V1 and V3, k31: rate constant between V3 and V1, k10: rate constant for drug elimination from V1

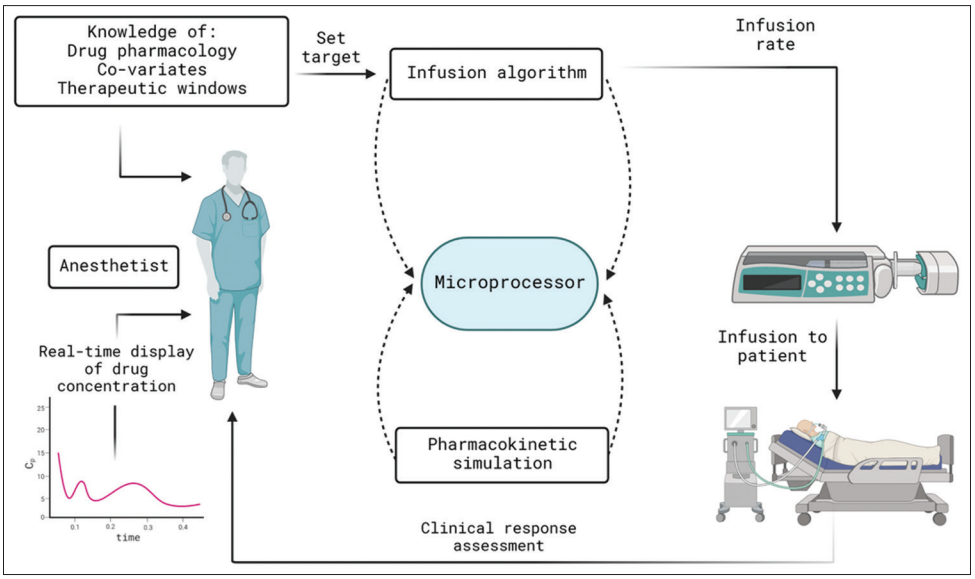

Figure 3: Components of TCI
TCI = target-controlled infusion

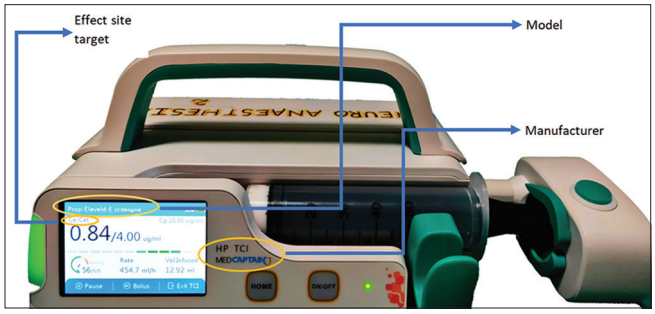

Figure 4: The three elements in a TCI apparatus
TCI = target-controlled infusion

The first-generation TCI systems came into practice in 1996 with the "Diprifusor™" module (AstraZeneca, Macclesfield, UK), which used the Marsh PK model for administration of only Diprivan™-labeled propofol.[12] Absalom *et al.*[7] estimated that approximately 25,000 such first-generation TCIs were sold from their inception till 2013, after which their production was stalled for want of second-generation open-system TCIs. They are "open" because the clinician is free to choose propofol as well as syringes from any manufacturer and to administer other select anesthetic drugs based on their PK models. However, a plasma–brain equilibration hysteresis is observed in these TCI systems, wherein there is a delay in the onset of the drug effect after commencement of the infusion, and also, the drug continues to produce the desired effect briefly after stopping infusion as the brain recovers slower than the plasma. This is the basis for adding an "effect site" to the existing three-compartment model. In this model, a trivial volume of drug flows to the effect site and is removed by a clearance process that is defined by a single rate constant, k_{e0}. The k_{e0} is the ratio of changes in the plasma and the effect site concentration gradients with each unit of time. The rate of plasma–effect site equilibration depends on several factors such as cardiac output, cerebral blood flow, plasma–effect site concentration gradient, and rate of drug transfer across the blood–brain barrier and is determined by the value of k_{e0}. Its optimum value is key to titrating the drug concentration in the brain, where the drugs actually produce their effect.[13] Since a direct estimation of effect site concentration of intravenous anesthetic agents is not possible, it can be indirectly inferred from measuring the clinical effects these drugs produce. The integrated PK/PD models thus created facilitate more precise drug delivery. Table 1 lists the commonly available models for various intravenous anesthetic agents.

