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Total intravenous anaesthesia in paediatrics.

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INTRODUCTION

Total intravenous anaesthesia (TIVA) refers to the use of intravenous anaesthetic agents for the induction and maintenance of anaesthesia. The history of intravenous anaesthesia dates as far back as 1657, when a quill was used to inject a cocktail of opium, wine, and ale intravenously into dogs. Since then, progress has been made as by 1855 hollow needles and syringes were available which made injecting drugs easier; in 1932 hexobarbitone was reported as the first rapidly acting intravenous anaesthetic drug; sodium thiopental was introduced for clinical use in 1932; chlordiazepoxide (the first benzodiazepine) was discovered in 1955; in 1966 ketamine was used in clinical anaesthesia; and by 1977, trials of propofol for induction and short-term maintenance of anaesthesia were underway. The French professor, Peirre-Cyprian Ore, was one of the first pioneers of intravenous anaesthesia. In 1872 he used chloral hydrate as an intravenous aesthetic in the treatment of 36 patients with tetanus; unfortunately the high mortality rate delayed further developments in the field (1).
Today we have advanced knowledge of the pharmacokinetics and pharmacodynamics of several intravenous agents with much better safety profiles; we are also able to control the plasma level of our intravenous agents quite accurately by using Target Controlled Infusion (TCI) models. However, TIVA is generally utilized only when a volatile anaesthetic agent is contraindicated (as in the case of known malignant hyperthermia) or not practical (as in the case of the shared airway). TIVA in the paediatric population is further complicated by the lack of certified depth of anaesthesia monitors for this age group.

My talk will focus on the pros and cons of TIVA related to paediatric anaesthesia and give a practical approach to TIVA.

What are the benefits of TIVA

The advantages of TIVA can be categorized according to patient factors, surgical factors and other:

Patient	Surgical	Other
Reduces PONV*	Shared airway.	Remote anaesthesia.
Reduces emergence delirium*	Neuro monitoring.	Patient transport.
Reduces perioperative respiratory complications*	Neuroanaesthesia.	Environmental concerns.
Not a trigger for MH and AIR.		
Reduces negative post op behavioural changes*		

We will consider the ones which are of relevance to paediatric patients specifically*

Patient factors: TIVA has been demonstrated to improve several clinical outcomes; the following is a description of some of the important ones.

- Postop nausea and vomiting (PONV): Several studies show that propofol TIVA has a beneficial effect on reducing the incidence of PONV (2-5). The Fourth

Consensus Guidelines for the Management of Postoperative Nausea and Vomiting, published in 2020, recommends the use of two pharmacological agents (5HT3 receptor antagonist and dexamethasone) and the consideration of propofol TIVA for the prevention of post operative nausea and vomiting in high-risk paediatric patients (6). The evidence shows that even sub-hypnotic doses of propofol combined with a single pharmacological agent (dexamethasone or 5HT3 antagonist) is superior to a single pharmacological agent alone in preventing post operative vomiting in children who have undergone tonsillectomies (4, 5). A 2018 systematic review and meta-analysis compared TIVA and inhalation anaesthesia in preventing anaesthesia related complications among paediatric inpatients undergoing strabismus surgery (7). Results showed that while the incidence of PONV was significantly less in the propofol TIVA group as compared to the inhalation anaesthesia group, the incidence of the oculocardiac reflex was much higher in the propofol TIVA group.

- Emergence delirium: A network meta-analysis looked at the emergence and recovery characteristics of common paediatric anaesthetic techniques; inhalation agents (Desflurane, Sevoflurane, Isoflurane and Halothane) and propofol TIVA (8). The outcome showed that propofol was clearly the superior technique with regards to PONV and emergence delirium and fared well with regards to emergence time, extubation time and time in the PACU.

