Original Article

EC_{50} of sevoflurane for classic laryngeal mask airway insertion in children at different time points: A randomized blind trial

Sameer Sethi, Nitika Goel, Babita Ghai, Mantoliya N. Sharma, Jagat Ram[1]

Departments of Anaesthesia and [1]Ophthalmology, PGIMER, Chandigarh, India

Abstract

Background and Aims: Literature documents EC_{50} (End-tidal) of sevoflurane for CLMA (Classic Laryngeal Mask airway) insertion between 1.5 and 2% and most of these studies suggest maintaining the required end-tidal sevoflurane concentration for 10-25 minutes before LMA insertion. Waiting for this long interval for blood brain sevoflurane equilibration may not be feasible in children especially during failed ventilation. We aimed to estimate EC_{50} of sevoflurane for CLMA insertion at equilibration time points of 2.5 min and 5.0 min.
Material and Methods: In this randomized trial, children aged 2-8 years of either sex having American Society of Anesthesiologists status I undergoing elective cataract surgery were included. After inhalational induction of general anesthesia with 8% sevoflurane and 100% oxygen, intravenous cannulation was secured. The sevoflurane vaporizer was finely adjusted to maintain an end-tidal sevoflurane concentration at 2% for 2.5 min for first child in group 2.5 and 5 min in group 5.0. This was followed by LMA insertion which was considered to be unsuccessful if there was "movement" and successful if "no movement" occurred. End-tidal concentration was increased/decreased (step-size 0.2%) using Dixon and Massey up and down method in the next patient depending upon the previous patient's response.
Results: EC_{50} of sevoflurane for insertion of classic LMA in children aged 2-8 yrs in 100% oxygen was 1.1% (0.9-1.2) at 2.5 min and 1.6% (1.5-1.7) at 5.0 min. Derived EC_{95} (95% CI) at 2.5 min was 1.8% (1.5-9.2) and at 5.0 min was 1.8% (1.4-8.8) respectively.
Conclusion: We suggest maintaining end-tidal sevoflurane of 1.6% for 2.5 min and 1.8% for 5 min for successful CLMA insertion.

Keywords: Classic laryngeal mask airway insertion, end-tidal sevoflurane, pediatric anesthesia.

Introduction

The optimum sevoflurane EC_{50} required for CLMA insertion in unpremedicated children is reported to be in the range of 1.5-2.0%.[1,2] In most of studies calculating EC_{50} and EC_{95}, the required end-tidal sevoflurane (Etsevo) has been maintained for 10-15 min in order to attain the blood brain partial pressure equilibrium for sevoflurane.[1-3] Waiting for such a long time may not be feasible especially in busy centers with long operating lists. Though studies are present which document time for attainment of partial pressure equilibrium of sevoflurane of approximately 2.25 min,[4,5] we could not find any literature where feasibility of CLMA insertion at shorter times has been checked. We aimed to check the feasibility of CLMA insertion at shorter equilibration time points of 2.5 min and 5 min and therefore the EC_{50} of sevoflurane for CLMA insertion at these shorter equilibration times respectively.

Material and Methods

This was a single-center, prospective, randomized, blind trial conducted in children who were recruited from the preoperative room, in the Advanced Eye Centre, PGIMER, Chandigarh between 1st August 2014 and 30th June 2015. After the approval of the Institutional Ethics Committee (NK/1726/

Address for correspondence: Dr. Nitika Goel,
Departments of Anaesthesia, PGIMER, Chandigarh, India.
E-mail: nitikagoel7@gmail.com

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MD/10029-30 dated 18.09.2014), this trial was registered with Clinical Trial Registry of India (CTRI/2015/05/005775). Written informed consent from the parents/guardians was taken before recruitment in the study. Children aged between 2 and 8 years of either sex and ASA status I, undergoing elective cataract surgery were recruited in this trial. Those with upper respiratory tract infection, any airway anomaly, anticipated difficult airway, history of asthma, any cardiac anomaly, psychiatric disease or seizure, or any psychotropic medication use were excluded from this study.

After confirming their fasting status (8 h for solids and 2 h for clear fluids), children were randomized into one of the two groups using (computer-generated randomization schedule; Software Random-RANDOMIZER) i.e,

Group 2.5: the insertion of CLMA was attempted at 2.5 min of equilibration of a predetermined Etsevo concentration.

Group 5.0: the insertion of CLMA was attempted at 5.0 min of equilibration of a predetermined Etsevo concentration.