TCI models for propofol

The Marsh model, one of the first TCI models of propofol, was adapted from Gepts three-compartment model and used a dataset of 150 patients.[14] It did not use allometric scaling, and body weight was the only covariate incorporated. The model did not include the rate constant k_{e0} when it was originally developed. Subsequently, a rate constant of 0.26/min[15] was used, which was later increased to 1.2/min[16] in some of the commercial TCI pumps, and it came to be known as the modified Marsh model. The faster k_{e0} enabled better manipulation of the plasma concentration when effect site targeting was used.

The much larger volume of central compartment in the Marsh model leads to a four-fold difference in the calculated peak plasma concentrations when a per kilogram bolus is administered. Since weight is the only covariate in Marsh model, the volumes of V1 and 2 are independent of patient age, and an identical volume of propofol is administered to

Table 1: TCI models for commonly used intravenous anesthetic agents

Drug	Models	Cut-offs for use	Fixed parameters	Variable parameters	Covariates
Propofol	Marsh (1991)[12]	More than 16 years	All rate constants	V1 (0.227 L/kg) V2, 3	Weight
	Schnider (1998)[19]	25–81 years	V1=4.7 L V3, k13, k31	V2 k12, k21 k10	Age, gender, Height, weight, LBM
	Eleveld (2018)[26]	0.5–88 years	-	-	Age, gender, Height, weight, fat-free mass, Comedication
	Kataria (1994)[23]	3–16 years, minimum weight 15 kg	All rate constants	V1, 2, 3	Weight
	Paedfusor (2003)[24]	1–16 years, 5–61 kg	All rate constants except k10	V1, 2, 3 k10	Weight
Fentanyl	Shafer (1990)[4]	-	All rate constants	V1	BSA
Remifentanil	Minto (1997)[38]	20–85 years	V3=5.42 L	V1, V2, and rate constants	Age, LBM
	Kim-Obara-Egan (2017)[39]	20–85 years	-	-	Age, weight, fat-free mass
Alfentanil	Maitre (1987)[45]	-	All rate constants except k31	V1, k31	Age, weight, gender
	Scott and Stanski (1987)[15]	-	All rate constants	-	No covariates
Sufentanil	Gepts (1995)[42]	-	All rate constants	-	No covariates
	Bovill (1984)[43]	-	All rate constants	V1	Weight
Midazolam	Greenblatt (2004)[60]	24–37 years, 60–79 years	Two-compartment model	-	Age, weight, gender
Ketamine	Domino (1982)[61]	-	All rate constants	V1, 2, 3	Weight
Dexmedetomidine	Dyck (1993)[30]	18–50 years	All rate constants except k10	-	Height
	Hannivoort (2015)[31]	20–70 years			Weight

TCI=Target-controlled infusion, V1: Central compartment, V2: Rapidly equilibrating, well-perfused tissue group, V3: Slowly equilibrating, poorly perfused tissue group, k12: Rate constant between V1 and V2, k21: Rate constant between V2 and V1, k13: Rate constant between V1 and V3, k31: Rate constant between V3 and V1, k10: Rate constant for drug elimination from V1

patients of all ages with the same body weight for a given target plasma concentration. Age is incorporated in the TCI pump only to ensure its usage in patients above 16 years of age, and not for drug titration. Also, the Marsh model tends to deliver a high induction dose of propofol when total body weight is used in the morbidly obese patients, resulting in significant hemodynamic instability. This is because the central compartmental volume does not increase significantly in obesity and the induction dose varies better with the lean body mass (LBM).[17,18] Conversely, it is seen that the maintenance dose requirements are better predicted using the total body weight and do increase significantly in the obese. This leads to a confusion regarding the ideal input weight while using the Marsh model for administration of propofol.

The Schnider model uses a small, fixed value of V1, which leads to attainment of a given target plasma concentration at lower induction doses, which may be inadequate to produce the desired clinical effect. Consequently, the Schnider model is recommended for use in the effect site target mode. Based on serial arterial samples from 24 study subjects, the Schnider model uses covariates such as patient age, gender, height, weight, and a gender-specific parameter known as LBM, which is used for calculating k_{10}. The LBM is derived using James formula,[19] which is given as follows:

$$\text{Males: LBM} = 1.1 \times \text{weight} - 128 \times (\text{weight/height})^2$$

$$\text{Females: LBM} = 1.07 \times \text{weight} - 148 \times (\text{weight/height})^2$$

This formula gives an accurate prediction of k_{10} in normal and moderately obese patients. However, for a body mass index (BMI) exceeding 42 kg/m^2 in males and 37 kg/m^2 in females, the calculated value is paradoxically lower, resulting in a large increase in k_{10}. Most TCI systems using the Schnider model, therefore, do not allow higher values of BMI. The major differences between Marsh, Schnider, and Eleveld models are summarized in Table 2.

