

# Total intravenous anaesthesia in neonatal surgery: a case series using the Eleveld model

Chan Weng Ken<sup>1</sup>, Sanah Mohtar<sup>2</sup>, Teo Shu Ching<sup>2</sup>

<sup>1</sup>Department of Anaesthesiology and Intensive Care, Hospital Canselor Tuanku Muhriz, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia; <sup>2</sup>Department of Anaesthesiology and Intensive Care, Hospital Umum Sarawak, Kuching, Malaysia

## Abstract

The practice of total intravenous anaesthesia (TIVA) target-controlled infusion of propofol (TCI-propofol) during neonatal surgery was limited by the lack of an appropriate pharmacokinetic-pharmacodynamic model and safety concerns. This is due to the physiological differences between the adult and neonate populations as well as inter-individual pharmacodynamic variation. Eleveld is the latest propofol pharmacokinetic model commercially available and the only model with the neonatal population in its algorithm design. We present a case series of neonates that underwent neonatal surgery under TIVA TCI-propofol utilising the Eleveld pharmacokinetic model. There was no observable clinically significant hypotension intra-operatively. Careful titration of TCI-propofol was necessary for timely emergence and maintaining haemodynamic stability. All neonates were extubated well post-operatively and recovered uneventfully. These demonstrated good and desirable anaesthetic effects using TCI-propofol without undesirable short-term side effects, especially clinically significant hypotension.

**Keywords:** Eleveld model, neonatal surgery, target-controlled infusion, total intravenous anaesthesia, tracheoesophageal fistula repair

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**Correspondence:** Dr. Sanah Mohtar, M.Med (Anaes), Department of Anaesthesiology and Intensive Care, Hospital Umum Sarawak, Jalan Hospital, 93586 Kuching, Sarawak, Malaysia. E-mail: shazsm75@gmail.com

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## Introduction

Propofol (2,6-diisopropylphenol) is a common anaesthetic and sedative agent in the adult population but less common in neonates due to the differences in pharmacokinetic and unknown safety profile, especially clinically significant hypotension.<sup>1,2</sup> There is limited pharmacokinetic data in the literature on total intravenous anaesthesia (TIVA) target-controlled infusion of propofol (TCI-propofol) and practice experience among neonates, which is likely attributed to the unavailability of the TCI model designed for neonates in commercial pumps. Eleveld is the latest propofol pharmacokinetic model commercially available and the only model with the neonatal population in its algorithm design.<sup>3</sup> This was made possible by incorporating data from 30 published studies, including from Allegaert *et al.*, who provided most of the data for neonates.<sup>4</sup> Hence, the Eleveld model can cater to a wide range of ages from 27 weeks post-menstrual age to 88 years old with a weight range 0.68–160 kg.<sup>3</sup> We present a case series of 6 patients who underwent neonatal surgery under TIVA using the TCI-propofol Eleveld model.

## Case presentation

This is a retrospective case series of 6 patients who underwent neonatal surgery using the TIVA TCI-propofol Eleveld pharmacokinetic model from November 2021 to January 2022 in a tertiary centre in Sarawak, Malaysia. Demographic details of all 6 patients are summarised in Table 1. We obtained written informed consent on the anaesthetic technique from the patients' parents before surgery.

Intraoperatively, standard monitoring of non-invasive blood pressure, pulse oximeter, and electrocardiogram was applied on patients before induction of anaesthesia. Induction with TCI-propofol (Fresofol 1% MCT/LCT) using the Eleveld model (effect-site target) was set up on Medcaptain HP TCI-Pump (Medcaptain Medical Technology, China), except for Baby-A, for whom plasma-site target infusion was selected. Intravenous (IV) remifentanyl was administered using Perfusor® Space infusion pump (B. Braun, Germany) utilising mass infusion rate. Propofol, remifentanyl, and maintenance IV drip were connected to two three-way stopcocks with antireflux valves to prevent backflow as standard practice. All patients received regional blockade as well as IV paracetamol as multimodal analgesia. Intraoperative vital parameters, including capnography and temperature, were monitored, and TIVA-TCI was titrated accordingly by the attending anaesthesiologist.