Anesthesia was induced using circuit prefilled with sevoflurane 8% in 100% at 6 L of oxygen using a face mask with *Datex Ohmeda Aespire view* anesthesia workstation (GE healthcare, GE medical systems, information technologies Asia). Intravenous agents or muscle relaxants were not used during induction. Once the loss of eye reflex and loss of muscle tone was noted, intravenous cannulation was performed and the vaporizer dial setting was finely adjusted to attain ET_{sevo} to the predetermined target concentration level. This predetermined target concentration was Etsevo concentration of 2% which was sustained for 2.5 min in group 2.5 and 5 min in group 5.0 in the first child by finely altering the vaporizer dial settings. ET_{sevo} for the next child was decided based on the response of the previous child's by using Modified Dixon's Up and Down Method (MDUDM),[6] with 0.2% step up (if there was movement in the previous child) or decreased by 0.2% (if there was no movement in the previous child). In those children where movement was seen, for the child's safety, a bolus of intravenous propofol (1 mg/kg) was injected and sevoflurane was increased immediately to 8% of vaporizer dial concentration, to avoid adverse events. Movement and adverse events were recorded. Each child provided one dot point towards the estimation of EC_{50} for CLMA insertion in the up and down study groups.

A single experienced CLMA user, the primary investigator (with an experience of more than 50 CLMA insertions), performed insertion of CLMA *(Classic laryngeal mask airway, Laryngeal Mask Silken; Romsons Sci. & Surg. India Pvt. Ltd., Agra, India)* and fixed it as per standard practice. Movements during and within 1 min of CLMA placement were observed by an independent observer and were recorded as "movement" or "no movement". They were recorded as "movement", if mouth opening was difficult while CLMA insertion or if there was any coughing, gagging, breath holding, biting, laryngospasm, or purposeful movements of head and neck or the extremities while insertion or within 1 min after CLMA insertion.

The predicted number of movement-no movement pairs needed for the present study has been computed using power analysis which is based on Modified Dixon and Massey method (MDUDM).[6,7] At least 20 patients in each group were included in the study to complete 8 pairs (successful pairs or unsuccessful pairs).[8] The primary outcome of this study was EC_{50} of end-tidal sevoflurane for successful CLMA insertion at 2.5 min and 5 min of equilibration time. The secondary outcome was to determine EC_{95} of end tidal sevoflurane for successful CLMA insertion at 2.5 min and 5 min of equilibration time points, CLMA success rate and adverse events (recorded as coughing, gagging, breath holding, laryngospasm, biting, purposeful movement of extremities) at LMA placement.

Statistical analysis

Statistical analysis was performed using SPSS version 22.0 for windows (Chicago, IL, USA). Patient characteristics were presented as mean (SD) or absolute numbers (percentages). Continuous variables were analyzed by t-test and categorical variables were analyzed by Chi-Square test. The mean of mid-point of all unsuccessful/successful pairs was used to determine EC_{50} using Dixon and Massey's up and down method (MDUDM).[6,7] Probit analysis of the data was then performed to determine the dose-response relationship. Data for successful responses for each category was used to plot a sigmoid dose-response curve and a log dose-response relation. EC_{50} and EC_{95} were obtained by extrapolation of the sigmoid curve. The difference of EC_{50} and EC_{95} between the groups was analyzed by student's t-test. Hemodynamic measures were analyzed by Student's t-test. A *P*-value of less than 0.05 was considered significant.

Results

Eighty children were assessed for eligibility, among them 63 met the inclusion criterion. Parents of eight children denied consent. We also excluded 6 children as the children were exposed more than twice for anesthesia and they needed premedication.

Forty-nine children aged 2-8 years were included in this study. A CONSORT diagram showing patients recruitment, randomization and data collection has been provided in Figure 1. Demographic profiles of the children are depicted in Table 1.

The calculated EC_{50} of sevoflurane for successful LMA insertion using Dixon and Massey was 1.1 (0.9-1.2) for

Group 2.5 and 1.6 (1.5-1.7) for Group 5.0. Figures 2 and 3 depict ETsevo concentrations at which insertion of LMA was successful or unsuccessful in the up and down plot at 2.5 min and 5 min, respectively. Results of Student's t-test of the EC_{50} of sevoflurane for CLMA insertion in Group 2.5 compared to Group 5.0 were significantly lower ($P = 0.002$).

The result obtained from the Dixon and Massey was further analyzed with the probit regression analysis to confirm the EC_{50} (95% CI) and derive the EC_{95} (95% CI) for LMA insertion with sevoflurane. The EC_{50} and EC_{95} for Group 2.5 were 1.1 (0.4-1.4) and 1.8 (1.5-9.2) respectively, and the EC_{50} and EC_{95} were 1.2 (0.6-1.8) and 1.8 (1.4-8.8) for Group 5.0 respectively. The probit analysis of the data for both the groups was performed to determine dose- response relationship. Dose-response curve and a log-dose relationship for both the groups were plotted [Figures 4 and 5].

