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Lidocaine Reduces Sevoflurane Consumption and Improves Recovery Profile in Children Undergoing Major Spine Surgery

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Background: Intravenous lidocaine administered during surgery improves postoperative outcomes; however, few studies have evaluated the relationship between intravenous lidocaine and volatile anesthetics requirements. This study assessed the effects of lidocaine treatment on sevoflurane consumption and postoperative consciousness disorders in children undergoing major spine surgery.





Material/Methods: Patients were randomly divided into 2 treatment groups: lidocaine and placebo (control). The lidocaine group received lidocaine as a bolus of 1.5 mg/kg over 30 min, followed by a continuous infusion at 1 mg/kg/h to 6 h after surgery. The following data were assessed: end-tidal sevoflurane concentration required to maintain a bispectral index BIS between 40 and 60, intraoperative blood pressure, heart rate, demand for fentanyl, and consciousness level assessed after surgery using the Richmond Agitation-Sedation Scale. Any treatment-related adverse events were recorded.

Results: Compared to the control group, lidocaine treatment reduced by 15% the end-tidal sevoflurane concentration required to maintain the intraoperative hemodynamic stability and appropriate level of anesthesia (P=0.0003). There were no intergroup differences in total dose of fentanyl used, average mean arterial pressure, or heart rate measured intraoperatively. The postoperative level of patient consciousness did not differ during the first 6 h between groups. After 9 h, more patients in the control group were still sleepy (P=0.032), and there were fewer perioperative complications in the lidocaine group.

Conclusions: Lidocaine treatment decreases sevoflurane consumption and improves recovery profiles in children undergoing major spine surgery.

MeSH Keywords: **Adjuvants, Anesthesia • Consciousness Disorders • Intensive Care Units, Pediatric • Lidocaine • Spinal Fusion**

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Background

The perioperative administration of intravenous (IV) lidocaine improves postoperative analgesia, accelerates restoration of normal gastrointestinal function, allows for earlier mobilization of the patients, and improve their postoperative quality of life [1]. The systemic use of lidocaine also reduces the requirement of intravenous anesthetic agents [2], but its effect on the intraoperative usage of sevoflurane and on postoperative consciousness disorders has not yet been carefully characterized. Animal studies have shown that IV lidocaine reduces the minimal alveolar concentration (MAC) of volatile anesthetic agents [3], which may have important clinical implications for the optimal and safe administration of anesthesia in humans. To date, few studies have evaluated the relationship between IV lidocaine and volatile anesthetics requirements in surgical patients [4–9]. There are also no reports in the literature describing the relationship between the use of lidocaine and the intraoperative request for sevoflurane or the postoperative level of sedation in children undergoing major operations.

Objective

The objective of this study was to evaluate the effect of IV lidocaine infusion on intraoperative sevoflurane consumption, postoperative consciousness level, and safety of use in pediatric patients undergoing major spine operations.

Material and Methods

The protocol of the study was approved on 28 05 2015 by the Jagiellonian University Bioethical Committee [No. 122.6120.89.2015]. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All the parents or legal guardians of the patients, as well as patients over 16 years of age, provided written informed consent prior to inclusion in the study.

Participants

All patients undergoing spine surgery between May 2015 and June 2016 were assessed for study eligibility. Inclusion criteria were multilevel spine surgery, the American Society of Anesthesiologists (ASA) Physical Status <3, and age below 18 years. The exclusion criteria were allergy to topical anesthesia agents, liver disease, renal impairment, epilepsy, planned long-term postoperative mechanical ventilation, body mass index (BMI) >30, chronic opioid therapy, medical history of organ transplant, arrhythmia, and long QT syndrome.

Randomization

We performed a randomized, double-blind, placebo-controlled study. Patients were randomized to the lidocaine or the control group using a computer-generated random numbers table. The randomization sequence was generated by a hospital pharmacist who was not involved with the study. Before the surgery, an appropriately coded syringe was prepared by a hospital pharmacist, which contained a blinded fluid (BF): either Fresenius multi-electrolyte fluid (Fresenius Kabi, Warsaw, Poland) or lidocaine 20 mg/ml (Lignocainum hydrochloricum WZF 2%: Polfa S.A. Warsaw, Poland). In the lidocaine group, patients received IV infusion of lidocaine (a bolus of 1.5 mg/kg over 30 min before skin incision, followed by infusion of 1 mg/kg/h up to 6 h after surgery), and in the control group patients received an equal volume of placebo. The anesthesiologists, surgeons and medical personnel responsible for perioperative patient care, as well as the patients themselves, were blind to the treatment administered. The study coordinator was responsible for maintaining the flow of the study.

