

Received: 2019.05.10
Accepted: 2019.07.16
Published: 2019.10.24

Minimum Alveolar Concentration of Sevoflurane with Cisatracurium for Endotracheal Intubation in Neonates

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 **Bin Zhang**
ABCDEF 2 **Junxia Wang**
ABCDEF 3 **Mingzhuo Li**
ABCDEFG 4 **Feng Qi**

1 Department of Anesthesiology, Qilu Hospital of Shandong University, Jinan, Shandong, P.R. China
2 Department of Pediatrics, Qianfoshan Hospital of Shandong Province, Jinan, Shandong, P.R. China
3 Department of Biostatistics, School of Public Health, Shandong University, Jinan, Shandong, P.R. China
4 Department of Anesthesiology, Qilu Hospital of Shandong University, Jinan, Shandong, P.R. China

Corresponding Author: Feng Qi, e-mail: zb000307@hotmail.com

Source of support: This study was funded in part by the National Natural Science Foundation of China (No. 81672250) and the Major Project and Development Plan of Shandong Province (No. 2017ZD943002)

Background: Sevoflurane inhalation induction is widely used in pediatric anesthesia, but the minimum alveolar concentration for endotracheal intubation (MAC_{E1}) when combined with neuromuscular blockade in neonates has been largely unexplored. This study assessed the MAC_{E1} of sevoflurane combined with cisatracurium in neonates.

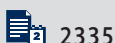
Material/Methods: Anesthesia induction was commenced by inhaling 4% sevoflurane with 2 l/min of 100% oxygen via mask. Neonates were administered cisatracurium 0.2 mg/kg followed by adjustment of inspired sevoflurane to target end-tidal concentration based on intubation condition of the preceding subject. When the steady-state end-tidal sevoflurane concentration target was maintained for at least 15 min, endotracheal intubation by direct laryngoscope was performed. The intubation condition was considered failed if either heart rate (HR) after intubation increased by 20% or mean arterial blood pressure (MAP) by 30% or more than that before intubation. Otherwise, the intubation condition was regarded as successful. Dixon's up-and-down method was used with 0.2% as the step size to determine the target end-tidal sevoflurane concentration.

Results: The MAC_{E1} of sevoflurane combined with cisatracurium in neonates was $2.76 \pm 0.24\%$. Using probit analysis, the 50% effective end-tidal sevoflurane concentration (ED_{50}) for successful condition of endotracheal intubation was 2.61% (95%CI 2.07–2.88%) and the 95% effective end-tidal sevoflurane concentration (ED_{95}) was 3.28% (95%CI 2.95–7.19%). Hypotension and bradycardia occurred in 2 neonates during induction.

Conclusions: Sevoflurane combined with cisatracurium is feasible and effective for intubation in neonates, and the MAC_{E1} of sevoflurane in this subpopulation is $2.76 \pm 0.24\%$. However, cardiovascular adverse effects should be taken into consideration.

MeSH Keywords: Anesthetics • Atracurium • Infant, Newborn • Intubation

Full-text PDF: <https://www.medscimonit.com/abstract/index/idArt/917472>



2335



2



2



27



Background

Sevoflurane, as an inhaled anesthetic, has a low partition in blood gas. It has short equilibrium time from pulmonary alveoli to brain tissues and is widely used for anesthesia induction and maintenance in children [1,2]. Compared with other volatile anesthetics, sevoflurane is a preferred inhalation induction anesthetic in children due to its minimal airway irritation and low cardiovascular adverse effects [3,4]. Sevoflurane inhalation induction can adequately inhibit the stress response in children with congenital heart diseases [5]. High concentrations of sevoflurane result in significant risk of hemodynamic instability [3,6], while low concentrations cannot inhibit stress response caused by intubation in shallow-depth anesthesia.

