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Research Article

The effects of intravenous lidocaine infusion on hospital stay after major abdominal pediatric surgery. A randomized double-blinded study

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KEYWORDS

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Abstract *Background:* Lidocaine attenuates the stress response to surgery when given intravenously. This study investigated the effect of perioperative lidocaine infusion on hormonal responses, bowel function and hospital stay after major abdominal surgeries in pediatrics.
Methods: After obtaining the Research Ethics Board (REB) approval and written informed parental consent, 80 pediatric patients aged 1–6 years, ASA II, III scheduled for abdominal major surgery were randomly allocated into two groups, each of forty children. Twenty minutes before induction, children in placebo group received saline in a rate of 1.5 ml/kg/h and those in lidocaine group received lidocaine 1.5 mg/kg intravenously then infusion of 1.5 mg/kg/h up to 6 h postoperatively. Length of hospital stay and return of bowel function were reported. Plasma cortisol was recorded at baseline, 10 min after continuous infusion, 5 min after intubation and 10 min after extubation. Serum lidocaine concentrations were recorded 10 min after start of infusion, 10 min and 4 h after extubation.
Results: Patients in placebo group showed significant higher plasma cortisol concentrations ($P = 0.001$) in response to induction of anesthesia and extended postoperatively when compared to lidocaine group.

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Hospital stay was significantly less in lidocaine group (5 ± 2 days) compared to placebo group (7 ± 2 days; $P = 0.03$). Also, fentanyl (μg/kg/d) requirement was significantly less in lidocaine group (5.4 ± 2.9 on 1st postoperative day and 4.1 ± 2.6 on 2nd postoperative day) compared to placebo group (14.4 ± 2.5 on 1st postoperative day and 12.6 ± 3.3 on 2nd postoperative day). Moreover, return of bowel function was earlier in lidocaine group compared to placebo group (19 ± 6.2 h *vs.* 23 ± 3.65 h respectively).

Conclusion: Intravenous lidocaine infusion, started preoperatively and continued for 6 h postoperatively, attenuated stress response to major abdominal pediatric surgery. It also decreased hospital stay, opioid requirement and hastened return of bowel function.

1. Introduction

Postoperative pain is a major concern after any surgical intervention especially major abdominal surgery. Pain is associated with increased duration of hospital stay; and as a component of inflammatory response following surgery; it also leads to delay in bowel movement and development of ileus as a result of activation of nocireceptors by inflammatory mediators [1–3]. For such reasons, control of postoperative pain is a major concern, and traditionally was achieved by administration of opiates. However, opiate administration has its own side effects and limitations, especially in pediatric group of patients. Hence, administration of local anesthetics to epidural space gains its own role. It blunts stress response; provides rapid mobilization, leads to early extubation with rapid recovery of bowel function [4]. However, insertion of an epidural catheter carries its own risks especially in pediatric population [5]. Therefore, seeking for alternative and/or adjunct drugs and techniques should continue specially in the era of fast track surgery and enhanced recovery programs.

Lidocaine has been shown to have analgesic, antihyperalgesic, and anti-inflammatory effects when administrated intravenously [6]. Several studies have shown the role of intravenous lidocaine administration during abdominal surgery in improving postoperative analgesia, reducing postoperative opioid requirements, accelerating postoperative recovery of bowel function, decreasing postoperative fatigue, reducing the duration of hospitalization, and enhancing acute rehabilitation in patients undergoing major abdominal surgery [6,7]. However, all of these studies were carried out in adult population and were not involving pediatrics' one. In the current study we aim at evaluating the role of systemic lidocaine administration in children undergoing elective major abdominal surgery as regard the length of hospital stay as a primary outcome. Also studying its effect on hormonal response, opioid requirement and return of bowel function.

2. Methods

Over a period of 8 months, all patient aged 1–6 years who were scheduled for elective major abdominal surgery at Mansoura University children hospital were assessed for eligibility. Patients with hepatic, cardiac, or renal morbidity, allergy to local anesthetics, and/or epilepsy were excluded. The study was approved by the Research Ethics Board (REB). A detailed explanation of the study including the principles and instructions of PNCA (Parent-/Nurse-Controlled Analgesia) was given to parents/legal guardians of children; and an informed consent was signed. All surgical procedures were done by a well-trained team of pediatric surgeons. All patients received a premedication in the form of i.v. midazolam and morphine, in a dose of 0.02–0.1 mg/kg respectively 15 min before induction.