- Perioperative respiratory complication: The beneficial effects of TIVA, particularly propofol, can be seen on its effect on laryngospasm and clearance of bronchial secretions.

    i) Laryngospasm: A randomised control trial looked at the effect of propofol and sevoflurane on the protective airway reflexes in children (9). Children were randomised to be anaesthetised by either sevoflurane or propofol at two different levels of hypnosis (BIS 40 and 60). Laryngeal irritation was induced by spraying water on the laryngeal mucosa and the evoked response was assessed by a blinded reviewer. Results showed that apnoea and laryngospasm occurred more frequently in the sevoflurane group irrespective of the depth of hypnosis.
    ii) Bronchial secretions: A randomized, double blinded study compared the effect of propofol/remifentanil TIVA to a sevoflurane/remifentanil anaesthetic on bronchial mucus transport velocity (BTV) (10). Twenty-two ASA 1 and 2 patients were included in this study and BTV was assessed by placing a drop of methylene blue in the right main bronchus 30 minutes after induction of anaesthesia. The position of the drop was then assessed bronchoscopically after 2, 4 and 6 minutes by a blinded observer. The TIVA group had a BTV of 4.8±2.1 (2.3-8.8) mm/minute, far superior to the Sevoflurane group which came in at 1.5±0.7 (0-2.3) mm/minute.

- Post op behaviour: Negative post op behaviour changes (NPOBCs) are common after surgery and anaesthesia; risk factors include preop anxiety and post op delirium. Changes in behaviour can manifest as anxiety, tantrums and disobedience, sleeping disorders or fear of doctors. A link between the type of anaesthesia and the development of NPOBCs has been demonstrated (11). A propofol TIVA reduces the incidence of NPOBCs.

Complications/Contraindications of TIVA

Major complications of TIVA include accidental awareness and complications related to the specific anaesthetic drug being used.

Awareness

Accidental awareness under general anaesthesia refers to intraoperative consciousness and post operative recall of intraoperative events. The 5th National Audit Project looked at accidental awareness under general anaesthesia (AAGA). The overall incidence of certain/probable AAGA was 0.005% (1:19 600); the highest incidence was during caesarean sections, 0.15% (1:670) and the average incidence of AAGA in children aged 3 to 16 years was 0.002% (1 : 61 100). As the NAP5 relies on patients spontaneously reporting events of AAGA, it is possible that the actual incidence among children is higher than 0.002%.

Factors contributing to AAGA during TIVA were reported as follows

- Equipment failures preventing the delivery of the intended anaesthetic dose: disconnection or clamping of the IV cannula, disconnection of the infusion tubing, pump failure due to low battery or infusion paused for too long, back tracking of anaesthetic drugs into intravenous fluid infusion tubing when the infusions are given through the same cannula, drug errors such as using the wrong drug or wrong concentration of the correct drug for the intended TIVA protocol.
- Starting an infusion too late or ending the infusion too early when neuromuscular blocking agents are used.
- Initiating an infusion prior to transporting a patient to theatre or after surgery for transport and treatment elsewhere.

Notably, fewer cases of AAGA were reported when a TCI based TIVA was used as compared to non-TCI infusions. Contributors to this were that lack of a loading dose and use of a low dose fixed rate infusion.

Monitoring depth of anaesthesia in the paediatric population is challenging. Several publications have demonstrated that using processed electroencephalograph (EEG) monitors (such as BIS or Narcotrend) may improve hemodynamic stability, reduce intraoperative drug consumption, shorten awakening time, and reduce time in the PACU (12-14). However, their ability to monitor depth of anaesthesia is unreliable in the paediatric population as the EEG changes as the brain develops. EEG activity stabilizes around twelve years of age (15). Studies have also shown that BIS values vary depending on age, with older children (above five years of age) having lower BIS

values than younger children (aged one to five years) (16), and that BIS values may actually increase at deeper planes of Sevoflurane anaesthesia (17).

Propofol based TIVA should be used with caution if there is an increased risk of propofol related infusion syndrome, mitochondrial disease, hemodynamic instability, or significant cardiac dysfunction.