Neuromuscular relaxant can facilitate tracheal intubation in adults and children and is frequently used for anesthesia induction. Excellent intubation conditions are less frequently associated with intubation sequelae and thus are preferred by anesthesiologists. Neuromuscular relaxant in rapid induction can improve intubation conditions and facilitate tracheal intubation [7–9]. Although succinylcholine retains its value in critical situations, it is not a routine option in elective pediatric anesthesia due to its life-threatening adverse effects [10]. Rocuronium has shown more influence on lung function in children than cisatracurium [11]. Cisatracurium, as a non-depolarizing neuromuscular relaxant, produces excellent intubation conditions and maintains hemodynamic stability in neonates and children [12]. Sevoflurane combined with neuromuscular relaxant is preferred in infants due to lower hemodynamic and respiratory adverse events [13]. However, there is scant data on use of sevoflurane combined with neuromuscular relaxants (such as cisatracurium) for intubation in neonates, and the minimum alveolar concentration for endotracheal intubation (MAC_{EI}) of sevoflurane remains unclear in this subpopulation.

The MAC_{EI} is the end-tidal concentration of volatile anesthetic, at which there is a 50% possibility of smooth endotracheal intubation for patients. Previous studies reported that the MAC_{EI} of sevoflurane in children younger than 6 months who only inhaled sevoflurane for intubation was 3.2–3.43% [14,15]. The aim of the present study was to determine the MAC_{EI} of sevoflurane to produce successful intubation conditions in neonates in combination with cisatracurium. We hypothesized that the value of MAC_{EI} is lower in neonates than that in the closest age group in consideration of the presumed muscle relaxant effect.

Material and Methods

Study population

Neonates who underwent endotracheal intubation general anesthesia by direct laryngoscope were included from April 2017

to March 2018 in a single tertiary hospital in China. The inclusion criteria were: 1) neonates gestational age above 37 weeks, 2) neonates without respiratory diseases or cardiac diseases, 3) neonates without airway malformations and having no potential difficult airway in preoperative evaluation, and 4) neonates with no risk of regurgitation or aspiration. The exclusion criteria were: 1) neonates with airway or thoracic malformations, 2) neonates with cardiac diseases, 3) neonates with severe physical status greater than III according to the American Society of Anesthesiologists, and 4) neonates who presented with hypotension and hypothermia during monitoring in the operating room before induction. All neonates were fasted for water and breast milk for 2 h and 4 h before surgery, respectively. There were no premedications administered to any neonates prior to induction of anesthesia. Demographic data were collected. This clinical trial was approved by the Medical Ethics Committee of the hospital and parents of each patient signed written informed consent before surgery.

Anesthesia procedures

All the neonates were infused with 15 ml/kg of saline to complement fluid loss during fasting and to reduce the risk of hypovolemia before anesthesia induction. The condition of each neonate was monitored with pulse oximetry, electrocardiography, noninvasive arterial blood pressure measurement, and nasopharyngeal temperature after they were transferred to the operating room. A warming unit was used to maintain normal neonatal body temperature. Concentrations of sevoflurane and end-tidal carbon dioxide partial pressure were analyzed and measured continuously using the gas analyzer of the anesthesia machine (Dräger, Primus. Dräger Werk AG & Co., Lübeck, Germany). A catheter was inserted within the sealed face mask. Sampling and measurements of end-tidal gases were obtained through the catheter. Once endotracheal intubation was completed, the reading from the catheter connected to the endotracheal tube was taken and recorded by the anesthetic machine. General anesthesia was commenced with sevoflurane inhalational induction in 100% oxygen with a fresh gas flow rate of 2 liter/min⁻¹ through a semi-closed-circuit system. Sevoflurane was delivered via a vaporizer (Dräger Vapor 2000, Dräger Werk AG & Co., Lübeck, Germany). The breathing circuit was pre-infused by 2% sevoflurane for at least 2 min before anesthesia induction. Neonates initially inhaled 4% of sevoflurane spontaneously via mask. When the limb movements of neonates stopped, cisatracurium (0.2 mg·kg⁻¹) was administered and flushed into the body by saline. Then, lung ventilation was controlled manually to keep SpO₂ above 95% and maintain end-tidal carbon dioxide partial pressures at 35–45 mmHg. Anesthesiologist adjusted the inspired concentration of sevoflurane to obtain the target end-tidal sevoflurane concentration according to results of the preceding neonate. When the target end-tidal sevoflurane concentration was

achieved, it was maintained for at least 15 min before endotracheal intubation. A train of 4 twitch monitors was used to verify that the neonates were indeed paralyzed. HR and MAP were measured before tracheal intubation. An appropriate uncuffed tracheal tube was selected, and the tracheal intubation by direct laryngoscope was performed. No analgesics were used in this study. Once endotracheal intubation was completed, the value of end-tidal sevoflurane concentration measured automatically by the anesthesia machine was recorded immediately. HR and the MAP were also measured immediately within 5 s after intubation.

