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Influence of intravenous lidocaine infusion on haemodynamic response to tracheal intubation and metabolic-hormonal responses during laparoscopic procedures in children: a randomised controlled trial

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Abstract

Background Lidocaine, a widely used local anaesthetic, also serves as an adjuvant in pain management. However, its use in children is off-label. This study aimed to determine if intravenous lidocaine alleviates the haemodynamic, metabolic, and hormonal responses to intubation and laparoscopic surgery in children.

Methods A single-centre, parallel, double-masked, randomised, placebo-controlled trial. 132 patients, aged 18 months to 18 years, with no contraindications to lidocaine administration and qualified for laparoscopic appendectomy were enrolled. The intervention studied was a lidocaine bolus of 1.5 $mg \cdot kg^{-1}$ over 5 min given before induction of anaesthesia, followed by intraoperative lidocaine infusion at 1.5 $mg \cdot kg^{-1} \cdot h^{-1}$ intraoperatively. Patients in the control group were administered a placebo. Mean arterial pressure, glucose, cortisol, lidocaine blood levels, lidocaine-related side effects, and intraoperative opioid requirements were analysed.

Results 132 participants completed the trial. The number of patients who experienced an excessive cardiovascular response to induction of anaesthesia or intubation was 23 (37%) in the control group and 21 (34%) in the lidocaine group ($p = 0.707$). No statistically significant difference was found between the control and lidocaine groups in the hormonal and metabolic responses, as well as intraoperative fentanyl requirements. Serum lidocaine levels remained below the toxic threshold in all patients.

Conclusions Although the studied intervention appears to be safe, with no clinical side effects observed and serum lidocaine levels remaining below the toxic threshold, its intraoperative administration is not recommended, as it does not demonstrate any significant benefit during the anaesthesia period when compared to placebo.

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Keywords Haemodynamic response, Intravenous lidocaine, Multimodal anaesthesia, Opioid consumption, Paediatric anaesthesia, Serum levels of lidocaine

Background

Lidocaine, the first amino amide-type local anaesthetic, has been used in a variety of applications for over seventy years. Besides regional anaesthesia, it is also utilised as an antiarrhythmic, anticonvulsant, antitussive, and as an adjunct in acute and chronic pain management protocols. Lidocaine and its active metabolites, monoethylglycinexylidide (MEGX) and glycinexylidide (GX), interact with numerous ion channels, neurotransmitter pathways, and affect the immune system [1]. Despite its long history of clinical use and numerous preclinical studies, some important questions remain unanswered.

Prevention of significant cardiovascular responses to induction of anaesthesia and tracheal intubation plays a critical role in the management of patients with cardiovascular disease, intracranial bleeding, and those at risk of or with existing increased intracranial pressure requiring surgery. There are several well-established rules to follow during the induction of anaesthesia to maintain cerebral perfusion pressure. These include ensuring correct positioning of the patient, effective pain management, minimising coughing and vomiting reflexes, maintaining adequate haemoglobin levels and appropriate coagulation parameters, maintaining normocapnia and normoxia, and maintaining stable haemodynamic parameters by avoiding both excessive increases and decreases in arterial blood pressure [2, 3].

Particularly, the latter may be easier to achieve with the use of lidocaine [4, 5]. However, although some recommendations exist [2], the level of evidence supporting them remains low. Therefore, the decision to use lidocaine, especially in children, remains an off-label option.

As the multimodal approach to pain management became standard, interest in lidocaine as an adjuvant surged. Its well-recognised opioid-sparing properties, as well as its ability to promote recovery after certain surgical interventions in adults, have consequently led to guidelines being published by scientific societies [6, 7]. However, due to limited evidence, the use of lidocaine in the paediatric population has a weaker level of recommendation; therefore, its efficacy and safety profile require further investigation [8–10].

The primary objective of this study was to evaluate the ability of lidocaine to alleviate the haemodynamic response to tracheal intubation. Safety concerns were addressed through the close monitoring and assessment of haemodynamic parameters, as well as serum lidocaine concentrations. Cortisol and glucose levels were measured as markers of hormonal and metabolic responses to surgery. The final parameter assessed was the use of opioids during anaesthesia to determine if lidocaine had an opioid-sparing effect in the paediatric population.

Methods

Study design

In accordance with current Polish law and the Declaration of Helsinki, the study was approved by the Ethics Committee of the Medical University of Warsaw on 13 December 2021 (KB/204/2021). The trial was registered with the US National Institutes of Health (ClinicalTrials.gov): NCT05238506. The date of first registration: 14/02/2022.

The study was conducted in a single teaching hospital – the University Clinical Centre of the Medical University of Warsaw. Patients were enrolled between 12 March 2022 and 8 August 2023.

Written informed consent was obtained from patients' parents or legal guardians, as well as from all patients over the age of 16 years.

In this double-masked, randomised controlled trial, children were randomly assigned to two groups according to the use of intraoperative intravenous lidocaine infusions to compare haemodynamic responses to tracheal intubation. Secondary outcomes included the metabolic response to laparoscopic surgery, serum lidocaine levels, the hormonal response to laparoscopic surgery, and side effects of lidocaine. Finally, the requirement for opioids during anaesthesia was also assessed.