Propofol related infusion syndrome

This is a rare, but potentially fatal complication occurring in both children and adults. The pathophysiology of propofol infusion syndrome is not fully understood, but theories put forward so far suggest that propofol affects mitochondrial function and ATP production (18). The primary features of propofol infusion syndrome are metabolic acidosis, ECG changes and rhabdomyolysis. Additional findings can include cardiac failure, AKI, hyperkalaemia, lipidaemia, fever, elevated liver transaminases and serum lactate. Risk factors for developing propofol infusion syndrome are large cumulative dose of propofol (more than 5mg/kg/hour or more than 48hours of infusion), critical illness (traumatic brain injury) and use of inotropes and steroids.

Paediatric TCI models

TCI models are essentially infusion protocols which are based on pharmacokinetic algorithms for a specific drug. These algorithms consider the patients age, height, weight, and gender, and calculates the expected blood concentration for the drug being administered. The algorithm calculates the infusion rate based on a three-compartment model, with the intention of maintaining a stable plasma concentration. The three compartments can be described as follows:

V_1 : The central compartment. This is where the drug is delivered to and eliminated from, it is also regarded as the initial volume of distribution.

V_2 : This compartment represents well perfused organs and tissues; and is also called the fast redistribution compartment as drugs rapidly distribute between V_1 and V_2.

V_3 : Tissues with poor blood supply make up this compartment and it is therefore referred to as the vessel poor or the slow compartment.

Volume of distribution (Vd) relates the total amount of drug administered to the measured plasma concentration and can be calculated as follows:

Vd (L) = Amount of drug given (mg) / Plasma concentration of the drug (mg/L).

The sum of V_1, V_2 and V_3 is the volume of distribution at steady state, i.e., the point at which the transfer of drug between the compartments is equal. Drug elimination and transfer between compartments is described using rate constants which are represented by the letter *k.*

k_{10} is the elimination rate constant for drugs in the central compartment (the subscripts refer to the compartments the drug is moving from and where it is going to).

k_{12} is the rate constant for the transfer of drugs from V_1 to V_2 and k_{21} is the rate constant for the transfer of drugs from V_2 to V_1. Similarly, there are rate constants for the vessel poor compartment and they are represented as k_{13} and k_{31}.

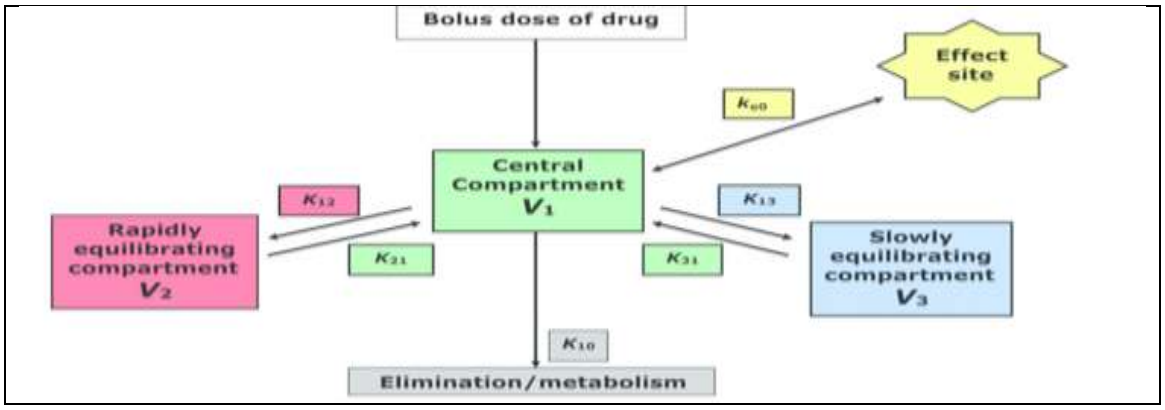

Image 1: *The three-compartment model*

Additional concepts that need to be understood is that of clearance, elimination half-life and context-sensitive half-time. Clearance refers to the volume of blood from which the drug is eliminated per unit time. While elimination half-time is the time it takes for the drug concentration in blood to decrease by 50%. For these reasons, if an infusion of a drug is given at a fixed rate without a bolus, it would take 5 half lives of that drug for plasma levels to reach steady state (19).