Propofol models for pediatric patients

It is known that the PK of propofol differs significantly between adults and children.[20,21] A performance study of the adult

Table 2: Major differences between Marsh, Schnider, and Eleveld propofol models

	Marsh model	Schnider model	Eleveld model
Target	Plasma concentration (modified Marsh – effect site targeting)	Effect site (inaccurate in plasma–effect site- targeting mode)	Plasma concentration and effect site targeting
Covariates	Weight	Age, weight, height, gender, LBM	Fat-free mass (weight, height, sex)
Central compartment (V1)	0.228×weight (bigger than Schnider model)	4.27 L	6.28 × ($F_{central}$ [weight]/$F_{central\ [ref]}$)
Rate constants	Fixed	V2, Keo, K10 variable	Keo is a function of weight
Advantage	Faster induction due to large V1	Lower induction dose Reduced rate of adverse events	Universal PK/PD model Adjusted for concurrent opioid use
Disadvantage	Higher loading dose required	Inaccurate dose prediction in obese patients	Less evidence base for PD model Underrepresentation of 12–20 years age group in dataset

LBM=Lean body mass, PD=Pharmacodynamics, PK=Pharmacokinetic

Marsh model on 20 children receiving propofol showed that the model overpredicted plasma propofol concentration.[12] Hence, it is necessary to calculate and validate TCI models specifically adapted to the pediatric population. Two commercially used models for TCI administration of propofol in children are the Kataria and the Paedfusor models. The compartmental volumes in the Kataria model are a linear function of weight, whereas all the rate constants are fixed. In the prototype Paedfusor infusion system, the compartment volumes are linearly related to weight, the distribution rate constants are fixed, and the clearance is a power function of weight.[22,23] Kataria can be used from 3 to 16 years of age and has a minimum weight limit of 15 kg. Paedfusor can be used for children aged 1–16 and weighing between 5 and 61 kg.[24] Both the models have an overall acceptable performance in the age range of their respective dataset, but can result in administration of larger bolus doses than necessary when used in younger children due to overestimation of the initial volumes of distribution.[25]

Panacea for TCIs – One model for all?

The model proposed by Eleveld *et al.*[26] in 2018 is built on a robust scaffold of pooled data from 30 PK and five PD studies, including 1033 patients aged 0.5–88 years and weighing between 0.68 and 160 kg. The large number of covariates used makes it an almost universal model that is representative of the patient population a clinician encounters in everyday practice. The model uses a fat-free mass predictor described by Al-Sallami *et al.*,[27] which is a better size descriptor than LBM used in the Schnider model. The Eleveld model also incorporates adjustments for the concurrent use of opioids and is bispectral index (BIS) calibrated for providing both anesthetic and sedative doses of propofol. In clinical validation studies, the Eleveld model is found to have the lowest prediction error in adult patients compared to the Marsh and Schnider models.[28] In a prospective study involving 100 patients, Vellinga *et al.*[29] concluded that for PK, the Eleveld model showed a bias $< \pm 20\%$ in children, adults, and obese adults, but a greater bias (27%) in older subjects. Precision was < 30% in all groups. For PD, the bias was negligible (<5 BIS units) and the precision was close to 10 BIS units in all groups.

However, the proponents of the Eleveld model cited two chief limitations to their study. First, the BIS observations and hence the PD model have the weakest support in children and the elderly and no support in young children and adolescents. Second, patients from 12 to 20 years of age are underrepresented in the dataset. Hence, despite the well-perceived advantages, further evaluation and clinical validation of the model is needed to determine its safety and efficacy.

TCI models for dexmedetomidine

Dexmedetomidine has been administered by a TCI device both in the operation theater as well as in ICUs. The preliminary model proposed by Dyck *et al.* used height as the only covariate and suffered from inaccuracy at higher drug concentrations.[30] The Hannivoort model has recently been proposed as an optimized model of dexmedetomidine infusion, based on studies performed with 18 healthy volunteers, using weight as the only covariate.[31] Selection of healthy volunteers who are not otherwise on multiple medications avoids the effect of drug–drug interactions on PK/PD models and facilitates study of a stratified population with a wider age and weight range. The model also uses compartmental allometric scaling to adjust the intercompartmental clearances, which improves its prediction accuracy. Although BMI exceeding 30 kg/m^2 is an exclusion criterion in this study, the results include data from patients with BMI up to 29.3 kg/m^2. Because it is based on a small number of volunteers, with an age range of 20–70 years, its performance in children still needs to be validated. However, a subsequent study by Morse *et al.*[32] states that the Hannivoort model has good prediction accuracy in children above 1 year of age. In fact, using datasets from the well-known Hannivoort model and from four other dexmedetomidine models, namely, the Potts,[33] Cortinez,[34] Rolle,[35] and Talke[36] models, Morse *et al.*[32]