Patients were randomly assigned into two groups based on a computer-generated sequence, which was kept in sealed envelopes. Immediately before surgery, the envelope was opened by a pharmacist; who has no role in the data collection or analysis. Based on the allocation of patient; a solution was prepared from saline (placebo group); or lidocaine 15 mg/ml in similarly looking syringes. Patients, anesthetists, surgeons, and nurses were completely blinded about the patients' allocation. Twenty minutes before induction of anesthesia, patients received i.v. bolus 0.1 ml/kg followed by i.v. infusion at 0.1 ml/kg/h of the prepared solution, then throughout surgery and infusion was continued for 6 h postoperatively.

Heart rate, noninvasive blood pressure, oxygen saturation, and end tidal carbon dioxide ($EtCO_2$) concentrations were monitored. Induction was performed with thiopental 3–5 mg/kg and cisatracurium 0.09 mg/kg. Anesthesia was maintained with 2% sevoflurane, air in oxygen (1:1). The target of ventilation is to maintain an $EtCO_2$ of 4–4.5 kPa. Sevoflurane was discontinued at the start of skin closure. Ketoprofen (2 mg/kg IV) and 15 mg/kg i.v. paracetamol was used for intraoperative analgesia. All patients were started on Parent-/Nurse-Controlled Analgesia (PNCA) by bolus dose 0.5 μg/kg followed by 0.25 μg/kg/h fentanyl solution, with 30 min lockout interval and a maximum of four boluses within 6 h, once the peritoneum was closed. Residual neuromuscular block was reversed with neostigmine 50 μg/kg and atropine 20 μg/kg at the end of surgery.

Blood samples were withdrawn preoperatively, and at 10 min after start of infusion, 5 min after intubation and 10 min after extubation for assay of serum cortisol level. Also serum level of lidocaine was checked at 10 min after start of infusion, 10 min after extubation and 4 h after extubation. As regard assessment of cortisol level, all samples were centrifuged immediately and kept at −60 °C; and all samples were analyzed using radioimmunoassay technique (LI4003K, Adaltis, Italy). However, the lidocaine level was assessed quantitatively (The TDx/TDxFLx; Abbot Diagnostic, USA [8]) immediately because of possibility of toxicity, by a biochemist who was completely uninvolved in the study and was instructed only to disclose the results if the toxic level was reached in any given sample, otherwise all the results should be kept confidential till the study end.

Patients were transferred to postanesthetic care unit (PACU), and assessed for severity of postoperative pain every 10 min by the trained nurse, using FLACC scale (Face, Legs,

Activity, Cry, Consolability), which is an observer assessment scale based on 5 items and each item is graded from 0 to 2 [9]. Patients were allowed to leave PACU to ward when they achieve modified Aldrete Score of ten [10]. Furthermore postoperative pain was assessed regularly at 2, 6, 12, 24, 36, and 48 h. in the ward using the same FLACC scale. Also patients were assessed for degree of sedation using modified Ramsay sedation scale [11].

Ketoprofen at a dose of 2 mg/kg IV and. Paracetamol at a dose of 15 mg/kg i.v was used every 8 h postoperatively for 48 h. The lockout interval of the PNCA was decreased to 15 min, when FLACC scale reaches more than 3, return it to 30 min if modified Ramsay sedation scale rises more than 4; and the total opioid requirement was documented. A well-trained nursing team was responsible for assessment of return of bowel function by auscultation, starting 6 h postoperatively, and every 2 h later. Furthermore the nursing team was instructed to assess the ability of patients to tolerate oral intake, and to report if any intolerance happens. All the patients started to ambulate on the first postoperative day with guidance, and assistance of the physiotherapist. The physiotherapy team was responsible for assessment of patients' activity based on a standardized hospital protocol. Seizures were reported if happen. Children were allowed to leave the hospital once they are able to tolerate light diet, pain free and/or controlled pain with oral analgesics; and when they can ambulate unaided.

3. Statistical analysis

Data were tested for normality using the Kolmogorov–Smirnov test. Serial changes in cortisol were analyzed with repeated-measures analysis of variance, and Bonferroni correction was used to set a more stringent P value. Student's t-test and the Mann–Whitney U-test were used for comparisons between and within groups. Chi-square test was used for qualitative data. Data were expressed as mean ± standard deviation or frequency (%), or medians with interquartile ranges. Data analysis was done using SPSS 16.0 software (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered as statistically significant.