Context-sensitive half-time (CSHT) refers to the time a drugs plasma concentration takes to decrease following an infusion (the context being the duration of the infusion). This phenomenon occurs because the drug distributes from the central compartment to the vessel rich and vessel poor compartments during an infusion, and when the infusion is stopped the drug returns from the peripheral compartments to the central compartment from which it is eliminated. For example, fentanyl will have a short CSHT when given by infusion over a short period, but this dramatically increases as the duration of the infusion increases.

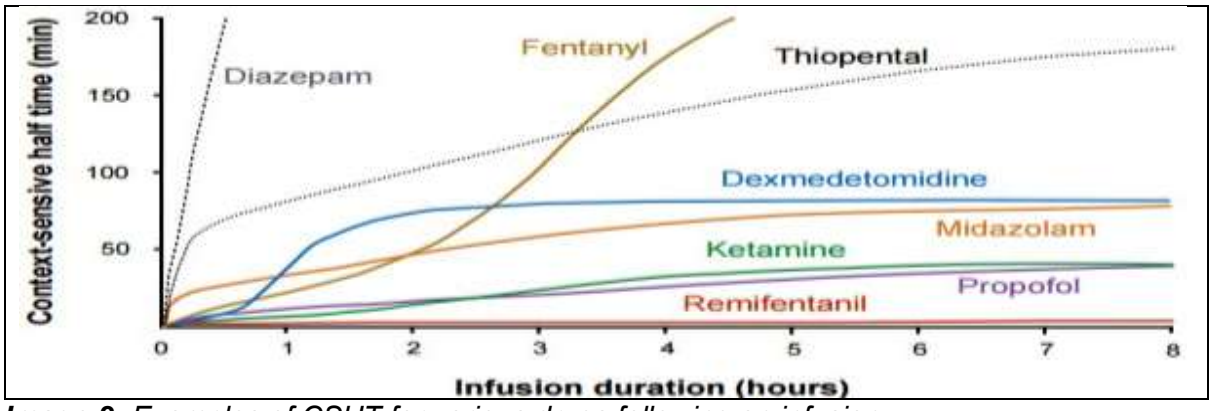

Image 2: *Examples of CSHT for various drugs following an infusion*

It should be noted that an increase in Vd or a reduction in clearance (or both) will result in an increase in the elimination of a drug.

Developing a TCI model that works correctly across all age groups is challenging as drug pharmacokinetics change as we grow. Two simple examples of this would be volume of distribution and clearance.

Factors affecting Vd can be divided into drug properties and patient factors. Drug properties influence protein and tissue binding; and include size of the molecule, its charge, pKa, and lipid/water partition coefficient. Patient factors include age, gender, body composition (muscle vs fat), hydration, distribution of water (for example oedema, effusions, ascites, and pregnancy) and extracorporeal sites of distribution (such as circuit, filters, and oxygenators). As such, Vd for a given drug can vary markedly from the neonatal period through to adulthood.

Clearance involves the processes of metabolism and excretion. A major factor affecting metabolism and excretion is organ maturity which develops as we grow.

Propofol has been extensively studied in the paediatric population and several attempts at designing a TCI model for the paediatric population have been made (Paedfusor, Kataria, Marsh, Short, Rigby- Jones, Coppens, Saint-Maurice, Shangguan, Murat, Schüttler and Eleveld). The most widely used models are Paedfusor and Kataria. The effectiveness of these two models has been compared in a prospective, double blinded, randomized control trial involving 38 patients aged 3 to 12 years (20). Results show that they are equivalent with regards to success rate of induction and induction time; however, a statistically significant difference lies in the plasma concentrations at recovery, with the Kataria group being lower than the Paedfusor group (1.5*u*g/ml ±0.1 versus 1.6*u*g/ml ±0.1, *p* 0.01). Recover time was also better in the Kataria group (14.6 minutes ±2.3 versus 15.1 minutes ±2.5, *p* 0.51).