Protocol of the study

Intraoperative management

The general anesthesia and the perioperative management protocol were identical in the lidocaine and the control groups, according to a predetermined standard. Four hours before surgery, the first dose of oral gabapentin (Gabapentin Teva, Teva Pharmaceuticals, Warsaw, Poland) (15 mg/kg, max. 600 mg) was given. In the induction to the general anesthesia, fentanyl 1 µg/kg (Fentanyl, Polfa, Poland), propofol 2 mg/kg (Plofed, Polfa S.A, Warsaw, Poland) and rocuronium 0.6 mg/kg (Roqurum, Jelfa S.A., Jelenia Góra, Poland) were used. Half an hour before the skin incision, the following medications were given: dexamethasone

0.1 mg/kg (Dexaven, SUN-FARM, Łomianki, Poland), acetaminophen 15 mg/kg (Paracetamol Kabi, Fresenius Kabi, Warsaw, Poland), and a BF as a bolus of 0.075 ml/kg over 30 min. After tracheal intubation, anesthesia was based on the supply of inhaled oxygen, air, and sevoflurane (Sevorane, AbbVie, Warsaw, Poland).

Fentanyl was administered in fractionated doses for the prevention and treatment of intraoperative pain. The first intravenous dose of 0.1 mg/kg morphine (Morphini Sulfas WZF, Polfa S.A, Warsaw, Poland) was given at the beginning of anesthesia and the second was given at the end. BF was administered intravenously at a rate of 0.05 mg/kg/h throughout the operation and for 6 h after surgery.

Extended monitoring was used, including continuous ECG, the invasive arterial blood pressure measurement, pulse oximetry, end-tidal sevoflurane concentration (ET-Sevo) measured in the exhaled air, body temperature, diuresis, and assessment of blood biochemistry parameters. The depth of anesthesia was monitored using a BIS monitor (bispectral index – a compact module BISx Power Link™, Warsaw, Poland). Sevoflurane concentration was adjusted according to the hemodynamic and BIS values. The ventilatory frequency was adjusted to obtain an end-tidal carbon dioxide concentration (ET-CO₂) between 35 and 40 mmHg. Intraoperatively hypotension was treated with fluid therapy and iv dopamine infusion, if necessary. The neuromuscular blockade was assessed by measuring the train-of-four (TOF) and was reversed by sugammadex (Bridion, Hoddesdon, UK), if necessary.

After the operation was completed, the patient was extubated in the operating room and then transferred to the Intensive Care Unit (ICU).

Postoperative management

Using the Richmond Agitation-Sedation Scale (RASS), the medical staff assessed the postoperative level of consciousness. The rating was performed immediately after surgery and at 2, 6, 9, 15, 24, 30, 40, and 48 h postoperatively. Any possible adverse events of therapy were monitored and recorded in the patient's documentation.

During treatment of postoperative pain, IV morphine (concentration – 1 mg/ml) was administered for the first 2 days as patient-controlled anesthesia (PCA). In the first 16 h, morphine was administered as bolus and a background infusion of 0.5–1 mg/h (on the night immediately after surgery). The bolus was 1 mg, blockade for 15 min, maximum dose 0.03 mg/kg/4 h. In the following hours, morphine was administered only as bolus.

If the NRS for pain exceeded 3, an additional bolus of morphine was given by a nurse. Later, morphine was given in subcutaneous boluses 0.1 mg/kg, depending on demand. The following non-opioid analgesic agents were given intravenously in the first dose during the operation: acetaminophen 15 mg/kg every 6 h and metamizole 0.5–1 g every 8 h (Pyralgin, Polpharma S.A, Starogard Gdański, Poland). Oral gabapentin 5 mg/kg (max. 300 mg per dose) was administered every 8 h for 3 consecutive days.

Study outcomes

The primary aim of this study was to assess the effects of intraoperative IV lignocaine on ET-Sevo concentration required to maintain hemodynamic stability and the appropriate level of anesthesia during spine surgery in children. The secondary

objectives were to assess the effect of perioperative administration of systemic lidocaine on postoperative patient consciousness disorders and to assess the possible adverse effects of lidocaine use.