Study population

Children admitted for emergency laparoscopic appendectomy during shifts covered by the anaesthesiologists participating in the study were assessed for eligibility criteria.

The inclusion criteria are listed below:

Age between 18 months and 18 years;

American Society of Anesthesiologists (ASA) physical status class 1E, 2E, 3E;

Patients undergoing laparoscopic appendectomy.

The exclusion criteria are listed below:

Allergy to local anaesthetics or contraindications for the use of lidocaine;

ASA physical status class 4E or higher;

Severe cardiovascular disease;

Preoperative bradycardia;

Preoperative atrioventricular block;

Renal failure;

Chronic treatment with analgesics;

Legal guardians' refusal.

Study interventions

Participants were randomly assigned to the lidocaine or control group. The enrolment team consisted of three physicians who were blind to patient allocation. Only patients operated on during the shifts of the recruitment team were evaluated for eligibility criteria (Fig. 1). The other patients were labelled "Not available to the study team".

Patients in the experimental arm received intravenous lidocaine bolus of 1.5 $mg \cdot kg^{-1}$ over 5 min before induction of anaesthesia, followed by lidocaine infusion at 1.5 $mg \cdot kg^{-1} \cdot h^{-1}$ intraoperatively. The infusion was discontinued before the patients' transfer to the postanaesthesia care unit (PACU).

Patients in the control arm received intravenous normal saline bolus of 0.15 $ml \cdot kg^{-1}$ over 5 min before induction of anaesthesia, followed by normal saline infusion at 0.15 $ml \cdot kg^{-1} \cdot h^{-1}$ intraoperatively. The infusion was discontinued before the patients' transfer to the PACU.

Both solutions, 1% lidocaine, and normal saline, are transparent and indistinguishable from each other. Syringes were prepared by a separate staff member who was not involved in patient enrolment or anaesthesia. Each syringe was labelled only with the participant's number. Therefore, the attending anaesthesiologist was effectively blinded to the intervention given. Both groups of participants were treated according to the same fixed intraoperative care protocol.

Anaesthesia protocol description (Fig. 1)

The peripheral intravenous catheter was inserted in the Emergency Department or in the Surgery Ward when obtaining blood samples. No local anaesthetics were used.

Due to the primary diagnosis of acute appendicitis, all cases were classified as emergencies (E) and all patients were treated as if they had a "full stomach" and were therefore at risk of pulmonary aspiration. Rapid sequence intubation was performed with a high dose of rocuronium without applying cricoid pressure (Sellick manoeuvre).

Upon admission to the operating wing, intravenous midazolam at 0.05 $mg \cdot kg^{-1}$ was administered for anxiolysis. The patient was then transferred to the operating theatre, where their vital signs were captured. In both groups, identical syringes containing an unidentifiable substance (1% lidocaine or normal saline) were connected, and a bolus of 0.15 $ml \cdot kg^{-1}$ was administered over five minutes. Induction of anaesthesia was achieved with IV propofol 4 $mg \cdot kg^{-1}$, fentanyl 0.003 $mg \cdot kg^{-1}$ and rocuronium 1.0-1.2 $mg \cdot kg^{-1}$. Five minutes after tracheal intubation the first blood sample was collected into a blood collection tube (S-Monovette Serum CAT, 4.9 ml), and the infusion of the masked solution was initiated.

This was followed by intravenous acetaminophen 15 $mg \cdot kg^{-1}$ and metamizole 15 $mg \cdot kg^{-1}$. Anaesthesia was maintained with sevoflurane. The minimum alveolar concentration of the volatile agent was adjusted to maintain the bispectral index (BIS) near the target of 45.

Additional fentanyl doses of 0.001 $mg \cdot kg^{-1}$ were given when the increase in heart rate or blood pressure exceeded 20% of baseline readings.

The second blood sample was collected into a blood collection tube (S-Monovette Serum CAT, 4.9 ml) immediately after the end of surgery (last dressing applied) and before the endotracheal tube was removed. After extubation, the children were transferred to the PACU.

Haemodynamic and respiratory parameters were continuously monitored, recorded, and automatically stored in the study database for future analysis.

Randomisation

Eligible children were allocated to groups according to a computer-generated permuted block randomisation list. The list was generated using the Sealed Envelope Ltd. 2022, available from: https://www.sealedenvelope.com/simple-randomiser/v1/lists.

Block sizes were 4, 6, 8; Seed 20,412,912,460,056; list length: 138; allocation ratio 1:1.

