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A randomized study of the effects of perioperative i.v. lidocaine on hemodynamic and hormonal responses for cesarean section

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Abstract
Purpose. Intravenous infusion of lidocaine attenuates the stress response to surgery. We aimed to evaluate the effects of perioperative lidocaine on the hemodynamic and hormonal responses for cesarean delivery.
Methods. After the gaining of ethical approval, 90 patients scheduled for elective cesarean delivery were randomly allocated to receive either lidocaine 1.5 $mg \cdot kg^{-1}$ i.v. bolus 30 min before induction, followed by an infusion of 1.5 $mg \cdot kg^{-1} \cdot h^{-1}$ until 1 h after surgery (n = 45), or saline placebo (n = 45). Anesthesia was maintained with 50% nitrous oxide in oxygen with 0.7% isoflurane. Hemodynamic variables, plasma cortisol, maternal and neonatal lidocaine concentrations, Apgar scores at 1 and 5 min, neonatal acid-base status, and the neurologic and adaptive capacity score (NACS) were recorded.
Results. After induction, patients receiving lidocaine had a smaller increase in heart rate and mean arterial blood pressure ($P < 0.02$) and lower plasma cortisol concentrations (31.1 ± 9.91 vs 45.6 ± 8.43 $\mu g \cdot dL^{-1}$; $P < 0.001$). There were no differences between the two groups in Apgar scores, NACS, or neonatal acid-base status. After delivery, maternal and umbilical venous concentrations and umbilical vein-to-maternal vein ratios of lidocaine were 2.05 ± 0.42 $\mu g \cdot mL^{-1}$ and 1.06 ± 0.31 $\mu g \cdot mL^{-1}$, and 0.52 ± 0.07, respectively.
Conclusion. Perioperative lidocaine is safe and effective in attenuating the maternal stress response to surgery for cesarean delivery.

Key words Anesthesia · Cesarean section · Stress response · Lidocaine

Introduction

Regional anesthesia has become the anesthetic of choice for cesarean section in most countries; however, in our region many women still prefer general anesthesia rather than regional techniques. The pharmacological modifications of the sympathetic response to laryngoscopy, tracheal intubation, and surgical stimulation, including opioids, have been well documented [1,2]. However, opioid administration to the mother before delivery has adverse effects on the neonate [2]. Intravenous lidocaine is appealing as a simple and inexpensive method to gain the same benefits as more invasive and costly techniques in reducing the hemodynamic and hormonal responses of endotracheal intubation [3]. The perioperative systemic administration of lidocaine, at a nontoxic low dose [3], was able to attenuate the cardiovascular responses to tracheal intubation and extubation [4], reduce requirements for various volatile anesthetics [4,5], and provide stable clinical anesthesia [2,4]. Lidocaine has been extensively used in obstetrics, and its presence can be easily detected in umbilical cord blood [6,7].

We postulated that the use of i.v. lidocaine from the preanesthesia period to the postoperative period for uncomplicated cesarean delivery would reduce the maternal hemodynamic and hormonal responses, without harmful effects on either mother or baby. Therefore, the present study was designed to evaluate the effects of i.v. lidocaine on surgical stress responses and neonatal outcome during cesarean delivery.

Patients, materials, and methods

After we had obtained approval from the Institutional Ethics Committee [34/8-2006] and written informed consent from the participants, the study was performed in 90 women (American Society of Anesthesiologists [ASA] I and II), with uncomplicated, singleton pregnancies of at least 36 weeks' gestation, who refused regional anesthesia and were scheduled for elective cesarean delivery under general anesthesia. Exclusion

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criteria included women with a history of cardiac, liver, or kidney diseases; allergy to amide local anesthetics; epilepsy; those taking cardiovascular medications; and those with pregnancy-induced hypertension, evidence of intrauterine growth restriction, or fetal compromise. All parturients received oral ranitidine 150 mg on the night before and on the morning of surgery and 30 mL of 0.3 $mol \cdot L^{-1}$ sodium citrate 15 min before induction. Lactated Ringer's solution (500 mL) was infused over 20 min. Left uterine displacement was maintained before induction.