Laboratory analysis

Perioperatively, at 4 timepoints (before skin incision, after completion of surgery, 6 h after surgery, and on the next morning) blood samples were collected from the arterial line. Routine biochemistry parameters were measured using a Vitros®5600 (Ortho Clinical Diagnostic, Raritan, USA) analyzer, and routine hematology parameters were determined using a Sysmex XN-1000 hematological analyzer (Sysmex Corp., Japan). Plasma concentrations of lidocaine were measured using modified sandwich enzyme-linked immunosorbent assay (ELISA) kits from Neogen Corporation (Lexington, USA). The intra-assay and inter-assay coefficients of variation were 5.2% and 6.7%, respectively, and the detection range was 0.005–10.0 µg/ml. Assay was performed without knowledge of whether the sample was from the control or the lidocaine group.

Statistical analysis

The intergroup differences were compared using the t-Student or t-Welch test, depending on variance equality (variance equality was assessed by the Levene test) for variables with normal distribution. The Mann-Whitney U test was performed for continuous variables with a distribution other than normal. Normality was assessed by the Shapiro-Wilk test. Categorical variables were compared by the Fisher exact test. Additionally, within-group comparisons made over time using repeated measures analysis of variance (ANOVA) with the Bonferroni post hoc test, when necessary. The correlation between laboratory results was evaluated by the Pearson correlation test or the Spearman rank-order correlation test, with the Bonferroni correction adjusted for the total number of analyses. The significance level in all analyses was set to $\alpha=0.05$ and the power needed to detect significant inter- and intra-groups differences was 96–99%. The calculations were done with STATISTICA v.13.5 software (StatSoft, Inc., Tulsa, OK, USA).

Results

Of 66 patients assessed for eligibility, 41 were recruited for our study: 22 of them were randomized to the lidocaine group and 19 to the control group (Figure 1). There were no differences in the remaining variables characterizing patients, surgical procedures, and the general anesthesia course in both groups (Tables 1, 2). During surgery, we observed that the mean end-tidal sevoflurane concentration (ET-Sevo) required to maintain the intraoperative hemodynamic stability and a

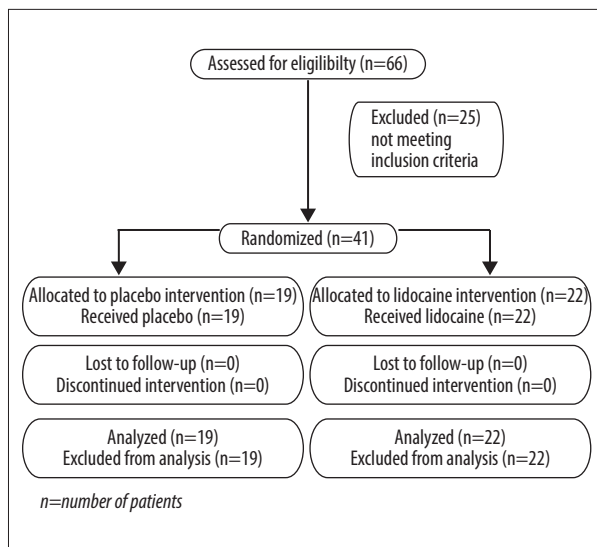


Figure 1. Patient flow chart.

bispectral index (BIS) of 40–60 was about 15% lower in the lidocaine group compared to the control group (P=0.0003) (Table 2, Figure 2). We did not note differences between groups in regard to the total dose of fentanyl, the average mean arterial pressure, or heart rate measured intraoperatively (Table 2). We found that during surgery, only 1 patient in the control group required extra cardiovascular support of the infusion of dopamine. We found no significant differences

in the amount of fluid infused during surgery or perioperative total amounts of packed red blood cells (PRBCs) and fresh frozen plasma (FFP) administered. The lidocaine concentration in the blood was within a safe range (<5 µg/ml) at each measurement point (Figure 3). In the postoperative period, we observed that awareness assessed using the RASS did not differ between groups during the first 6 h, while at 9 h we noted significantly better consciousness level in children in the lidocaine group compared to the control group (P=0.032) (Figure 4). We noted lower morphine requirements in the initial 48 h in the lidocaine group (P=0.03) compared to the controls (Table 2). There were no differences in perioperative complications between groups (P>0.5) (Table 2).

