Comparison of speed of inhalational induction in children with and without congenital heart disease

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ABSTRACT

Background: Conduct of stable inhalational anesthetic induction in children with congenital heart disease (CHD) presents special challenges. It requires in-depth understanding of the effect of congenital shunt lesions on the uptake, delivery, and equilibration of anesthetic drugs. Intracardiac shunts can alter the induction time and if delivery of anesthetic agent is not carefully titrated, can lead to overdosing and undesirable myocardial depression. Aims: To study the effect of congenital shunt lesions on the speed of inhalational induction and also the impact of inhalational induction on hemodynamics in the presence of congenital shunt lesions. Setting: Tertiary care hospital. Design: A prospective, single-center clinical study. Materials and Methods: Ninety-three pediatric patients undergoing elective surgery were segregated into three equal groups, namely, Group 1: no CHD, Group 2: acyanotic CHD, and Group 3: cyanotic CHD. General anesthesia was induced with 8% sevoflurane in 6 L/min air-oxygen. The time to induction was noted at loss of eyelash reflex and decrease in bispectral index (BIS) value below 60. End-tidal sevoflurane concentration, minimum alveolar concentration, and BIS were recorded at 15 s intervals for the 1st min followed by 30 s interval for another 1 min during induction. Hemodynamic data were recorded before and after induction. Results: Patients in Group 3 had significantly prolonged induction time (99 ± 12.3 s; \( P < 0.001 \)), almost twice that of the patients in other two groups (51 ± 11.3 s in Group 1 and 53 ± 12.0 s in Group 2). Hypotension occurred after induction in Group 1. No other adverse hemodynamic perturbations were observed. Conclusion: The time to inhalational induction of anesthesia is significantly prolonged in patients with right-to-left shunt, compared to patients without CHD or those with left-to-right shunt, in whom it is similar. Sevoflurane is safe and maintains stable hemodynamics in the presence of CHD.

Key words: Congenital heart disease; Electrical velocimetry; Inhalational anesthesia; Speed of induction

INTRODUCTION

Conduct of stable inhalational anesthetic induction in pediatric patients requires sound knowledge of the fundamental physiology specific to the age group and underlying pathology. This practice is all the more important for children with congenital heart disease (CHD) and a shunt lesion which can alter the induction time. Delivery of anesthetic agent if not carefully titrated can consequently lead to overdosing, undesirable myocardial depression, and hemodynamic instability. Therefore, for safe conduct of anesthesia in the pediatric population with
or without congenital cardiac lesions, knowledge of the factors governing the relationship between the delivered anesthetic and the achieved brain concentrations is necessary. There are three factors which determine inhalational anesthetic uptake: Anesthetic gas solubility (λ), cardiac output (Q), and alveolar to venous anesthetic partial pressure difference (P_a − P_v). The speed of induction is determined by the anesthetic equilibration between the alveoli and arterial blood and, in turn, the brain. The speed of inhalational induction is not altered substantially in patients with left-to-right shunt but is delayed in the presence right-to-left intracardiac shunt. Data to substantiate these theories have been obtained from computerized models, electrical analogs, and canine studies. Huntington et al. performed a study on six children with right-to-left shunts using inhalational anesthetic induction and found a delay in rise in arterial volatile anesthetic concentration with poorly soluble volatile agents, expecting delayed induction. Controversies still exist over the impact of left-to-right shunt lesions on the rapidity of inhalational induction and the actual prolongation of induction with right-to-left shunts, as no clinical study involving adequate number of patients has been done till date. This study was done to objectively compare the speed of induction of inhalational anesthesia using sevoflurane in pediatric patients with acyanotic, cyanotic, and without CHD. This study also evaluated the safety and hemodynamic effects of sevoflurane during induction as assessed by electrical velocimetry-based cardiac output monitoring in these patients.

