ORIGINAL ARTICLE

Anesthesia using target-controlled infusion of propofol during elective pediatric surgery: Kataria versus Paedfusor pharmacokinetic model

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ABSTRACT

Background: Kataria and Paedfusor are two validated target-controlled infusion (TCI) pharmacokinetic (PK) models in pediatric population. The aim of this study was to compare the effectiveness of these two different PK models of TCI in pediatric patients during elective surgery.

Methodology: 38 patients of ASA I and II, aged 3-12 year-old, who underwent elective surgery under general anesthesia, were randomized into two groups; Group Kataria (Group K) (n = 19) and Group Paedfusor (Group P) (n = 19). All patients initially received 1 µg/kg loading dose of intravenous (IV) remifentanil over 1 minute 15 seconds and followed with infusion at 0.1-1 µg/kg/min. Group K was subsequently started with Kataria model at target plasma concentration (Cpt) of 6 µg/ml, whereas Group P was started with Paedfusor model also at Cpt of 6 µg/ml. Success rate of induction and induction time were recorded. Anesthesia for both groups was maintained at Cpt of 3-6 µg/ml. After completion of surgery, remifentanil infusion and TCI propofol were stopped. Recovery time and plasma concentration (Cp) of propofol at recovery were recorded.

Results: All patients in both groups were successfully induced at Cpt of 6 µg/ml and induction time was also comparable. Cp at recovery was significantly lower in Group K than Group P; [1.5± 0.1 vs. 1.6 ± 0.1; p = 0.01]. However, there was no significant difference in time of recovery.

Conclusions: Kataria and Paedfusor PK models were comparably effective for induction of anesthesia and recovery of pediatric patients. However, Cp at recovery was lower in Kataria than Paedfusor model.

Key words: Kataria; Paedfusor; Paedfusor PK model; Propofol; Remifentanil; Target-controlled infusion; Pharmacokinetic

INTRODUCTION

Total intravenous anesthesia (TIVA) is a method of anesthesia using solely combination of intravenous anesthetic drugs which is becoming more popular technique in pediatric anesthesia. It can be

administered either in manually controlled or target-controlled infusion (TCI) techniques.[1] TCI is an advanced method of TIVA using a special infusion pump which is incorporated with software, consisted of an algorithm that based on pharmacokinetics (PK) profile of the specific drugs and age appropriate parameters. The PK concepts related to TIVA/TCI in children are different from adults. Children tend to have a large central compartment volume and rapid clearance of IV drugs. Therefore they require relatively higher dose of intravenous (IV) agent per-unit of body weight and higher maintenance infusions rates than the weight corrected dose for adults.[2] TCI for pediatric is currently available with the availability of infusion pump that is incorporated with validated PK models for pediatric. The only currently available and validated PK models are Kataria and Paedfusor for propofol.[3]

The Paedfusor system was developed in the early 1990s as a variant of the Diprifusor, which is an adult TCI software and its performance was found to be within the accepted limits.[4] The lower age limit for the use of Paedfusor is 1 year and the lower weight limit is 5 kg. Another validated TCI model for pediatric is Kataria model which was developed from the study over 600 plasma propofol samples from 53 children at various stages of induction, maintenance and recovery from anesthesia. The lower age limit for the use of Kataria model is 3 years and the lower weight limit is 15 kg.[5] The two models of TCI differ in PK profile. The derived k_{eo} (the constant for rate of drug removal from the effect site) values for the Paedfusor model is 0.91/min ($t_{1/2}$ k_{eo} 0.8 min) and for Kataria models is 0.41/min ($t_{1/2}$ k_{eo} 1.7min) for children aged between 3 to 11 years.[6] Other differences are initial volume of distribution (V_D) and clearance. V_D for Paedfusor is 9.2 l and Kataria is 7.6 l, whereas clearance in Paedfusor is 0.58 l/min and Kataria is 0.74 l/min.[7]

There were limited studies comparing the use of different PK models of propofol in pediatric patients and the question was raised in term of the difference in clinical effects between these two PK models. We hypothesized that Paedfusor PK model might provide better anesthetic effects than Kataria PK model in pediatric patients. Therefore, our aims were to compare the success rate of induction, induction time recovery time and plasma concentration at recovery of these two models for elective pediatric surgery.

