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# Intravenous lidocaine reduces perioperative opioids without negatively affecting the electrical stapedial reflex threshold in pediatric cochlear implants

W. Z. Bakhet[1,2*], L. M. El Fiky[3] and H. A. Debis[4]

## Abstract

**Background:** Total intravenous anesthesia (TIVA) with propofol and remifentanil is frequently used for pediatric cochlear implants (CIs) surgery as it does not suppress the electrical stapedial reflex threshold (ESRT). However, high doses of remifentanil exacerbate postoperative pain and increase opioid consumption. Intravenous lidocaine reduces pain and opioid requirement. This study investigated the effect of intravenous lidocaine on perioperative opioid consumption and ESRT in pediatric CIs.

**Results:** The mean (95% CI) remifentanil consumption was significantly lower in lidocaine group than in placebo group [0.57 (0.497–0.643) vs 0.69 (0.63–0.75)] μg/kg/min, $P = 0.016$. The mean (95% CI) propofol consumption was significantly lower in lidocaine group than in placebo group [155.5 (146–165) vs 171 (161–181) μg/kg/min, $P = 0.02$. MBP and HR were significantly lower after surgical incision, laryngeal mask airway (LMA) removal, and at PACU admission in the lidocaine group compared with the placebo group. The PACU pain score was significantly lower in the lidocaine group compared to the placebo group. The mean (95% CI) pethidine consumption in PACU was significantly lower in the lidocaine group than in the placebo group 7.0 (6.17–7.83) vs. 8.9 (7.84–9.96) mg, $P = 0.012$. There were no differences between groups regarding ESRT response.

**Conclusions:** Intravenous lidocaine infusion reduced perioperative opioid requirements without altering the ESRT in pediatric CIs.

**Trial registration:** Clinical registration number: NCT04194294.

**Keywords:** Cochlear implant, Electrical stapedial reflex threshold, Intravenous lidocaine, Pediatric anesthesia, Total intravenous anesthesia

## Background

Cochlear implants (CIs) are an established therapeutic option for children with profound irreversible sensorineural hearing loss (Gordon et al. 2004). Anesthesia technique for CIs should be modified to achieve a bloodless surgical field, facilitate the intraoperative stapedial reflex measurement, provide adequate analgesia, and prevent postoperative vomiting.

The stapedial reflex protects ears from the excessive noise exposure. The measurement of the electrically evoked stapedial reflex threshold (ESRT) during CIs surgery is used to confirm that the implant is functioning correctly and to determine the maximum comfortable level (Gordon et al. 2004). Total intravenous anesthesia (TIVA) with propofol and remifentanil is frequently used for pediatric CIs as it does not suppress the ESRT. However, high doses of

* Correspondence: Wahba_zak@hotmail.com
[1]Department of Anesthesia, Ain Shams University, 4 Abdelhamed El Wardany street, El-Zeitoun, Cairo 11725, Egypt
[2]Present Address:, Kuwait City, Kuwait
Full list of author information is available at the end of the article

remifentanil used intraoperatively have been found to exacerbate postoperative pain and increase the opioid consumption (Angst and Clark 2006).

Lidocaine has been used safely in children for a variety of indications (Lemming et al. 2019). At clinically relevant doses, it reduces pain, opioid requirement, and postoperative nausea/vomiting (Dunn and Durieux 2017). Recent studies found that intravenous (IV) lidocaine could be used as an adjuvant to TIVA without adversely affecting motor and sensory evoked potentials (Sloan et al. 2014; Urban et al. 2017). However, these studies have been done in adults undergoing spine surgeries. Moreover, it has been shown that in children the cortical responses are more sensitive to anesthetics (Helmers and Hall 1994). Thus, it remains unclear whether systemic lidocaine can negatively affect ESRT in pediatric CIs.

Therefore, this double-blind-controlled randomized study was designed to determine if IV lidocaine would result in a reduction of opioid requirements without altering ESRT in pediatric CIs. The primary outcome of the study was the intraoperative remifentanil consumption. The secondary outcomes included propofol consumption, ESRT response, hemodynamics (MBP, HR), maximum PACU pain scores, PACU pethidine consumption, and incidence of side effects.

