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Research Article

Nebulized lidocaine and fentanyl before sevoflurane induction of anesthesia in congenital diaphragmatic hernia repair: Prospective double blind randomized study

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KEYWORDS

Fentanyl;
Lidocaine;
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Abstract *Introduction:* Gastric overdistension by mask ventilation during induction of anesthesia in congenital diaphragmatic hernia (CDH) repair may worsen hypoxemia. Topical airway anesthesia may improve the intubating conditions during sevoflurane induction without muscle relaxation. The present study was designed to evaluate the effect of nebulized lidocaine and fentanyl on the intubating conditions without muscle relaxation during sevoflurane induction of anesthesia in infants undergoing CDH repair. The secondary aim was studying hemodynamic changes during induction.
Patients and methods: Forty patients scheduled for (CDH) repair were randomly selected and blindly categorized to the following: Nebulizer group: Nebulized solution of 4 mg kg^{-1} lidocaine 1% plus 2 μg kg^{-1} fentanyl, Control group: Nebulized solution of comparable volume/weight normal saline 0.9%. Nebulizer of either solution was applied 15 min before sevoflurane induction.
Results: Heart rate (HR) and mean arterial blood pressure (mABP) statistically significantly increased in the control group following intubation and for 2 min regarding HR and for 5 min regarding mABP in comparison with the base line and relative to the nebulizer group. There was a statistical significant improvement regarding the intubation conditions in the nebulizer group relative to the control group ($p \leqslant 0.001$). The same was noticed regarding the intubation time and the number of intubation attempts ($p \leqslant 0.001$).
Conclusions: Premedication of infants undergoing CDH repair with nebulized solution containing 4 mg kg^{-1} lidocaine 1% plus 2 μg kg^{-1} fentanyl improves the intubating conditions under inhalational sevoflurane induction without muscle relaxation. The studied combination can suppress patients' hemodynamic changes to intubation.

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1. Introduction

Congenital diaphragmatic hernia (CDH) occurs in approximately 1 of 2500 newborn infants [1]. Outcome in CDH is variable between different centers in the world regarding prognosis with reported mortality rates between 20% and 60%. The morbidity and mortality of CDH is traditionally related to the mechanical compression of the herniated viscera on the developing lung leading to pulmonary hypoplasia and pulmonary hypertension [2]. After birth, gut distension at any time due to face mask ventilation exacerbates the ventilatory compromise by further compression of the lungs. Positive pressure ventilation by mask at induction of anesthesia should be avoided as the passage of gas into the esophagus may increase the stomach volume and further compromise the pulmonary function [3]. Sevoflurane is frequently used for inhalational induction in pediatrics because of its relatively pleasant smell, low airway irritability, rapid onset of action and cardiovascular stability [4]. Several methods have been described to improve intubating conditions with sevoflurane. These include the use of $\alpha 2$ agonists for premedication [5], extended exposure to sevoflurane [6], high inspired fraction of sevoflurane [7], addition of nitrous oxide [8], opioids [9], or propofol [10]. Local anesthesia to the airway may be an important adjunct of this technique [11]. Lidocaine is a cheap, widely available drug with a good safety profile when nebulized [12]. Several authors documented the presence of peripheral opioid receptors and explored the action of opioids peripherally [12,13].

2. Aim of the study

The primary aim was to evaluate the effect of premedication by a combination of nebulized lidocaine and fentanyl on the intubating conditions without muscle relaxation during high inspired concentration of sevoflurane induction of anesthesia in infants undergoing CDH repair. The secondary aim was to study the effect of the same nebulized solution on the hemodynamic response to endotracheal intubation.

3. Patients selection

This prospective, double-blind, randomized, and placebo-controlled study was performed at Alshatby university hospital from March 2014 to October 2014. Forty patients of any gestational age ASA physical status II–III scheduled for congenital diaphragmatic hernia (CDH) repair were selected from those admitted to Alshatby pediatric intensive care unit. Patients were calculated according to the following formula:

$$n = \frac{t^2 \times p(1-p)}{m^2}$$

where n = required sample size, t = confidence level at 95% (standard value of 1.96), p = estimated measurements, m = margin of error at 5% (standard value of 0.05)

The power of the study was 80%

Patients were excluded if they were already intubated, with suspected neuromuscular disorders, having history of opioid intake or infusion during the past three hours and finally those with anticipated difficult intubation in the form of known congenital airway anomalies.