We used Dixon's up-and-down method with 0.2% end-tidal concentration as a step size to determine the target end-tidal sevoflurane concentration, and the initial end-tidal sevoflurane concentration was starting at 3.0%. If either the HR or the MAP of the preceding subject increased by 20% or 30% or more after intubation than that before intubation, the intubation condition was considered failed; as a result, the end-tidal sevoflurane concentration was increased by 0.2% in the next patient. Otherwise, the intubation condition was considered successful and the end-tidal sevoflurane concentration was reduced by 0.2% in the next patient.

Observation of adverse effects

The hemodynamic and respiratory adverse effects occurring during anesthesia induction were recorded. Respiratory adverse effects included hypoxemia ($SpO_2 < 90\%$ lasting over 1 min), laryngospasm, and bronchospasm. Hemodynamic adverse effects included hypotension (MAP below 40 mmHg on 2 consecutive readings), bradycardia (HR $< 100/\text{min}$), tachycardia (HR $> 180/\text{min}$) and arrhythmia.

Statistical analyses

All statistical analyses were performed using SPSS 19.0 software (SPSS Inc., USA). Data are presented as mean \pm SD. The mean \pm SD of the MAC_{Ei} was obtained through the Dixon's up-and-down method by calculating the midpoint concentration of all independent pairs of neonates involving a crossover (failed to succeed). The mean of MAC_{Ei} was calculated as the average of the crossover midpoints in each pair, and the SD of MAC_{Ei} was the SD of the crossover midpoint in each pair. Dixon's up-and-down data were analyzed with probit regression analysis to obtain the effective sevoflurane concentration required for successful endotracheal intubation condition in 50% and 95% (ED₅₀ and ED₉₅, respectively) of neonates. Sample size was calculated based on the fact that a minimum of 6 crossover pairs were required for the statistical analysis [16]. Indeed, 6 pairs are considered optimal for a clinical study [17].

Results

Thirty-seven neonates were screened for enrollment and 6 neonates were excluded. One neonate was excluded because of the presentation of hypotension before induction. Two neonates had cardiovascular adverse effects during anesthesia induction and thus were excluded. The other 3 neonates were excluded due to the difference in value of end-tidal concentration before and after intubation. In our final analysis, 31 neonates were included and analyzed. The neonates' characteristics and type of surgery are shown in Table 1. End-tidal sevoflurane concentration, HR, and MAP before and after intubation are shown in Table 2. Consecutive end-tidal sevoflurane concentration and condition of tracheal intubation are shown in Figure 1. The MAC_{Ei} of sevoflurane in neonates when combined with cisatracurium was $2.76 \pm 0.24\%$. From probit analysis, the ED₅₀ of end-tidal sevoflurane concentration for successful condition of endotracheal intubation was 2.61% (95% CI 2.07–2.88%), and the ED₉₅ of that for successful intubation condition was 3.28% (95% CI 2.95–7.19%). Dose-response data for each neonate obtained by the up-and-down method are shown in Figure 2.

Cardiovascular adverse effects occurred in 2 neonates during induction, who were eliminated from the consecutive patients, and their results were excluded from this study. One 21-day-old neonate with intestinal malrotation had hypotension (MAP 32 mmHg) and was rescued by discontinuing sevoflurane and by liquid supplementation. Bradycardia occurred in a 4-day-old neonate whose HR decreased from 126 min^{-1} to 89 min^{-1} during inhalation induction and was corrected by infusing atropine 0.05 mg. The intubations were successful at first attempt in all other patients and no respiratory adverse events were observed.