## Methods

This prospective, randomized-controlled, double-blind study was carried out during the period from August 18, 2015, to June 5, 2019, after the approval of the local hospital ethical committee (05/06/2015). All parents provided written informed consent. The study included 70 children, aged 1–6 years, ASA physical statuses I or II, undergoing cochlear implant surgery. Children with an allergy to lidocaine, liver/renal dysfunction, or predicted operative difficulty (i.e., syndromic hearing loss, congenital cochlear abnormalities, or cochlear ossification) were excluded.

Children were randomized in a 1:1 ratio using computer-generated random numbers into two groups; lidocaine group ($n$ = 35) or placebo group ($n$ = 35). Allocation concealment was done using number-coded, sealed-opaque envelopes. Anesthesia nurse not involved in the study prepared the study infusions as per allocation to either lidocaine or normal saline 0.9% in a master-coded, covered 60 mL syringe. The otologist and the outcome assessor were unaware of group allocation. The attending anesthesiologist who managed the anesthesia was aware of the group allocation.

No premedication was used. In addition to standard monitors, the bispectral index (BIS) was used to monitor the depth of anesthesia. A 22-G IV canula was inserted after induction of anesthesia with 8% sevoflurane. After an IV bolus of 3 mg/kg propofol, an appropriate size flexible laryngeal mask airway (LMA) was placed. The lungs were mechanically ventilated using an oxygen/air mixture ($FIO_2$ = 0.5) with an end-tidal $CO_2$ of 30–35 mmHg.

Immediately after induction, children in the lidocaine group received a slow IV bolus of lidocaine (Lidocaine HCL® 2%, preservative-free, 20 mg/ml, Fresenius, USA) 1.0 mg/kg, followed by 1.0 mg/kg/h IV until the start of skin closure as follows: lidocaine of 60 mg (3.0 ml) was drawn up to 57 ml saline in 60 ml syringe (each ml containing 1 mg lidocaine). 1 ml $kg^{-1}$ (1 mg $kg^{-1}$) were given slow IV bolus followed by 1 ml $kg^{-1}$ $h^{-1}$ (1 mg $kg^{-1}$ $h^{-1}$) IVI. Similarly, children in the placebo group received equivalent volumes of normal saline 0.9% instead of lidocaine. The study solutions were infused using an infusion pump.

Anesthesia was maintained with propofol and remifentanil. The initial rate for propofol infusion was 200 μg/kg/min, then it was titrated up or down by 20 μg to maintain the BIS between 40 and 60. The initial rate for remifentanil infusion was 0.5 μg/kg/min, then it was titrated up or down by 0.1 μg to maintain the MBP between 50 and 60 mmHg. Bradycardia was defined as a 30% reduction of baseline HR. Hypotension was defined as a 30% reduction of baseline MBP. Bradycardia was treated with atropine 0.02 mg/kg IV, and hypotension was treated with ephedrine 0.3 mg/kg IV. All children received lactated Ringer at 5 $mL.kg^{-1}.h^{-1}$, dexamethasone 0.2 mg $kg^{-1}$ IV, and paracetamol 15 mg/kg IV. Normothermia was maintained using forced-air warming devices.

Before surgical incision, the surgeon infiltrated 0.5 $ml^{-1}$ $kg^{-1}$ of saline with adrenaline 1:200,000 subcutaneously along the surgical incision. After drilling of the device seat in a tight periosteal pocket, the ESRT responses were assessed by the surgeon using direct microscopic examination after insertion of the electrode (MED-EL®SONATA Ti cochlear implant system electrode) at the base, middle, and apex of the electrode array by visual monitoring of the stapedius muscle (Almqvist et al. 2000).

All infusions were stopped at the end of surgery and children in both groups received fentanyl 0.5 mcg/kg IV. The LMA was removed once the child was awake and had adequate spontaneous breathing and then the child was transferred to PACU.