MATERIALS AND METHODS

Ninety-three pediatric patients undergoing elective cardiac surgery or noncardiac surgery were studied prospectively after obtaining approval from the Institutional Review Board and written informed parental consent. The exclusion criteria were emergency surgery, previous cardiac surgery, presence of respiratory tract infection, asthma, pneumonia, bronchospastic lung disease, cardiogenic shock, unstable hemodynamics requiring inotropes, patient on mechanical ventilation, renal dysfunction, musculoskeletal disorder (malignant hyperthermia), liver disease, and neurological disorder. The children were categorized into three equal groups based on presence or absence of CHD. Group 1 included children with no cardiac lesion undergoing elective surgery; Group 2 included acyanotic children with left-to-right shunt undergoing cardiac surgery; and Group 3 included cyanotic children with right-to-left shunt undergoing cardiac surgery. All children were kept nil per oral for 6 h for solids, 4 h for breast milk or formula milk, and 2 h for clear fluids. Children weighing >5 kg were premedicated with syrup promethazine 0.5 mg/kg administered orally 30 min before shifting to the operation theater. After arrival in the operation theater, hemodynamic monitoring was established with 5-lead electrocardiography, pulse oximetry, noninvasive blood pressure, bispectral index monitor (BIS™ Monitoring System, Aspect Medical Systems Inc., Newton, MA, USA), and noninvasive cardiac output monitor (ICON® Osypka Medical GmBH, Berlin, Germany). Baseline readings of the following hemodynamic parameters were taken: Heart rate, systolic/diastolic/mean blood pressure, stroke volume, stroke index, cardiac output, cardiac index, index of contractility, and arterial saturation. In addition, baseline BIS values were recorded.

All the patients were anesthetized by overpressure technique of induction: Immediate 8% sevoflurane inhalation using 6 L/min of fresh gas flow. Children in Groups 1 and 2 received air-oxygen at FiO_2 0.5, and children in Group 3 received 100% oxygen. A Hygroboy DAR™ Infant-Pediatric Electrostatic Filter Heat and Moisture Exchanger (Covidien, Ireland) was interposed in the Jackson Rees modified Ayre’s T-piece circuit between the fresh gas tubing and the elbow connector. The end-tidal sevoflurane (EtSevo) and carbon dioxide (EtCO_2) gas concentrations were continuously measured by the multigas analyzer (Datex-Ohmeda S/5, Instrumentarium Corp., Helsinki, Finland), which was calibrated before every case. The time of induction was determined by the time taken to loss of eyelash reflex and decrease in BIS value <60. BIS values, EtSevo, and its minimum alveolar concentration (MAC) multiple were recorded at 15 s intervals for the 1st min (T1–T4) followed by 30 s interval for another 1 min (T5–T6) during the period of induction. Hemodynamic variables were recorded again at the end of induction of anesthesia.

The conduct of anesthesia, surgery, and cardiopulmonary bypass was according to standard institutional protocol.

Statistical analysis

Statistical package SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The power of the study was 90%. All values were expressed as frequency (n) or mean ± 1 standard deviation. Qualitative data were analyzed by Chi-square test. Quantitative data were analyzed by paired t-test. All
changes in hemodynamic parameters before and after induction of anesthesia were analyzed with ANOVA. *P* ≤0.05 was considered statistically significant.

**RESULTS**

Demographically, children in Group 1 were comparatively older (5.7 ± 2.08 years vs. 3.6 ± 1.23 years [Group 2] and 3.4 ± 1.11 years [Group 3], *P* < 0.05), and therefore, had significantly higher weight, height, and body surface area (*P* < 0.05). However, the demographic profile of patients in Groups 2 and 3 did not differ from each other [Table 1].

The time of induction as determined by the loss of eyelash reflex and achievement of BIS value <60 was considerably longer in Group 3 (99 ± 12.3 s) compared to 51 ± 11.3 s in Group 1 and 53 ± 12.0 s in Group 2 (*P* ≤0.001) [Table 2 and Figure 1].

The BIS values recorded at all time points were significantly higher in Group 3 as compared to the other two groups (*P* ≤0.01) [Table 3 and Figure 2].

In addition, EtSevo and MAC values were significantly higher at all time points in Group 3 compared to the other groups (*P* ≤ 0.05) [Table 3 and Figure 3]. Within Groups 1 and 2, EtSevo and MAC values peaked at time point T2, whereas in Group 3, EtSevo and MAC values peaked later at time point T3.

