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Effect of a Bolus Dose of Fentanyl on the ED_{50} and ED_{95} of Sevoflurane in Neonates

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Data Interpretation D
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Background: The minimum alveolar concentration (MAC) of sevoflurane in neonates is 3.3%, but this value has not been verified in Chinese neonates and the effect of different doses of fentanyl on MAC in neonates has not been investigated. This study was designed to determine the ED_{50} and ED_{95} values of sevoflurane in Chinese neonates with and without fentanyl.

Material/Methods: Ninety-three neonates were randomly assigned to receive sevoflurane alone (control group, n=30), 1 μg/kg sevoflurane (group $fent_1$, n=29), or 2 μg/kg fentanyl (group $fent_2$, n=32). Following inhalational induction and tracheal intubation, the end-tidal concentration of sevoflurane was adjusted to achieve the designated concentration, which was determined using the modified Dixon's up-and-down method starting with 3.0% in each group, with a 0.25% step size. Success was defined as no motor response within 60 s of skin incision.

Results: The MAC (standard deviation) values of sevoflurane were 2.91% (0.27) in the control group, 2.53% (0.31) in the $fent_1$ group, and 2.34% (0.33) in the $fent_2$ group according to Dixon's up-and-down method. Logistic probit regression analysis revealed that the ED_{50} and ED_{95} (95% CI) of sevoflurane in neonates were 2.82% (2.66–2.98) and 3.39% (2.89–3.89), respectively, in the control group; 2.44% (2.19–2.68) and 3.30% (2.51–4.09), respectively, in the $fent_1$ group; and 2.21% (1.97–2.45) and 3.11% (2.35–3.88), respectively, in the $fent_2$ group.

Conclusions: The MAC value of sevoflurane in Chinese neonates was lower than previously reported and was reduced by the addition of fentanyl.

MeSH Keywords: Anesthesia, Inhalation • Fentanyl • Infant, Newborn

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Background

Sevoflurane is widely used for the induction and maintenance of anesthesia in pediatric patients due to its beneficial pharmacological characteristics, including low blood tissue solubility, non-pungency, and limited cardiorespiratory depression. Previous studies of sevoflurane have shown that the minimum alveolar concentration (MAC) increases as age decreases in childhood and infancy, and it has a similar value in infants and neonates [1–3]. Lerman et al. reported that the MAC of sevoflurane in neonates was 3.3% [1], but this value has not been verified in Chinese neonates.

Opioids are often combined with sevoflurane to minimize the adverse effects of sevoflurane, but, to the best of our knowledge, no English or Chinese studies have been performed to evaluate the effect of different doses of fentanyl on MAC of sevoflurane in neonates. Therefore, the aim of our study was to determine the ED_{50} and ED_{95} values of sevoflurane in Chinese neonates. We also investigated the effects of different doses of fentanyl on the MAC of sevoflurane.

Material and Methods

Patients and study design

This clinical trial was reviewed and approved by the Ethics Committee of Guangzhou Women's and Children's Medical Center. Written informed consent was obtained from the parents or legal guardians of each pediatric patient. In total, 93 full-term healthy neonates with an American Society of Anesthesiologists physical status I-II and undergoing elective or emergency surgery under general anesthesia were enrolled into the study. Neonates were excluded if they had cardiorespiratory, renal, or hepatic dysfunction. Neonates were also excluded if they received medications known to affect anesthetic requirements. Neonates were randomly allocated using a computer-generated sequence of numbers to 1 of 3 groups. Patients received either sevoflurane alone (control group) or different doses of fentanyl combined with sevoflurane (group $fent_1$: 1 μg/kg; group $fent_2$: 2 μg/kg). The number of patients in each group was selected to obtain 8 pairs of crossover points in the Dixon's graph.

