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Research Article

The effect of nebulized lidocaine hydrochloride on emergence from sevoflurane anesthesia in children undergoing Tonsillectomy

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KEYWORDS

Lidocaine;
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Abstract *Background:* Sevoflurane-related emergence agitation (EA) is considered a significant problem that interferes with children's recovery; our aim was to evaluate the efficacy of nebulized lidocaine hydrochloride when given before sevoflurane anesthesia in attenuating EA in children undergoing tonsillectomy.

Materials and methods: A randomized clinical study was conducted on eighty children ASA I and II who underwent tonsillectomy. The children were randomized to one of two groups according to the nebulizer contents. Lidocaine group (group L) received nebulized solution of 4 mg/kg lidocaine hydrochloride and placebo group (group P) received nebulized solution contains 0.9% normal saline.

Results: The number of agitated patients were significantly lowered in the lidocaine group compared to the placebo group; *p* value (0.012).

Conclusion: The use of nebulized lidocaine before sevoflurane anesthesia for pediatric patients undergoing tonsillectomy attenuated the sevoflurane-related EA with no side effects.

1. Introduction

Sevoflurane is the most commonly used inhaled anesthetic in children, due to its pleasant smell and low blood gas solubility coefficient that lead to rapid induction and recovery [1]. However, emergence agitation (EA) occurs in up to 80% of pediatric patients receiving sevoflurane [2]. In addition to the stress imposed on both caregivers and the family, it is considered as a potentially serious complication due to the possibility of self-injury.

Otolaryngeal procedures are considered as one of the independent risk factors for EA [3]. Although the exact etiology of sevoflurane EA is still unclear, rapid emergence, variable neurological recovery, and increased sensation of pain are the proposed causes of EA related to sevoflurane (4). Different techniques have been used to attenuate the EA including propofol, narcotics, ketamine, and alpha 2-agonists [1,2,5–7]. However, these techniques may interfere

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with the goal of having a conscious child without excessive sedation on arrival to the recovery room.

Lidocaine hydrochloride is a widely available local anesthetic with a good safety profile when given by nebulization [8]. It is frequently nebulized before bronchoscopy procedures, allowing the bronchoscope to reach greater depths in the airway. Lidocaine levels in the blood after nebulization for adults at normal doses were found to be safe [9]. Also, lidocaine was given by nebulization for flexible bronchoscopy in children in doses 4 and 8 mg/kg of 2% lidocaine and was well tolerated with no side effects, or symptoms of toxicity [10].

We hypothesized that achieving preemptive analgesia using preoperative lidocaine nebulization for pediatric patients undergoing tonsillectomies with sevoflurane anesthesia can result in less EA without excessive sedation in recovery room.

We conducted this double-blind, placebo-controlled, randomized study to evaluate the efficacy of nebulized lidocaine when given before sevoflurane anesthesia for children undergoing tonsillectomy in attenuating EA.

1.1. Material and methods

After approval of the ethical committee at Saad Specialist Hospital, Saudi Arabia, written informed consents were obtained from the parents of 80 children ASA physical status I and II aged 4–6 years old, undergoing tonsillectomy under general anesthesia during the period from April to October 2012. Children with history of cardiovascular, neurologic and liver diseases, bronchial asthma, obstructive sleep apnea, recent upper respiratory tract infection within the previous 2 weeks, and patients in whom surgery had taken more than 1 h were excluded from this study.

The children were randomly divided using closed envelope technique for randomization to one of two groups according to the nebulizer contents:

Group L ($n = 40$): Lidocaine group received nebulized solution of 4 mg/kg lidocaine.
Group P ($n = 40$): Placebo group received nebulized solution contains 0.9% normal saline.

The study drug consisted of identically labeled 5 ML vials; the contents of the vials were only known to the pharmacy department, of either:

- Lidocaine hydrochloride (Astra Zeneca, New South Wales, Australia.) calculated to be equal to 4 mg/kg of lidocaine 2% and then normal saline is added to make the study solution up to 5 ml; hence, the lidocaine concentration was variable and dependent on the child's weight.
- Or 0.9% normal saline (placebo) 5 ml.

The solution was applied to the patient by face mask and a compressed gas-powered jet nebulizer with 6 L/min oxygen. The child was asked to inhale deeply.

The nebulizers were given by the nurses in the holding area according to the instruction written in the sealed envelope; the anesthesiologists in charge of the case were unaware of the component of the nebulizer except in emergency conditions in order to ensure the double-blind nature of the study.