Discussion

The main objective of this clinical trial was to determine the MAC_{Ei} of sevoflurane for successful intubation condition in combination with cisatracurium in neonates. Usually, MAC_{Ei} is assessed based on intubation conditions, such as jaw relaxation, ease of laryngoscopy, coughing, movements of the vocal cords or limbs, and whether tracheal intubation is smooth [15,18]. Because all the neonates in our study were paralyzed by cisatracurium, so we could not apply the above criteria to evaluate the intubation condition. However, insufficient depth of anesthesia cannot block the stress response caused by tracheal intubation, and consequent hemodynamic fluctuation cannot be masked. So, we used changes in HR and MAP before and after intubation as the criteria to evaluate the intubation condition according to previous descriptions [13,19–21].

Table 1. Clinical data of included neonates.

N	Age, days	Weight, kg	Sex	Disease type
1	9	4.0	Male	Congenital megacolon
2	8	3.2	Male	Intestinal malrotation
3	1	3.0	Male	Anal atresia
4	27	4.5	Male	Pyloric obstruction
5	26	3.8	Male	Congenital megacolon
6	6	2.4	Female	Intestinal malrotation
7	2	3.9	Female	Anal atresia
8	2	3.4	Male	Anal atresia
9	17	4.0	Male	Duodenal stenosis
10	21	3.5	Male	Congenital megacolon
11	3	2.7	Female	Rectal atresia
12	26	3.0	Female	Depressed fracture of skull
13	3	3.0	Female	Pyloric obstruction
14	2	4.6	Male	Intestinal atresia
15	6	3.2	Female	Intestinal atresia
16	7	2.9	Female	Intestinal malrotation
17	6	2.7	Female	Omphalocele
18	10	3.4	Male	Intestinal malrotation
19	3	3.1	Male	Intestinal atresia
20	3	3.0	Female	Intestinal atresia
21	16	3.1	Female	Intestinal atresia
22	2	4.0	Female	Duodenal stenosis
23	25	4.4	Male	Inguinal hernia
24	3	3.0	Female	Omphalocele
25	7	3.3	Female	Intestinal malrotation
26	26	3.9	Female	Depressed fracture of skull
27	10	3.1	Male	Congenital megacolon
28	23	3.6	Female	Inguinal hernia
29	21	3.3	Male	Omphalocele
30	5	2.9	Female	Intestinal atresia
31	3	3.0	Female	Duodenal stenosis

The MAC_{EI} of sevoflurane in infants 1–6 months old was 3.2–3.43% [14,15]. However, before we started conducting this clinical trial, we did not consult the MAC_{EI} value for sevoflurane in neonates with or without neuromuscular relaxant in the available literature. We suppose that under the effects of cisatracurium, there should be no laryngeal muscle resistance during tracheal intubation and the MAC_{EI} should be close to or less than the reported value. Chen et al. [15] reported that the MAC_{EI} of sevoflurane in infants 2–3 months, which was closest to the age of neonates in our study, was 3.43±0.18%. We showed that the MAC_{EI} value for sevoflurane

in neonates with cisatracurium was 2.76 ± 0.24%, which was lower than the value without muscular relaxant, further verifying our hypothesis. However, Inomata et al. [22] reported that the MAC_{EI} of sevoflurane without other adjuvants in children aged 1–9 years was 2.69%, which is slightly lower than our results. However, the 2 studies are quite different, making the results difficult to compare.

We also used probit regression analysis to calculate ED50 and ED95 values. Although this method has been questioned, it remains a reliable approach to determine ED₅₀ and ED₉₅ values.

Table 2. The end-tidal concentration of sevoflurane, HR, and MAP before and after intubation.