Surgical procedure and clinical observations

Neonates were fasted for 4 h before surgery, and scopolamine (0.01 mg/kg) was subcutaneously administered 30 min before surgery. Patients' electrocardiogram, oxygen saturation, noninvasive arterial pressure, and body temperature were monitored throughout the surgery. The temperature of the operating room was pre-warmed at 24°C before induction of anesthesia. The body temperature of each patient, which was measured at the deep pharynx nasalis, was kept at 36.5–37°C by applying a heating blanket. An overhead radiant heater and plastic sheets were used to cover exposed skin. All neonates were pre-oxygenated for 3 min with 100% oxygen through a tight-fitting mask. Patients were then connected to a semi-closed anesthetic circuit prefilled with 6% sevoflurane with the rate of fresh airflow set at 6 L/min. After losing the eyelash reflex, a 24-gauge intravenous cannula was inserted if the patient did not have an intravenous catheter before being taken to the operation room, and 0.9% normal saline was infused at a rate of 10 ml/kg/h.

After tracheal intubation, the lungs were mechanically ventilated with 1 L/min of air and 1 L/min of oxygen. The ventilator rate was adjusted to maintain an end-tidal carbon dioxide partial pressure of 4.7–6.0 kPa. Arterial blood gas analysis was performed to determine the arterial blood carbon dioxide partial pressure and to adjust the balance of blood electrolytes. The end-tidal sevoflurane concentration and carbon dioxide partial pressure were continuously monitored using a Datex Capnomac airway gas monitor (Datex-Ohmeda, Helsinki, Finland) during the study. The end-tidal concentration of sevoflurane was changed to achieve the target concentration by another anesthesiologist who was unaware of the patients' assignment. As soon as the target concentration of sevoflurane was achieved, 1 μg/kg and 2 μg/kg fentanyl were infused, over a period of 1 min in neonates in the $fent_1$ and $fent_2$ groups, respectively. In the control group, saline was infused. Drugs were prepared in unlabeled 5-ml syringes by a nurse anesthetist who did not participate in the intraoperative management. The target end-tidal concentration of sevoflurane was maintained for 20 min to allow for equilibration between the alveolar and brain partial pressures. The sevoflurane end-tidal concentration during maintenance was considered as the MAC for that study if the neonate had not moved. After the skin incision, cisatracurium (0.2 mg/kg) was given for muscular relaxation. For each neonate, a total volume of 1 ml/kg 0.2% ropivacaine was infiltrated into the wound as postoperative wound analgesia at the end of surgery. The study protocol is shown in Figure 1.

For each neonate, the target end-tidal concentration of sevoflurane was determined using the modified Dixon's up-and-down method starting with 3.0% in each group, with a 0.25% step size. Increasing or decreasing the target end-tidal sevoflurane concentration was determined by the response of the previous neonate in the same group. The response of each neonate was observed for 60 s after the skin incision and evaluated as "successful" or "unsuccessful". Unsuccessful was recorded when the skin incision caused withdrawal of the neonates' hand or foot. If the response was determined to be unsuccessful, the end-tidal concentration of sevoflurane

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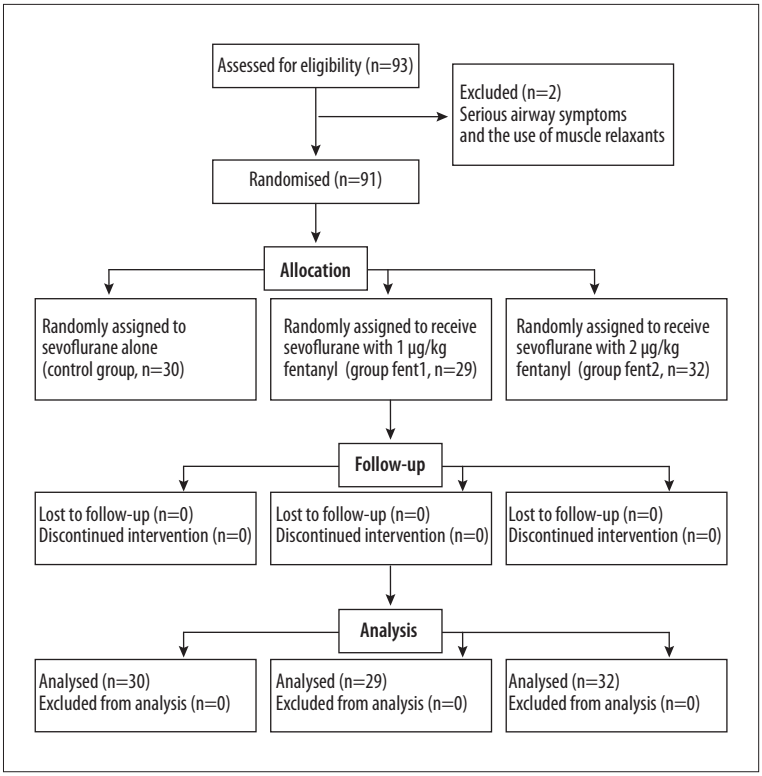