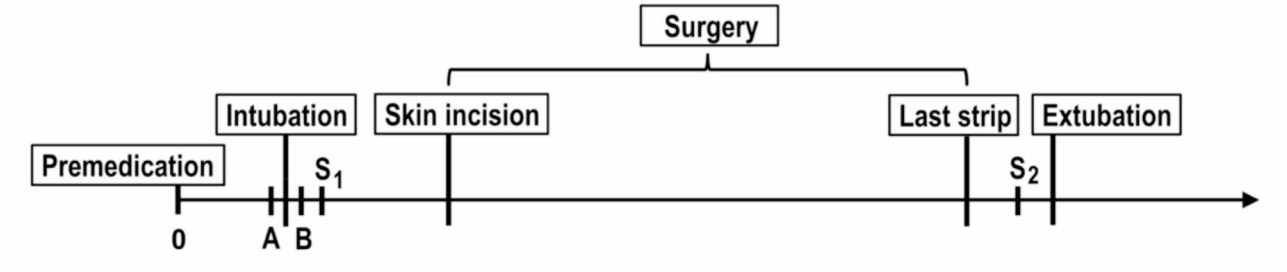

Fig. 1 Study timeline diagram. **A**, **B** – time points representing haemodynamic baseline status (**A**) and haemodynamic parameters immediately after tracheal intubation (**B**). S_1, S_2 – time points for the first (S_1) and second (S_2) collection of blood samples to measure initial and final levels of glucose, cortisol, and lidocaine

Information on participant allocation was only available to the principal investigator and a dedicated staff member responsible for providing the solution. Personnel with knowledge of the allocation were not involved in patient enrolment, anaesthesia administration, or intervention application. The statistician was also blinded by being provided with a randomisation list labelled "group W" and "group G". These specific letters were deliberately chosen to avoid any association with words such as "control", "intervention", "lidocaine", "saline", "study", etc. Laboratory technicians were not given any randomisation list at all. Participants and their parents or legal guardians were not informed of the allocation at any time until the end of data analysis.

Throughout the study, patients received all medications according to their allocation. To check for potential mistakes, lidocaine levels were measured in both groups.

The attending surgical team was not informed of the patients' participation in the study. No additional information sheet about the patients' enrolment was included in the medical records. In the anaesthesia protocol, information about the infusion was recorded as "solution X" with the infusion rate in $ml \cdot h^{-1}$. Written information about the trial and the informed consent forms were given to the participants' parents or legal guardians, and were not part of the medical records. In the event of lidocaine-specific adverse reactions, researchers were required to contact the principal investigator to reveal the composition of "solution X".

Study outcomes

Data were collected in the operating wing while the anaesthesia team were responsible for the participants, from admission and premedication to tracheal tube removal and discharge to the PACU.

The primary outcome was defined as the proportion of patients in each group who experienced an excessive cardiovascular response, characterized by a change in mean arterial blood pressure (MAP) exceeding 20% from baseline during induction of anaesthesia or intubation.

Furthermore, the occurrence of excessive increases in mean arterial pressure due to tracheal intubation and excessive decreases in mean arterial pressure due to induction of anaesthesia were analysed separately.

The secondary outcomes of this study were defined as follows.

- The metabolic response to anaesthesia and laparoscopic procedure was assessed by comparing glucose levels [$mg \cdot dl^{-1}$] before and after the laparoscopic procedure.
- The hormonal response to anaesthesia and laparoscopic procedure was assessed by comparing cortisol levels [$\mu g \cdot dl^{-1}$] before and after the laparoscopic procedure.
- Serum lidocaine levels [$\mu g \cdot ml^{-1}$] were measured after the initial bolus and immediately before the end of the drug infusion.

For all the above tests, the first blood sample was taken 5 min after tracheal intubation, and the second blood sample was taken just before extubation.

- The side effects of lidocaine administration were assessed by recording the rates of the following complications: arrhythmia, hypotension (defined as 2 standard deviations below the 50th percentile), and allergic reactions. Monitoring began at the start of the drug infusion and continued until transfer to the PACU, approximately 10 min after extubation.
- Opioid requirements during anaesthesia were assessed by comparing the total amount of fentanyl, measured in micrograms per kilogram of body weight, used from the induction of anaesthesia to admission to the PACU, approximately 10 min after extubation.

There were no amendments to the study protocol after the commencement of the study.

Sample size and statistical analysis

In order to detect a difference of at least 25% between the fractions of patients with a change in mean arterial blood pressure of more than 20% from baseline, with a type 1 error rate of 0.05 and a power level of 80%, the study needed 60 subjects in each group.

The rate of children lost to follow-up due to incomplete medical records and other reasons was expected to reach 10%. Therefore, the final recruitment target of 132 was divided into two cohorts of 66 patients each.

Categorical data are expressed as the number of participants and the corresponding percentage of the group. Differences between the proportions of qualitative data were assessed with the $\chi 2$ test. Quantitative data were assessed for normal distribution using the Shapiro-Wilk test. Normally distributed data are expressed as mean (standard deviation - SD) and Student's t-test was used for inter-group comparison. Non-parametric data are reported as median (interquartile range – IQR) and were compared using the Mann-Whitney U test. A p-value < 0.05 was considered to be statistically significant. All analyses were conducted using the Statistica software version 13.1 (Statsoft Co.).