have synthesized a universal PK three-compartmental model, which applies to a wide age range, including preterm neonates and elderly patients up to 70 years. More recently, concerns that the Morse model tends to deliver a higher loading dose of dexmedetomidine have been raised, which can lead to hypertension and bradycardia. Hence, when using Morse model in a TCI system, care should be taken to limit the rate of infusion to safe levels.[37] Table 3 enlists the various dexmedetomidine models and their potential pros and cons.

TCI models for opioids

A number of PK/PD models have been developed for remifentanil, of which only the one proposed by Minto *et al.*[38] is commercially available. The Minto model is based on a dataset of 65 nonobese patients between 20 and 77 years of age. The use of LBM mathematically limits its use in patients with higher BMI. The calculations of the Kim–Obara–Egan model are drawn from nine published PK datasets, achieving nearly 20% accuracy in normal and obese individuals.[39] The model uses the equations published by Janmahasatian *et al.*[40] to calculate the fat-free mass, which is implemented for deriving the rate of remifentanil infusion. Eleveld *et al.*,[41] on the other hand, have recently developed a model for remifentanil that can be scaled to both adults as well as children. Their model incorporates a robust database of 131 subjects aged between 5 days and 85 years and weighing between 2.5 and 106 kg. The PK covariates include total body weight and fat-free mass, as described by Al-Sallami *et al.*[27] However, the PD measurements are available from adults from a single dataset and can be less accurate than the PK counterpart. The Eleveld model predicts a reduction in remifentanil clearance in young children due to immaturity of the nonspecific tissue esterase enzyme. This data needs to be confirmed in prospective studies.

Sufentanil has a much longer duration of action compared to remifentanil, hence increasing the risk of accumulation, postoperative respiratory depression, and delayed recovery when infused for a prolonged period. The common models available for sufentanil administration are those proposed by Gepts *et al.*[42] and Bovill *et al.*[43] In a clinical evaluation of the Bovill model, Zhao *et al.*[44] stated that recovery from sufentanil took approximately 6 min when an effect site concentration target of 4 ng/mL was set and around 7 min at 6 ng/mL.

The most common model used for alfentanil is the Maitre model. It is essentially a three-compartmental model using age, weight, and gender as the covariates.[45]

Practical aspects of TCI

Errors during TCI can lead to various complications, including underdosing and accidental overdosing of anesthetic agents. The National Audit Project 5 (NAP5) mentions lack of understanding of underlying pharmacologic principles and failure of drug delivery as the two most common causes of awareness during TIVA.[8] Following proper guidelines during administration of TIVA ensures a safe and standard practice and helps avoid complications.[8] A few commonly encountered setups for TCI use has been described in Supplementary File 1.

First, an appropriate PK/PD model should be chosen to serve the purpose. The commonly used target concentrations in routine practice are summarized in Table 4. A large peripheral vein should be cannulated and made accessible and

Table 3: Newer dexmedetomidine models for TCI

Model	Covariates	Advantages	Limitations
Hannivoort model (2015)[31]	Weight	Wide age range (20–70 years)	Not validated for infants and those with BMI exceeding 30 kg/m^2
Rolle model (2018)[35]	Lean body weight	Considers the role of hepatic blood flow in dexmedetomidine elimination	PK profile of dexmedetomidine may have been affected by the effect of general anesthesia and surgery and by the drug interactions with remifentanil and propofol
Talke model (2018)[36]	Weight	PD modeling was done taking into account dexmedetomidine-induced vasoconstriction, which was continuously measured during the study	Small patient cohort. Gender, age, and diseases could not be studied as covariates
Cortinez model (2010)[32]	Age, TBW	Applicable for obese and nonobese individuals	Small sample size limits covariate prediction accuracy

PD=Pharmacodynamics, PK=Pharmacokinetic, TCI=Target-controlled infusion, TBW=Total body weight

Table 4: Commonly used effect site target concentrations in routine practice

Drug	Effect site target concentration at induction	Effect site target concentration at maintenance	Effect site target concentration at eye-opening[7]
Propofol	4–6 μg/mL	Without opioids: 3–6 μg/mL With opioids: 2.5–4 μg/mL	Without opioids: 1.4–1.6 μg/mL With fentanyl: 1.2–1.4 μg/mL With remifentanil: 0.9–1.1 μg/mL
Remifentanil	2–6 ng/mL	Usually titrated to monitor the depth of anesthesia	-

visible throughout the infusion. The entire setup should be devoid of excess dead space, kinks, air bubbles, or leakages. Luer lock mechanisms prevent inadvertent disconnections and are desirable. An anti-siphon valve should be present on the drug delivery line to prevent overdosing from a damaged syringe. The presence of an anti-reflux valve ensures that there is no backflow of drug into the infusion tubing when multiple infusions are in use. It is also important to apply the blood pressure cuff to a limb other than the one used for administering TCI.