METHODOLOGY

This study was a prospective, double-blinded, randomized controlled trial, conducted in Hospital Universiti Sains Malaysia, which is the teaching university hospital. After approval from the university ethics committee and written inform consent from all parents of the patients, 38 patients undergoing elective surgery under general anesthesia, with age between 3 to 12 years and American Society of Anesthesiologists (ASA) class I-II, were randomized into two groups; Group Kataria (Group K) (n = 19) and Group Paedfusor (Group P) (n = 19). Those patients with history of allergy to study drugs, co-morbidities related to the heart and history of inborn error metabolism of lipid were excluded from the study. Patients were withdrawn from the study if they were not cooperative during IV line insertion and developed either severe hypotension or bradycardia after starting infusion of study drugs, which required optimization with rescue drugs, for instance IV atropine or IV ephedrine. The randomization was based on computer-generated randomization.

This study was a double blinded study where the patient and the second medical officer who assessed the patient in the operation theatre did not know which model of TCI propofol was actually used. Both groups received TIVA/TCI from standard Alaris™ PK TIVA/TCI pump, United Kingdom, for TCI propofol and manual infusion of remifentanil. The set up and conduct of TCI pump was performed based on randomization by the anesthesiology registrar in charge in that particular OT. The conduct of anesthesia was performed by a second medical officer and data collection was done by the first investigator.

All selected patients were applied eutectic mixture of local anesthetic cream on both hands during pre-operative visit and IV cannula was inserted after an hour in the ward. No premedication was prescribed in the morning of the surgery. In OT, all patients were monitored for non-invasive blood pressure, pulse oximeter, electrocardiogram, capnography and bispectral index (BIS) monitoring. After pre-oxygenation for 3 minutes, all patients received a slow bolus of 1 μg/kg remifentanil infusion for 1 minute 15 seconds as initial analgesia. During induction, Group K was induced with the Kataria model of TCI propofol at target plasma concentration (Cpt) of 6 μg/ml, whereas Group P was induced with a Paedfusor model also at Cpt of 6 μg/ml. Success rate of induction and induction time was recorded. After successful induction, the laryngeal mask airway (LMA) was inserted and the patients were breathing spontaneously throughout the surgery. During maintenance of anesthesia, both groups were maintained at Cpt of 3-8 μg/ml based on BIS index of 40-60 with combination of remifentanil infusion at 0.1-1.0 μg/kg/min. Supplement analgesia was

provided appropriately with suppository paracetamol 20 mg/kg and/or suppository diclofenac sodium 1 mg/kg. The regional block was given to patients if no contraindication. After completion of surgical closure, TCI propofol and remifentanil infusion were discontinued and patients were extubated when they were fully recovered. Plasma concentration (Cp) at recovery and the recovery time during emergence were recorded. The success rate of induction was defined as successful loss of consciousness and verbal response at starting Cpt. The induction time was defined as the time taken from starting of infusion of propofol to loss of consciousness. Cp at recovery was defined as the concentration of propofol at the plasma level, which was displayed on the TCI pump monitor at extubation. The recovery time during emergence was defined as the time taken from discontinuation of propofol to extubation. The sample size calculation was based on expected significant difference in the time to peak effect of 0.4, standard deviation of 0.35, power of 0.8 and $\alpha = 0.05$. The calculated sample size was 17 per group using Power and Sample size software, version 3.0.10. After considered 10 % of potential drop out, the total samples were 38 patients.

All measurement data were analyzed for normal distribution and homogeneity variance. Categorical data were analyzed with either khi-square or Fisher exact test, whereas numerical data were analyzed with either independent t-tests or Mann Whitney test. The statistical analysis was performed by SPSS version 22 software and $p < 0.05$ was considered as a significant difference.