Figure 1. Consort flow diagram.

given to the next neonate was increased by 0.25%. If it was successful, the end-tidal concentration of sevoflurane given to the next neonate was decreased by 0.25%. All responses were assessed by an independent observer who was unaware of the sevoflurane concentration and group assignment. Each neonate contributed to 1 data point toward the measurement of sevoflurane MAC in each study group. The midpoint between an unsuccessful response and a successful response in 2 consecutive neonates was defined as a pair of crossover, and the study in each group ended after 8 pairs of crossover were obtained.

Baseline measurements of systolic, diastolic and mean arterial blood pressures, heart rate, SpO2, and temperature were recorded at 4 time intervals as follows: awake, before intubation, at the steady-state target concentration of sevoflurane before the skin incision, and at steady-state concentration approximately 1 min after the skin incision. Hypotension was defined as a ≥30% decrease in mean arterial blood pressure compared to blood pressures when the neonate was awake. Dopamine (1–10 ug/kg/min) was used to treat hypotension during sevoflurane anesthesia. The incidence of vomiting and moderate and severe airway responses, including breathholding (>15 s), coughing, laryngospasm (>5 s of phonation or inability to ventilate), bronchospasm (bilateral wheezing), and secretions (requiring suctioning) were recorded during the induction of anesthesia and emergence from anesthesia.

The primary endpoint of the study was the end-tidal concentration of sevoflurane. The secondary endpoints were postoperative airway responses and adverse events.

Statistical analysis

Sample size determination, when using Dixon's up-and-down method, is relatively speculative. The Dixon method is a useful statistical approach of MAC calculation, requiring a moderate sample size of subjects. Indeed, 6 pairs are considered as optimal for a clinical study [4]. All statistical analyses were performed using SAS (SAS Institute Inc, Cary, NC, USA) statistical software. The end-tidal concentration of sevoflurane was analyzed by calculating the midpoint concentration of all independent pairs of crossover points. The MAC was defined as the mean of the median crossover concentration. The up-and-down data was also subjected to logistic probit regression analysis to estimate the 50% and 95% effective sevoflurane concentrations (ED_{50} and ED_{95}, respectively) and the 95% confidence interval (95% CI). ANOVA or a Kruskal-Wallis test was used to analyze the differences between patient age, weight, time to loss of eyelash reflex, time to successful tracheal intubation, and operation time. Sex, cause of surgery, airway response, emergence agitation, and vomiting were analyzed with a chi-square analysis or Fisher's exact test. Intraoperative hemodynamic variables were analyzed using repeated measures analysis of variance and the Newman-Keuls test. A $p<0.05$ was considered statistically significant.

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Table 1. Neonates' demographic and experimental data. Data are expressed as mean (range) for age, or mean (SD) or number of cases (n).

Group	Control group (n=30)	Group $fent_1$ (n=29)	Group $fent_2$ (n=32)
Age (day)	12 (1–28)	13 (1–25)	12 (1–28)
Gender (male/female)	17/13	16/13	17/15
Weight (kg)	2.99 (0.31)	2.95 (0.28)	2.90 (0.26)
Time to loss of eyelash reflex (s)	27 (4)	25 (5)	26 (6)
Time to successful tracheal intubation (s)	105 (17)	103 (14)	107 (16)
Operative time (min)	66 (17)	63 (14)	63 (15)
Cause of surgery (n)			
Duodenal obstruction	9	8	7
Intestinal malrotation	7	6	9
Intussusception	6	6	7
Intestinal atresia	4	5	5
Pneumoperitoneum	2	3	2
Incarcerated hernia	2	1	2

Patients in control group received sevoflurane alone. Patients in groups $fent_1$ and $fent_2$ received sevoflurane and either 1 $\mu g \cdot kg^{-1}$ fentanyl or 2 $\mu g \cdot kg^{-1}$ fentanyl, respectively.