All children were fasting 6 h before surgery and an intravenous cannula (24 or 22 gauge) was inserted to all of them on admission to the hospital. Lactated Ringer's solution started at the standard maintenance fluid therapy according to the patient's weight.

All patients received atropine 0.01 mg/kg followed by ketamine 1 mg/kg intravenously as a premedication and to facilitate separation from the parents just before shifting to the operating room. In the operating room, the ECG, pulse oximeter, and noninvasive arterial blood pressure monitor were attached and the anesthesia was induced to all patients with fentanyl 2 μg/kg, sevoflurane 2–8%, and atracurium 0.5 mg/kg. Orotracheal intubation was done using a suitable size, lubricated tube. Anesthesia was maintained with sevoflurane 2% in 50:50% O_2/N_2O with pressure controlled mode of ventilation aiming to maintain $etco_2$ between 30 and 35 mmHg. Spo_2, $etco_2$, heart rate, and noninvasive arterial blood pressure were monitored. Immediately after intubation, a suppository of paracetamol (Adol, Julphar Pharmaceutical Industries, UAE) 20 mg/kg was given.

The same surgeon performed all the operations; at the end of surgery, sevoflurane and N_2O were discontinued, muscle relaxant was reversed using neostigmine and atropine after return of at least two of the train-of-four by peripheral nerve stimulator and proper suction of the throat under vision, and the patients were put in the recovery position and extubated after displaying a regular respiratory pattern, purposeful movement, and return of the swallow reflex. After extubation, 100% O_2 were applied by face mask till the patient open his eyes in response to verbal commands and then shifted to the recovery room for observation and monitoring until they reach a score 9 or more on Modified Aldrete score [11] before discharging to the ward.

The following variables were recorded during the study.

- Demographic data.
- The duration of operation: (the time between application and removal of the mouth gag).
- The duration of anesthesia: (the time from induction of anesthesia till extubation).
- The duration of extubation: (the time from discontinuation of the anesthetic till extubation).
- The duration of emergence: (the time from the discontinuation of anesthesia to the time of eye opening on verbal command).
- State of emergence at the time of admission to recovery room using emergence agitation scale [12], Table 1; for our study, the score of 4 or more was considered agitation and needs treatment with increments of fentanyl 1 μg/kg slowly intravenously with close monitoring for any signs of respiratory depression and can be repeated if needed at 10 min intervals.

Table 1 Five-point emergence agitation scale [12].

Score	
1	Obtunded with no response to stimuli
2	Asleep, but responsive to movement and stimuli
3	Awake and appropriately responsive
4	Crying and difficult to console
5	Wild thrashing behavior that requires restraint

- The number of patients needed postoperative fentanyl.
- The duration of discharge from the recovery room (from arrival to the recovery room until discharge).
- Vital signs (heart rate, blood pressure, and oxygen saturation) were monitored in recovery room on admission (T0) and every 10 min until discharge.
- Nausea and vomiting using a 4-degree scale [6]: 0 = no nausea and vomiting; 1 = nausea only; 2 = single vomiting episode; 3 = multiple vomiting episodes. (Treated with Ondansetron 0.15 mg/kg).
- Respiratory depression detected by O_2 desaturation.
- Hallucination.

1.2. Statistical analysis

Data were statistically described in terms of mean ± standard deviation (±SD), or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student *t* test for independent samples. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. *P* values less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

The sample size was calculated to be 36 patients in each group depending on the results from previous studies; we assumed a reduction in the incidence of agitation from 60% to 30% with the α-error level fixed at 0.05 and the power was set at 90%. We were expecting some exclusions and failure to follow up during the course of the study, so we increased the number of the sample size to 40 patients per each group.

Table 2 Demographic data and duration of operation.

Variables	Group L (n = 38)	Group P (n = 39)	p value
Age (year)	5.17 ± 1.08	5.24 ± 1.14	0.783
Gender (male/female)	20/18	19/20	0.906
Body weight (kg)	17.3 ± 2.5	16.90 ± 3.4	0.559
Duration of operation	40.43 ± 1.0	40.32 ± 1.2	0.664

Data are presented as mean ± SD or numbers. No significant differences between groups.

2. Results

The demographic data and anesthesia time were presented in Table 2. Two patients in group L were excluded from the study both due to surgery exceeded 1 h, one patient in group P was excluded due to bleeding at the surgical site after extubation. The two groups were comparable regarding age, sex, weight, and operative time.