Results

Study population

Of the 162 patients who were screened, 5 did not meet the inclusion criteria (1 with renal failure, 1 with heart failure, 1 with coexisting heart and renal failure, 1 currently undergoing diagnostic testing for porphyria, and 1 with uncertain initial surgical eligibility for appendicitis/Meckel's diverticulum). Additionally, 8 patients could not be enrolled due to a language barrier, and 15 patients refused to participate. In 2 cases, the dedicated operating theatre was unavailable.

Between March 2022 and August 2023, 132 children aged between 35 months and 17 years and 10 months met the eligibility criteria and were randomised: 66 patients were assigned to the control group and 66 were assigned to the lidocaine group. 132 participants completed the trial. A total of 130 patients ultimately underwent laparoscopic appendectomy. Despite 2 procedures being converted from laparoscopic to open, 1 patient receiving a higher dose of lidocaine and 1 patient receiving morphine preoperatively, the intention-to-treat analysis principle was followed. Therefore, no patient was excluded from the analysis for any reason.

Baseline demographic and clinical characteristics are presented in Table 1.

Perioperative clinical data and non-opioid analgesic use

There were no differences between the groups in mean haemodynamic parameters, bispectral index, minimum alveolar concentration of sevoflurane, duration of surgery, duration of anaesthesia, time to emergence from anaesthesia, time from extubation to hospital discharge, and intraoperative fentanyl requirement. The doses of acetaminophen and metamizole administered were also the same in both groups (Table 2).

Primary outcome

A primary outcome defined as an excessive cardiovascular response to intubation or induction of anaesthesia occurred in 23 participants (37%) in the control group and 21 participants (34%) in the lidocaine group; $\chi^2 = 0.141$ (df = 1, 2 × 2), $p = 0.707$.

An excessive increase in mean arterial pressure due to tracheal intubation occurred in 3 participants (5%) in the control group and 5 participants (8%) in the lidocaine group, whereas an excessive decrease in mean arterial pressure due to induction of anaesthesia occurred in 20 participants (32%) in the control group and 16 participants (26%) in the lidocaine group, $\chi^2 = 1$ (df = 2, 3 × 2), $p = 0.606$.

Secondary outcomes

- The metabolic response to anaesthesia and laparoscopic procedure.

In the Mann-Whitney test, there were no significant differences between the control and lidocaine groups in glucose levels measured immediately after intubation (Z = 0.571, $p = 0.568$) and immediately before extubation (Z = 0.913, $p = 0.361$).

The differences between the baseline and the final glycemia levels within both groups were statistically significant: 88.08 ± 20.76 mg·dl^{-1} vs. 96.02 ± 24.3 mg·dl^{-1} (control group) and 85.68 ± 19.44 mg·dl^{-1} vs. 91.91 ± 20.28 mg·dl^{-1} (lidocaine group); $P < 0.001$ according to Wilcoxon's test (Fig. 2a).

Finally, the difference between the groups was not statistically significant in the Kruskal-Wallis ANOVA test: H (1,130) = 0.328, $p = 0.567$.

- The hormonal response to anaesthesia and laparoscopic procedure.

Table 1 Patient characteristics in each cohort

Variable	Lidocaine group *n* = 66	Control group *n* = 66
Age		
(year) Mean (SD)	10.82 (3.75)	12.04 (3.81)
Sex		
Male		
n (%)	39 (59)	36 (45.5)
Female		
n (%)	27 (41)	30 (54.5)
Weight		
(kg) Median (IQR)	40 (27–57)	46.5 (32–56)
ASA		
(IE/IIE/IIE)	39/26/1	45/21/0

Normally distributed data are expressed as mean (SD, standard deviation) and Student's t-test was used for group comparison. Non-parametric data are expressed as median (IQR, interquartile range) and were compared using the Mann-Whitney U test or χ2 test

Table 2 Perioperative clinical data

Variable	Lidocaine group *n* = 66	Control group *n* = 66	*p*-value
Mean arterial pressure – skin incision			
(mmHg) mean (SD)	67 (10.3)	64.2 (10.4)	0.128
Mean arterial pressure – end of surgery			
(mmHg) mean (SD)	70.4 (11)	70.2 (12)	0.933
Heart rate – skin incision			
(bpm) Median (IQR)	97.8 (18.5)	92.7 (16.9)	0.105
Heart rate – end of surgery			
(bpm) Median (IQR)	87.9 (18.7)	85.6 (17.8)	0.472
Bispectral index			
Mean (SD)	44.9 (2.9)	45.1 (3.3)	0.808
Minimum alveolar concentration of sevoflurane			
Mean (SD)	0.62 (0.114)	0.636 (0.097)	0.399
Duration of surgery			
(min) Median (IQR)	56 (39–79)	54.5 (42–70)	0.942
Duration of anaesthesia			
(min) Median (IQR)	86.5 (70–98)	89.5 (70–104)	0.689
Time from the end of surgery ("last strip") to extubation			
(min) Median (IQR)	12.5 (9–16)	12 (10–15)	0.909
Time from extubation to discharge			
(days) Median (IQR)	4.51 (3.59–6.66)	3.98 (3.37–6.53)	0.458
Fentanyl before intubation			
(µg) Median (IQR)	120 (80–170)	145 (100–160)	0.389
(µg·kg^{-1}) Median (IQR)	3.00 (2.94–3.08)	3.01 (2.88–3.13)	0.698
Cumulative dose of fentanyl			
(µg) Median (IQR)	150 (100–190)	150 (110–200)	0.578
(µg·kg^{-1}) Median (IQR)	3.20 (3.0-4.09)	3.13 (2.98–4.06)	0.577
Number of patients who received additional fentanyl dose			
n (%)	31 (47)	28 (42.4)	0.599
Total perioperative non-opioid analgesic use			
Acetaminophen (paracetamol)			
(mg) Median (IQR)	600 (400–1000)	700 (450–800)	0.534
(mg·kg^{-1}) Median (IQR)	15.00 (14.49–15.48)	15.00 (13.95–15.52)	0.629
Metamizol			
(mg) Median (IQR)	600 (450—850)	700 (450–850)	0.404
(mg·kg^{-1}) Median (IQR)	15.00 (14.58–15.38)	15.09 (14.29–15.56)	0.848