At least three studies have looked at the ability of the various propofol TCI models to accurately predict blood plasma levels of propofol in paediatric patients (21-23). In all studies performance was assessed by calculating a prediction error (PE) for the different TCI models. Median prediction error (MDPE) assessed accuracy and a value of zero indicated greater accuracy. Median absolute prediction error (MDAPE) assessed precision and a value of zero indicated greater precision.

The table below compares the results of these studies for the commonly used TCI models:

Model	**Hara et al (21)**		**Coppens et al (22)**		**Sepúlveda et al (23)**	
	MPDE(%)	MPADE(%)	MPDE	MPADE	MPDE	MPADE
Paedfusor	-27.3	27.9	10.4	19	5.0	22.8
Kataria	-8.3	17.9	31.3	34.1	8	21.1
Marsh	-28.6	29.9	-1.3	15.9	-20.1	23.6
Short	-10.5	17.5	17.0	23.1	5.4	18.2
Schüttler	-19.9	21.3	10.2	21.8	NA	NA

Results varied across the studies, however Hara et al and Sepúlveda et al determined that the Short model performed the best. TCI models are developed for specific patient groups, therefore a possible explanation for the variable results seen above would be differences in populations studied such as age, sex, height, weight and possibly ethnicity. The Eleveld model was created by incorporating data from several studies. The patient population was therefore much bigger and variable, representing patients from the neonatal period up to adulthood and patients with comorbid conditions such as obesity, liver disease, cancer, and alcoholism. The Eleveld model was prospectively validated in children, adults, elderly patients and obese adults (24). It performed well across all groups except elderly patients: the MDPE for children was -4.42% and the MDAPE was 16.8%.

Adjuncts

Propofol does not have any analgesic properties and additional drugs are required for this reason. Options available are regional anaesthetic techniques and intravenous (IV) agents.

Among the IV agents are remifentanil, ketamine and dexmedetomidine.

Remifentanil is an excellent adjunct to a propofol based TIVA as it is a potent analgesic agent and has a short context sensitive half-life. TCI models do exist for it, but it can also be administered as a constant infusion or bolus dose for when intense analgesia is needed for a brief period (for example blunting the intubation response). The Minto model is the only commercially available TCI model for remifentanil. It uses the patients age, sex, weight, and height to calculate the lean body weight. Unfortunately, it cannot be used in children less than 12 years or less than 30 kgs body weight. The recommended infusion rate is 0.1 to 0.5ug/kg/min and boluses of 3ug/kg have been used for tracheal intubation without a muscle relaxant (25). Bradycardia should be monitored for, and boluses should be given over 30 seconds.

Some clinicians combine propofol and remifentanil in the same syringe (the concentration of remifentanil varying from to 2.5 to 5 to 10ug per ml of propofol) depending on the clinical situation. However, this practice is not endorsed by regulators, is not practical when individual agent titration is needed and is not recommended for children under ten kilograms.

Ketamine is a versatile drug with a favourable pharmacodynamic profile. It is both analgesic and hypnotic and can be administered via multiple routes. It can therefore be used for premedication, as an induction agent, for procedural sedation and as an analgesic adjunct during general analgesia (26). When used as part of a propofol TIVA, the recommended infusion rate is 0.1 to 2.5mg/kg/hour, bearing in mind that ketamine does accumulate during prolonged procedures.

Dexmedetomidine is both sedative and analgesic; it can be administered nasally (40% bioavailability), buccal (81% bioavailability) and orally (16% bioavailability). It is not yet licensed for use in paediatric patients, however studies have shown its beneficial effect in a variety of situations, including awake craniotomies, open inguinal hernia repairs in neonates when combined with a caudal, and sedation in the out of theatre environment (27). Bolus doses vary depending on age, with doses as high as 3ug/kg

being used in neonates. Heart rate and blood pressure can decrease by as much as 30% after a loading dose of 1ug/kg of dexmedetomidine in children; these hemodynamic changes are partly attenuated when 2mg/kg of ketamine is co-administered (28). As the side effects of dexmedetomidine are dose dependent and its use in paediatrics is still “off label”, it would be wise to use it as an adjunct rather than a sole analgesic/hypnotic agent. A sensible regime would be a loading dose of 0.5 – 1ug/kg over 20 minutes, followed by an infusion of 0.2-0.5ug/kg/hour. TCI models do exist for dexmedetomidine, but they are yet to be validated in the paediatric population.