The duration of anesthesia, extubation, and emergence was prolonged in group L compared to group P; (46.10 ± 1.6 min) versus (44.31 ± 3.2 min) *p* value 0.003, (5.11 ± 1.3 min) versus (4.2 ± 1.0 min) *p* value 0.001 and (10.30 ± 2.1 min) versus (7.44 ± 3.3 min) *p* value 0.00, respectively. While the duration of stay in recovery room were comparable in both group L and group P (29.12 ± 3.3 min) and (30.10 ± 2.1 min) respectively, *p* value 0.123, (Fig. 1).

In the recovery room, there was a significantly lower values of heart rate and mean arterial blood pressure in group L compared to group P, (Figs. 2 and 3). The mean heart rate for group L and P, at T0 (111 ± 2.4) and (119 ± 3.2), at T10 (105 ± 2.3) and (110 ± 1.2), at T20 (103 ± 2.5) and (108 ± 1.1), at T30 (102 ± 3.1) and (107 ± 2.5) respectively, *p* value (0.00).

The mean arterial blood pressure for group L and group P; at T0 (59 ± 3.2) and (63 ± 1.0), at T10 (60 ± 1.2) and (64 ± 2.2), at T20 (62 ± 2.3) and (64 ± 4.1), at T30 (62 ± 1.0) and (64 ± 1.4) respectively, *p* value at all times was (0.00).

The peripheral oxygen saturation was comparable in both groups, (Fig. 4) shows the mean oxygen saturation (%) in the recovery room in group L and group P respectively; at T0 (96.4 ± 2) and (97.02 ± 1.6), *p* value (0.137), at T10 (97.63 ± 1.3) and (97.23 ± 1.7), *p* value (0.249), at T20 (98.1 ± 2) and (97.51 ± 1.2), *p* value (0.120), at T30 (98.61 ± 1.6) and (99.04 ± 1.4), *p* value (0.213).

The incidence and degree of agitation in both groups are represented in Table 3.

The number of agitated patients (⩾ grade 4) who required fentanyl was significantly lower in group L; 8 out of 38 (20.5%) than in group P; 20 out of 39 (51.5%), *p* value (0.012), Fig. 5.

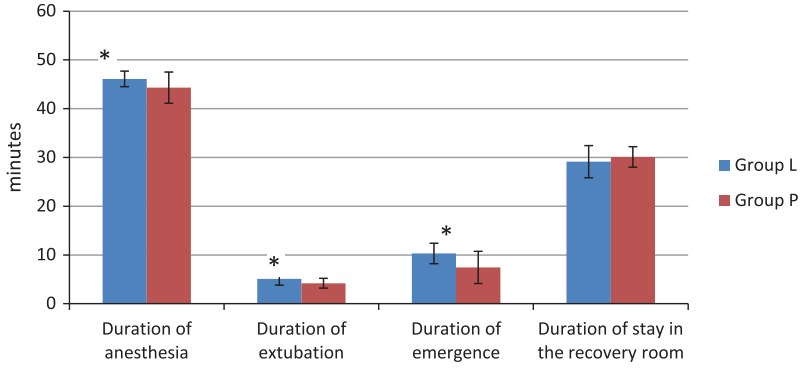

Figure 1 Mean duration of anesthesia (min), extubation (min), emergence (min), and stay in the recovery room (min) between the study groups. *p value is significant. Group L (lidocaine group), group P (placebo group).

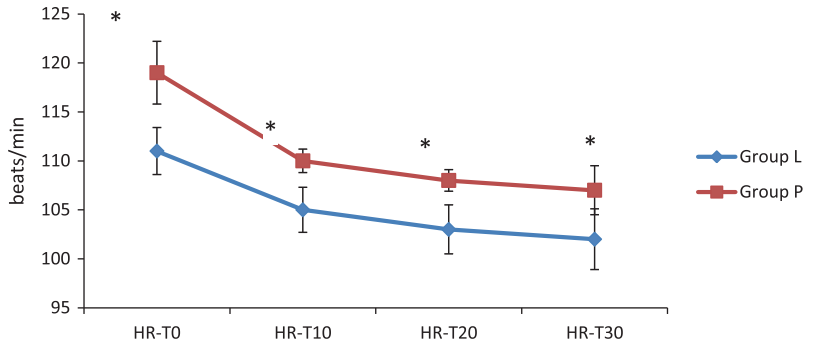

Figure 2 Mean heart rate (beats/min) between the 2 groups over the study period in the recovery room T0 (at admission), T10 (after 10 min), T20 (after 20 min), and T30 (after 30 min). Group L (lidocaine group), group P (placebo group). *p value was significant.