Table 1: Demographic characteristics in both groups

Parameters	Group Kataria (n = 19)	Group Paedfusor (n = 19)	p-value
Age (years)	6.2 ± 2.7	6.3 ± 2.9	0.61
Height (cm)	105.0 ± 21.4	108.7 ± 20.4	0.90
Weight (kg)	22.8 ± 11.5	23.5 ± 11.5	0.92
ASA:			
I	18 (94.7)	17(89.4)	0.32
II	1 (5.3)	2 (10.6)	
Sex:			
Males	18 (94.7)	19 (100)	0.32
Females	1 (5.3)	0 (0)	
Type of Surgery:			
General Surgery	15 (78.9)	17(89.4)	0.32
Orthopedic	4 (21.1)	2 (10.6)	

Data were expressed as Mean ± SD or n (%)

RESULTS

There was no significant difference in terms of age, height, weight, genders, types of surgery and ASA health status between the two study groups (Table 1).

All patients in both groups were successfully induced at Cpt of 6 μg/ml and induction time was also comparable [Group K, 0.5 ± 0.1 vs. Group P, 0.5 ± 0.1 μg/ml; p = 0.89]. Cp at recovery was significantly lower in Group K than Group P; [1.5± 0.1 vs. 1.6 ± 0.1 μg/ml; p = 0.01]. However, there was no significant difference in time of recovery [Group K, 14.6 ± 2.3 vs. Group P, 15.1 ± 2.5 μg/ml; p = 0.51] (Table 2).

Table 2: Success rate of induction, induction time, plasma concentration at recovery and time of recovery in both groups

Parameters	Group Kataria (n = 19)	Group Paedfusor (n = 19)	p-value
Success rate of induction	19 (100)	19 (100)	-
Induction time (min)	0.5 ± 0.1	0.5 ± 0.1	0.89
Plasma concentration at recovery (μg/ml)	1.5± 0.1	1.6 ± 0.1	0.01*
Time of recovery (min)	14.6 ± 2.3	15.1 ± 2.5	0.51

Data were expressed as Mean ± SD or n (%). $p < 0.05$ *was significant*

DISCUSSION

The use of TIVA for pediatric anesthesia is not quite popular before the availability of TCI pump with validated models for pediatric population. A survey concerning the use of propofol infusions among 388 pediatric anesthetists in United Kingdom showed that 26% of anesthetists used propofol infusions with at least a monthly frequency and only 2% regularly used BIS monitoring.[8] The availability of TCI pump with both validated models for pediatric, Kataria and Paedfusor models has facilitated the practice of TIVA and has increased the safety of its practice. The comparison between Kataria and Peadfusor models of TCI propofol in our study showed that both models were comparable in success rate of induction, induction time and recovery time. The significant difference was only in Cp at recovery where Cp for Kataria model was lower than Cp for Paedfusor model.

In our study, Cpt of propofol 6 μg/ml with remifentanil infusion was used for induction. The plasma concentration 6 μg/ml had been chosen based on the Malaysian protocol on pediatric TCI.[9] To the best of