Table 1. Summary of all patients

Baby	Age (days)	CGA (weeks)	Weight (kg)	Diagnosis	Operation	IOTCI-PT (mcg/ml)	AT (minutes)	POO
A	2	37	2.41	TOF*	Right thoracotomy, ligation of TOF, primary anastomosis, direct laryngoscopy	2.0–4.0	330	Extubated in OT
B	1	33	1.39	Duodenal atresia	Laparotomy, duodenoduodenostomy	2.0–3.0	220	Extubated in OT
C	2	35	2.77	TOF	Right thoracotomy, ligation of TOF, primary anastomosis, direct laryngoscopy	2.0–3.8	460	Extubated in OT
D	1	37	2.75	Anorectal malformation	Colostomy	2.0–2.5	130	Extubated in OT
E	5	36	2.21	Omphalocele	Omphalocele minor repair	2.5–3.3	95	Extubated in OT
F	2	38	2.05	Anorectal malformation	Left transverse colostomy	2.5–3.3	155	Extubated in OT

CGA: corrected gestational age; IOTCI-PT: intraoperative TCI-propofol target; AT: anaesthetic time; POO: postoperative outcome; TOF: tracheoesophageal fistula; OT: operating theatre

Postoperatively, patients were extubated and monitored in the anaesthetic recovery area before being discharged to the ward or neonatal intensive care unit (NICU). The parents of the patients have consented to the publication of this case series. We describe the details of the first 3 cases as the subsequent 3 were managed similarly under TIVA-TCI with regional analgesia.

### Case 1

Baby-A, term at 37 weeks, was diagnosed with tracheoesophageal fistula (TOF) and was posted for emergency bronchoscopy, right thoracotomy, fistula ligation, and primary anastomosis at day 2 of life. Baby-A was noted to be cyanosed during feeding, and the chest radiograph showed a coiled orogastric tube. A provisional diagnosis of TOF was made. Antibiotic was started for presumed sepsis because of low-grade fever and possible aspiration. Systemic examination was unremarkable except for a small patent ductus arteriosus on the echocardiogram. Preoperatively, Baby-A was active with blood pressure (BP) 65/37 mmHg, heart rate (HR) 136 beats-per-minute (bpm), respiratory rate 30–36 per minute with oxygen saturation (SpO<sub>2</sub>) 100% on nasal-prong (NP).

During anaesthetic induction, TCI-propofol was commenced at 2 mcg/ml with IV remifentanil 0.1 mcg/kg/min aiming for spontaneous breathing. The airway was topicalised with lidocaine 1% before rigid bronchoscopy by a paediatric otorhinolaryngologist. Saturation was maintained via NP oxygen 2 L/min during the airway assessment. TOF type-C was confirmed, and Baby-A was then intubated at TCI-propofol 3 mcg/ml and remifentanil 0.1 mcg/kg/min. A caudal epidural was inserted as analgesia.

IV rocuronium was given before the surgical incision. TCI-propofol was maintained at 2.7–3.0 mcg/ml throughout the operation based on clinical parameters. Remifentanil infusion was kept at 0.1 mcg/kg/min, which was subsequently off, while epidural continued as the mainstay of analgesia. IV paracetamol was given as part of multimodal analgesia. Vital signs were stable throughout the operation, with BP in the range of 40–58/20–30 mmHg, HR 130–150 bpm, SpO<sub>2</sub> 95%–98%, and temperature at 35.8–37.2°C. IV fluid QSD 10% maintenance was kept at 12 ml/hour with a total of 15 ml/kg intermittent boluses of gelafluidin. Postoperatively, Baby-A was reversed and extubated to NP oxygen. The total anaesthetic duration was approximately 6 hours, with 62 mg (4.5 mg/kg/hour) of propofol infused. Baby-A was discharged to the NICU with an epidural infusion.

Baby-A recovered uneventfully in NICU, was discharged from NICU the following day, and went home after 2 weeks once feeding was established.

## Case 2

Baby-B was a 1.39-kg premature baby born at 33 weeks' gestation who had duodenal atresia and was posted for emergency laparotomy and duodenoduodenostomy on day 1 of life. TCI-propofol was started at 3 mcg/ml upon induction and increased to 3.2 mcg/ml during intubation, while remifentanil was started at 0.1 mcg/kg/min and increased to 0.2 mcg/kg/min before intubation. Baby-B was intubated after being paralysed with IV rocuronium. TCI-propofol was titrated from 3 mcg/ml to 2.5 mcg/ml, and remifentanil was kept at 0.1 mcg/kg/min. A caudal epidural was inserted and maintained with 0.1% ropivacaine 0.4 ml/hour.