Normally distributed data are expressed as mean (SD, standard deviation) and Student's t-test was used for group comparison. Non-parametric data are expressed as median (IQR, interquartile range) and were compared using the Mann-Whitney U test or χ2 test

The Mann-Whitney (M-W) test showed that there were no significant differences between the control and lidocaine groups in the level of cortisol measured immediately after intubation (S_1: $Z = 0.571$, $p = 0.568$) and immediately before extubation (S_2: $Z = 0.913$, $p = 0.361$); Fig. 2a.

Wilcoxon's tests showed that cortisol levels increased significantly in both groups when comparing S_1 and S_2 measurements ($P < 0.001$); from 12.7 ± 8.8 µg·dl^{-1} to 19.3 ± 9.8 µg·dl^{-1} in the control group and from 11.4 ± 8.2 µg·dl^{-1} to 19.9 ± 10.3 µg·dl^{-1} in the lidocaine group (Fig. 2b). However, these cortisol increases (ΔCortisol) were not statistically different between groups; Z=-0.989, $p = 0.322$ (M-W test); Fig. 2b. Lidocaine did not affect the hormonal response to anaesthesia and laparoscopic surgery as assessed by the change in cortisol levels.

- Serum lidocaine levels [µg·ml^{-1}].

Serum lidocaine levels were tested in both groups to detect potential errors in the preparation of the masked solutions. No discrepancies were found. In the 64 lidocaine patients from whom appropriate samples were taken, serum lidocaine levels did not exceed the maximum therapeutic level of 5 µg·ml^{-1} (Fig. 3). The two patients excluded from the analysis had blood samples