The heart rate was significantly higher in Group 2 patients both before (140 ± 28.1 bpm) and after induction (125 ± 16.2 bpm) (*P* ≤ 0.05) as compared to patients in the other two groups. It decreased after induction in all groups. The mean arterial pressure decreased significantly after induction in Group 1 (88 ± 10.5 mmHg to 66 ± 7.5 mmHg, *P* ≤ 0.05). Children in Group 1 had significantly higher stroke index as compared to the patients in other two groups both before and after anesthetic induction. Children in Group 3 had significantly lower cardiac index as compared to the children in other two groups both before and after anesthetic induction. The index of contractility and systemic arterial oxygen saturation was lower in Group 3 both before and after induction as compared to the other two groups [Table 4].

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**Table 1: Demographic characteristics**

| Variable                        | Group 1 (mean±SD) | Group 2 (mean±SD) | Group 3 (mean±SD) |
|---------------------------------|-------------------|-------------------|-------------------|
| Age (years)                     | 5.7±2.08*         | 3.6±1.23          | 3.4±1.11          |
| Gender (male/female) (n)        | 21/10             | 18/13             | 23/8              |
| Weight (kg)                     | 18.9±6.10*        | 11.2±4.14         | 12.2±4.43         |
| Height (cm)                     | 110.8±19.55*      | 87.4±16.67        | 91.2±17.87        |
| BSA (m²)                        | 0.76±0.097*       | 0.52±0.091        | 0.55±0.089        |

*P*≤0.05. SD: Standard deviation

**Table 2: Comparison of induction times**

| Group | Induction time (s) (mean±SD) |
|-------|-----------------------------|
| 1     | 51±11.3                     |
| 2     | 53±12.0                     |
| 3     | 99±12.3*                    |

*P*≤0.001. SD: Standard deviation

**Table 3: Inhalational agent characteristics and depth of anesthesia**

| Time | ET sevo (mean±SD) | MAC (mean±SD) | BIS (mean±SD) |
|------|-------------------|---------------|---------------|
|      | Group 1 | Group 2 | Group 3 | Group 1 | Group 2 | Group 3 | Group 1 | Group 2 | Group 3 |
| T1   | 2.9±0.85 | 3.9±0.81* | 4.3±1.42* | 1.5±0.33 | 1.9±0.43 | 2.1±0.78* | 93±3.0 | 93±2.7 | 92±2.9 |
| T2   | 4.4±1.40* | 4.6±1.16* | 4.7±1.59* | 2.2±0.72* | 2.2±0.52* | 2.4±0.70* | 80±7.4 | 79±6.2 | 82±4.7 |
| T3   | 4.3±1.34 | 4.1±1.29* | 5.0±1.61* | 2.1±0.83 | 2.1±0.76* | 2.6±0.52* | 62±8.6 | 64±9.8 | 74±4.8* |
| T4   | 2.4±0.81 | 3.0±1.05* | 4.6±1.70* | 1.5±0.53 | 1.5±0.63 | 1.9±0.81* | 35±9.1 | 41±14.7 | 67±13.3* |
| T5   | 0.6±0.24* | 0.7±0.32* | 4.3±1.49* | 0.3±0.11* | 0.4±0.17* | 2.1±0.78* | 21±7.3 | 25±9.5 | 61±15.5* |
| T6   | 0.3±0.13* | 0.4±0.18* | 2.8±1.06* | 0.2±0.08* | 0.2±0.09* | 1.5±0.53* | 13±5.3 | 19±7.5 | 50±14.4* |

*P*≤0.05, *P*≤0.01, *P*≤0.001 for intergroup comparisons, †*P*≤0.01, ‡*P*≤0.001 for within group comparisons from baseline. ET-sevo: End-tidal sevoflurane concentration (%), MAC: Minimum alveolar concentration, BIS: Bispectral index

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**Figure 1: Comparison of speed of induction, *P* ≤ 0.001**
No arrhythmias or other adverse hemodynamic perturbations occurred at the MAC used for induction.

**DISCUSSION**

Induction of anesthesia in pediatric patients, especially neonates and infants is challenging, more so in the presence of CHD. Whether intravenous or inhalational method of anesthetic induction is employed, the goals remain to maintain cardiopulmonary homeostasis and prevent adverse events.