The subjects were allocated randomly to two groups, using a computer-generated randomization code. The placebo group (n = 45) received an i.v. infusion of 0.1 $mL \cdot kg^{-1}$ saline 0.9%, infused for 10 min, at 30 min before induction of anesthesia, followed by a constant infusion at 0.1 $mL \cdot kg^{-1} \cdot h^{-1}$. The lidocaine group ($n$ = 45) received i.v. infusion of 1.5 $mg \cdot kg^{-1}$ lidocaine 1.5% infused for 10 min, at 30 min before induction of anesthesia, followed by a constant infusion at 1.5 $mg \cdot kg^{-1} \cdot h^{-1}$ of the same solution. The placebo and the lidocaine solutions looked identical and their infusions were continued until 60 min after skin closure. The test solution was prepared by one anesthesiologist before induction of anesthesia. Another anesthesiologist, who was blinded to the study solution, gave the anesthetic and was instructed to avoid using local anesthetics, and a third performed the assessments. All staff in the operating room were unaware of the randomization code.

Maternal monitoring included electrocardiography, noninvasive blood pressure, pulse oximetry, and end-tidal isoflurane and carbon dioxide ($EtCO_2$) concentrations. After preoxygenation for 5 min, a rapid-sequence induction was performed with thiopental 5–7 $mg \cdot kg^{-1}$ and suxamethonium 1.5 $mg \cdot kg^{-1}$. Cricoid pressure was applied, laryngoscopy was performed after the 1-min blood pressure recording, and tracheal intubation was completed before the 2-min reading. Anesthesia was maintained with an end-tidal concentration of 0.7% isoflurane, in combination with 50% nitrous oxide in oxygen and vecuronium 0.06 $mg \cdot kg^{-1}$. The patients' lungs were ventilated to maintain an $EtCO_2$ of 4–4.6 kPa. After the umbilical cord was clamped, infusions of 10 U oxytocin, midazolam 0.05 $mg \cdot kg^{-1}$, and fentanyl 2 $\mu g \cdot kg^{-1}$ were given, and nitrous oxide was increased to 70%. Isoflurane was discontinued at the start of skin closure and the nitrous oxide was discontinued after the last skin suture was applied. At the end of surgery, residual neuromuscular block was antagonized with neostigmine 50 $\mu g \cdot kg^{-1}$ and atropine 20 $\mu g \cdot kg^{-1}$, and the trachea was extubated. Times for induction to delivery (I-D), extubation (time from discontinuation of nitrous oxide to extubation), and spontaneous ventilation (time between beginning of spontaneous breathing and extubation) were recorded. The quality of tracheal extubation was evaluated using a 5-point rating scale: 1, no coughing or straining; 2, very smooth, minimal coughing; 3, moderate coughing; 4, marked coughing or straining; and 5, poor extubation, very uncomfortable [8].

Heart rate and mean arterial pressure (MAP) were recorded before and 15 min after bolus infusion; at 1, 2, 3, 4, 5, 6, 10 min after induction; 15 and 30 min after delivery; and 0, 1, 5, 15, 30, and 60 min after extubation.

The obstetrician assessed uterine tone by palpation every 5 min after delivery of the placenta, using a 10-cm visual analogue score (VAS; 0, well contracted; 10, completely relaxed). If uterine tone remained unsatisfactory after 3 min, an additional 5-U bolus of oxytocin was administered.