An approach to paediatric TIVA

In 2019 the Association of Anaesthetists and the Society for Intravenous Anaesthesia published guidelines for the safe practice of TIVA (29). These guidelines are not specific to paediatric anaesthesia, but the do provide a framework for the junior anaesthetist who is new to TIVA.

Getting started…..

There are a few considerations that need to be addressed before embarking on a TIVA:

Firstly, how are you going to establish IV access in your patient? An older child may cooperate for the insertion of an IV canula, however younger children may find this distressing; this is further complicated if the child has poor peripheral veins as in the case of the obese. Premedication with a sedative and early application of a local anaesthetic cream will greatly facilitate this process.

Provided that there are no contraindications to volatile agents, an inhalation induction can be performed and then changed to TIVA once IV access is obtained.

We need to establish whether propofol is safe to use? Mitochondrial myopathy is an important contraindication to its use.

How are you going to deliver propofol? An infusion pump (with an appropriate TCI model) will be needed.

- Use Paedfusor for children aged 1 to 16 years and weighing 5 to 61 kg.
- Use Kataria for children aged 3 to 16 years and weighing 15 to 61 kg.

Target a plasma site concentration of 3 to 6ug/ml.

If your infusion pump does not have TCI capabilities, there are two manual infusion regimes you can use for propofol:

- McFarlan regimen, based on Kataria pharmacokinetics and used in children aged 3 to 11 years. Will maintain blood plasma concentrations of 3ug/ml.
- Steur regimen, for children aged 0 to 3 years.

McFarlan propofol infusion regimen

Bolus dose	2.5mg/kg
Infusion rates	mg/kg/hour
0-15 minutes	15
15-30 minutes	13
30 – 60 minutes	11
1 – 2 hours	10
2 – 4 hours	9

Steur propofol infusion regimen starts with an induction dose of 3-5mg/kg across all age groups, then an infusion rate as shown below:

Age	0-10min	10-20min	20-30min	30-40min	40-100min	>100min
0-3months	25*	20	15	10	5	2.5
3-6months	20	15	10	5	5	2.5
6-12months	15	10	5	5	5	2.5
1-3years	12	9	6	6	6	6

*mg/kg/hour

Consider whether depth of anaesthesia monitoring can be employed during the anaesthetic. No monitor is applicable to children less than 1 year and processed EEG monitors are based on data from adult studies. Nevertheless, it does provide an additional tool we can use to prevent awareness during TIVA. If a BIS monitor is used aim for a value of 40 -60.

Add an adjunct, either remifentanil, ketamine or dexmedetomidine together with a regional anaesthetic technique if possible.

Before we conclude, what about the obese child?

Obesity adds to the challenges of TIVA in the paediatric patient as it is associated with an increase in perioperative adverse respiratory events and makes dosing of our anaesthetic agents difficult. Incorrectly dosing anaesthetic agents can lead to problems such as accidental awareness, hemodynamic instability, and delayed emergence. The following recommendations are made for dosing of some common anaesthetic agents in the obese child(30):

Drug	**Loading dose**	**Maintenance dose**
Propofol	IBW	TBW or ABW
Etomidate	LBW	
Ketamine	IBW	
Benzodiazepines	ABW/LBW	IBW
Remifentanil	LBW	LBW
Alfentanil	LBW	LBW
Paracetamol	LBW	
Ibuprofen	LBW	

(IBW, ideal body weight. TBW, total body weight. ABW, adjusted body weight. LBW, lean body weight.)

Formulae:

IBW can be calculated in several ways.

Firstly, IBW= BMI at 50^{th} percentile x height^2 (in meters).