For over a century and half, volatile anesthetic agents have been the mainstay for induction and maintenance of anesthesia with continuous evolution of newer and better inhalational agents. There are three factors which determine inhalational anesthetic uptake (V): Anesthetic gas solubility (λ), cardiac output (Q), and alveolar to venous anesthetic partial pressure difference (\(P_A - P_V\)) as given by the Fick’s equation:

\[
V = \lambda \times Q \times (P_A - P_V)/P_B.
\]

Where \(P_B\) is the barometric pressure.

The speed of induction with an inhalational anesthetic is determined by the rate of anesthetic equilibration between the alveoli and arterial blood followed by equilibration between the arterial blood and the brain tissue and therefore is influenced by fresh gas inspired concentration, concentration effect, minute ventilation, functional residual capacity, blood/gas solubility of the anesthetic, presence of intracardiac shunts, and cardiac output. There is ample literature documenting rapid onset of anesthetic induction with sevoflurane in different pediatric populations with different methods of administration, namely, overpressure technique (immediate 7–8% inhalational induction), incremental dosing (tidal volume technique) and single breath vital capacity. While induction was most rapid with the single breath vital capacity technique, it lacks applicability in young children and has no proven significant advantage over overpressure technique. Similarly, induction time was found almost twice as much prolonged when compared...
with the overpressure technique because of slow rise of alveolar partial pressures and hence delayed equilibration in brain tissue.\(^{[18-16]}\) Moreover, in most of these referenced studies, sevoflurane was administered along with nitrous oxide-oxygen mixture in varying proportions and the patients were premedicated with midazolam, both of which have MAC-sparing effects thereby affecting the observed time of induction.\(^{[20-22]}\)

There was a lack of representative data providing actual time of induction with the use of 8% sevoflurane in children without the use of any other MAC-sparing agent.

Furthermore, there is a dearth of literature elaborating the effect of shunt lesions on the magnitude of difference in the time of induction using exclusive inhalational anesthesia in patients with congenital lesions. Indeed, books do mention about delayed onset of anesthetic induction with poorly soluble volatile anesthetic agents in cyanotic children with right-to-left shunt,\(^{[6,23,24]}\) but the observation is based on physiological postulations from computerized models,\(^{[1]}\) electrical analogs,\(^{[2]}\) canine studies, and a few children with tetralogy of Fallot.\(^{[3,4]}\) Zeyneloglu et al. recently investigated the induction characteristics of sevoflurane in cyanotic and acyanotic children with CHD compared with healthy controls and found a significant difference between the patients with acyanotic and cyanotic CHD.\(^{[25]}\) They employed sevoflurane in 7% concentration and had subjectively identified the time of induction based on loss of eyelash reflex. The present study was designed to fill a lacuna and add objectivity to the understanding of inhalational induction technique in children with CHD, who present not only for cardiac surgeries but also for various other surgical procedures including outpatient procedures.

The results of this study not only confirm the popular physiological assertion of delay in the time of inhalational anesthetic induction in patients with cyanotic CHD but also give the magnitude of delay in induction which is almost twice of that in patients with acyanotic CHD or without CHD [Table 2]. This observation corroborates the findings of Huntington et al.\(^{[4]}\) and previous other experimental studies\(^{[1,2,24]}\) that with decrease in pulmonary blood flow due to right-to-left shunt, the rate of rise of partial pressure of poorly soluble inhalational anesthetic (sevoflurane in this study) in arterial blood also decreases. For the same reason, we found significantly higher EtSevo concentrations and MAC equivalents throughout induction in Group 3 patients, in addition to the finding that EtSevo and MAC values peaked later in this group (~45 s) than in Groups 1 and 2 (~30 s) [Table 3]. The decrease in pulmonary blood flow coupled with dilution of inhalational anesthetic due to mixing of blood in left ventricle prolonged the rise of partial pressures in brain resulting in delayed induction. In the present study, the BIS values were significantly higher in Group 3 at all time points as compared to the other two groups, implying that the equilibration of sevoflurane between arterial blood and brain was delayed.