Maternal venous blood samples (MV) were collected for assay of cortisol and lidocaine concentrations, at five points: preoperatively, immediately after bolus infusion, 5 min after intubation, 1 h after delivery, and 1 h after continuous infusion. Plasma cortisol levels were determined using a radioimmunoassay technique (Gamma Coat Cortisol 125IRIA; Nihon Sheering, Chiba, Japan), and plasma lidocaine levels were measured using the Therapeutic Drug Monitoring Tests (TDx) automated immunoassay method (Abbot Diagnostic, Eden Prairie, MN, USA) with a lower detection limit of 0.1 $\mu g \cdot mL^{-1}$ and a cross-reactivity of less than 0.05% to lidocaine metabolites [9]. Additionally, neonatal umbilical artery (UA) and umbilical vein (UV) samples were collected from a double-clamped segment of umbilical cord for the measurement of blood pH, gas tensions, base excess, and lidocaine levels. Fetal/maternal (F/M) lidocaine concentration ratios were calculated by dividing UV or UA lidocaine values by MV values for lidocaine.

All neonates were assessed by a pediatrician unaware of the mothers' randomization. Apgar scores at 1 and 5 min, and newborns' blood pressure, heart rate, temperature, arterial oxygen saturation, and the neurologic and adaptive capacity score (NACS) were recorded at 15 min and at 2 and 24 h after delivery. NACS gives a total score: the maximum is 40, and a score of 35–40 denotes vigor [10]. The percentages of infants scoring 35 or less were determined.

The presence of perioperative side effects, including arrhythmia, sedation, nausea and vomiting, light-headedness, headache, perioral numbness, tunnel vision, or seizures was reported.

Statistical analysis

Data were tested for normality using the Kolmogorov-Smirnov test. Serial changes in hemodynamic, cortisol, and lidocaine data at induction were analyzed with

repeated-measures analysis of variance. Comparisons between and within groups were undertaken using Student's *t*-test and the Mann-Whitney *U*-test, with a significance level of $P < 0.05$. Data values were expressed as frequency (%), means ± SD, or medians (ranges). A prior power analysis indicated that 45 patients in each group would be sufficient to detect a 20% reduction in post-induction blood pressure values, with a type-I error of 0.05 and a power of approximately 90%.

Results

All 90 patients completed the study: 45 patients in the placebo group and 45 in the lidocaine group. Maternal age, weight, height, gestational age, I-D time, and duration of anesthesia, and neonate birth weight, did not significantly differ between the groups (Table 1).

Baseline heart rate and MAP were similar in the two groups (Figs. 1, 2). Changes in heart rate from baseline were significantly greater in the placebo group than in the lidocaine group throughout the study period ($P < 0.02$; Fig. 1). Similarly, changes in MAP from baseline were significantly greater in the placebo group than in the lidocaine group throughout the study period ($P < 0.001$). In addition, MAP increased significantly in the placebo group at 1, 2, and 3 min after induction compared to the baseline values (Fig. 2).

There was no significant difference between the two groups in the surgical assessment of uterine tone, the spontaneous ventilation time, or the time of extubation (Table 2). However, the extubation quality scores were significantly higher in the placebo group than in the lidocaine group ($P = 0.001$; Table 2).

Baseline maternal cortisol concentrations in the placebo group (26.4 ± 10.81 $\mu g \cdot dL^{-1}$) were similar to those in the lidocaine group (29.6 ± 10.48 $\mu g \cdot dL^{-1}$). Plasma cortisol concentrations were significantly greater at 5 min after intubation, 1 h after delivery, and 1 h after continuous infusion in the placebo group than in the lidocaine group, and the concentrations at these times were higher than the preoperative values ($P < 0.001$). The cortisol level was significantly decreased in the lidocaine group at 1 h after continuous infusion compared to the preoperative value (Fig. 3).