Intraoperatively, BP was in the range of 60–70/32–36 mmHg, with HR 130–160 bpm, SpO<sub>2</sub> 99%–100%, and temperature 36.1–37°C. Total parenteral nutrition was continued at 8.7 ml/hour, with 14 ml/kg intermittent fluid boluses in total. The entire duration of anaesthesia was 3.5 hours, with an accumulative 17.7 mg (3.6 mg/kg/hour) of propofol. Postoperatively, Baby-B was extubated to room air and continued with the epidural infusion. Postoperative recovery in the NICU was uneventful, with stable vital signs and no metabolic acidosis (Table 2).

Table 2. Perioperative investigations of Case 1 and Case 2

	Case 1: Baby-A			Case 2: Baby-B		
	Preop	POD 1	POD 2	Preop	POD 1	POD 2
pH	7.26	7.29	7.3	7.43	7.38	7.35
HCO <sub>3</sub> <sup>-</sup>	22.9	17.3	21	24.3	23.9	23.1
BE	-4.9	-8.4	-3.8	-0.4	-0.1	-1.1
Urea (mmol/L)	4.6	4.5	2.75	3.1	2.6	-
Creatinine (umol/L)	75	70	54	27	52	-
Albumin (g/L)	38	-	33	39	32	-
ALT (U/L)	10	-	6	8	9	-
AST (U/L)	68	-	31	-	33	-

Preop: Preoperative; POD: postoperative day; HCO<sub>3</sub><sup>-</sup>: bicarbonate level in blood; BE: base excess; ALT: alanine transaminase; AST: aspartate aminotransferase

### Case 3

A premature, 2.77-kg infant born at 35 weeks' gestation presented at day 2 of life for bronchoscopy, fistula ligation, and primary anastomosis of TOF. During airway assessment, TCI-propofol was started gradually from 2 to 3 mcg/ml and remifentanyl 0.1–0.15 mcg/kg/min, maintaining spontaneous respiration. Intubation was achieved with TCI propofol 3.8 mcg/ml and remifentanyl 0.2 mcg/kg/min without muscle relaxant, as a Type-C fistula was confirmed near the carina. Caudal epidural ran at 0.7 ml/hour 0.1% ropivacaine following a bolus, with supplementation of IV paracetamol. Intraoperatively, TCI-propofol was slowly titrated down based on clinical parameters from 3 to 2 mcg/ml and remifentanyl 0.1 mcg/kg/min at the end of surgery. Muscle relaxant was only given once the fistula was ligated. There were no significant haemodynamic changes. Muscle paralysis was reversed, and the tracheal tube was removed after 15–20 minutes of stopping the TIVA. A total of 65.8 mg (3.1 mg/kg/hour) of propofol was given for 7 hours of anaesthesia. Postoperative recovery was uneventful, and the baby was discharged well.

### Cases 4–6

Babies D, E, and F were term babies who underwent colostomy and omphalocele repair with either transabdominal-plane block or local infiltration. Total propofol 4.3, 6.0, and 5.5 mg/kg/hour was infused respectively during the anaesthetic duration.

## Discussion

Propofol is widely used in adults as an anaesthetic and sedative agent. Several studies have demonstrated that propofol infusion may be administered safely despite its off-label usage in neonatal anaesthesia.<sup>1,4-6</sup> However, TIVA TCI-propofol usage in neonatal surgery is limited due to differences in pharmacokinetics and unknown safety profiles. In their attempt to find the optimal dose of propofol to provide sedation without side effects, De Kort *et al.* concluded that it was difficult to achieve and carried a high risk of hypotension.<sup>2</sup>

The Eleveld propofol pharmacokinetic model was recently introduced, enabling TCI-propofol to be used on a broader range of populations, including neonates.<sup>3</sup> This pharmacokinetic-pharmacodynamic model has also recently been validated in various groups of patients, including paediatric patients, with predictive precision of less than 30% and low population bias.<sup>7</sup> However, to our knowledge and literature search, there is a lack of reported use of the Eleveld model among neonates and its short-term side effects among this population. Before the Eleveld model, we used the Paedfusor model, a paediatric plasma-site targeting model with a lower limit of 1 year old and 5 kg. As such, Baby-A started with a plasma-site targeting of the Eleveld model for transitioning familiarity.