The success rate of LMA insertion was comparable in both the groups. In Group 2.5, out of 26 children, successful CLMA insertion was performed in 17 children (65%) and CLMA . In Group 5, out of 23 children, CLMA was successfully placed in 14 children (61%). The incidence of adverse events in the two groups has been shown in Table 2. The heart rate of children at baseline in both the groups was similar ($p = 0.571$). Hemodynamic responses at intravenous cannula insertion and at CLMA insertion were similar in the two groups. End-tidal carbon dioxide ($EtCO_2$) in both the groups remained in the range of 33-41 mmHg. Overall, we did not observe any clinically significant changes in SpO_2 during the study, and no child had a reduction in SpO2 to below 95% during the study.

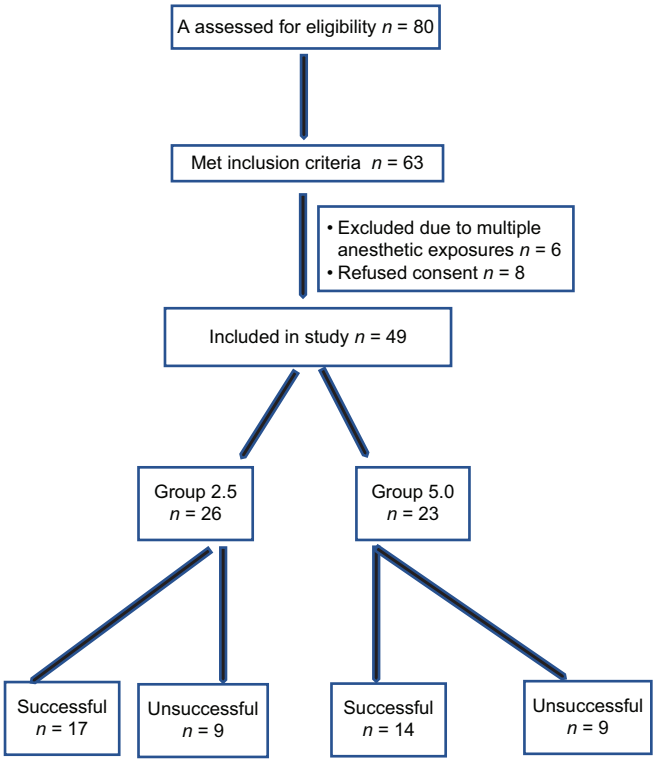

Figure 1: CONSORT flow diagram for patients' recruitment, randomization and data collection

Discussion

The results of this study showed that EC_{50} of sevoflurane for the insertion of CLMA in children aged 2-8 years in 100% oxygen was 1.1% (± 0.3%) at 2.5 min and 1.6% (± 0.2%) at 5.0 min. Derived EC_{95} (95% CI) from probit regression analysis at 2.5 min was 1.6%(1.4-2.3%) and at 5.0 min was 1.8%(1.6-8.8%).

This study shows the feasibility of LMA insertion at 2.5 min and 5 min of blood-brain partial pressure equilibration time. In contrast to the previous studies where the time allowed of

Table 1: Patients' demographic profile in two groups

VARIABLE	Group 2.5	Group 5
Age (year)	5.1±2.2	5.1±2.0
Sex (M/F)	10/16	15/8
Weight (kg)	16.3±4.5	16.3±3.4
LMA size 2/2.5	11/15	16/7
Primary disease (Congenital/ traumatic cataract)	8/18	7/16

Data expressed as mean±SD or absolute numbers

Table 2 Incidence of adverse effects in two groups

Complications	Group 2.5 (*n*=26)	Group 5.0 (*n*=23)
Movement of head and neck	7 (27)	5 (22)
Clenching	1 (4)	2 (9)
Coughing	3 (12)	2 (9)
Laryngospasm	0	0

Values are expressed as absolute numbers (%)