Plasma concentrations of lidocaine during the study in the lidocaine group are given in Fig. 4. After delivery, the maternal venous concentration of lidocaine was

Table 1. Patient data

	Placebo group ($n = 45$)	Lidocaine group ($n = 45$)
Age (years)	26.5 ± 4.56	28.1 ± 4.20
Weight (kg)	75.4 ± 9.21	75.3 ± 10.91
Height (cm)	163 ± 4.81	164 ± 5.32
Gestational age (weeks)	38.9 ± 1.83	38.2 ± 1.91
Induction to delivery time (min)	9.12 ± 1.13	9.01 ± 0.91
Duration of anaesthesia (min)	40.8 ± 6.65	43.2 ± 5.51
Birth weight (kg)	3.2 ± 0.23	3.1 ± 0.17

Data values are means ± SD

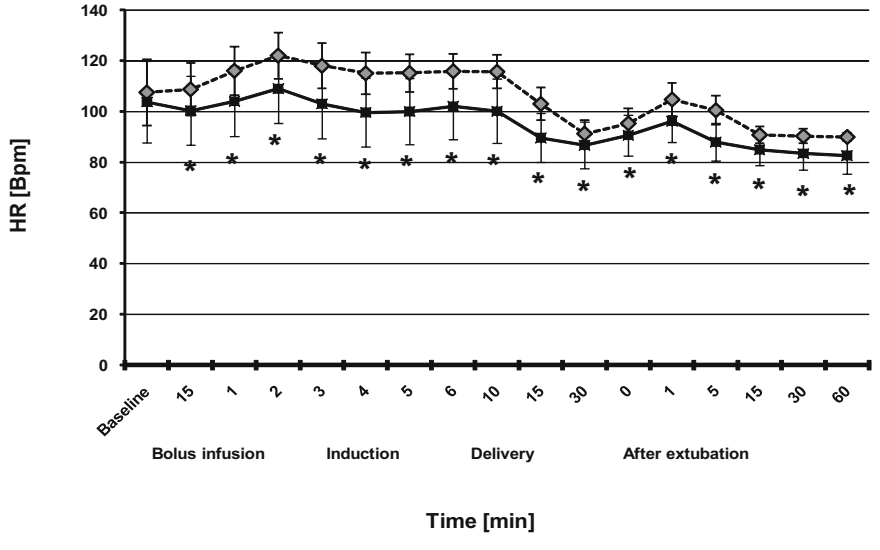

Fig. 1. Perioperative heart rate (*HR*). Data values are means ± SD. *$P < 0.05$ compared with the placebo group. *Diamonds*, placebo group; *squares*, lidocaine group

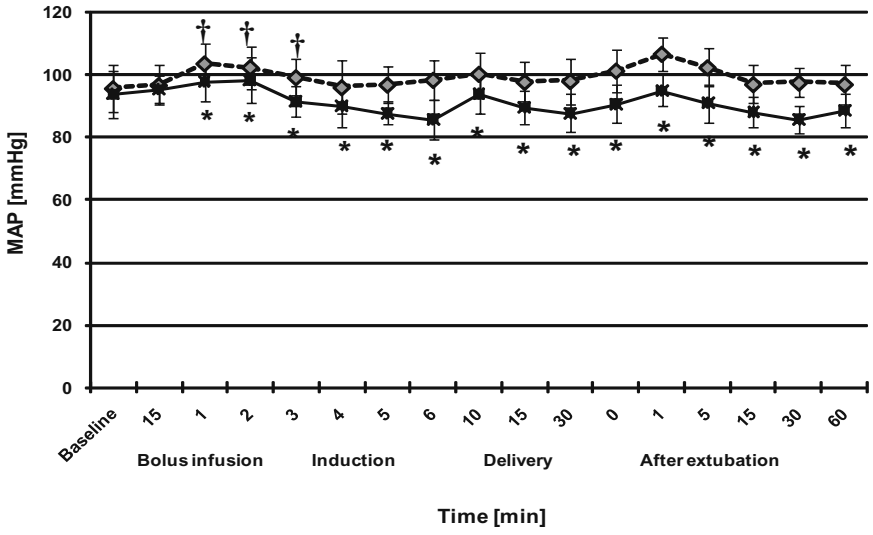

Fig. 2. Perioperative mean arterial pressure (*MAP*). Data values are means ± SD. **P* < 0.001 compared with the placebo group. †*P* < 0.05 compared with the baseline values. *Symbols*, as in Fig. 1