The pumps should have audible alarms for high line pressure, stopped infusion, empty syringe, interruption of the main electric supply, and low battery. A visual display should indicate the status of infusion. Accidental disconnections in the TCI apparatus can be detected in certain TCI pumps which are enabled with alarms for drop in line pressure. The "keep vein open" (KVO) feature, which allows a reduction in the infusion rate when the syringe is near empty, should not be used for propofol or remifentanil.

Performing a thorough pre-use check and meticulous labeling of syringes minimize the risk of drug errors. When multiple TCI pumps are in use, there should be a fixed sequence in which these pumps are fitted on the pole. The same concentration of drugs should be used for all patients for bolus as well as during infusion to avoid inadvertent administration of wrong drug dose. The TCI pump is started after appropriate programming, and both clinical response and the depth of anesthesia are monitored during the course of infusion.

Future directions

TCI pumps have recently made their way into the ICUs, given the many advantages they offer when compared to manual infusions. Adequate analgosedation is imperative for patients requiring intensive care, and the advent of TCI makes titration of opioids with a short half-life easy. It allows infusion at higher doses than are normally administered with traditional opioids, but minimizes cardiorespiratory depression or delayed recovery resulting from drug accumulation. Patient-controlled hydromorphone TCI offers satisfactory analgesia with moderate side effects in those undergoing cardiac surgeries.[46] TCI administration of alfentanil and remifentanil targeted to attain postoperative pain scores of less than 3 provides superior analgesia when compared to conventional syringe pump, without resulting in significant cardiorespiratory depression.[47]

Besides postoperative pain, patients in ICU are subject to various other sources of discomfort, such as clinical procedures, presence of noninvasive ventilation (NIV) mask or endotracheal tube, daily dressings and wound care, and others. In a select group of patients with NIV failure due to low tolerance who would otherwise have warranted an endotracheal intubation, TCI of propofol improves mask acceptance and patient comfort during NIV sessions in the ICU.[48] TCI administration of remifentanil and propofol is a safe choice for improving patient cooperation and preventing desaturation during fiberoptic bronchoscopy.[49,50]

Recently, administration of nonopioid analgesic adjuncts such as lidocaine, magnesium, ketamine, and so on via TCI pumps is also being explored as a possible option to decrease intraprocedural propofol or opioid consumption and its attendant side effects.[51]

Even more recent and still experimental, closed loop TCI systems facilitate the user to titrate drug concentrations by targeting a PD endpoint such as blood pressure, BIS, and so on. The computer forms a closed feedback loop by automatically adjusting the target concentration and hence the rate of infusion based on the patient's PD data. A closed loop vasopressor (CLV) controller for norepinephrine infusion, recently studied in 40 patients admitted to the ICU after they underwent cardiac surgery, results in significant reduction in postoperative hypotension.[52] Using a BIS-guided closed loop system for propofol allows attainment of different hypnotic–anesthetic levels while maintaining clinical stability in all stages.[53] BIS-guided automated systems decrease the dose of propofol used, are associated with fewer episodes of hypotension or hypertension, and significantly reduce postoperative cognitive dysfunction.[54] Since the PD targets most relevant to the anesthesiologist are the degree of hypnosis and the balance between nociception and anti-nociception, it is desirable that the drugs used should obtain stable clinical effects for both components. The technology required to realize this goal is known as multiple-input–multiple-output (MIMO). It uses BIS to titrate propofol doses and Analgoscore, which is based on the combination of heart rate and arterial blood pressure to administer remifentanil. When compared to manual infusion schemes, MIMO provides a superior control of hypnosis and analgesia as is inferred from the BIS and Analgoscore values.[55]