Age < 1 year, IBW (kg) = 0.5 x (age in months + 9).

1 – 4 years, IBW = 2 x (age in years + 5).

5 – 14 years, IBW = 4 x age in years.

LBW, or ABW, considers the increase in organ mass that occurs with obesity and is calculated as follows:

LBW (or ABW) = IBW + 0.3(TBW – IBW).

CONCLUSION

There are clear benefits for the use of TIVA in the paediatric population and few complications which can be avoided by adequate preparation and close attentiveness. TCI models, while not perfect, reduce the need for manual calculations and the associated errors. Adequate training, use of depth of anaesthesia monitors and having a departmental protocol/set of standards will improves the quality of our TIVA techniques and the clinician's confidence in providing TIVA to children.

REFERRENCES

1. Sear JW. When and How Did It All Begin? A Brief History of Intravenous Anesthesia. In: Absalom AR, Mason KP, editors. Total Intravenous Anesthesia and Target Controlled Infusions: A Comprehensive Global Anthology. Cham: Springer International Publishing; 2017. p. 3-8.
2. Tramèr M, Moore A, McQuay H. Propofol anaesthesia and postoperative nausea and vomiting: quantitative systematic review of randomized controlled studies. Br J Anaesth. 1997;78(3):247-55.
3. Sneyd JR, Carr A, Byrom WD, Bilski AJ. A meta-analysis of nausea and vomiting following maintenance of anaesthesia with propofol or inhalational agents. Eur J Anaesthesiol. 1998;15(4):433-45.
4. Erdem AF, Yoruk O, Silbir F, Alici HA, Cesur M, Dogan N, et al. Tropisetron plus subhypnotic propofol infusion is more effective than tropisetron alone for the prevention of vomiting in children after tonsillectomy. Anaesth Intensive Care. 2009;37(1):54-9.
5. Erdem AF, Yoruk O, Alici HA, Cesur M, Atalay C, Altas E, et al. Subhypnotic propofol infusion plus dexamethasone is more effective than dexamethasone alone for the prevention of vomiting in children after tonsillectomy. Paediatr Anaesth. 2008;18(9):878-83.
6. Gan TJ, Belani KG, Bergese S, Chung F, Diemunsch P, Habib AS, et al. Fourth Consensus Guidelines for the Management of Postoperative Nausea and Vomiting. Anesthesia & Analgesia. 2020;131(2):411-48.
7. Scheiermann P, Herzog F, Siebenhofer A, Strametz R, Weberschock T. Intravenous versus inhalational anesthesia for pediatric inpatient surgery - A systematic review and meta-analysis. J Clin Anesth. 2018;49:19-25.
8. Guo J, Jin X, Wang H, Yu J, Zhou X, Cheng Y, et al. Emergence and Recovery Characteristics of Five Common Anesthetics in Pediatric Anesthesia: a Network Meta-analysis. Molecular Neurobiology. 2017;54(6):4353-64.
9. Oberer C, von Ungern-Sternberg Britta S, Frei Franz J, Erb Thomas O. Respiratory Reflex Responses of the Larynx Differ between Sevoflurane and Propofol in Pediatric Patients. Anesthesiology. 2005;103(6):1142-8.
10. Ledowski T, Paech MJ, Patel B, Schug SA. Bronchial Mucus Transport Velocity in Patients Receiving Propofol and Remifentanil Versus Sevoflurane and Remifentanil Anesthesia. Anesthesia & Analgesia. 2006;102(5).
11. Stipic SS, Carev M, Kardum G, Roje Z, Litre DM, Elezovic N. Are postoperative behavioural changes after adenotonsillectomy in children influenced by the type of anaesthesia?: A randomised clinical study. European Journal of Anaesthesiology | EJA. 2015;32(5):311-9.
12. Sargin M, Uluer MS, Ozmen S. The effects of bispectral index monitoring on hemodynamics and recovery profile in developmentally delayed pediatric patients undergoing dental surgery. Pediatric Anesthesia. 2015;25(9):950-5.
13. Weber F, Walhout LC, Escher JC. The impact of Narcotrend™ EEG-guided propofol administration on the speed of recovery from pediatric procedural sedation—A randomized controlled trial. Pediatric Anesthesia. 2018;28(5):443-9.
14. Weber F, Pohl F, Hollnberger H, Taeger K. Impact of the Narcotrend Index on propofol consumption and emergence times during total intravenous anaesthesia with propofol and remifentanil in children: a clinical utility study. Eur J Anaesthesiol. 2005;22(10):741-7.
15. Eisermann M, Kaminska A, Moutard ML, Soufflet C, Plouin P. Normal EEG in childhood: From neonates to adolescents. Neurophysiologie Clinique/Clinical Neurophysiology. 2013;43(1):35-65.
16. Wang F, Zhang J, Yu J, Tian M, Cui X, Wu A. Variation of bispectral index in children aged 1–12 years under propofol anesthesia: an observational study. BMC Anesthesiology. 2019;19(1):145.