4. Study design

The study protocol was reviewed and approved by the Ethics Committee of the Alexandria Main University Hospitals. The study was registered in the PACTR database under a number of PACTR201410000871409. A written consent was obtained from the parents for participation of their kid in the study. Complete history was taken from the parents and from the intensive care staff members and all patients were subjected to thorough examination and routine laboratory investigations. Patients were randomly categorized using a computer-generated program to one of two groups undergoing induction of anesthesia with sevoflurane. An independent participant prepared the nebulized solution which was given to patients in the intensive care 15 min preoperatively at a flow of $3\,l\,min^{-1}$ and patients were blindly categorized into the two following groups according to the components of the nebulized solution:

- *Nebulizer group:* The nebulized solution contained $4\,mg\,kg^{-1}$ lidocaine 1% plus $2\,\mu g\,kg^{-1}$ fentanyl.
- *Control group:* The nebulized solution contained a comparable volume according to weight of normal saline 0.9%.

After admission to the operative theater, all patients were monitored by continuous electrocardiography, heart rate, pulse oximetry, non-invasive arterial blood pressure, endtidal capnography and transrectal temperature probe. An intravenous line was already existing. Anesthesia was induced with 8% sevoflurane in 100% oxygen for 90 s using an appropriate sized face mask via a primed pediatric circle system. The proper sized endotracheal tube was inserted by Macintosh blade size 0 or 1. Failed trial of intubation was defined as failure to insert the endotracheal tube between the vocal cords before the arterial oxygen saturation reaches 80%. In case of failure of intubation, a second attempt was tried after intravenous injection of $1\,mg\,kg^{-1}$ propofol and application of 8% sevoflurane in 100% oxygen via a face mask for 30 s. After insertion of the endotracheal tube, anesthesia was maintained with fentanyl $1\,\mu g\,kg^{-1}$, rocuronium $0.6\,mg\,kg^{-1}$ and sevoflurane 2–3%.

5. Measurements

5.1. Hemodynamic parameters

- *Heart rate (HR)*
- *Mean arterial blood pressure (mABP)*
- *Arterial oxygen saturation (SpO_2)*

The previous parameters were recorded at the following times:

- Before nebulizer setting.
- Before induction of anesthesia.
- After induction of anesthesia.

- Immediately after intubation.
- Every one minute after intubation for 5 min.

5.2. Intubating conditions

were assessed by a single anesthetist who is 8 years experienced in pediatric anesthesia after residency according to the Copenhagen scale [14]. Intubating conditions were considered excellent when all the categories were excellent, good if one of the variables was good and clinically unacceptable (poor) if any variable was poor. The number of intubation attempts and the duration of intubation (time between the initial introduction of the laryngoscope and fixation of the endotracheal tube) were also measured (see Table 1).

6. Statistical analysis

Data were presented as means and standard deviations, numbers and percent. Categorical data were compared by Chi square test and quantitative data were compared by student *t* test. The level of significance was 0.05. Data were entered into the computer and were analyzed using Statistical Program for Social Sciences (SPSS) Version 20.

7. Results

Patients enrolled in the study were ranging as regards age from 7 days to 2 months and 25 days. All patients completed the study 20 in each group. Heart rate increased statistically significantly after intubation and for 2 min in the control group. There was a statistical significant increase during this period in the control group relative to the nebulizer group ($p \leqslant 0.001$) (Fig. 1). Mean arterial blood pressure statistically significantly increased in the control group after intubation and during the whole remaining periods of follow up in comparison with the base line and relative to the nebulizer group ($p \leqslant 0.001$) (Fig. 2). There was no significant difference between the two groups regarding the oxygen saturation at all periods of follow up (Fig. 3). There was a statistical significant improvement as regards the intubation conditions in the nebulizer group relative to the control group ($p \leqslant 0.001$). The same was noticed