Ongoing clinical research also indicates the possibility of extending TCI technology to precise antibiotic dosing in the ICU. The simulation model proposed for TCI of piperacillin shows superior PK/PD profiles and a 30% reduction in total daily drug usage. For piperacillin, TCI is cost-effective, safe, and offers potential advantages when compared to continuous infusion or intermittent bolus dosing.[56] Recently, the standard therapeutic drug monitoring (TDM)–based regimen of vancomycin has been compared with an adaptive TCI (aTCI) system. Based on the Thomson model of vancomycin drug

dosage, the aTCI combines TCI with infrequent TDM sampling.[57] The study shows superior performance of aTCI for vancomycin administration in terms of PK/PD attainment and minimizing the potential toxic overshoot.[58]

The current usage of TCIs in the operation theater or ICU is primarily restricted to hypnotics and analgesics. The number of studies advocating their use for other drugs and in other clinical settings is limited. The patient numbers in the existing studies are small, and hence, they may be underpowered for some clinically relevant endpoints. At present, loading two different drugs such as propofol and remifentanil in the same syringe for TCI administration is not feasible due to differences in PK, pharmaceutical compatibility, and so on. Whether such syringes can be made commercially available in future is a matter of conjecture.[59] Majority of the TCI models in current use do not take into account the altered PK in the critically ill patient and the dynamic PK/PD changes during the course of treatment. Future expansion of the software models to different drugs and diverse patient populations such as pediatric, elderly, obese, and others are the order of the day.

Despite its perceived limitations, TCI technology holds promise for future use in the field of anesthesiology and critical care. As more anesthetists gain access to TCI systems, it is likely that their popularity and frequency of use in the operation theaters and ICUs will increase manifold. The environmental impact of inhaled anesthetics warrants a change in the current practice. TCI is one of the remedies to this predicament, and more research into the field of TCI and its widespread usage are cornerstones to a safer future.

Conclusion

TCI technology is a recent, yet invaluable addition to the anesthetist's armamentarium, enabling more accurate and safe infusion of intravenous anesthetic agents to patients in operation theaters and ICUs. A comprehensive understanding of the three-compartment model, plasma–effect site kinetics, and the interplay between patient covariates and drug pharmacokinetics is crucial for minimizing errors during TCI administration. Majority of the drug models in common use lack generalizability because their datasets are drawn from age- and sex-limited patient populations and are based solely on PK analyses. The Eleveld model, developed for the administration of propofol and remifentanil, is a universal PK/PD model that caters to a wide age and weight spectrum. Though preliminary studies yield optimistic data on its prediction accuracy, further clinical validation is necessary to ascertain the safety and efficacy of this model. Similarly, the Hannivoort model, recently proposed as an optimized model for dexmedetomidine infusion, awaits further performance evaluation, especially among the pediatric population. Besides the newer models of drug infusion, the TCI technology itself has undergone significant evolution since its inception. Recent developments such as the closed loop TCI, patient-controlled TCI, MIMO, and others are fertile areas of research, holding promise for the future. The incorporation of TCI technology into ICU has resulted in better NIV mask tolerance, improved patient cooperation during clinical procedures, cost-effective antibiotic usage, and superior postoperative analgesia. As the environmental concerns of inhaled anesthetic agents mount, it can be hoped that the TCI technology will permeate further into anesthetic practice and will be ubiquitously used in the days to come.

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Supplement 1: Commonly Encountered Case Scenarios for Administration of TCI in Routine Practice

Case 1: TCI in obese patient.

Case 2: TCI in elderly patient.

Case 3: TCI in a child.

Case 4: TCI for neurosurgery with intraoperative neurophysiological monitoring.

Case 5: TCI for laparoscopy with history of post-operative nausea and vomiting.

Case 6: TCI for sedation during endoscopy.

Case 1: Mrs. A, aged 42 years, has breast cancer and requires left modified radical mastectomy. She weighs 105kg, and her height is 164 cm. Her body mass index (BMI) is 39.1 kg/m^2. She has no other known comorbidities

Anesthetic technique

Induction of anesthesia for Mrs. A will be initiated with a target-controlled infusion (TCI) of remifentanil (Minto model) at an effect-site target of 4 ng/ml. After 2 minutes, effect-site targeted TCI of propofol will be started using the Eleveld PKPD model with a target of 2-4 mcg/ml. The infusions will be maintained to target BIS values of 40-50. Muscle relaxation during the surgery will be maintained with Inj. Vecuronium. The infusions will be stopped during skin closure. Mrs. A will be extubated after complete neuromuscular recovery, guided by the train of four (TOF) ratio.