Our case series demonstrated good anaesthetic quality using TCI-propofol with the Eleveld model. For Baby-A and Baby-C, TIVA used during rigid bronchoscopy provided the surgeon with an optimal view while maintaining the anaesthesia with spontaneous ventilation amid endoscopic airway assessment. This is particularly useful as TIVA minimises the risk of inadequate anaesthesia due to inefficient delivery of volatile agents, especially during airway procedures, avoids theatre air pollution, and has fewer airway complications such as laryngospasm due to inadequate depth-of-anaesthesia (DOA).<sup>8</sup>

All cases in this series demonstrated that TCI-propofol with the Eleveld model allows stable haemodynamics with careful titration to clinical effects during induction, maintenance, and emergence.<sup>5</sup> Clinical vigilance, understanding of pharmacokinetic models of TIVA and interindividual variability in pharmacodynamic response are essential to minimise undesirable side effects such as clinically significant hypotension and delayed emergence.<sup>9</sup> Coadministration with remifentanyl infusion and targeting a lower concentration of propofol during maintenance is beneficial in the TIVA-TCI technique, especially in long surgery for neonates and small infants, considering their immature organs and elimination pathways.<sup>6,10</sup> Supplementation of regional blockade and paracetamol as multimodal analgesia also reduces TCI-propofol requirement.

Given immature brains in neonates and infants, the risk of under- or overdosage with TIVA-TCI, anaesthesia should be guided with DOA monitoring as recommended in older children and adults. However, correlation with processed electroencephalogram (EEG) was unavailable due to a lack of validated equipment for its use in small children. Recently, we have started using raw EEG waveform and non-proprietary EEG parameters monitoring as there is an increasing trend with the potential use of frontal EEG signals to guide the depth of anaesthesia in infants.<sup>11</sup> Nevertheless, to date, there is no validated electroencephalographic monitor to titrate propofol administration in this group of the population; in regards to the EEG power spectrum, target spectral edge frequency and density spectral array for anaesthesia, particularly in premature and term neonates as well as young infants remains unclear.<sup>11</sup> This might be due to substantial changes in EEG frequency and amplitude from birth to 3 years of age, in which delta-dominating waves with brief isoelectric intervals are common until 34 weeks post-menstrual age in premature infants. In contrast, theta and delta frequencies dominate in term neonates.<sup>12</sup> We also observed that most of our patients woke up spontaneously when the predicted effect-site concentration (Ce) was 1.5 mcg/ml, compared to 2.0 mcg/ml for predicted Ce-awake in older children.<sup>13</sup> They were subsequently extubated well and monitored closely. Postoperatively, all neonates recovered uneventfully, and no short-term adverse effects related to propofol were observed (Table 1). For Baby-A, metabolic acidosis resolved after fluid boluses and escalation of antibiotics as the baby was presumed to be septic due to aspiration pneumonia.

Additionally, TIVA is advantageous compared to volatile anaesthetics in reducing operating theatre pollution and is possibly an alternative in our practice to promote the reduction of greenhouse gases in the environment.<sup>14</sup>

Although our case series demonstrated stable haemodynamics among neonates, a larger sample size is needed to ascertain the safety profile of TIVA TCI-propofol in both the short and long term. The developmental milestones of neonates should be assessed and followed up as they grow to determine the long-term effects of TIVA TCI-propofol. A large sample size reduces the interindividual variability in pharmacodynamic response and provides the power to detect rare complications such as propofol infusion syndrome. Propofol use in patients born with metabolic disorders should be avoided as much as possible. We advise DOA monitoring for septic neonates with inotropes and exert caution when using TIVA or inhalation to avoid overdosage. We also highlight the potential use of frontal EEG signals to guide the DOA in neonates and young infant populations, especially to minimise the risk of hypotension.<sup>15</sup>

## Conclusions

The Paedfusor and Kataria models, being the more widely used TCI-propofol model in children, have their limitations in infants and neonates. The Eleveld model has overcome this by allowing infants and neonates weighing more than 680 g to be anaesthetised with TCI-propofol. Our case series has shown this model to have good and desirable anaesthetic effects without short-term adverse outcomes with careful titration, clinical vigilance, and an understanding of the pharmacokinetics of the drugs and models. However, a larger sample is needed to evaluate the short-term and long-term safety of TIVA among neonates using TCI-propofol.

## Declarations

### Informed consent for publication

The parents of all patients consented to the publication of the clinical data contained in this case series.

### Competing interests

The department received a small honorarium from Medcaptain Medical Technology for the data collected.

### Funding

None to declare.

### Acknowledgments

None to declare.

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