Table 2. Neonates' demographic and experimental data. Values are mean (SD) or numbers.

Group	Control group (n=30)	Group $fent_1$ (n=29)	Group $fent_2$ (n=32)
Postoperative airway responses (n)	0	0	1
MAP; mmHg			
Awake	53.1 (5.4)	53.8 (4.7)	53.9 (4.5)
Before intubation	36.0 (5.7)**	36.2 (4.3)**	36.3 (4.0)**
Before skin incision	46.5 (5.2)**	46.7 (4.1)**	46.0 (5.0)**
1 min after skin incision	47.6 (5.9)**	47.4 (3.9)**	47.2 (4.8)**
HR; beat min-1			
Awake	147 (17)	147 (16)	146 (12)
Before intubation	150 (14)	148 (12)	149 (13)
Before skin incision	133 (12)**	134 (13)**	130 (11)**
1 min after skin incision	135 (10)**	136 (10)**	133 (13)**

** $p<0.01$ as compared with awake MAP. Patients in Control group received sevoflurane alone. Patients in groups $fent_1$ and $fent_2$ received sevoflurane and either 1 $\mu g \cdot kg^{-1}$ fentanyl or 2 $\mu g \cdot kg^{-1}$ fentanyl, respectively.

Results

Ninety-three neonates were enrolled in this study. Two neonates were excluded from the study because of serious airway symptoms necessitating the use muscle relaxants before the skin incision. There was no difference between the 3 groups in demographic data (Table 1). Hemodynamic responses were maintained within 20% of baseline measurements during the maintenance period. An airway response was not observed in the control group or the $fent_1$ group during the emergence from anesthesia. One neonate in the $fent_2$ group exhibited breathholding during the emergence from anesthesia (Table 2) and was treated with assisted mask ventilation. Vomiting was not observed during the induction of anesthesia in any of the groups.

Figures 2–4 showed individual responses to skin incision according to the up-and-down sequence. The MAC of sevoflurane at which a successful skin incision was possible in 50% of neonates was 2.91% (0.27) in the control group, 2.53% (0.31)

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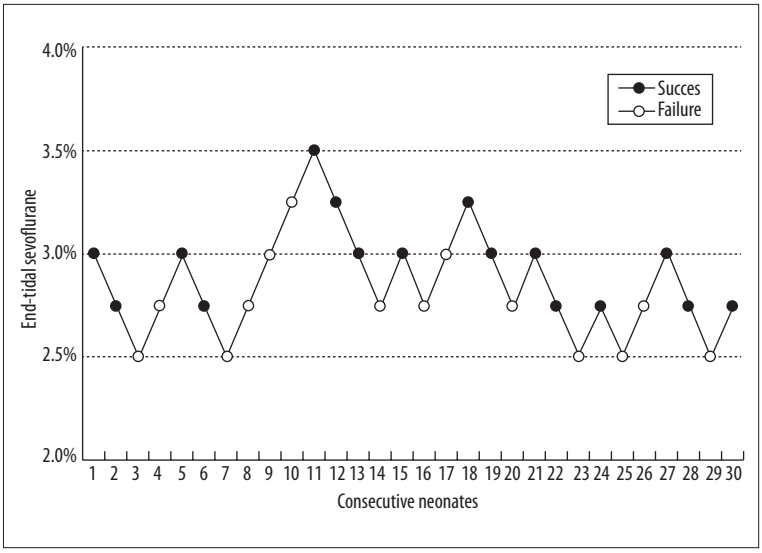

Figure 2. The responses of 30 consecutive neonates. Skin incisions were attempted at different end-tidal concentrations of sevoflurane. The MAC of sevoflurane in neonates was 2.91% (0.27).