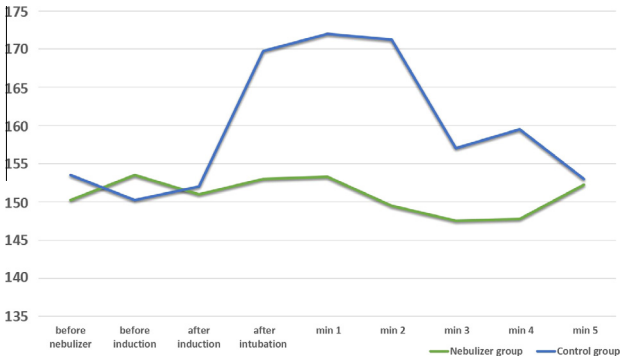

Figure 1 Comparison between the two studied groups regarding the heart rate at different period of follow up.

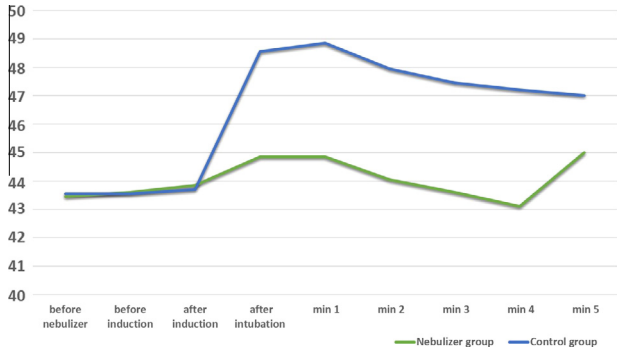

Figure 2 Comparison between the two studied groups regarding mean arterial blood pressure at different period of follow up.

regarding the intubation time and the number of intubation attempts which were statistically significantly less in the nebulizer group relative to the control group ($p \leqslant 0.001$) (Table 2).

8. Discussion

In the present study, the combination of nebulized 4 mg kg^{-1} lidocaine 1% plus 2 μg kg^{-1} fentanyl achieved excellent

Table 1 Copenhagen scale.

Variables	Intubating conditions		
	Clinically acceptable		Not acceptable
	Excellent	Good	Poor
Laryngoscopy[a]	Easy	Fair	Difficult
Vocal cords			
Position	Abducted	Intermediate	Closed
Movement	None	Moving	Closing
Response to intubation			
Movement of the limbs	None	Slight	Vigorous
Coughing	None	Diaphragm	Sustained

Fair: jaw not fully relaxed, slight resistance to blade.
Difficult: poor jaw relaxation, active resistance of the patient to laryngoscopy
[a] Laryngoscopy. Easy: jaw relaxed, no resistance to blade in the course of laryngoscopy.

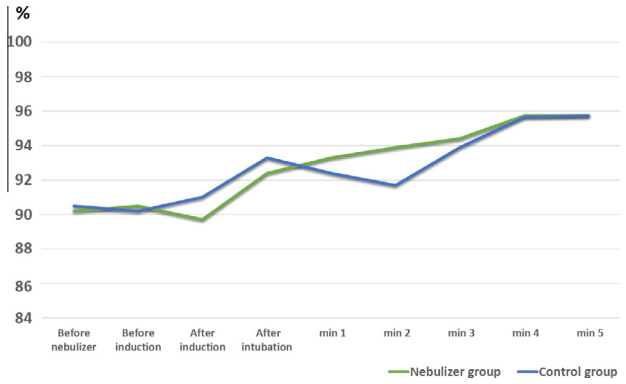

Figure 3 Comparison between the two studied groups regarding O_2 saturation at different period of follow up.

Table 2 Comparison between the two studied groups regarding intubation condition, number of intubation attempts and intubation time in seconds.