our knowledge, there was no study that investigated the comparison of anesthesia effects between these two different TCI PK models for pediatric. There were few available studies looking more into the predictive performance of various PK models of TCI including pediatric models. Varveris DA, et al. conducted a study to evaluate the ease of use and efficacy of the Paedfusor for children down to the age of 6 months and weighing 5 kg which involved thirty ASA I children. Target plasma and calculated effector site propofol readings were recorded on insertion of the LMA, insertion of regional block, surgical incision and on removal of LMA. The results showed that Cpt level of 8 μg/ml induced sleep universally within 1 minute. Mean calculated effector site concentration was 4.29 μg/ml for insertion of the LMA and 2.78 μg/ml for LMA removal.[10] Our result in Paedfusor group also showed 100% success rate at Cpt 6 μg/ml which was even lower than 8 μg/ml as in Varveris DA et al. study. The induction time for Paedfusor group in our study was 0.5 $\pm$ 0.1 min, which was faster than described in above study. If based on Kataria PK model, Fuentes et al. has conducted a study to determine effect-site concentration (Ce) targets associated with induction success rates of 50% (Ce50) and 95% (Ce95) among children 3-11 years of age. The results identified useful propofol targets to be used with the Kataria effect-site model were 3.8 μg/ml (95% CI: 3.1-4.4 μg/ml) for Ce50 and 6.1 μg/ml (95% CI: 4.6-7.6 μg/ml) for Ce95.[11] The result was almost similar in our study where success rate of induction in Kataria group at Cpt 6 μg/ml was 100%. Although Kataria and Paedfusor differ in PK algorithm dataset, but from our study all subjects were successfully induced with TCI propofol at Cpt of 6 μg/ml and no significant difference in induction time between Kataria and Paedfusor. Furthermore, remifentanil might have reduced Cpt of propofol that was required for induction and also shortened the induction time. On top of remifentanil, we also provided appropriate supplement of analgesia either suppository medication or regional block for both groups which might also contribute to reduction of anesthesia and analgesia requirement intraoperatively.

This study was also aimed to look for any differences between Kataria and Paedfusor PK models on the emergence. Our study failed to demonstrate the difference in emergence time between these two groups of TCI models. The mean emergence time following termination of propofol infusion was 14.6 $\pm$ 2.3 min in Kataria group and 15.1 $\pm$ 2.5 min in Paedfusor group respectively. There were no Ce-awake displayed on TCI pump for pediatrics;

therefore we could only compare the Cp of the patient during recovery. Cp at recovery was significantly lower in Group Kataria than Group Paedfusor; [1.5 $\pm$ 0.1 vs. 1.6 $\pm$ 0.1; μg/ml; p = 0.01]. McCormack JG et al. conducted a study on the predictability of recovery from anesthesia using Paedfusor as TCI model, using k_{e0} of 0.26 min^{-1}. The result from 90 patients between aged 3 months to < 10 years, showed that a wide variation in emergence time was observed, with a mean $\pm$ standard deviation (SD) of 16.9 $\pm$ 7 min, and a trend to more rapid emergence in older subjects. Emergence time was the time of first purposeful spontaneous movement occurred at a mean $\pm$ SD predicted Ce of 2.0 $\pm$ 0.5 μg/ml and state entropy of 79 $\pm$ 11.[12]

There were few studies comparing between these two PK models. Munoz et al. conducted a study to estimate the value of ke0 for propofol in children using the time to peak effect (tpeak) method and two pharmacokinetic models of propofol for children, Kataria and Paedfusor models. The median ke0 in children was 0.41 min^{-1} with the model of Kataria and 0.91 min^{-1} with the Paedfusor model (P < 0.01). The corresponding $t_{1/2} k_{e0}$ values, in minutes, were 1.7 and 0.8, respectively. This study showed that the values of k_{e0} of propofol calculated for children depend on the pharmacokinetic model used and only can be used with the appropriate set of pharmacokinetic parameters to target effect site in this population.[13]

Cortinez et al. studied the dose-response relationship by comparing the predicted effect-site concentration (Ce) and the level of hypnosis measured by a monitor of depth of anesthesia based on auditory evoked potential in the adult based on Schnider and for children based on the models of Kataria and of the Paedfusor system. The Ce associated with auditory evoked potentials at 50% of the maximum effect (Ce50) estimated by Kataria was, 2.06 [0.24] μg/ml and Paedfusor was 3.56 [0.22] μg/ml.[14] In term of cost, there should not be much difference between the two pharmacokinetic models because both models are available in current TCI/TIVA infusion pump. As in our study, we used Alaris™ PK TIVA/TCI pump, United Kingdom, whereby both models are available and either one can be selected. To the best of our knowledge, there is no study comparing the amount of propofol consumption between the two pediatric pharmacokinetic models to compare the cost of drugs consumed by different techniques. In term of user interface, Paedfusor model has advantage in term of usage for lower age limit at minimum age of one year old and lower body weight limit at minimum of 5 kg. The age limit for Paedfusor model is between

1-16 years and body weight limit is between 5-60 kg. Whereas for Kataria model, the age limit is between 3-16 years and body weight limit is between 30-60 kg.[9]

CONCLUSION

Kataria and Paedfusor PK models are comparably effective for target controlled infusion of propofol for induction of anesthesia and in recovery of pediatric patients. However, Kataria model shows a lower Cp at recovery than Paedfusor model.