A priori power analysis, assuming mean hospital stay after major pediatric abdominal surgeries was 7 ± 2 days, showed that 40 patients in each group were needed to detect day and half less in hospital stay, with a power of 90%.

4. Results

All the patients completed the study successfully with no dropouts (Fig. 1). No significant difference was observed in baseline characteristics between the two groups. Type of surgery was similar between the groups, with no significant difference in duration of surgery (96 ± 11.6 *vs.* 98 ± 13.2; $P = 0.35$) (Table 1).

Basal serum cortisol concentrations in both groups were similar (27.8 ± 7.23 *vs.* 29.4 ± 8.34 μg/dl; $P = 0.23$). Placebo group showed significantly greater plasma cortisol concentrations 10 min after start of infusion, 5 min after intubation and 10 min after extubation ($P = 0.001$, 0.002, 0.002 respectively) compared with lidocaine group and these concentrations were also higher than the preoperative values (Fig. 2).

There was a significant decrease in daily fentanyl consumption in the lidocaine group when compared with placebo group

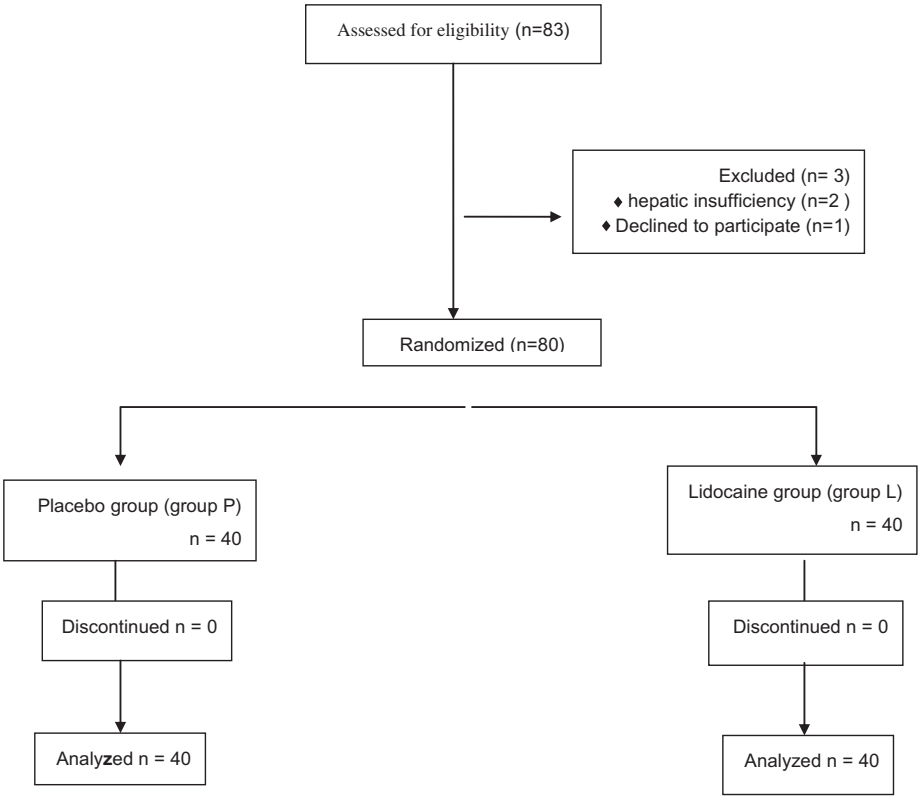

Figure 1 Study flowchart.

Table 1 Demographic data, duration of surgery and type of surgery.

Variable	Placebo group	Lidocaine group	*P* value
Age (year)	3.7 (2–5)	3.5 (1.5–5)	0.21
Weight (kg)	17 ± 6.1	16 ± 5.2	0.55
Sex			
Male	24 (60%)	23 (57.5%)	0.43
Female	16 (40%)	17 (42.5 %)	0.54
Duration of surgery (min)	96 ± 11.6	98 ± 13.2	0.35
Type of Surgery			
Fundoplication	18 (45%)	18 (45%)	
Splenectomy	8 (20%)	7 (17.5%)	
Megacolon	8 (20%)	7 (17.5%)	
Other[a]	6 (15%)	8 (20%)	

Data values are mean ± standard deviation, or median (range) or number (%).
[a] Intestinal malrotation, neuroblastoma.