In the PACU, the pain was assessed every 15 min using the FLACC scale (faces, legs, activity, cry, and consolability) (Manworren and Hynan 2003). The total FLACC score ranges from 0 to 10 (0 = no pain, 10 = worst). Pethidine 1 mg/kg IV was administered to maintain FLACC score <4. Total pethidine consumption in the PACU was recorded. Vomiting and signs of lidocaine

toxicity (twitching in the upper extremities or tongue, confusion, seizures, oxygen desaturations, or refractory hypotension) were also recorded.

The primary endpoint in this study was the intraoperative remifentanil requirement. Based on previous studies (Bergmann et al. 2012), a sample size of 24 patients per group would be required to detect a difference in mean intraoperative remifentanil requirement of 25%, with a standard deviation of 30%, a level of significance of 0.05, and a power of 0.8. Considering a protocol violation of 30%, we recruited 35 patients in each group.

All data was analyzed using Statistical Package for the Social Sciences (SPSS 20, SPSS Inc., Chicago, IL, USA). Data was presented as number (percentage), mean (standard deviation), mean (95% CI), or median (range). Shapiro-Wilk test was used to test the normality of distribution. Non-normally distributed data was compared using Mann-Whitney *U* test (MWU). Normally distributed data was compared using independent Student's *t* test. Nominal data was compared using Fisher's exact test or chi-squared test ($X^2$ test), as appropriate. MBP and HR were analyzed by repeated-measures ANOVA. Statistical tests were two-tailed and a *P* value <0.05 was considered significant.

## Results

The flow of patients during the study is depicted in Fig. 1. The two groups were comparable with regard to the baseline characteristics (Table 1). Remifentanil and propofol consumption were significantly lower in the lidocaine group compared to the placebo group (Table 2). The ESRT obtained in all patients at the apex, middle and base was not significantly different between the two groups (Fig. 2). There were no significant differences in MBP and HR between the two groups at baseline, after induction, LMA insertion, hypotensive period, and at the end of surgery. However, the MBP and HR were significantly lower after surgical incision, LMA removal, and at PACU admission in the lidocaine group, compared with the placebo group, $P < 0.05$ (Fig. 3). The mean (95% CI) maximum FLACC pain score at PACU was significantly lower in the lidocaine group [4.22 (4–4.43)] than in the