Discussion

The Eleveld model for propofol is preferred in this patient over other existing TCI models, due to the following reasons:

- Marsh model: In this model, all volumes scale linearly with weight, leading to administration of very large induction doses.[1] and allow either plasma- or effect-site targeting. With effect-site targeting the goal is to achieve a user-defined target effect-site concentration as rapidly as possible, by manipulating the plasma concentration around the target. Currently systems are pre-programmed with the Marsh and Schnider pharmacokinetic models for propofol. The former is an adapted version of the Gepts model, in which the rate constants are fixed, whereas compartment volumes and clearances are weight proportional. The Schnider model was developed during combined pharmacokinetic–pharmacodynamic modelling studies. It has fixed values for V1, V3, k13, and k31, adjusts V2, k12, and k21 for age, and adjusts k10 according to total weight, lean body mass (LBM. This is of concern in obese patients, as is our case. Also, because age is not a co-variate, an identical volume of propofol is administered to patients of all ages with the same body weight for a given target plasma concentration.
- Schnider model: This model uses lean body mass (LBM) using James formula[2] for making drug calculations, which requires three input variables: total body weight, height, and gender. However, the formula does not apply to obese patients, where it yields paradoxically low values of LBM.
- Eleveld model: This model uses fat-free mass based on the Al-Sallami formula,[3] which is a better size-descriptor when compared to LBM. It requires the user to input patient demographic data, such as, gender, height, weight, and age. The software then calculates the drug infusion rates based on the data provided. The Eleveld model has been studied in a wide age and weight- range and has been found to deliver more accurate drug dosages than the pre-existing TCI models.

Case 2: Mrs. B, aged 78 years, has developed an incisional hernia, for which she requires hernia repair and meshplasty. She weighs 58 kg, and her height is 162 cms. She is a known hypertensive and diabetic for 10 years, controlled on oral medications

Anesthetic technique

The anesthetic plan for Mrs. B will include general anesthesia with TCI and placement of an epidural catheter. The epidural catheter will be secured at L2-L3 interspace and local anesthetic infusion will be started. Induction will be carried out with effect-site targeted TCI of remifentanil (Minto model) at an initial target of 4 ng/ml. After 2 minutes, effect-site targeted TCI of propofol will be initiated (Eleveld PKPD model) at the patient-individualized predicted EC50 of 2.27 mcg/ml (EC50: concentration needed to

attain BIS of 47). Muscle relaxation during the surgery will be maintained with TOF- guided doses of Inj. Vecuronium. Propofol and remifentanil infusions will be titrated to maintain BIS values between 40 and 50. The infusions will be stopped during skin closure, and Mrs. B will be extubated when she is awake, obeying commands, and with a TOF ratio of 0.95.

Discussion

Caution should be exercised when using TCI in elderly patients, as they often have altered pharmacokinetics, when compared to healthy, young individuals. Also, due to enhanced receptor sensitivity, standard doses of anesthetic agents tend to cause more profound pharmacodynamic effects in this patient population. Hence, these patients are prone to cardio-respiratory compromise at higher doses and warrant careful titration of drugs during induction and maintenance of anesthesia.

Improved cardiovascular stability can be attained by using a combination of moderately high doses of remifentanil (target concentration 6-8 ng/ml), and lower doses of propofol (target concentration 1.5-2.5 mcg/ml). Alternatively, a patient-individualized EC50 dose of propofol can be used, which is described as the effect-site concentration required to attain a BIS of 47. Induction of anesthesia in the elderly with TCI propofol should start at very low target concentrations and should gradually be increased in small steps every few minutes, to ensure cardiovascular stability. For further insight into the concept of EC50, the reader is advised to refer to the study conducted by Eleveld *et al*.[4]

Case 3: C is scheduled to undergo laparoscopic appendicectomy for acute appendicitis. He is 6 years old, weighs 18 kgs, and his height is 150 cms

Anesthetic technique

Initially, TCI remifentanil (Minto model) will be instituted at a target of 4 ng/ml. After 2 minutes, an effect-site targeted TCI of propofol will be started (Kataria model) at 4 ng/ml. The infusions will be titrated to clinical response. Muscle relaxation will be maintained with Inj. Atracurium throughout the surgery. The infusions will be stopped during commencement of skin closure.

Discussion

The pharmacokinetics of propofol vary significantly between adults and children, and adult models tend to overpredict the required doses of propofol in the latter group. The most commonly used TCI models for propofol in children are the Kataria and Paedfusor models. Kataria can be used from 3 to 16 years of age and has a minimum weight limit of 15 kg. Paedfusor can be used for children aged 1 to 16 years and weighing between 5 and 61 kg. Both the models have an overall acceptable performance in the age range of their respective dataset but can result in administration of larger bolus doses than necessary when used in younger children, due to overestimation of the initial volumes of distribution. The Eleveld general purpose model, as the name describes, is applicable over a wide age and weight range and can be used for infants and smaller children. The Minto model for remifentanil also can be used for children, without dose modifications.