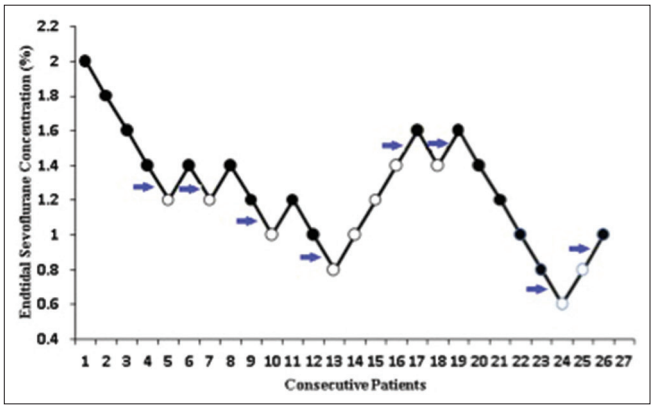

Figure 2: The ETsevo concentrations at which insertion of LMA was successful marked as (•, no movement) or unsuccessful marked as (○, movement) in the up and down plot for group 2.5. The consecutive responses of 26 unpremedicated children depicted as arrows (->) show the average of crossover (movement–no movement) patient pairs. The concentration of sevoflurane (EC_{50}) required for smooth insertion of CLMA was determined to be 1.003 (0.843-1.142)

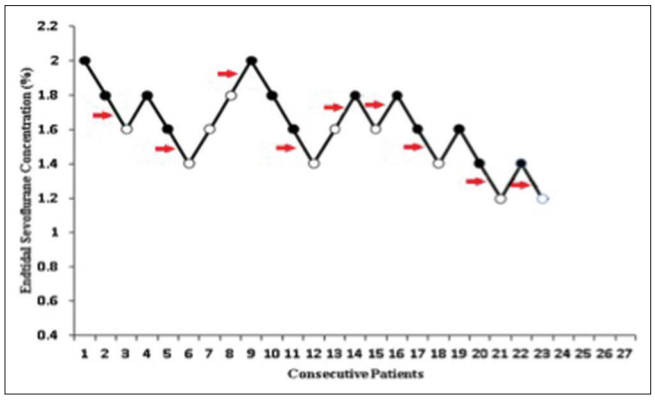

Figure 3: The ETsevo concentrations at which insertion of LMA was successful marked as (•, no movement) or unsuccessful marked as (○, movement) in the up and down plot for group 5. The consecutive responses of 23 unpremedicated children depicted as arrows (->) shows the average of crossover (movement–no movement) patient pairs. The concentration of sevoflurane (EC_{50}) required for smooth insertions of CLMA was determined to be 1.508 (1.127-1.832)

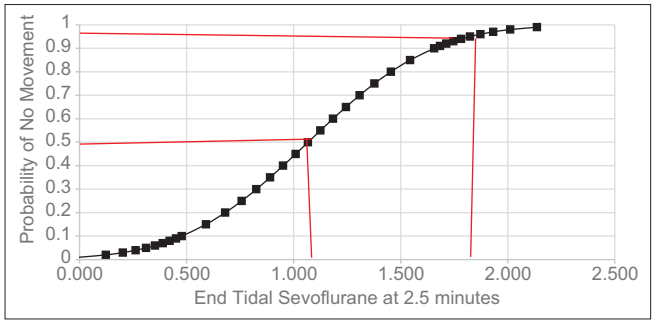

Figure 4: Dose–response curves of sevoflurane concentration plotted from the probit regression analyses of individual end-tidal concentrations (EC) showing EC_{50} and EC_{95} values in GROUP 2.5

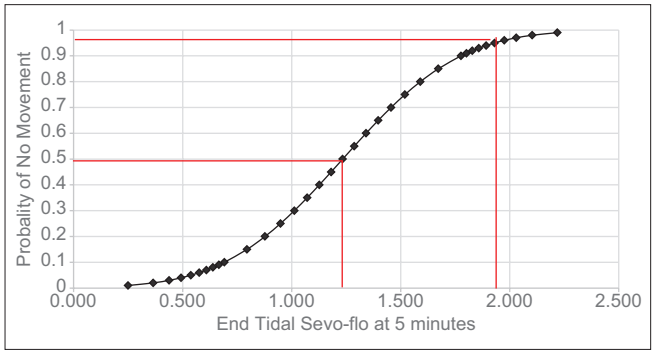

Figure 5: Dose–response curves of sevoflurane concentration plotted from the probit regression analyses of individual end-tidal concentrations (EC) showing EC_{50} and EC_{95} values in GROUP 5.0

equilibration has been reported to be 10-25 minutes,[9-15] we waited for 2.5 min and 5 min, respectively for equilibration, before insertion of CLMA. We were successfully able to insert CLMA at 2.5 min in 62% and at 5 min in 61% of our study population.