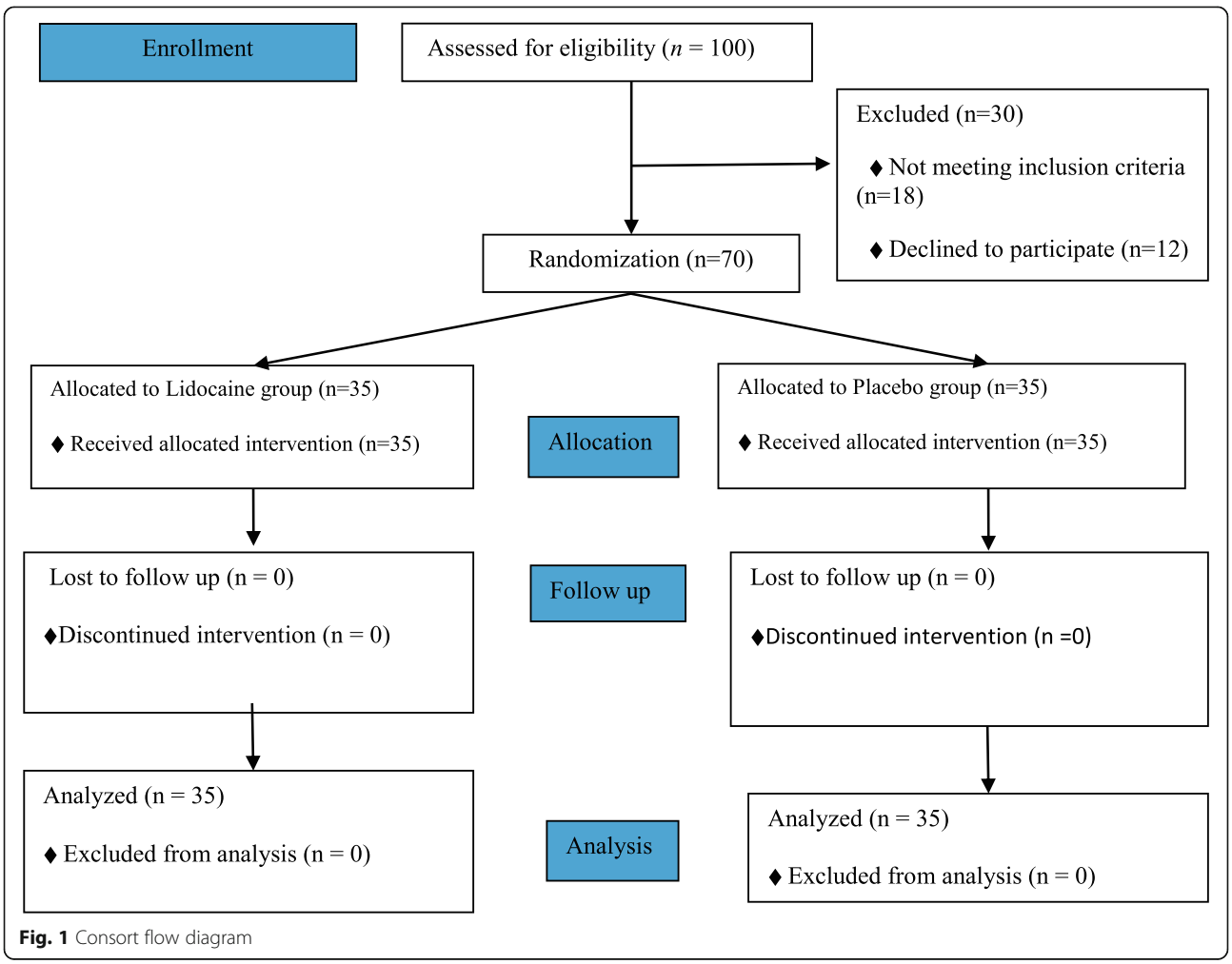


**Fig. 1** Consort flow diagram

**Table 1** Comparison of demographic data in the two groups

| Parameters | Lidocaine group (*n*=35) | Placebo group (*n*=35) | *P* value |
|---|---|---|---|
| Age in years | 3.0 (1.0–6.0) | 3.0 (2.0–6.0) | 0.57 |
| Gender (girls and boys) | 22/13 | 17/18 | 0.33 |
| Weight in kg | 14.0 (10.0–20.0) | 14.0 (12.0–20.0) | 0.57 |
| ASA-PS classification (I/II) | 30/5 | 27/8 | 0.54 |
| Duration of surgery in minutes | 70.6 (8.4) | 69.2 (11.7) | 0.78 |
| Duration of ansthesia in minutes | 77.7(9.2) | 76.3(12.8) | 0.72 |

Values are median (range), mean (SD), or numbers
*ASA PS* American Society of Anesthesiologists physical status

placebo group [4.74 (4.41–5.07), $P = 0.02$] (Table 2). The mean (95% CI) pethidine consumption at PACU was significantly lower in the lidocaine group than in the placebo group [7.0 (6.17–7.83) vs. 8.9 (7.84–9.96) mg, $P = 0.012$] (Table 2). There was no significant difference in the incidence of vomiting in PACU between the two groups [5.7% in lidocaine group vs. 14.2% in placebo group, $P = 0.42$] (Table 2). No other adverse events were reported.

## Discussion

Our study found that intravenous lidocaine infusion decreased perioperative opioid requirement without altering the ESRT in pediatric CIs. Additionally, it decreased propofol consumption and postoperative pain.

Intravenous lidocaine has analgesic and anti-hyperalgesic properties via sodium channel and NMDA receptor blockade, potentiation of GABA receptors, and mechanosensitive nociceptors (Kundra and Vinayagam 2020; Gottschalk et al. 2012; Koppert et al. 2000). Further, lidocaine has antinociceptive properties in the presence of surgical stimulation via modulation of synaptic transmission at the spinal dorsal horn. Lidocaine was shown to have blunted a rise in BIS and hemodynamics with surgical stimulation (Hans et al. 2010). The pharmacokinetics of lidocaine in children have been studied and showed an elimination half-life of 58 min, volume of distribution of 1.1 l/kg, and clearance of 11.1 ml/kg/min (Finholt et al. 1986). The usual recommended dose is a bolus of 1–2 mg/kg followed by 1–2 mg/kg/h continuous infusion. At this infusion rate, serum level remains below 5.0 ug/mL (Daykin 2017).