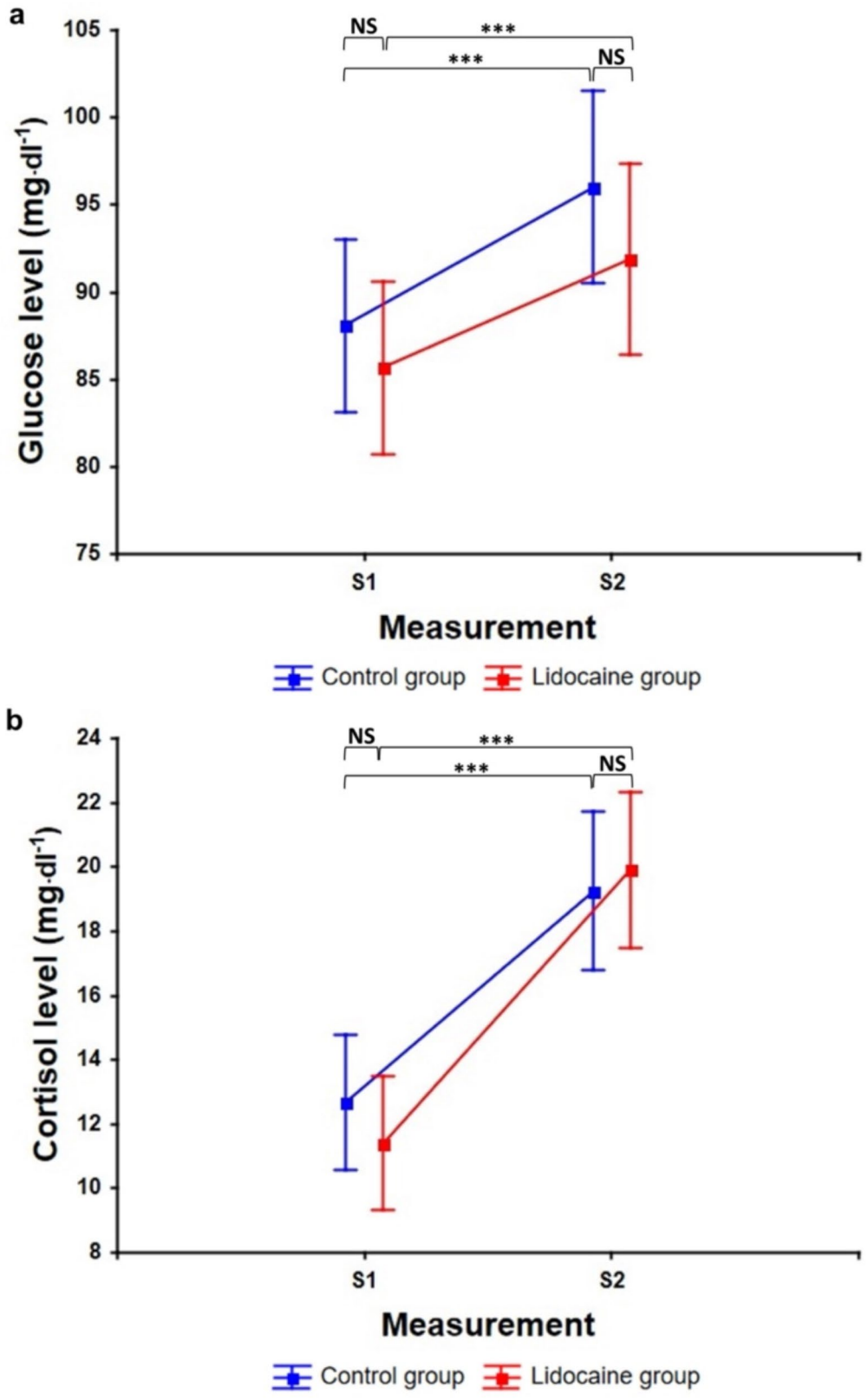

Fig. 2 Glucose (**a**) and cortisol (**b**) levels in the lidocaine and control groups, in blood samples taken 5 min after intubation (S_1) and immediately before extubation (S_2); the data are: mean ± 95% CI (confidence interval). $P < 0.00$ (***), nonsignificant difference (NS)

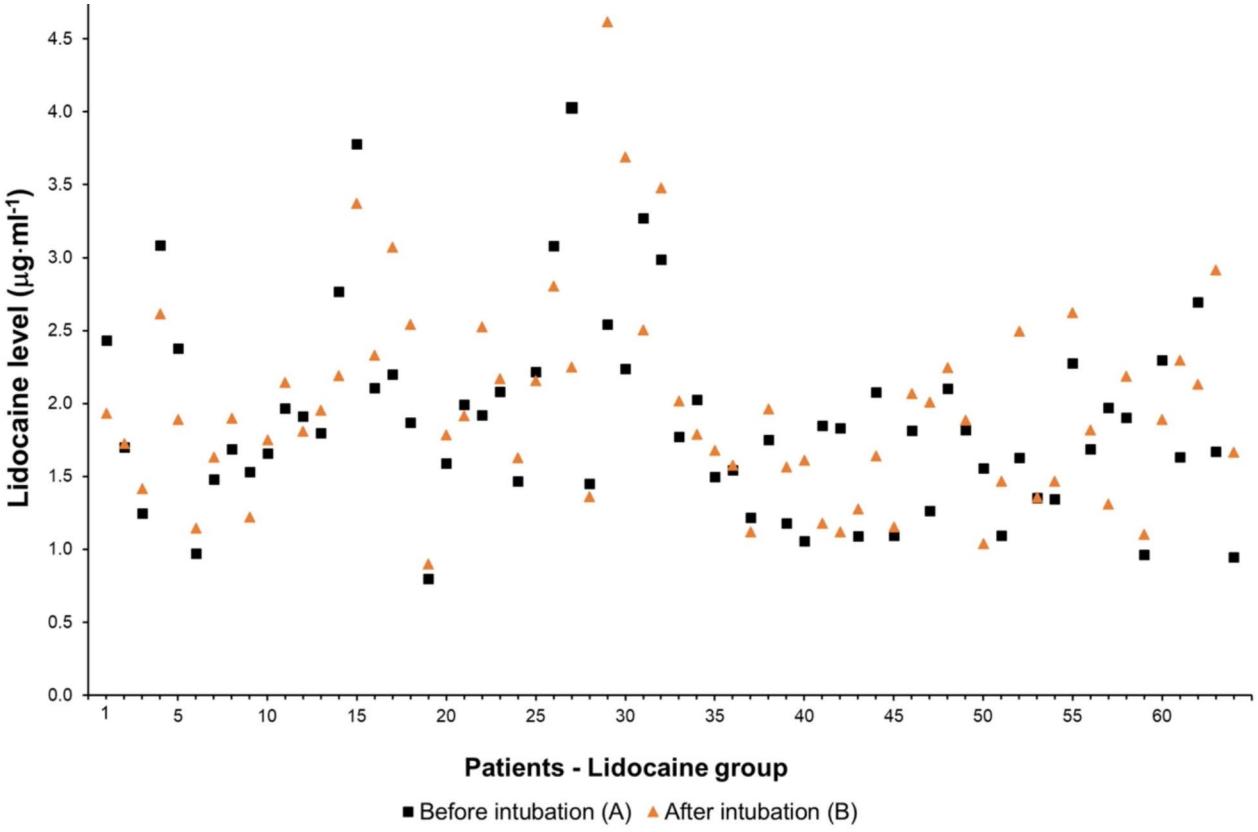

Fig. 3 Lidocaine levels in consecutive patients in the lidocaine group, measured in blood samples taken 5 min after intubation (S_1) and immediately before extubation (S_2) (see Fig. 1)

collected from veins located slightly above the vessels receiving the lidocaine infusion.