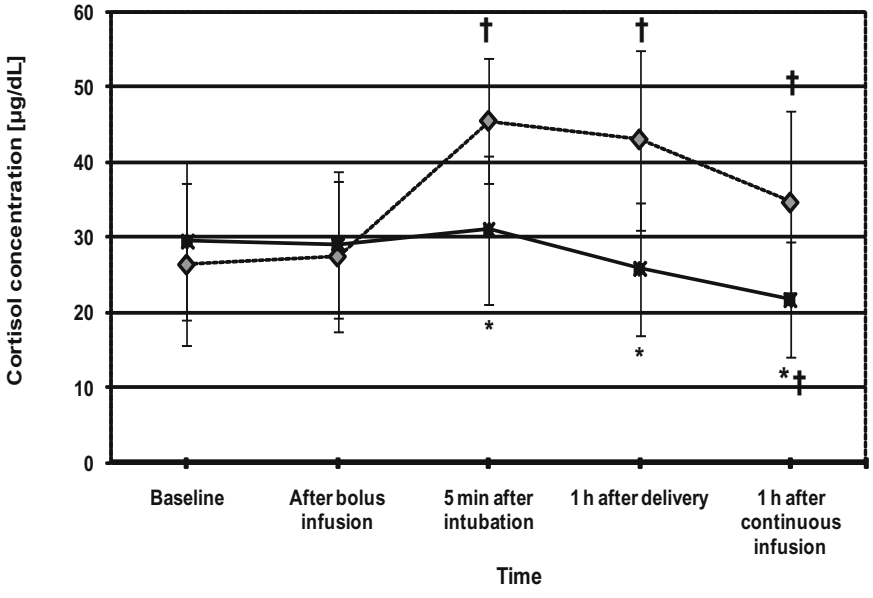

Fig. 3. Plasma cortisol concentrations. Data values are means ± SD. **P* < 0.05 compared with the placebo group. †*P* < 0.05 compared with the values at baseline and after bolus infusion. *Symbols*, as in Fig. 1

Table 2. Perioperative data

	Placebo group (n = 45)	Lidocaine group (n = 45)	P value
VAS assessment of uterine relaxation	0 (0–3)	1 (0–3)	0.484
Spontaneous ventilation time (min)	3.9 ± 1.51	4.2 ± 1.11	0.712
Time of extubation (min)	7.4 ± 1.47	8.1 ± 1.76	0.654
Extubation quality score	3 (1–5)	1 (1–3)	0.001
Patients experiencing nausea and vomiting	7 (15.6%)	5 (11.1%)	0.611

* $P < 0.05$ significant compared with the placebo group
Data values are medians (ranges), means ± SD, or n (%)

2.05 ± 0.42 µg·mL^{-1}. In no case did lidocaine plasma concentrations approach a toxic level (>5 µg·mL^{-1}). UA and UV concentrations of lidocaine and the F/M ratio were 1.09 ± 0.39 µg·mL^{-1}, 1.06 ± 0.31 µg·mL^{-1}, and 0.52 ± 0.07, respectively.

There were no reported serious side effects during the study. There were no differences between groups in the frequency of sedation or nausea and vomiting. No woman reported perioperative arrhythmia, light-headedness, headache, perioral numbness, tunnel vision, or seizures.