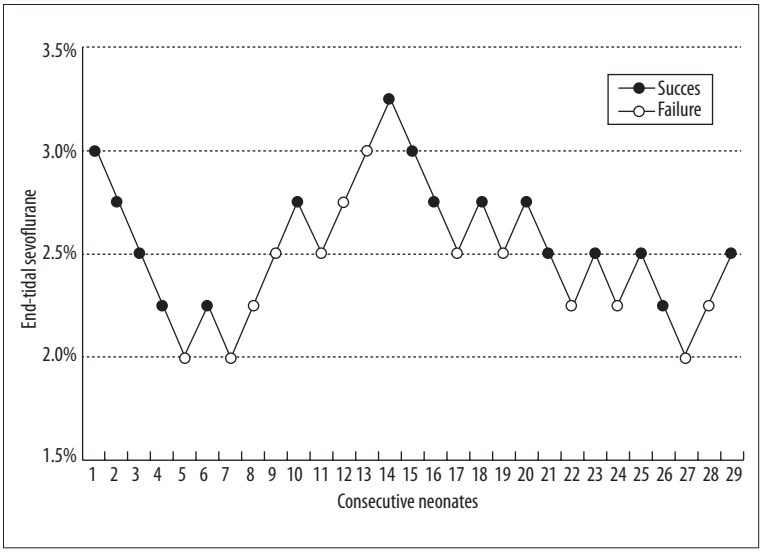

Figure 3. The responses of 29 consecutive neonates. Skin incisions were attempted at different end-tidal concentrations of sevoflurane with 1 ug/kg fentanyl. The MAC of sevoflurane in neonates receiving 1 ug/kg fentanyl was 2.53% (0.31).

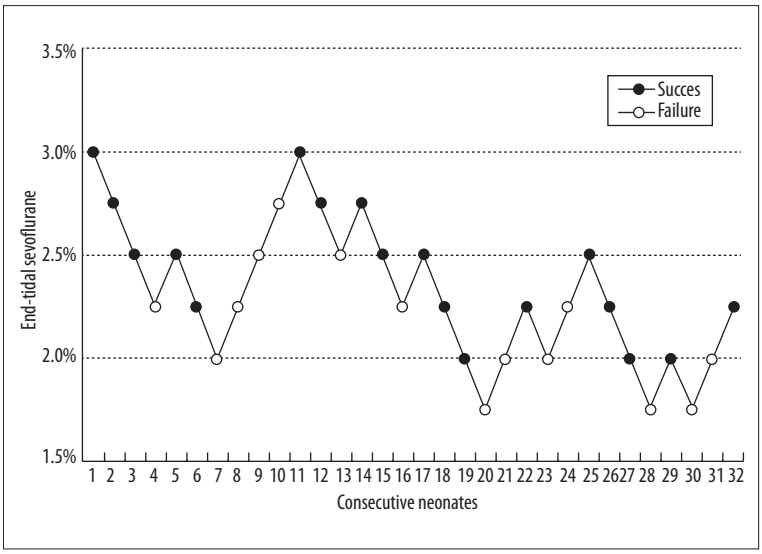

Figure 4. The responses of 32 consecutive neonates. Skin incisions were attempted at different end-tidal concentrations of sevoflurane with 2 ug/kg fentanyl. The MAC of sevoflurane in neonates receiving 2 ug/kg fentanyl was 2.34% (0.33).

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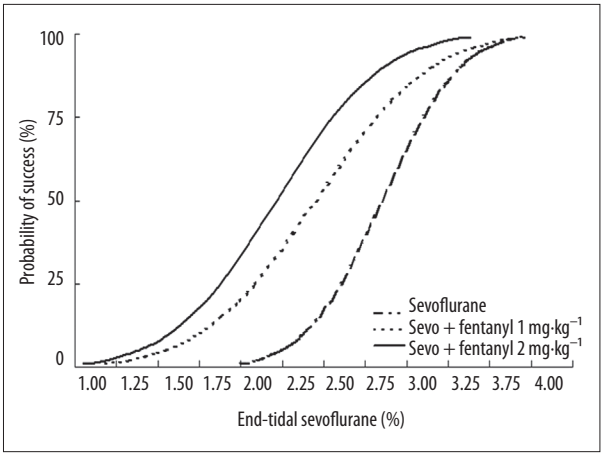