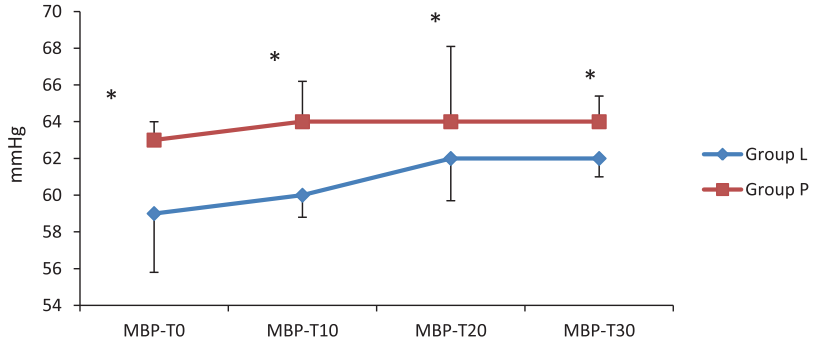

Figure 3 Mean mean arterial blood pressure (mmHg) between the 2 groups over the study period in the recovery room T0 (at admission), T10 (after 10 min), T20 (after 20 min), and T30 (after 30 min). Group L (lidocaine group), group P (placebo group). *p value was significant.

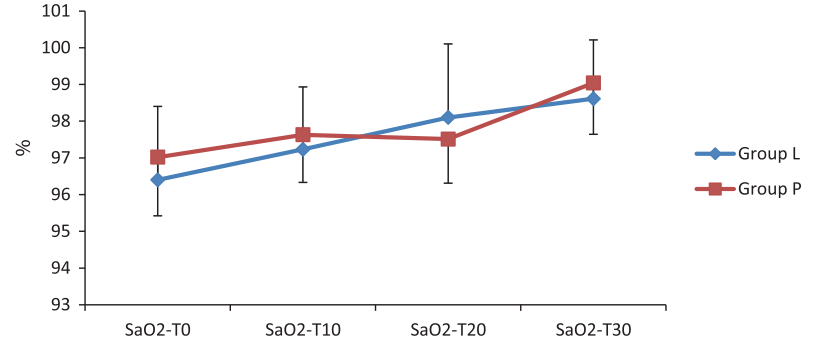

Figure 4 Mean oxygen saturation (%) between the 2 groups over the study period in the recovery room T0 (at admission), T10 (after 10 min), T20 (after 20 min), and T30 (after 30 min).Group L (lidocaine group), group P (placebo group).

There were no significant differences in both groups regarding the incidence of nausea, vomiting, respiratory depression, and hallucination Table 4.

3. Discussion

Sevoflurane-related EA was reported to be up to 80% and is considered as a significant post-anesthetic problem that interferes with safe and smooth recovery [2]; usually, it is self-limited (15–30 min) [13]. The exact etiology of sevoflurane-related EA is still unclear. Studies have reported EA despite adequately treated pain [14,18] or even when pain was absent [18]. Also, it was thought that rapid awakening after the use of the insoluble anesthetics, as sevoflurane, may cause EA [19]. But the recovery from propofol which is also rapid and pleasant was associated with less incidence of EA [18]. However, inadequate analgesia may play an important role, especially after short surgical procedures as adenotonsillectomy since the maximum effect of analgesics may be delayed until the child is completely awake [13,14]. Hence, adequate analgesia as a goal to approach is very essential to prevent EA. Different pharmacological interventions had been tested

Table 3 Incidence and degree of agitation.

Agitation score	Group L (n = 38)	Group P (n = 39)	p value
Grade 1	0(0)	0(0)	1
Agitated patients			0.031*
Grade 2	8(21%)	6(15%)	
Grade 3	22(58%)	13(33.5%)	
Grade 4	7(18.5%)	13(33.5%)	
Grade 5	1(2.5%)	7(18%)	
Number of patients with agitation score ⩾ 4	8(20.5%)	20(51.5%)	0.012*

Values are presented as number of patients and percentages. Group L = lidocaine group, group P = placebo group.
* p value is significant.

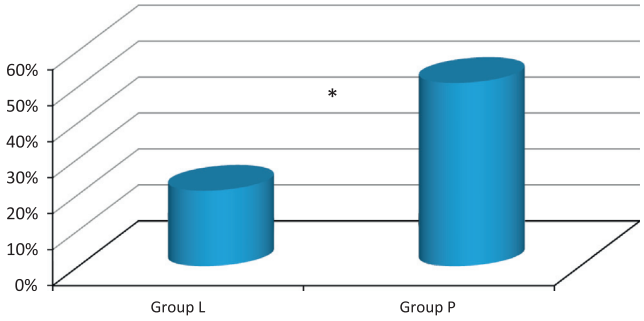

Figure 5 Percentage of cases who needed fentanyl treatment between the 2 study groups. *p value was significant, group L; lidocaine group, group P; placebo group.