17. Rigouzzo A, Khoy-Ear L, Laude D, Louvet N, Moutard M-L, Sabourdin N, et al. EEG profiles during general anesthesia in children: A comparative study between sevoflurane and propofol. Pediatric Anesthesia. 2019;29(3):250-7.
18. Hemphill S, McMenamin L, Bellamy MC, Hopkins PM. Propofol infusion syndrome: a structured literature review and analysis of published case reports. Br J Anaesth. 2019;122(4):448-59.
19. MANI V, MORTON NS. Overview of total intravenous anesthesia in children. Pediatric Anesthesia. 2010;20(3):211-22.
20. Hassan WMNW, Mansor A, Zaini RHM, editors. Anesthesia using target-controlled infusion of propofol during elective pediatric surgery: Kataria versus Paedfusor pharmacokinetic model2019.
21. Hara M, Masui K, Eleveld DJ, Struys MMRF, Uchida O. Predictive performance of eleven pharmacokinetic models for propofol infusion in children for long-duration anaesthesia. Br J Anaesth. 2017;118(3):415-23.
22. Coppens MJ, Eleveld DJ, Proost JH, Marks LAM, Van Bocxlaer JFP, Vereecke H, et al. An Evaluation of Using Population Pharmacokinetic Models to Estimate Pharmacodynamic Parameters for Propofol and Bispectral Index in Children. Anesthesiology. 2011;115(1):83-93.
23. Sepúlveda P, Cortínez LI, Sáez C, Penna A, Solari S, Guerra I, et al. Performance evaluation of paediatric propofol pharmacokinetic models in healthy young children. Br J Anaesth. 2011;107(4):593-600.
24. Vellinga R, Hannivoort LN, Introna M, Touw DJ, Absalom AR, Eleveld DJ, et al. Prospective clinical validation of the Eleveld propofol pharmacokinetic-pharmacodynamic model in general anaesthesia. Br J Anaesth. 2021;126(2):386-94.
25. SAMMARTINO M, GARRA R, SBARAGLIA F, DE RISO M, CONTINOLO N. Remifentanil in children. Pediatric Anesthesia. 2010;20(3):246-55.
26. Simonini A, Brogi E, Cascella M, Vittori A. Advantages of ketamine in pediatric anesthesia. Open Medicine. 2022;17(1):1134-47.
27. Lin R, Ansermino JM. Dexmedetomidine in paediatric anaesthesia. BJA Education. 2020;20(10):348-53.
28. Mason KP, Lerman J. Dexmedetomidine in Children: Current Knowledge and Future Applications. Anesthesia & Analgesia. 2011;113(5).
29. Nimmo AF, Absalom AR, Bagshaw O, Biswas A, Cook TM, Costello A, et al. Guidelines for the safe practice of total intravenous anaesthesia (TIVA). Anaesthesia. 2019;74(2):211-24.
30. Lerman J, Becke K. Perioperative considerations for airway management and drug dosing in obese children. Current Opinion in Anesthesiology. 2018;31(3):320-6.