Figure 5. Relationship between sevoflurane concentration and response to skin incision in the 3 groups. The concentration-effect curves were defined from the data of the 3 groups by using logictical regression (ED_{50}: control group *vs.* group $fent_1$, $p<0.05$; control group *vs.* group $fent_2$, $p<0.01$).

with 1 μg/kg fentanyl, and 2.34% (0.33) with 2 μg/kg fentanyl. There were significant differences between the 3 groups in the MAC for sevoflurane (control group *vs.* $fent_1$ group, $p<0.01$; control group *vs.* $fent_2$ group, $p<0.01$).

The ED_{50} and ED_{95} (95% CI) values of sevoflurane obtained from the logistic probit regression analysis were respectively 2.82% (2.66–2.98) and 3.39% (2.89–3.89) in the control group, 2.44% (2.19–2.68) and 3.30% (2.51–4.09) in the $fent_1$ group, and 2.21% (1.97–2.45) and 3.11% (2.35–3.88) in the $fent_2$ group (Figure 5).

The mean arterial blood pressure and heart rate are shown in Table 2. In total, 70% of neonates in the 3 groups had hypotension after receiving high induction doses of sevoflurane, especially before intubation. However, mean arterial pressure returned toward normal levels after reducing the sevoflurane concentration following intubation and remained less than at the steady state target concentration of sevoflurane.

Discussion

In this study, we found that the MAC of sevoflurane in Chinese neonates was lower than previously reported in white neonates [1]. Additionally, single doses of 1 μg/kg and 2 μg/kg fentanyl significantly reduced the end-tidal concentration of sevoflurane required for skin incision by 13% and 20%, respectively, in Chinese neonates.

Few studies have evaluated the MAC of sevoflurane in neonates [1]. Lerman calculated the MAC of sevoflurane in neonates as 3.3%, which has been considered as a reference value for sevoflurane anesthesia in neonates [1]. Our study showed that the MAC of sevoflurane in neonates was 2.91% according to Dixon's up-and-down method and 2.82% according to logistic probit regression curves. The MAC of sevoflurane for Chinese neonates is less than that of white neonates, which is consistent with a previous study showing that the MAC value of sevoflurane in Asians is less than in whites.[4]

The MAC value is affected by the method of determination, type of surgery, patient age, body temperature, arterial carbon dioxide tension, and physiologic and genetic factors [1–6]. It is difficult to measure the alveolar concentration of inhaled anesthetics in the same subject repeatedly. In most studies, MAC is determined using the up-and-down method because it permits a small number of individuals to be studied. However, the up-and-down method can be affected by the starting concentration, the number of crossovers, increment size of concentration adjustments, and inter-individual variability [7]. The starting concentration of sevoflurane in our study was 3.0%, which is similar to that used in the clinic, but higher than the starting concentration of 2.4% in Lerman's study [1]. Furthermore, compared to Lerman's study, which had 4 crossover pairs and a total of 12 neonates, our study had 8 crossover pairs and a total of 28 neonates. More crossover pairs decreases the likelihood of reporting an inaccurate estimate and incurs minimal additional costs [7].

Physiologic, genetic, and pharmacologic conditions may alter MAC, such as body temperature, hypercapnia, and hypotension. For each 1°C decrease in core temperature, anesthetic requirements decrease by 5% [6]. Hypotension and hypercapnia may decrease MAC by affecting central nervous system function.[6] The differences in body temperature, carbon dioxide, and the type of surgical operation could have contributed to the differing results in our study and Lerman's study. Scopolamine, which was used as an anticholinergic pre-anesthetic medication in our study, has a weak sedative effect. A study in cats suggested that scopolamine does not affect the MAC of halothane [8]. However, the effect of scopolamine on the outcome of sevoflurane in humans has not yet been reported. Thus, our results provide a more accurate reference value for clinical sevoflurane anesthesia, especially in Chinese neonates.