N	Concentration of Sevoflurane (%)	HR, min ⁻¹		MAP, mmHg	
		Before intubation	After intubation	Before intubation	After intubation
1	3.0	152	161	53	55
2	2.8	146	160	51	56
3	2.6	141	171	48	59
4	2.8	138	163	55	74
5	3.0	129	132	55	55
6	2.8	161	158	42	43
7	2.6	143	182	43	60
8	2.8	148	178	46	62
9	3.0	126	154	47	58
10	3.2	132	133	56	60
11	3.0	152	149	58	50
12	2.8	138	132	51	53
13	2.6	131	150	48	56
14	2.4	155	183	43	61
15	2.6	130	161	51	53
16	2.8	141	152	55	53
17	2.6	152	160	48	51
18	2.4	140	166	40	55
19	2.6	118	156	41	49
20	2.8	129	160	44	45
21	3.0	147	140	56	52
22	2.8	156	149	48	43
23	2.6	139	158	62	66
24	2.4	149	139	60	55
25	2.2	141	171	42	61
26	2.4	121	155	46	58
27	2.6	148	149	51	50
28	2.4	143	160	53	63
29	2.2	145	170	51	69
30	2.4	135	168	41	47
31	2.6	131	150	44	46

N – number of consecutive neonates; HR – heart rate, MAP – mean blood pressure.

Nishikawa et al. [23] found that the ED₅₀ and ED₉₅ end-tidal sevoflurane concentrations for intubation in children ages 3–8 years were 3.10% and 4.68%, respectively. Another study reported that the ED₅₀ and ED₉₅ values in children ages 3–8 years were 5.12% and 5.60%, respectively [24]. The results in these 2 studies were higher than in ours, likely due to the following 2 reasons. First, there was no administration of muscular relaxant

in their studies. Second, they used a rapid induction method by inhaling a high inspired concentration, and a constant end-tidal concentration was maintained for a shorter time. Our study used the conventional method to maintain the target end-tidal concentration constantly for at least 15 min to allow adequate time for sevoflurane partial pressure to achieve equilibrium in alveoli, arterial blood, and brain before tracheal intubation.

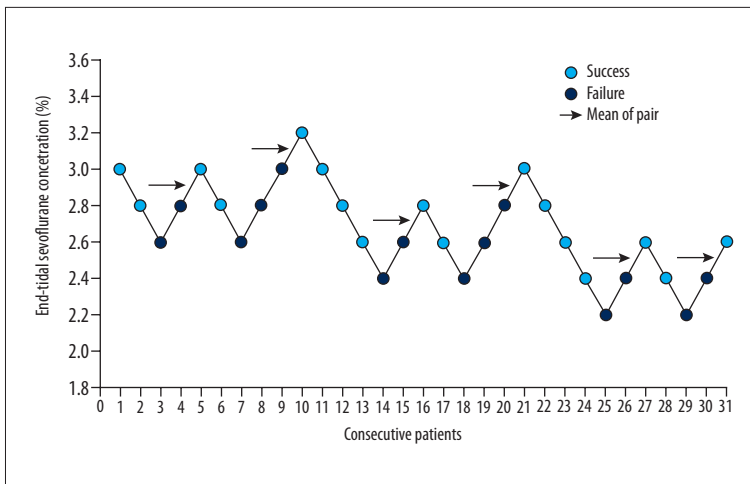


Figure 1. Thirty-one consecutive neonates at target end-tidal sevoflurane concentration and the condition of endotracheal intubation. Arrows indicate the midpoint end-tidal concentration of all neonates involving a crossover (i.e., failed to succeed).

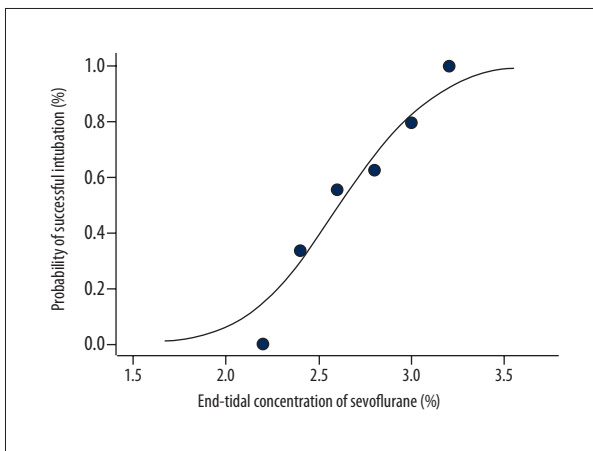


Figure 2. The dose-response curve of individual end-tidal sevoflurane concentration combined with cisatracurium and the condition of endotracheal intubation. Probit analysis was used.