Case 4: Mr. X, aged 54 yrs, weighing 72 kg, and 169 cms tall, requires resection of an intramedullary spinal cord tumor in the prone position. Intraoperative neuromonitoring (IONM) with somatosensory evoked potential (SSEP), transcranial motor evoked potential (tcMEP), and dorsal column mapping (DCM) are also planned during tumor resection

Anesthetic technique

Induction for Mr. X will be initiated with effect-site targeted TCI of remifentanil (Minto model) at an initial target of 4 ng/ml, followed by effect-site targeted TCI of propofol (Schnider model), at 2-4 mcg/ml. A single bolus dose of Inj. Vecuronium (0.10 mg/kg) will be administered to facilitate endotracheal intubation, prone positioning, and placement of head pins. Further doses of muscle relaxants will be avoided in order to obtain reliable neuromonitoring data during tumor resection. Intraoperative BIS will be maintained between 40 and 50. After completion of tumor resection and termination of IONM, vecuronium administration will be re-instituted. Propofol and remifentanil infusions will be stopped during commencement of skin closure.

Discussion

IONM during neurosurgeries facilitates identification and prevention of inadvertent injuries to crucial neural structures present in the field of surgery. It is vital to avoid usage of muscle relaxants during IONM, as they interfere with MEP readings. Routinely used inhalational agents decrease the amplitude and increase the latency of evoked potentials, hence hindering seamless neuromonitoring. Administration of TCI in neurosurgeries circumvents this problem, as the evoked potentials are minimally affected by the intravenous agents, when used in routine doses. The concurrent use of TCI and depth of anesthesia monitors decreases the risk of awareness during these surgeries.

Case 5: Mrs. Y, aged 35 yrs, has been admitted for undergoing laparoscopic tubectomy as a day care procedure. Her weight and height are 62 kg, and 165 cms respectively. She gives a past history of nausea and vomiting after undergoing fibroadenoma excision under general anesthesia 5 years ago and expresses concern regarding the same during her pre-anesthetic checkup

Anesthetic technique

The anesthetic plan for Mrs. X will comprise of TCI with propofol and remifentanil, given her increased risks of developing post-operative nausea and vomiting. An effect-site targeted TCI of remifentanil (Minto model) at an initial target of 4 ng/ml will be started. After 2 minutes, effect-site targeted TCI of propofol will be initiated (Schnider model) at 2 mcg/ml, which will be increased stepwise up to 6 mcg/ml over 3 minutes, to achieve target BIS values (40-50). A bolus of Inj. Atracurium (0.50 mg/kg) will be given to facilitate endotracheal intubation, followed by intermittent doses (0.10 mg/kg) at regular intervals. Intraoperatively, propofol and remifentanil infusions will be titrated to maintain BIS values between 40 and 50, without causing hemodynamic instability.

Discussion

The administration of intravenous anesthetic agents in day care procedures offers myriad advantages, such as reduced incidence of post-operative nausea and vomiting (PONV), lesser agitation during emergence, earlier recovery and discharge from hospital. Usage of TCI in such setups ensures maintenance of adequate depth of anesthesia and thwarts any possibility of intraprocedural awareness. The concurrent administration of dexmedetomidine allows considerable reduction in the doses of opioids and may even facilitate opioid-free anesthesia.

Case 6: Mrs. Z, aged 24 yrs, is planned for an upper gastrointestinal endoscopy for peptic ulcer workup. She weighs 54 kg and is 160 cms tall

Anesthetic technique

The endoscopy for Mrs. Z will be performed under sedation with an effect-site targeted TCI of propofol (Schnider model). The concentration of propofol will be titrated stepwise, from 1 mcg/ml up to 3 mcg/ml over 3 minutes, to achieve a state of deep sedation (Richmond Agitation and Sedation Scale score of -4). Supplemental oxygen will be provided with nasal cannula and Mrs. Z will be observed for episodes of hypotension, hypoventilation or apnea during the procedure.

Discussion

The use of propofol as a sedative agent during endoscopic procedures has been shown to possess multiple benefits, such as a rapid onset of action, predictable sedation depth and recovery time, and improved overall patient satisfaction.[5-7] Due to its narrow therapeutic window, inadvertent overdosage of the drug can culminate in cardio-respiratory compromise. The use of TCI technology ensures an adequate plane of sedation for the performance of endoscopy, without increasing the risks of hypotension or hypoventilation.

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