Discussion

The most important finding of the present study was that the loading dose of IV lidocaine followed by the intraoperative infusion reduced by 15% the mean ET-Sevo concentration required to maintain the hemodynamic stability and the appropriate level of anesthesia during spine surgery in children. These observations agree with results of other studies that analyzed the beneficial effect of lidocaine on intraoperative sevoflurane and desflurane consumption in non-spine surgery in adults. Saadawy et al. [6] reported that, in laparoscopic cholecystectomy, lidocaine decreased the mean ET-Sevo concentration by

Table 1. Demographic characteristics and type of surgeries.

Variable	Lidocaine n=22	Control n=19	P value
Age, years	13 (8–15)	13 (9–15)	0.986
Females, n (%)	13 (59.1)	11 (57.9)	0.938
SDS-BMI	18.3 (14.6–22.8)	18.7 (14.7–23.3)	0.989
ASA n (%)			
I	10 (45.5)	10 (52.6)	0.646
II	12 (54.5)	9 (47.4)	0.645
Superior vertebral region, n (%)			
Cervical	1 (4.5)	1 (5.3)	0.916
Thoracic	3 (13.6)	2 (10.5)	0.207
Thoracolumbar	16 (72.7)	15 (78.9)	0.643
Lumbosacral	2 (9.1)	1 (5.3)	0.639
Surgical range, number of vertebrae	13 (9–13)	13 (8–14)	0.922
Number of vertebrae with anchored instrumentation, n	7 (4–8)	7 (6–8)	0.83

Categorical variables were presented as counts and percentages; continuous variables were expressed a median and interquartile range (IQR). BMI – body mass index; ASA – American Society of Anesthesiologists Physical Status I–II; n – number of patients.

Table 2. Perioperative data.

Variable	Lidocaine n=22		Control n=19		P value
Intraoperative data					
Time of operation, min	260	(170–285)	300	(270–340)	0.057
Time of anesthesia, min	335	(225–355)	365	(330–400)	0.054
Fentanyl use, µg/kg/h of anesthesia	1.5	(1.36–2.1)	1.3	(1.16–2.19)	0.465
Mean end-tidal sevoflurane concentration, vol%	1,83	(1,63–1,9)	2,19	(2,06–2,33)	0.0003
Mean BIS	45	(40–48)	49	(47–52)	0.14
Mean MAP, mmHg	60	(58–69)	70	(65–74)	0.054
Mean HR, n/min	77	(71–86)	85	(74–100)	0.083
Hematocrit level,%	34.5	(26–37)	30	(26–33)	0.121
Glucose concentration, mmol/l	6.8	(5.4–7.9)	7.1	(6.5–7.2)	0.623
Lactates concentration, mmol/l	1.5	(1–1.9)	1.4	(1–1.8)	0.856
Base excess (BE), mEq/l	1.3	(0.1–2.5)	–0.35	(–2.0–1.6)	0.18
Cardiovascular support of the infusion of dopamine, n	0		1		N/S
PRBCs transfusion (intra- and postoperative), ml/kg	12.2	(6.5–23.2)	12.5	(8.1–29.4)	0.245
FFP transfusion (intra- and postoperative), ml/kg	12.3	(6.2–15.4)	12.1	(4.4–16.4)	0.913
The amount of fluid infused during surgery (crystalloid) ml/kg	40.7	(27.9–55.7)	42.6	(32.1–68.1)	0.6
Morphine usage up to 48 h postoperatively, mg/kg	0.9	(0.6–1.3)	1.3	(0.8–1.8)	0.030
Postoperative complications, n (%)	5	(22.3)	8	(42.1)	0.183
Disturbed carbohydrate metabolism in diabetic patients	0		1		0.275
Recurrent urinary tract infections with interstitial nephritis	0		1		0.275
Opioid-induced respiratory depression	2		1		0.639
Pneumonia	1		1		0.916
Reoperation associated with faulty implants	1		2		0.463
Surgical wound infection	0		1		0.275
Sensory disturbances due to incorrect body positioning)	1		1		0.916
Transient sensory disturbances in the extremity where lidocaine was administered	1		0		0.346

Categorical variables were presented as counts and percentages; continuous variables were expressed as a median and interquartile range (IQR). BIS – bispectral index; MAP – mean arterial pressure; HR – heart rate; BE – base excess; PRBCs – packed red blood cells; FFP – fresh frozen plasma; n – number of patients; N/S – no statistical difference.

about 48%, without significant differences in intraoperative mean arterial pressure (MAP) and heart rate (HR) compared to the placebo group. In breast plastic surgery, Choi et al. [7] found a 5% reduction in mean ET-Sevo concentration in patients receiving IV lidocaine. Kaba et al. [5] reported significantly lower MAP, HR, and mean ET-Sevo concentration (by 36%) when IV lidocaine was administered in laparoscopic colectomy.