- Side effects.

There were no side effects from lidocaine administration.

- Opioid requirements.

Opioid requirements, expressed as the total amount of fentanyl administered in $\mu g \cdot kg^{-1}$, and additional boluses of the drug, did not differ between the groups (Table 2).

Discussion

Intravenous lidocaine is widely used as an adjuvant to enhance the perioperative period. Its risk profile, beneficial properties, and dosing regimen are well-established in the adult population, providing sufficient evidence to formulate guidelines [5, 6]. In 2021, Foo and colleagues [11] published guidelines aimed at enhancing patient safety by recommending restrictive formal procedures, including obtaining separate consent from the patient, as well as approval from the local hospital and medication governance committee, or an equivalent body. The guidelines also provide explicit dosing recommendations. This document establishes well-defined rules, albeit specifically for the adult population. By contrast, there remains a lack of large, prospective studies in the paediatric population, making it impossible to formulate similar recommendations for children [8–10].

In line with our previous trial [12] and a publication focused on the paediatric population by El-Deeb and colleagues [13], we adopted a protocol that, in many aspects, closely resembles the one proposed by Foo and colleagues. An initial bolus of 1.5 $mg \cdot kg^{-1}$ was administered over 5 min prior to induction of anaesthesia, followed by an infusion at 1.5 $mg \cdot kg^{-1} \cdot h^{-1}$ intraoperatively. In the 64 patients from whom appropriate samples were taken, serum lidocaine levels did not exceed the maximum therapeutic level of 5 $\mu g \cdot ml^{-1}$. These results are consistent with those reported by El-Deeb et al. [13] and with findings compiled in the current review article by Heath et al. [10].

One patient was mistakenly given an initial bolus of 2.06 $mg \cdot kg^{-1}$, but the subsequent infusion rate was in accordance with the protocol. This patient developed no clinical side effects, and the serum lidocaine level was 3.08 $\mu g \cdot ml^{-1}$ in the first sample collected and

2.61 μg·ml^{-1} after 65 min of drug infusion. Based on both clinical assessment and laboratory testing, the presented protocol appeared to be safe for children.

The percentage of patients experiencing a significant increase in MAP did not differ between groups; therefore, lidocaine did not attenuate the haemodynamic response to tracheal intubation. This finding is consistent with the results of a study conducted by Zou et al. [5], who also failed to demonstrate a significant influence of lidocaine on MAP in adult patients undergoing intubation.

Although in our study some patients experienced a decrease in MAP of more than 20% from the baseline, further analysis showed that none of them experienced a decrease in MAP below the low cut-off, defined as 2 standard deviations below the 50th percentile. The lowest mean arterial pressure among children in this subgroup was recorded in a 13-year-old boy weighing 68 kg, who experienced a decrease from 69 mmHg to 47 mmHg (31%), which was still within the normal range for a male of his age and weight during anaesthesia [14]. In contrast, in the adult population studied by Zou et al. [5], incidences of hypotension were observed in response to the induction of anaesthesia; however, no significant difference was found between patients who received lidocaine and those who received a placebo. This finding suggests that lidocaine is not an additional risk factor for hypotension in adults or children.

Surgical and anaesthetic stress is responsible for neurohormonal dysregulation, leading to metabolic abnormalities [15, 16]. Intraoperative hyperglycaemia is associated with postoperative complications such as surgical site infections, myocardial infarction, kidney injury, stroke, and death [16]. Glycemia is a feasible, easily obtainable, cost-effective, and objective marker resistant to researcher influence; therefore, we chose to assess the impact of lidocaine on this parameter. To avoid performance bias, we masked the intervention and prohibited any procedures in the study protocol that could affect blood glucose levels. Therefore, only balanced crystalloids without glucose were administered, and dexamethasone, although considered an adjuvant and antiemetic, was excluded from use during anaesthesia.

In our study, glucose and cortisol levels proved to be reliable markers of metabolic and hormonal responses during minor laparoscopic procedures such as appendectomy, as both parameters increased significantly during anaesthesia and surgery. However, lidocaine had no significant effect on them.