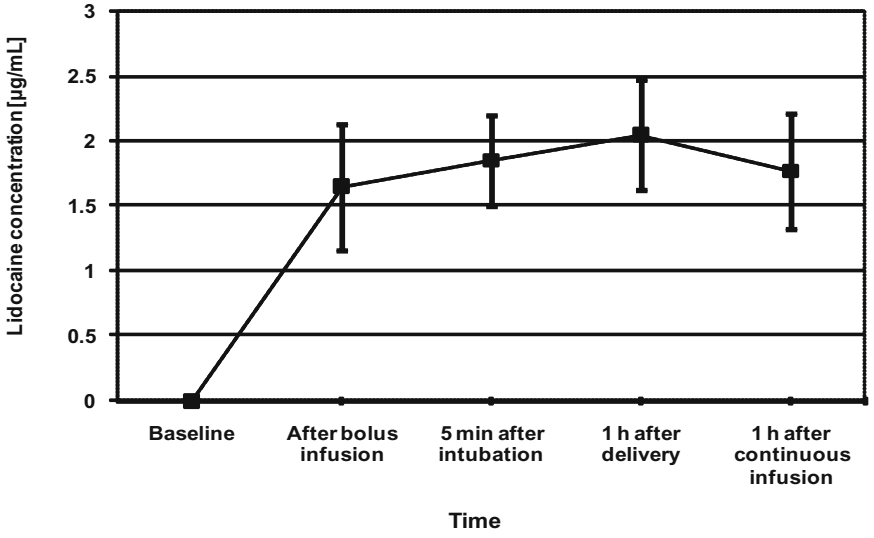

Fig. 4. Plasma lidocaine concentrations in mothers who received continuous lidocaine infusion. Data values are means ± SD

Table 3. Neonatal data

	Placebo group (n = 45)	Lidocaine group (n = 45)	P value
Apgar score			
1 min	7 (5–10)	7 (6–10)	0.171
5 min	9 (7–10)	9 (7–10)	0.742
Adaptive capacity score (NACS)			
15 min	37 (74%)	35 (70%)	0.331
2 h	41 (82%)	39 (78%)	0.512
24 h	48 (96%)	47 (94%)	0.910
Umbilical vein			
pH	7.32 ± 0.04	7.33 ± 0.03	0.811
Pa_{CO_2}	42.4 ± 8.21	44.3 ± 6.74	0.744
Pa_{O_2}	31.4 ± 6.21	34.3 ± 3.91	0.921
Base excess ($mEq \cdot L^{-1}$)	–4.6 ± 1.2	–4.9 ± 1.4	0.657
Umbilical artery			
pH	7.26 ± 0.03	7.25 ± 0.09	0.631
Pa_{CO_2}	49.9 ± 7.21	51.7 ± 4.91	0.711
Pa_{O_2}	24.7 ± 4.21	26.9 ± 2.25	0.652
Base excess ($mEq \cdot L^{-1}$)	–5.1 ± 0.9	–5.3 ± 1.1	0.323

Data values are medians (ranges), numbers (%), or means ± SD

Apgar scores at 1 and 5 min and the percentage of infants who scored 35–40 on the NACS at 15 min and at 2 and 24 h after delivery were not significantly different in the two groups (Table 3). Umbilical arterial and venous acid-base status were within normal limits in the two groups (Table 3).

Discussion

The present study demonstrated that the systemic administration of nontoxic doses of lidocaine before cesarean delivery, compared with placebo, resulted in lower increases in heart rate, MAP, and cortisol levels in response to tracheal intubation and surgical stimulation, with better quality of extubation, and without adverse neonatal outcome.

Previous studies have demonstrated that the i.v. administration of lidocaine 1.5–2 $mg \cdot kg^{-1}$, 2 to 3 min before laryngoscopy, may blunt the increases in heart rate, systolic blood pressure (SBP), MAP, and catecholamine levels associated with intubation and extubation [11–13]. Others found that i.v. lidocaine [1.5 $mg \cdot kg^{-1}$] failed in controlling the hemodynamic response following laryngoscopy and intubation [14,15]. This controversy may be referred to the importance of the timing of administration of lidocaine. In our study, the blunted hemodynamic and cortisol responses to tracheal intubation and surgical stimulation at nontoxic plasma lidocaine concentrations (0.75–2.9 $\mu g \cdot mL^{-1}$) may have been related to the early (30 min preoperatively) initiation of prolonged continuous infusion of lidocaine and its continuation until 60 min after surgery. The postulated mechanism of i.v. local anesthetics in inhibiting the sym-