During open radical prostatectomy, Weinberg et al. [9] found that the ET-Sevo concentration required to maintain anesthesia was 21% lower in the lidocaine group, with a simultaneous significant reduction in the intraoperative systolic blood pressure, MAP, and HR. Kaba et al. [5] found that the mean end-tidal desflurane concentration was 18% lower in the lidocaine group in a study of patients undergoing elective colon

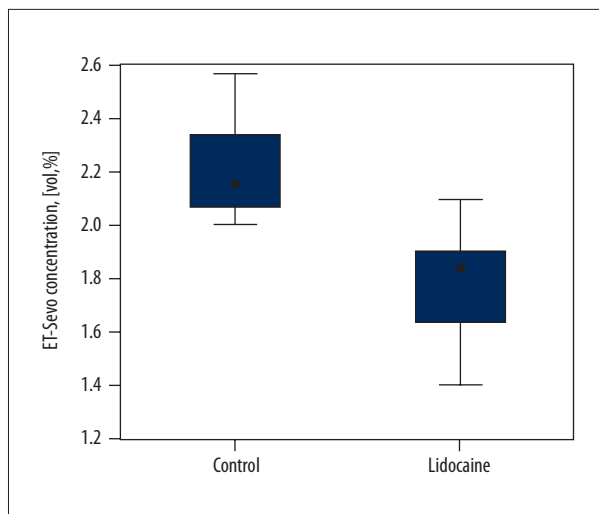


Figure 2. The mean end-tidal sevoflurane concentration (ET-Sevo) required to maintain intraoperative hemodynamic stability and a bispectral index (BIS) of 40–60.

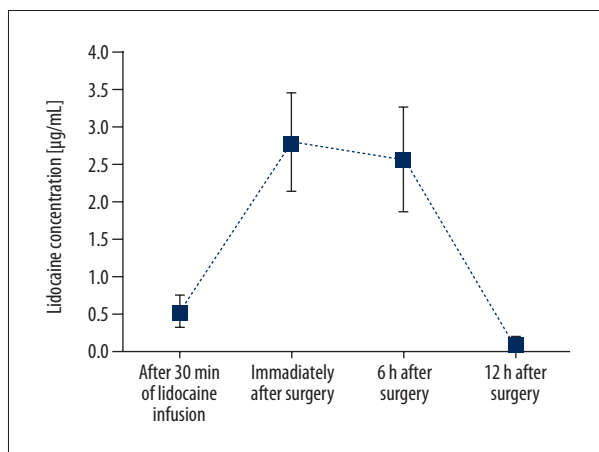


Figure 3. Blood serum lidocaine concentration.

surgery. The plasma concentrations of lidocaine in the above-mentioned studies were similar to those in the present study. The requirement of volatile anesthetics may depend on the way lidocaine is administered – it was reported that the mean MAC of sevoflurane was 12% lower when lidocaine was administered in continuous infusion compared to patients receiving only a loading dose in elective surgery [8]. Regardless of the route of administration, either epidural or intravenous, lidocaine has been shown to reduce the need for volatile anesthetics [4,10]. In the only published study that investigated the perioperative administration of IV lidocaine in adults undergoing spine surgery, no effects of this drug on the intraoperative use of volatile anesthetic were observed [11]. To the best of our knowledge, there are no published studies evaluating the effect of IV lidocaine on sevoflurane requirements of during surgery in children.

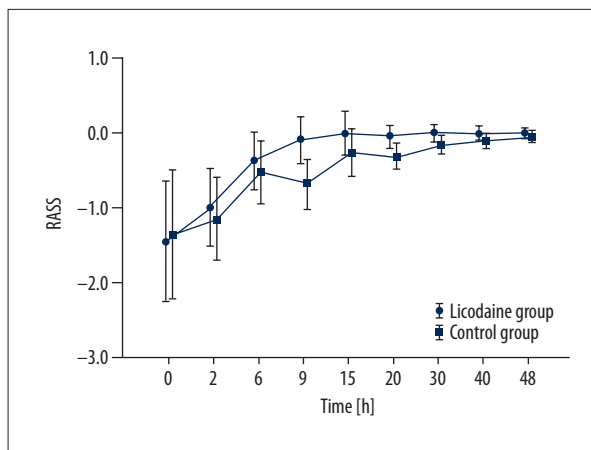


Figure 4. The postoperative level of consciousness assessed using the Richmond Agitation-Sedation Scale (RASS).