Although a large number of studies demonstrate that IV lidocaine infusion could reduce the requirement of opioid, propofol, and volatile agents and decrease postoperative pain (Sloan et al. 2014; Marret et al. 2008; Cui et al. 2010; Lauwick et al. 2008; Kaba et al. 2007; Kuo et al. 2006; Himes et al. 1977; Altermatt et al. 2012; Forster et al. 2018). This study is the first study to evaluate the effect of IV lidocaine infusion combined with TIVA in pediatric CIs.

A previous study, which examined the effect of IV lidocaine as an adjuvant to propofol remifentanil-based anesthesia in patient undergoing thoracic surgery, found that lidocaine could reduce morphine consumption and postoperative pain (Cui et al. 2010). Similarly, Lauwick et al. and Kaba et al. investigated the effect of intravenous lidocaine as an adjuvant to volatile anesthetic agents in patients undergoing laparoscopic cholecystectomy and colectomy and found that lidocaine could result in 35% reduction in sevoflurane and opioid requirements (Lauwick et al. 2008; Kaba et al. 2007). Other studies

**Table 2** Primary and secondary outcomes in the two groups

| Parameters | Lidocaine group (*n*=35) | Placebo group (*n*=35) | *P* value |
|---|---|---|---|
| Primary outcome | | | |
| • Remifentanil consumption (ug/kg/min) | 0.57 (0.49–0.64) | 0.69 ((0.63–0.75)) | 0.016* |
| Secondary outcomes | | | |
| • Propofol consumption (ug/kg/min) | 155.5 (146–165) | 171.0 (161–181) | 0.02* |
| • Max-FLACC pain score in PACU | 4.22 (4–4.43) | 4.74 (4.41–5.07) | 0.02* |
| • Total pethidine consumption at PACU (mg) | 7.0 (6.17–7.83) | 8.9 (7.84–9.96) | 0.012* |
| • Incidence of vomiting at PACU | 2 (5.7%) | 5 (14.2%) | 0.42 |

Values are the mean (95% CI) or number (%)
$P < 0.05$ considered significant
*FLACC* aces, legs, activity, cry, and consolability, *PACU* post anesthesia care unit
*Significant to the placebo group

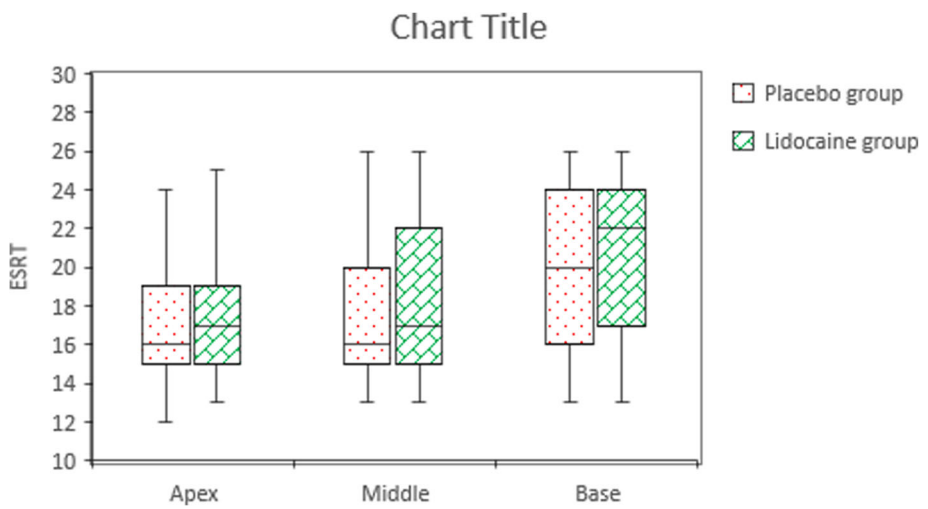


**Fig. 2** Box plots of the ESRT in both groups at the apex, middle, and base of the electrode. The median (IQR) values are shown as a solid line within the box of 25th and 75th percentile values. Whiskers represent 5th and 95th percentile values. ESRT electrical stapedial reflex threshold. No significant difference between groups, $P > 0.05$