pathetic response associated with tracheal stimulation appears to result from an increased threshold for airway stimulation, central inhibition of sympathetic transmission, and direct depression of cardiovascular responses [16]. Systemically administered lidocaine acts on voltage-gated sodium channels [17] and exerts analgesia at the spinal level [18], which is expected to decrease the minimum alveolar concentration of isoflurane and attenuate the stress response of surgical stimulation. In contrast, Kaba et al. [19] found that i.v. administration of 1.5 $mg \cdot kg^{-1}$ lidocaine at induction of anesthesia in 20 patients scheduled for laparoscopic colectomy, followed by an i.v. infusion of 2 $mg \cdot kg^{-1} \cdot h^{-1}$ intraoperatively and 1.33 $mg \cdot kg^{-1} \cdot h^{-1}$ for 24 h after surgery, resulted in a 35% reduction in the sevoflurane end-tidal concentration required to maintain hemodynamic stability ($P < 0.001$) and improved postoperative analgesia and outcome, with no significant changes in postoperative plasma concentrations of glucose, C-reactive protein, cortisol, epinephrine, and norepinephrine. They reported higher plasma lidocaine concentrations (0.7–4.6 $\mu g \cdot mL^{-1}$) compared to our results, which may be related to their use of prolonged infusion for 24 h after surgery [19]. Similarly, others have reported that lidocaine neither affected the perioperative stress response nor the metabolic responses [4,20,21]. These conflicting results may be attributed to the low power in these studies, unmeasured changes in catecholamine levels in our study, or our dependence on the clinical signs and end-tidal concentration of isoflurane (ETiso), rather than the changes in entropy or bispectral index values to assess the level of hypnosis during general anesthesia.

Lidocaine has non-monotonic effects on myometrial activity. At lower concentrations, an increase in contraction frequency with a depression in amplitude has been noted. As the concentrations increased, both amplitude and frequency were depressed until, eventually, activity was abolished [22]. We recorded no significant changes in the degree of uterine relaxation with low lidocaine plasma concentrations.

In all of the infusion studies, lidocaine was given in the 2–3 $mg \cdot min^{-1}$ range, resulting in plasma levels ranging from 1 to 5 $\mu g \cdot mL^{-1}$ [23]. We found that continuous lidocaine infusion led to a plateau of the plasma concentration of lidocaine well below the toxic range of 5.0 $\mu g \cdot mL^{-1}$, with no reported adverse effects. Transport of lidocaine through the placenta has been reported. In our study, the F/M plasma concentration ratio of lidocaine at the time of delivery (0.52 ± 0.07) was similar to the reported F/M ratio values after the perineal and systemic administration of lidocaine (0.46 and 0.52, respectively), with no neonatal adverse effects [7,24]. We recorded no difference in neonatal outcome, as assessed by Apgar scores, NACS, and blood gas analyses, with the perioperative use of i.v. lidocaine for cesarean delivery compared with placebo. However, there is evidence to suggest that the NACS is unreliable, and, therefore, any result would be impossible to interpret [25].

In conclusion, in the present study, i.v. lidocaine given from preinduction was found to be safe and effective in attenuating the maternal stress response in women undergoing elective cesarean delivery, in the absence of fetal compromise, with no detected adverse effects on neonatal outcome.

Further studies are needed to define the efficacy and safety of prolonged perioperative i.v. lidocaine on the changes in the depth of anesthesia, catecholamine levels, and postoperative analgesia after cesarean delivery and to define the safety of its use in the cesarean delivery of a compromised fetus.

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