The effect of lidocaine on the use of sevoflurane is unclear. The mechanisms underlying its anesthetic-sparing effects may include a direct sedative and hypnotic action facilitation of hypnotic agents via GABA-receptor effects in the central nervous system (CSN), blocking sensory transmission, or anti-nociception [10,12,13].

In the first 48 h after the operation, we assessed the level of consciousness using the RASS. This 10-level numerical rating scale is based on patient response to stimulation, from agitation to sedation [14]. We did not notice significant differences in the first 6 h after the operation: a comparable number of children in both groups were sleepy, waking up to verbal stimuli. In the following hours, more patients in the control group were still sleepy, awakening to voice, while in the lidocaine group more children were observant and calm. These observations can be explained by the reduction of intraoperative consumption of sevoflurane and lower postoperative demand for morphine in children in the lidocaine group, as well as the drug’s own properties. The neuroprotective properties of lidocaine have been the subject of many recent studies. A recent meta-analysis showed that, in cardiopulmonary bypass surgery, lidocaine reduces the postoperative cognitive deficit in adults, and this effect is enhanced by its higher plasma concentration [15,16]. The underlying mechanisms of postoperative brain functional changes are not fully understood, but it seems that the main causes are strong systemic inflammation, endothelial dysfunction, cerebral hypoperfusion, and microembolism [17,18]. Lidocaine is a sodium channel-blocking drug that crosses the blood-brain barrier and improves cerebral protection by modulation of inflammatory mediators, deceleration of ischemic ion fluxes, preservation of cerebral blood flow, and depletion of cerebral metabolism, and it has anti-apoptotic properties [17]. Lidocaine may also be an effective neuroprotective agent in treating early postoperative cognitive dysfunction in elderly patients undergoing spine surgery [19].

The mechanism responsible for this effect may be the inhibition of lidocaine release of the serum proteins IL-6, malonic aldehyde (MDA), S100b, and neuron-specific enolase (NSE) [19].

It is believed that the optimal therapeutic range of lidocaine is at a blood concentration of 1.1–4.2 µg/ml; plasma concentrations above 5 µg/ml are considered to be toxic [20,21]. The safety of lidocaine usage was proven by the analysis of 16 randomized, double-blind, placebo-controlled studies in which the dosage was standardized (1.5 mg/kg 30 min preoperatively, continuous infusion of 1.5–3 mg/kg intraoperatively, and 1–3 mg/kg postoperatively), and no serious adverse effects or complications of the therapy were observed [21,22]. After administration of lidocaine for up to 12 h in the regimen described above, the half-life of the drug is about 100 min and shows linear pharmacokinetics. About 90% of intravenous lidocaine undergoes hepatic metabolism by cytochrome P450. Less than 10% of lidocaine is excreted unchanged by the kidneys [20,21]. In children older than 6–7 months, lidocaine distribution and elimination is the same as in adults [23]. Early symptoms of local systemic anesthetic toxicity (LAST) include perioral numbness, metallic taste, tinnitus, visual and auditory disturbances, paresthesia, nausea, dizziness, and drowsiness. At higher blood concentrations, convulsions and respiratory and cardiac arrest may occur [20]. In the present study, blood lidocaine concentrations did not reach toxic levels. The only adverse effects of lidocaine we observed were transient skin sensory disturbances at the site of drug administration and the postoperative respiratory depression triggered by overestimated opioid requirements. There were fewer perioperative

complications (although the difference was not statistically significant) in the lidocaine group (a possible effect of low numbers of subjects in the groups), which suggests lidocaine is a safe medication.

A limitation of this study is the small number of subjects in each study group. This may be the reason for underestimating the possible association between variables. In addition, the research was carried out at a single center. Multi-center, prospective, randomized trials, with larger sample sizes and higher statistical power are necessary to overcome these limitations. None of our patients had a severe underlying disease causing organ failure. Therefore, the results of our study should not be generalized to other patients with serious comorbidities. We also did not examine the effects of lidocaine treatment on improvement of cognitive function in children using any validated neuro-psychometric tests.

Conclusions

We found that the loading dose of IV lidocaine followed by the intraoperative infusion reduces sevoflurane consumption and improves recovery profiles in children undergoing major spine surgery.

Conflict of interest

None.

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