Although sevoflurane is widely used for inhalation induction in children because it has the least myocardial depressant effects and lower cardiovascular adverse effects among all inhalational agents [25,26], hemodynamic instability cannot be neglected, especially when high-concentration sevoflurane was inhaled [3,4]. In our study, hypotension and bradycardia occurred in 2 neonates during anesthesia induction, and the target end-tidal concentration in both was 2.6%. Neonates are vulnerable to high-concentration sevoflurane due to their decreased myocardial reserve and high risk for hypotension [6]. Two MAC of sevoflurane can decrease the MAP in adults, while as much as 1 MAC of sevoflurane can reduce blood pressure by 30% in neonates [3,14]. Bradycardia is also reported in children when using sevoflurane induction [4,27]. Green et al. [26] demonstrated that bradycardia developed in 7 out of 60 infants during sevoflurane inhalation induction, and they found that the onset of bradycardia might be related to the depth of anesthesia. The immaturity of the autonomic nervous system

of neonates may make them more susceptible to arrhythmias, even in a relatively low inhalation concentration of sevoflurane.

There are several limitations in our study. First, it is likely that end-tidal concentrations measured by ventilation via mask were contaminated by inspired gas. Hence, it is difficult to keep the target end-tidal concentration absolutely stable within the 15 min before intubation. Fluctuation of no more than 0.1% within 1 min was acceptable in this study. However, subjects with slight differences in value of end-tidal sevoflurane concentration before and after endotracheal intubation were excluded. Second, some neonates in our study had gastrointestinal problems, and an inhalational induction may not be suitable due to potential risk of reflux aspiration. The contents of the stomach were preoperatively emptied. In fact, the children with high risk of reflux aspiration were excluded, and no reflux aspiration occurred in our study even though the duration of anesthesia induction was more than 15 min.

Conclusions

Use sevoflurane and cisatracurium for endotracheal intubation in neonates is acceptable and effective. The MAC_{EI} of sevoflurane in neonates with cisatracurium was $2.76 \pm 0.24\%$, which was less than the value in infants who only inhaled sevoflurane for endotracheal intubation. The ED₅₀ and ED₉₅ of sevoflurane combined with cisatracurium were 2.61% (95% CI 2.07–2.88%) and 3.28% (95% CI 2.95–7.19%), respectively. However, although sevoflurane combined with cisatracurium for endotracheal intubation is a good alternative and effective method in neonates, the cardiovascular adverse effects during anesthesia induction should be taken into consideration.

Conflicts of interest

None.

References:

1. Yao Y, Qian B, Lin Y et al: Intranasal dexmedetomidine premedication reduces minimum alveolar concentration of sevoflurane for laryngeal mask airway insertion and emergence delirium in children: A prospective, randomized, double-blind, placebo-controlled trial. *Pediatric Anesthesia*, 2015; 25: 492-98
2. Yu L, Sun H, Yao L et al: Comparison of effective inspired concentration of sevoflurane in preterm infants with different postconceptual ages. *Pediatric Anesthesia*, 2011; 21: 148-52
3. Michel F, Constantin JM: Sevoflurane inside and outside the operating room. *Expert Opin Pharmacother*, 2009; 10: 861-73
4. Bai W, Voepel-Lewis T, Malviya S: Hemodynamic changes in children with Down syndrome during and following inhalation induction of anesthesia with sevoflurane. *J Clin Anesth*, 2010; 22: 592-97
5. Wang CH, Luo J, Li J et al: Efficacy of inhalational sevoflurane anesthesia induction on inhibiting the stress response to endotracheal intubation in children with congenital heart disease. *Eur Rev Med Pharmacol Sci*, 2018; 22: 1113-17
6. Uejima T: Sevoflurane for intubation of neonates. *Paediatr Anaesth*, 2008; 18: 900
7. Aouad MT, Yazbeck-Karam VG, Mallat CE et al: The effect of adjuvant drugs on the quality of tracheal intubation without muscle relaxants in children: A systematic review of randomized trials. *Paediatr Anaesth*, 2012; 22: 616-26
8. Lundstrom LH, Duez CH, Norskov AK et al: Avoidance versus use of neuromuscular blocking agents for improving conditions during tracheal intubation or direct laryngoscopy in adults and adolescents. *Cochrane Database Syst Rev*, 2017; 5: CD009237
9. Same M, Smith J: Should neuromuscular blockers be used for every paediatric intubation? *Br J Hosp Med*, 2016; 77: 374
10. Sparr HJ, Johr M: [Succinylcholine – update]. *Der Anaesthesist*, 2002; 51: 565-75 [in German]
11. Yang CI, Fine GF, Jooste EH et al: The effect of cisatracurium and rocuronium on lung function in anesthetized children. *Anesth Analg*, 2013; 117: 1393-400
12. Meakin GH, Meretoja OA, Perkins RJ et al: Tracheal intubating conditions and pharmacodynamics following cisatracurium in infants and children undergoing halothane and thiopental-fentanyl anesthesia. *Paediatr Anaesth*, 2007; 17: 113-20
13. Devys JM, Mourissoux G, Donnette FX et al: Intubating conditions and adverse events during sevoflurane induction in infants. *Br J Anaesth*, 2011; 106: 225-29
14. Lerman J, Sikich N, Kleinman S, Yentis S: The pharmacology of sevoflurane in infants and children. *Anesthesiology*, 1994; 80: 814-24
15. Chen SQ, Ye HR, Chen YJ, Wang YW: MAC(EI) and MAC(awake) of sevoflurane in infants with obstructive jaundice. *Paediatr Anaesth*, 2014; 24: 282-89
16. Paul M, Fisher DM: Are estimates of MAC reliable? *Anesthesiology*, 2001; 95: 1362-70
17. Ezri T, Sessler D, Weisenberg M et al: Association of ethnicity with the minimum alveolar concentration of sevoflurane. *Anesthesiology*, 2007; 107: 9-14
18. Abdelhalim AA, Maghraby HH, ElZoughari IA et al: Using fentanyl and propofol for tracheal intubation during sevoflurane induction without muscle relaxants in children: A randomized prospective study. *Saudi J Anaesth*, 2017; 11: 312-18
19. Michel F, Lando A, Aubry C et al: Experience with remifentanyl-sevoflurane balanced anesthesia for abdominal surgery in neonates and children less than 2 years. *Paediatr Anaesth*, 2008; 18: 532-38
20. Hassid S, Nicaise C, Michel F et al: Randomized controlled trial of sevoflurane for intubation in neonates. *Paediatr Anaesth*, 2007; 17: 1053-58
21. Michel F, Viale R, Hassid S et al: Sevoflurane for central catheter placement in neonatal intensive care: A randomized trial. *Paediatr Anaesth*, 2010; 20: 712-19
22. Inomata S, Watanabe S, Taguchi M, Okada M: End-tidal sevoflurane concentration for tracheal intubation and minimum alveolar concentration in pediatric patients. *Anesthesiology*, 1994; 80: 93-96
23. Inomata S, Nishikawa T: Determination of end-tidal sevoflurane concentration for tracheal intubation in children with the rapid method. *Can J Anaesth*, 1996; 43: 806-11
24. He L, Wang X, Zhang XF, Tang SR: Effects of different doses of remifentanyl on the end-tidal concentration of sevoflurane required for tracheal intubation in children. *Anaesthesia*, 2009; 64: 850-55
25. Xing N, Wei X, Chang Y et al: Effects of low-flow sevoflurane anesthesia on renal function in low birth weight infants. *BMC Anesthesiol*, 2015; 15: 6
26. Green DH, Townsend P, Bagshaw O, Stokes MA: Nodal rhythm and bradycardia during inhalation induction with sevoflurane in infants: A comparison of incremental and high-concentration techniques. *Br J Anaesth*, 2000; 85: 368-70
27. Kundra P, Vinodhadevi V, Arimanickam G: Sevoflurane-induced arrhythmia in an adult and a child. *J Anaesthesiol Clin Pharmacol*, 2011; 27: 269-71