found that IV lidocaine could result in a 15% reduction in propofol requirement during TIVA (Altermatt et al. 2012; Forster et al. 2018). In addition, it stabilizes the hemodynamics and decreases the prevalence of patient movement during surgery (Forster et al. 2018).

TIVA with propofol and remifentanil is commonly used during neuromonitoring because propofol unlike halogenated inhalational agents and does not suppress the intraoperative motor evoked potential (Crawford et al. 2009). However, at a higher dose, propofol can depress intraoperative motor-evoked potential, exacerbate reduction in blood pressure, and increase cost (Crawford et al. 2009; Scheufler and Zentner 2002a; Scheufler and Zentner 2002b). Crawford et al. evaluated the effect of different doses of propofol on the intraoperative ESRT in pediatric CIs and found that the intraoperative ESRT could obtain in all patients; however, a small but significant increase in intraoperative ESRT at each target

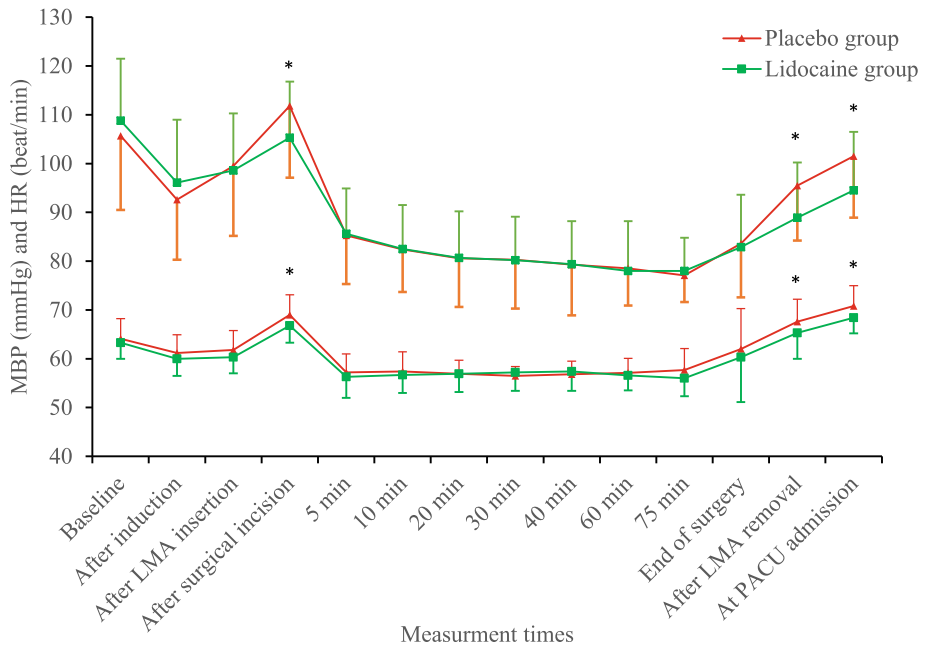


**Fig. 3** The mean (SD) of MBP and HR in both groups. MBP mean arterial blood pressure, HR heart rate, and PACU post-anesthesia care unit. $P < 0.05$ considered significant. *Significant to the placebo group

concentration of propofol. At 3 ug/ml, the intraoperative ESRT increased by 10% compared with baseline measurement before propofol administration. Additionally, the ESRT had not affected by the omission of nitrous oxide (Crawford et al. 2009).