Table 4 Incidence of side effects in the recovery room, represented by number of patients and percentages.

Variable	Group L (n = 38)	Group P (n = 39)	p value
Nausea	2(5%)	3(7.5%)	0.976
Vomiting	0(0%)	1(2.5%)	0.990
Respiratory depression	0(0%)	0(0%)	1
Hallucination	0(0%)	0(0%)	1

Values are represented as number or percentage. Group L = lidocaine group, group P = placebo group.

to prevent or attenuate this phenomena; Intraoperative injection of I.V. ketorolac 1 mg/kg for minor otorhinolaryngological procedures decreased the incidence of EA three to four times, after both halothane and sevoflurane anesthesia [15]. Fentanyl administered either I.V. 2.5 μg/kg [4] or intranasal 2 μg/kg [16] also decreased the incidence of EA. Similarly, propofol, ketamine, dexamethasone, and clonidine [5,7,1,17] have been found to be effective. Unfortunately, all the above mentioned pharmacological interventions can lead to undesired side effects especially for adenotonsillectomy pediatric patients, namely oversedation in recovery room or bleeding.

In this study, to optimize the pain management in our patients, we used low dose ketamine (1 mg/kg) intravenously as a premedication, intravenous fentanyl (2 μg/kg) with induction of anesthesia, and paracetamol suppository (20 mg/kg) immediately after intubation.

We chose nebulized lidocaine in a dose of 4 mg/kg; as it was reported by Gjonaj et al. to be safe and well tolerated when used in pediatric patients undergoing bronchoscopy and the lidocaine levels tested was found always below the toxic level [10]. Moreover, the standard nebulized dose in adult is 4 mL of 4% lidocaine which is approximately equal to 4 mg/kg for pediatric [20] and the maximum squirted pediatric dose was found to be 8.5 mg/kg [21].

Jee et al has compared lidocaine given by the intravenous route with lidocaine sprayed down the endotracheal tube (ETT), and they found that at the same dose, lidocaine sprayed directly down the ETT had attenuated the airway reflexes while the lidocaine administered intravenously did not. And they attributed this to the direct local-mucosal anesthetizing effect of the sprayed lidocaine rather than a systemic absorption from the airway [22].

In our study, the durations of anesthesia, extubation, and emergence were significantly prolonged in the lidocaine group, and this may be explained by the mucosal analgesia and blunted noxious stimulation as a direct topical effect of nebulized lidocaine; however, a systemic effect of nebulized lidocaine may has contributed as well.

Also, nebulized lidocaine had attenuated the cardiovascular response during the 30 min stay in the recovery room, which is an indication to patient comfort and adequate analgesia compared to the placebo group.

The incidence and degree of agitation have been significantly reduced by nebulized lidocaine, with no side effects, this again may be related to the preemptive analgesic effect of lidocaine, this analgesic effect seems to last to cover the emergence and early postoperative period, since the inhalation of lidocaine results in a much higher airway concentrations and lower plasma concentrations [23]. This finding also matches with Groeben et al., 1999 who tested the effect of lidocaine given by inhalation and by intravenous infusion on attenuating air way reflexes. And they found that the plasma concentrations of Meg X, which is the first metabolite of lidocaine, have a much longer-lasting plateau following lidocaine inhalation than following intravenous administration, suggesting prolonged absorption of lidocaine from the airway into the blood stream. Also, Meg X plasma concentrations continued to increase for 40 min after completion of inhalation, while its peak plasma concentrations were already reached after 10 min of termination of intravenous infusion of lidocaine [24].

In conclusion, the use of nebulized lidocaine hydrochloride before sevoflurane anesthesia for tonsillectomy in pediatrics attenuated the sevoflurane-related emergence agitation with no side effects.

Limitations of this study:

We used the five-point agitation scale for measuring the degree of agitation, although the Pediatric Anesthesia

Emergence Delirium (PAED) scale, which was developed in 2004 [25], seems to be the most reliable tool for the measurement of EA; but it was difficult for us to train the observers to apply it in a short time. Therefore, we depended on the simpler and rapidly applicable ''Five-point scale.''

This study was done only in children between 4 and 6 years, and further studies are needed on other age groups.

To keep it blinded, we had to fix the volume of tested drug which means variable lidocaine concentration, which might affected the pharmacokinetics of the drug.

Conflict of interest

We certify that there is no conflict of interest with any financial organization regarding the materials discussed in the manuscript.

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