Author's contribution:

WMNWH – Concept of study, statistical analysis, manuscript writing, editing

AM – Data collection, statistical analysis, manuscript writing

RHMZ - Manuscript writing, editing

REFERENCES

1. Strauss JM, Giest J. [Total intravenous anesthesia. On the way to standard practice in pediatrics]. Anaesthesist. 2003;52:763-77. [Pubmed]

2. Mani V, Morton NS. Overview of total intravenous anaesthesia in children. Paediatr Anaesth. 2010;20:211-22. [Pubmed] doi: 10.1111/j.1460-9592.2009.03112.x.

3. Constant I, Rigouzzo A, Louvet N. [Update on propofol TCI in children]. Ann Fr Anesth Reanim. 2013;32:e37-42.[Pubmed] doi: 10.1016/j.annfar.2012.10.023.

4. Absalom A, Amutike D, Lal A, White M, Kenny GN. Accuracy of the 'Paedfusor' in children undergoing cardiac surgery or catheterization. Br J Anaesth. 2003;91:507-13.[Pubmed]

5. McCormack JG. Total intravenous anaesthesia in children. Curr AnaesthCriti Care. 2008;19:309-314. [Free Full Text]

6. Munoz HR, Cortinez LI, Ibacache ME, Leon PJ. Effect site concentrations of propofol producing hypnosis in children and adults: comparison using the bispectral index. Acta Anaesthesiol Scand. 2006;50:882-87.[Pubmed]

7. Constant I, Rigouzzo A. Which model for propofol TCI in children. Pediatr Anesth. 2010;20:233-239. [Pubmed] doi: 10.1111/j.1460-9592.2010.03269.x.

8. Hill M, Peat W, Courtman S. A national survey of propofol infusion use by paediatric anaesthetists in Great Britain and Ireland. Paediatr Anaesth. 2008;18:488-93.[Pubmed] doi: 10.1111/j.1460-9592.2008.02459.x.

9. College of Anaesthesiologist, Academy of Medicine of Malaysia & Malaysian Society of Anaesthesiologists Total intravenous anaesthesia for paediatrics. A practical guidebook. 1st edition.2016. p1-26.[Free Full Text]

10. Varveris DA, Morton NS. Target controlled infusion of propofol for induction and maintenance of anaesthesia using the paedfusor: an open pilot study. Paediatr Anaesth. 2002;12:589-93.[Pubmed]

11. Fuentes R, Cortinez I, Ibacache M, Concha M, Munoz H. Propofol concentration to induce general anesthesia in children aged 3-11 years with the Kataria effect-site model. Paediatr Anaesth. 2015;25:554-559. [Pubmed] doi: 10.1111/pan.12657.

12. McCormack J, Mehta D, Peiris K, Dumont G, Fung P, Lim J, et al. The effect of a target controlled infusion of propofol on predictability of recovery from anesthesia in children. Paediatr Anaesth. 2010;20:56-62. [Pubmed] doi: 10.1111/j.1460-9592.2009.03196.x.

13. Munoz HR, Cortinez LI, Ibacache ME, Altermatt FR. Estimation of the plasma effect site equilibration rate constant (ke0) of propofol in children using the time to peak effect: comparison with adults. Anesthesiology. 2004;101:1269-74.[Pubmed] [Free Full Text]

14. Cortinez LI, Munoz HR, Lopez R. [Pharmacodynamics of propofol in children and adults: comparison based on the auditory evoked potentials index]. Rev Esp Anestesiol Reanim. 2006;53:289-96.[Pubmed]

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