Lidocaine is known to prolong the action potential via blocking voltage-gated sodium channels in the neural membrane and can adversely affect the evoked potential monitoring (Carpenter and Mackey 1989; Kasaba et al. 1991). However, studies found that IV lidocaine can be used as an adjuvant to general anesthesia in adult patients without affecting the motor and sensory evoked potentials (Sloan et al. 2014; Urban et al. 2017). Sloan et al. examined the use of IV lidocaine as an adjuvant to propofol-opioid TIVA during intraoperative neurophysiological monitoring and found no difference in motor and sensory-evoked potential amplitude (Sloan et al. 2014). Urban et al. investigated the effect of lidocaine infusion during spinal surgery and concluded that lidocaine could be used during multilevel spinal fusions without negatively affecting the intraoperative motor and sensory-evoked potential monitoring (Urban et al. 2017). Inghilleri et al. found no effect on the amplitude of motor evoked potential after 1mg/kg lidocaine; however, lidocaine increased successive amplitude of motor evoked potentials after repeated stimuli (Inghilleri et al. 2005). In line with these studies, we found no significant difference in the intraoperative ESRT monitoring between the groups.

In contrast, Schubert et al. found that IV lidocaine (3 mg/kg followed by 4 mg/kg/h) resulted in a 30% reduction of cortical somatosensory evoked potential, without affecting subcortical somatosensory-evoked potential in patients receiving GA with isoflurane, sufentanil, and nitrous oxide. They concluded that there is a synergistic interaction between sufentanil-based anesthesia and IV lidocaine at therapeutic levels to attenuate somatosensory-evoked potentials (Schubert et al. 1992). The use of a high lidocaine dose is another explanation for the attenuated somatosensory-evoked potentials (Inghilleri et al. 2005).

A limitation of this study is that the serum lidocaine levels were not measured. However, the dose of lidocaine in the present study corresponds to the lower end of the dose range in previous studies (1–2 mg/kg/h) (Ferrini and Paice 2004). The expected serum level for this infusion rate is under 3 μ g/ml; however, the side-effects are observed at 4–6 μg/ml, and the toxic effects are observed at 12–16 μg/ml in awake patients (Sloan et al. 2014; Kundra and Vinayagam 2020).

## Conclusion

IV lidocaine infusion combined with TIVA in pediatric CIs decreased perioperative opioid consumption, without altering the intraoperative ESRT monitoring in pediatric CIs. Additionally, it decreased propofol consumption and postoperative pain.

### Abbreviations

NMB: Neuromuscular blockade; TIVA: Total intravenous anesthesia; CIs: Cochlear implants; ESRT: Electrical stapedial reflex threshold; PACU: Post anesthesia care unit; LMA: Laryngeal mask airway; BSI: Bispectral index; FLACC: Faces, legs, activity, cry, and consolability; IV: Intravenous

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None.

### Authors' contributions

Concept, design, definition of intellectual content, literature search: Dr. Bakhet WZ. Experimental studies: Dr. Bakhet WZ, Dr. El Fiky LM, and Mr. Debis HA. Data acquisition, data analysis, statistical analysis: Dr. Bakhet WZ. Manuscript preparation: Dr. Bakhet WZ and Dr. El Fiky LM. Manuscript editing and manuscript review: Dr. Bakhet WZ, Dr. El Fiky LM, and Mr. Debis HA. The manuscript has been read and approved by all the authors that the requirements for authorship as stated earlier in this document have been met and each author believes that the manuscript represents honest work.

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### Availability of data and materials

Data supporting findings can be obtained from the corresponding author.

## Declarations

### Ethics approval and consent to participate

The study protocol was approved by the Bahteem-specialized hospital (05/06/2016) and was registered at ClinicalTrials.gov on November 12, 2019 (NCT04194294). The study was conducted in accordance with the Helsinki declaration. All parents provided written informed consent.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

### Author details

[1]Department of Anesthesia, Ain Shams University, 4 Abdelhamed El Wardany street, El-Zeitoun, Cairo 11725, Egypt. [2]Present Address:, Kuwait City, Kuwait. [3]Department of Otolaryngology, Ain Shams University, Cairo, Egypt. [4]Software Test Engineer, MED-EL Medical Electronics, Cairo, Egypt.

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## Publisher's Note