Traditionally, the anesthetic potency of inhalational agents is measured as the median effective concentration (EC_{50}).[4] EC_{50} is best described commonly as the minimum alveolar concentration,[16-18] at which 50% of subjects lack a response to a skin incision. It is accepted as the most widely used measure of anesthetic potency for volatile anesthetics including sevoflurane.[19]

Similarly, EC_{50} has been derived for various interventions. These EC_{50} concentrations have been estimated after achieving and sustaining the target concentration for a particular duration allowing equilibration of blood and brain anesthetic partial pressures. Therefore, the attainment of effect-site concentration (Ceff) is required for a given effect.[4]

The alveolar fraction is clinically measured as the end-tidal concentration because it approximates the partial pressure in the blood. The effect-site partial pressure is estimated as the plasma effect-site equilibration rate constant (k_{e0}) and the time for equilibration of anesthetic partial pressures is estimated by computing the time constant for equilibration in the tissue.[20,21] The predictable depth of anesthesia can be measured as the end-tidal concentration, under steady-state conditions. Thus, inhalational anesthesia is clinically achievable by closely observing and titrating the end-tidal concentration of the volatile anesthetic once equilibration between the alveolar and blood concentration occurs.[22]

End-tidal concentration can be used to derive effect-site concentration by using a real time predicted display based on pharmacodynamic modeling.[22] In pharmacokinetic modeling the time to half-equilibration ($t_{1/2}k_{e0}$) is reported to be 2.25 min for sevoflurane.[4] $t_{1/2}k_{e0}$ is defined as half time for sevoflurane distribution to effect site concentration.[4] Kennedy *et al.* showed that during clinical anesthesia it is possible to compute and display the estimates of Ceff in real time from ET_{sevo} and also had defined an appropriate $t_{1/2}k_{e0}$ for airway manipulation.[4] They compared the practicality of ET_{sevo} and Ceff guided LMA insertion using sevoflurane in 30 women aged 30-66 years.[4] The women were induced with 6% sevoflurane in 6 L of oxygen. LMA insertion was attempted using up and down methodology after achieving predetermined c_{eff} (in first patient was 2.5%).[4] They combined historical estimates of the equilibrium EC_{50} for insertion of LMA to derive a pooled EC_{50} of 2.17%.[4] They computed graphically the optimum $t_{1/2}k_{e0}$ corresponding to the target EC_{50} of 2.17% of sevoflurane for LMA insertion as 2.25 min.[4]

Muzi *et al.*, in their study also determined the time taken to achieve ideal acceptable conditions for successful LMA placement in (T_{50}) 50% of volunteers (unpremedicated adults aged 19-32 years) using 6-7% sevoflurane with 66% nitrous oxide in one of their group.[23] The time used in first volunteer was 3.5 min based on their pilot study, using Dixon and Massey method with step size of 30 s and found this time (T_{50}) to be 1.7 min (0.7-2.7 min).[23]

In an optimal safety time determination study in 25 children (3-8 years old), where the authors manually ventilated the children after attaining ETsevo of EC_{95} 3.91% for 5.0 min in first child and determined the time needed for lack of the response to insertion of the LMA in 50% children (T_{50}) to be 2.4 minutes (2.0-2.8 min) and extrapolated the time needed for lack of the response to insertion of the LMA in 95% children (T_{95}) as 3.2 minutes (2.8-4.6 min), with 1 minute as a step size.[24] Thus keeping all these studies in mind, we hypothesized that it would be feasible to insert CLMA at shorter equilibration times. Therefore we chose equilibration times of 2.5 min and 5 min, to evaluate the EC_{50} and EC_{95} of sevoflurane for CLMA insertion.

In busy paediatric centers, waiting for 10-25 minutes before airway manipulation can pose great economic burden in terms of unnecessary anesthetic agent usage. In addition, it can lead to delay in operation theater list, which not only prolongs fasting in children but also exposes them to unnecessary anaesthesia. Therefore checking for feasibility for LMA insertion at shorter times is important.

Our study should be read in light of some limitations. Since we included only unpremedicated children, the results may not be applicable in premedicated ones. Furthermore we used 8% sevoflurane in 100% oxygen for induction of anesthesia. The results may vary in the presence of nitrous oxide. Besides, the results may not be applicable to infants and older children.

Conclusion

Through this study, we endeavored to calculate EC_{50} and EC_{95} for CLMA insertion at equilibration times of 2.5 mins and 5 mins. We suggest maintaining an end tidal sevoflurane of 1.8%(1.5-9.2) at 2.5 min and 1.8%(1.4-8.8) at 5 mins for successful CLMA insertion in children aged between 2 and 8 years after inhalational induction with 8% sevoflurane.

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Conflicts of interest
There are no conflicts of interest.

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