The MAC of sevoflurane is highest in neonates (3.3% ± 0.2%) and decreases slightly in 1–6 months age infants (3.2% ± 0.1%) and is similar to adults in 1–12-year-old children (~2.5%).\(^{[6-12]}\) In the absence of an intracardiac shunt, it would be expected that patients in Groups 2 and 3 would be induced later than those in Group 1 as patients in latter group were older. Although the patients in Group 3 were demographically similar to those in Group 2, yet a significant delay in induction was found only in Group 3 patients, proving that the right-to-left shunt contributed to the significantly greater delay. Esper et al. in their recent study concluded that hematocrit does not have a significant effect on the blood solubility of isoflurane, sevoflurane, and desflurane.\(^{[26]}\) Thus, the high hematocrit in cyanotic patients (Group 3) would not have influenced their inhalational induction characteristics.

Our results also reaffirm the fact that inhalational induction in acyanotic patients with left-to-right shunt takes similar time as in patients without CHD as was reflected by the similar trend of BIS values, EtSevo concentrations, and MAC equivalents in both the groups. Recirculation through the lungs in the presence of left-to-right shunt reduces uptake from the alveoli. The resultant rise is alveolar partial pressure of the anesthetic is compensated by concomitant increase in pulmonary blood flow which enhances anesthetic uptake. Our finding was in agreement with that of Tanner et al., who showed patients with left-to-right shunt do not have substantially altered the rate of anesthetic induction.\(^{[1]}\)

Sevoflurane is routinely used for inhalational anesthetic induction in both cyanotic and acyanotic patients. Similar to previously published studies,\(^{[9,11,14,27,28]}\) 8% sevoflurane was found to be safe in pediatric patients with and without CHD. This observation
was drawn from the comparison of hemodynamic variables before and after induction, obtained by electrical velocimetry-based cardiac output monitoring, in agreement with conclusions drawn by impedance cardiometry and transthoracic echocardiography. Bernstein and Lemmens demonstrated the application of electrical velocimetry in the year 2005. It has been validated against thermodilution and Fick techniques of invasive cardiac output measurement and is interchangeable with Doppler ultrasound in varied patient population from very low birth weight babies to adults.

Evaluation of hemodynamic variables revealed that patients with left-to-right shunt had significantly higher heart rate both before and after anesthetic induction - a sign of heart failure prevalent in these patients at the time of presentation. There was a slight reduction of heart rate in all patients after anesthetic induction, attributable to the abolition of sympathetic drive with anesthetic agents. Hypotension, >20% drop in mean arterial pressure from baseline, was observed to occur in patients without CHD (Group 1). Hypovolemia commonly occurs after fasting and is unmasked after induction, once the sympathetic drive is obliterated. Patients with CHD (Groups 2 and 3) did not experience hypotension after induction as they generally have greater intravascular volume secondary to renin-angiotensin system activation resulting from a chronically underperfused state. Children in Group 1 had a significantly higher stroke index and index of contractility (ICON) as compared to children with CHD (Groups 2 and 3). Children with cyanotic CHD (Group 3) had significantly reduced cardiac index, index of contractility, and systemic arterial oxygen saturation both before and after anesthetic induction as compared to children in other two groups, owing to chronic hypoxia and ventricular dysfunction. Although patients with acyanotic CHD (Group 2) had a reduced stroke index, they could mount a tachycardic response and maintain their cardiac index. Children with cyanotic CHD and reduced pulmonary blood flow are invariably treated with β-blockers and are unable to manifest a similar response. Overall, sevoflurane was found to be safe and maintained stable hemodynamics in children with CHD.

Limitations of the study
The study population was not homogeneous as children without CHD were older than those in the other two groups. Children with cyanotic CHD were oxygenated with 100% oxygen, whereas patients in other two groups were oxygenated with 60% oxygen in air. Although nitrous oxide, which hastens induction by second gas effect, was not used; the effect of 100% oxygen on the uptake of inhalational agent cannot be ruled out. Since central venous catheterization was performed only after induction, the data derived from central venous pressure including systemic vascular resistance could not be obtained.

CONCLUSION
The time to inhalational induction of anesthesia is significantly prolonged in patients with right-to-left shunt, compared to patients without CHD or those with left-to-right shunt, in whom it is similar. Sevoflurane, in the clinically used concentrations, is safe and maintains stable hemodynamics in the presence of CHD.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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