	Nebulizer group	Control group	P
Intubation conditions			
Excellent	16 (80%)	4 (20%)	0.001*
Good	2 (10%)	13 (65%)	
Poor	2 (10%)	3 (15%)	
Number of intubation attempts			
Range	1–3	1–3	0.005*
Mean	1.4	2.1	
SD	0.7	0.9	
Intubation time in seconds			
Range	22–148	24–173	0.002*
Mean	53.1	105.4	
SD	42.3	62.6	

* *P* is significant if ⩽0.05.

intubating conditions in 80% of infants relative to 20% in the control group. In addition, intubation time decreased statistically significantly in the nebulizer group (53.1 s) relative to the control group (105.4 s) with a *P* value of 0.002. There was also a significant statistical decrease regarding the number of intubation attempts with a *P* value of 0.005. Hemodynamic response to endotracheal intubation in the form of the heart rate and mean arterial blood pressure was also suppressed by the application of nebulized lidocaine and fentanyl premedication.

Sevoflurane has long been known to provide favorable intubating conditions under spontaneous ventilation in children [5]. In the study carried out by Devys et al. [16], the rate of poor intubating conditions reached 37% in the sevoflurane group, despite a long exposure to 8% sevoflurane. Similar results were obtained by Lerman et al. [17] and Weber et al. [18]. The previous results are very close to those shown in the present study since the incidence of excellent intubating conditions was 20% in the control group.

High concentrations of sevoflurane for long periods, especially if accompanied by hyperventilation, may induce epileptiform activity [19] hence several authors tried to overcome such problem by combining other drugs with sevoflurane to facilitate intubation without muscle relaxation in infants and children.

N_2O 50–60% was combined with sevoflurane in several studies and the average of excellent intubating conditions was 44.6% and that of acceptable intubating conditions was 81.5% [3,20,21]. Excellent intubating conditions were achieved by Verghese et al. [22] in 91.7% of the children who received intranasal remifentanil combined with sevoflurane and 60 % N_2O. Different intravenous doses of remifentanyl were also tried by Park et al. [21] and Weber et al. [19] in addition to N_2O and achieved convergent results.

Intravenous lidocaine was shown by Aouad et al. [23] to decrease the amount of moderate or severe coughing and suppress the hemodynamic response to tracheal intubation in children under sevoflurane induction.

Previously, nebulized combination of lidocaine and fentanyl has been evaluated by the same author as a premedication in spontaneously breathing pediatric patients who have been subjected to tracheobronchial foreign body removal by rigid bronchoscopy [10]. The author concluded that children who have received nebulized fentanyl preoperatively have had less hemodynamic response to bronchoscopic manipulation relative to the other two groups who have not received fentanyl and at the same time, the incidence of intraoperative difficulties was less among patients in the fentanyl group. The previous results were attributed to a local or systemic opioid effect depending on the presence of peripheral opioid receptors on visceral fibers, and on neurons expressing substance P and/or calcitonin-gene-related peptide, consistent with the phenotype of nociceptors [24].

Relative to the previous reports studying the effects of different additives to sevoflurane, N_2O in variable concentrations was an essential component. In the present study, N_2O could not be used for fear of further distension of the stomach with added pulmonary compromise.

Several previous reports documented the beneficial effects of adding propofol to sevoflurane at a dose of 2 mg kg^{-1} improving the intubating conditions but at the expense of some hemodynamic compromise [25] which is not allowed in our patient population as most cases are associated with pulmonary hypertension. Doses less than 2 mg kg^{-1} have been shown to be less effective in improving the intubating conditions under sevoflurane without muscle relaxation [17].

From the present study we conclude that premedication of infants undergoing CDH repair with nebulized solution containing 4 mg kg^{-1} lidocaine 1% plus 2 μg kg^{-1} fentanyl improves the intubating conditions under inhalational sevoflurane induction without muscle relaxation. At the same time, the studied combination was found not to affect patients' hemodynamics.

Authors' contributions

Moustafa MA: Acquisition of data, analysis of results, interpretation of data and writing the final draft.

Osman YM: Design of the study, collection of data, sharing in writing the final draft.

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Conflict of interest

No conflict of interest declared.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.egja.2015.01.007.

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