In the study by El-Deeb et al. [13], a significant influence on cortisol levels was observed, which contrasts with the results of our study. In our opinion, this inconsistency might be explained by differences in the approach to induction of anaesthesia. El-Deeb et al. administered midazolam and 0.02–0.1 mg·kg^{-1} morphine as premedication and, after 15 min, induced anaesthesia using thiopental 3 mg·kg^{-1} and cisatracurium 0.09 mg·kg^{-1}. In our study, patients received propofol 4 mg·kg^{-1}, fentanyl 0.003 mg·kg^{-1}, and rocuronium 1.0–1.2 mg·kg^{-1} during the induction of anaesthesia. The differing choice and timing of opioid administration, in the authors' opinion, is the most likely explanation for the observed differences in hormonal responses to tracheal intubation.

According to the literature [9–11, 13, 17, 18], including a previous study by our team [12], lidocaine is thought to have opioid-sparing properties. However, in the present prospective, randomised, double-blind trial of lidocaine versus placebo, no statistically significant difference was found between the control and lidocaine groups in terms of the total intraoperative fentanyl dose and the need for additional rescue fentanyl boluses (see Table 2). We attribute this result to several factors. First, we examined only the intraoperative period, during which the pathophysiology of pain differs from that in the postoperative period. Moreover, participants underwent a rigorous randomisation process, and the administered solution (lidocaine or saline) was indistinguishable, ensuring that any intentional or unintentional influence by researchers on the opioid requirement assessment was eliminated. Additionally, our study group was homogenous in terms of the surgical procedures performed, meaning the results are primarily applicable to similar operations, such as short abdominal laparoscopies. Finally, it is important to emphasize that conclusions drawn from the intraoperative period cannot be extended to the remainder of the recovery process.

Study limitations

To ensure maximum adherence to the protocol, only three physicians were designated to enrol patients and administer anaesthesia. Only patients operated on during their shifts were assessed for inclusion criteria. As a result, the study duration increased. During this period, 362 patients underwent laparoscopic appendectomy (30 were excluded from the study), of whom 162 were available to the study team.

Lidocaine is believed to have anti-inflammatory properties [9, 10], so measuring levels of proinflammatory mediators, such as nerve growth factor (NGF) or interleukin 6 (IL-6), could be an important objective test of the hypothesis. However, due to economic constraints, such laboratory tests were unavailable.

Children enrolled in the study were aged between 35 months and 17 years and 10 months. In the lidocaine group, the mean age was 10.82 years (SD 3.75), whereas in the control group, it was 12.04 years (SD 3.81). The absence of extreme age groups (e.g., neonates, infants, or

adults) and the predominance of a single patient category precluded subgroup analyses.

The duration of the pain complaint period prior to surgery may influence the requirements for analgesics, anaesthetics, and the pain response. Hypothetically, this parameter could be a source of bias that might affect the results of our study. The most effective way to eliminate selection bias is through the process of randomisation. To address this, we took steps to ensure reliable randomisation and allocation concealment, which are described in detail in the "Methods" section.

According to hospital policy, all enrolled patients underwent surgery within six hours of being classified as emergencies. While awaiting surgery, patients received fluid therapy guided by the attending surgeon. Although the fluid management protocol was not formally analysed, the initial volume status was deemed optimal in all patients, as none exhibited hypotension during baseline measurements or experienced a decrease in MAP below the low cut-off, defined as two standard deviations below the 50th percentile. As the initial fluid status and intraoperative fluid management may influence haemodynamic responses to anaesthesia and laparoscopy, the lack of a standardised infusion strategy is recognised as a limitation of this study. Moreover, as previously discussed, the risk of bias was further minimised through a robust randomisation and allocation concealment procedure.

Conclusions

Intravenous lidocaine does not alleviate excessive increases in MAP in response to tracheal intubation in the paediatric population. Lidocaine does not affect the metabolic or hormonal response to anaesthesia and surgery. The studied intervention appears to be safe, as no clinical side effects were observed, and serum lidocaine levels did not exceed the toxic threshold.

Based on these data, the intraoperative administration of lidocaine is not recommended, as it does not demonstrate any significant clinical benefit compared to placebo.

Abbreviations

ASA	American society of anesthesiologists
BIS	Bispectral index
GX	Glycinexylidide
IL	6-interleukin 6
IQR	Interquartile range
MAP	Mean arterial pressure
MEGX	Monoethylglycinexylidide
PACU	Postanaesthesia care unit
NGF	Nerve growth factor
SD	Standard deviation

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Author contributions

M. Kaszyński conceived the study, collected, and analysed data and wrote the manuscript. A. Kuczerowska collected data and wrote the manuscript. J. Pietrzyk collected data and wrote the manuscript. P. Sawicki collected data and wrote the manuscript. P. Witt helped conceive the study and wrote the manuscript. B. Stankiewicz analysed data and wrote the manuscript. M. Darowski analysed data and wrote the manuscript. I. Pągowska-Klimek helped conceive the study, analysed data and wrote the manuscript. All authors read and approved the final manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Medical University of Warsaw (KB/204/2021). The trial was registered with the US National Institutes of Health (ClinicalTrials.gov): NCT05238506. The date of first registration: 14/02/2022. Written informed consent for participation in the trial was obtained from the parents or legal guardians of the patients, as well as from all patients aged 16 years or older.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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