The use of high doses of sevoflurane during anesthesia induction caused hypotension in our study. However, mean arterial pressure returned to normal values with the reduction of the sevoflurane concentration. Hypotension during sevoflurane anesthesia in neonates requires careful monitoring [9,10]. At equipotent doses, all of the potent inhalational anesthetics produce unacceptable hypotension in newborns [1,11]. Even at MAC concentrations, heart rate and blood pressure decrease by 12% and 30%, respectively, when using vapor anesthetics in

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newborns [6]. A newborn's myocardium is less compliant than that of an older child and has decreased contractile mass and a decreased velocity of shortening. Also, greater myocardial depression in neonates induced by volatile anesthetics may be mediated by the inhibition of Na-Ca^{2+} exchange and Ca^{2+} influx channels and at least in part by direct inhibition of cross-bridge cycling. Therefore, the negative inotropic and chronotropic effects associated with inhaled anesthetics are poorly tolerated [12–14]. The need for deeper levels of anesthesia to achieve satisfactory conditions for endotracheal intubation places the infant in a precarious position because there is a small safety margin between anesthetic overdose and inadequate depth of anesthesia. Uptake of potent anesthetics is more rapid in children because of an increased respiratory rate and cardiac index, as well as a greater proportional distribution of cardiac output to vessel-rich organs. This rapid rise in blood anesthetic levels, combined with functional immaturity of cardiac development, most likely explains why it is easy to deliver an inhaled anesthetic overdose to infants [15].

Opioids are frequently used for pain relief during surgical procedures, as well as to reduce the dose of inhalational anesthetics during pediatric anesthesia [16,17]. Fentanyl, a synthetic opioid with activity on μ_1 and δ-opioid receptors, is used frequently in neonates because it has a rapid onset, provides hemodynamic stability, blocks stress responses, and prevents pulmonary vascular resistance increases [18–20]. Furthermore, fentanyl does not significantly affect heart rate, blood pressure, cardiac output, or the regional distribution of blood flow to the major organs when it is administered in doses less than 3 mg/kg [20]. However, it can produce profound respiratory depression in newborns. Previous studies have shown that the plasma concentration of fentanyl in neonates vary slightly, between 30 min and 120 min after a bolus injection of the drug [21]. This prolonged elimination half-life of fentanyl has important clinical implications when repeated doses of fentanyl are used for the maintenance of analgesia, leading to the accumulation of fentanyl and its respiratory depressant effects. In our study, small single doses of 1 μg/kg and 2 μg/kg of fentanyl significantly decreased the MAC and concentration of sevoflurane in neonates, minimizing its adverse effects. Hence, although our study was not sufficiently powered to detect this effect, the use of fentanyl with sevoflurane had minimal respiratory depressant effects and improved the outcome of sevoflurane anesthesia in neonates.

In the current study, we used both logistic probit regression and the Dixon's up-and-down method to determine the ED_{50} and ED_{95} values of sevoflurane in Chinese neonates. The accuracy of the parameter estimates has been questioned, particularly when small samples, such as in the present study, are being evaluated [22]. Dixon's up-and-down method assumes that each measurement in a subject is independent and not correlated with any other measurements in that individual. The logistic regression technique uses the binary endpoint of success versus failure and does have potential weaknesses. In spite of these criticisms, the logistic regression model remains the only robust method to estimate both ED_{50} and ED_{95} values, and the 2 methods have been frequently used to study the potency of inhaled anesthetics in previous similar studies [1,23–26]. The end-tidal concentrations of sevoflurane in our study was measured with a sampling tube placed at the junction between the tracheal tube and the circuit, rather than measured in alveolar gas, which is the true MAC concentration. This method of monitoring expiratory concentrations of anesthetics is common in clinical anesthesia. Thus, the results can be used to guide clinical anesthesia.

Conclusions

In our study, the MAC value of sevoflurane in neonates was lower than previously reported. In addition, a single dose of fentanyl resulted in a dose-dependent decrease in the end-tidal concentration of sevoflurane required for skin incision. Fentanyl might also improve the outcome of sevoflurane anesthesia in neonates.

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Conflicts of interest

None declared.

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