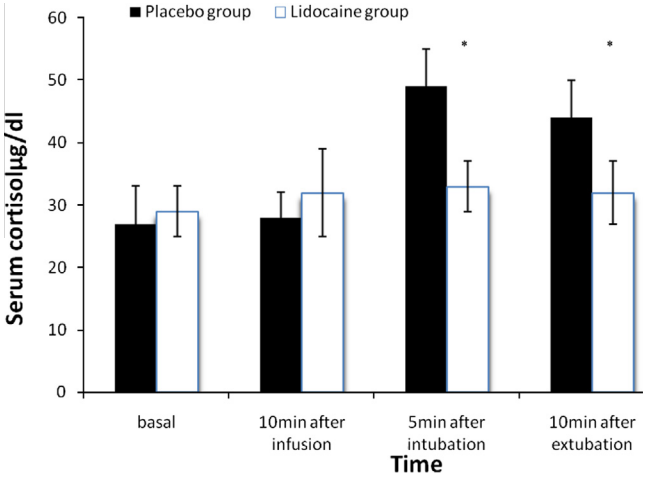

Figure 2 Perioperative serum cortisol (µg/dl), ∗Significant when compared with Placebo group.

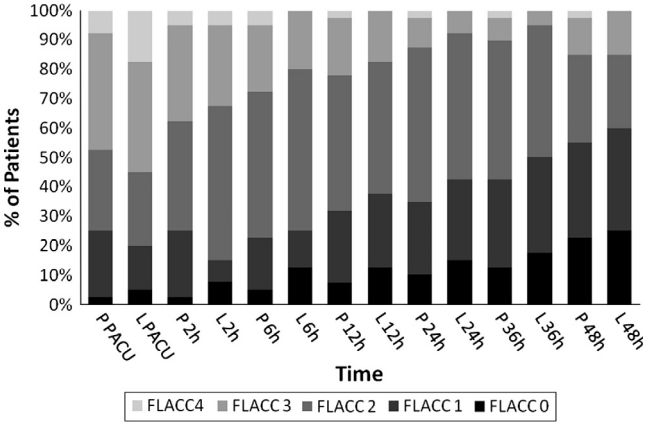

Figure 3 Postoperative FLACC scale in both groups, PACU; Postanesthetic care unit, P; Placebo group, L; Lidocaine group, FLACC; Face, Legs, Activity, Cry, Consolability Scale.

(5.4 ± 2.9, 4.1 ± 2.6 *vs.* 14.4 ± 2.5, 12.6 ± 3.3 µg/kg/d on 1st and 2nd postoperative day respectively). FLACC scale did not show any significant difference between the groups (Fig. 3). However, Sedation score did not differ significantly between the two groups (Table 2). Furthermore, the return of bowel function was earlier in the lidocaine group. And more interestingly the length of hospital stay was also significantly less in the lidocaine group (7 ± 2 *vs.* 5 ± 2; $P = 0.03$). Toxic plasma lidocaine level (5 µg/ml) was not reached, and no serious lidocaine related side effects was reported (Fig. 4).

5. Discussion

In the era of modern enhanced recovery programs aiming at decrease the length of hospital stay, the issue of pain control is of outmost importance [12]. In pediatrics, pain control is mainly achieved by opiate administration. A well-known side effect of which, is the delayed recovery of bowel function [13], and hence increase in hospital stay. This study showed that the perioperative intravenous administration of lidocaine in pediatrics undergoing elective major abdominal surgery was associated with decrease in dose of opiates and resulted in early return of bowel function with significant shortening of hospital stay.

To best of our knowledge based on a Medline search no previous studies dealt with lidocaine infusion in the perioperative period of major abdominal surgery in pediatric population. However, this topic was extensively studied in adult population. Intravenous lidocaine infusion decreases postoperative pain intensity in adults undergoing abdominal surgery [14]. It leads to early return of the bowel function, and shorten duration of hospital stay [1]. Also it has been suggested that stress hormones released as consequence for surgical trauma; can be used as an adjunctive method to assess the analgesic efficacy [15,16] .

The present study showed that a perioperative intravenous infusion of lidocaine attenuated the hormonal responses to tracheal intubation and surgical trauma. In a study carried on healthy volunteers; Dirks et al. found that lidocaine infusion inhibits the sympathetic response associated with tracheal stimulation and they assumed that effect was due to an increased threshold for airway stimulation, central inhibition of sympathetic transmission, and direct depression of cardiovascular responses [17]. A more recent study by El-Tahan et al., carried on pregnant women undergoing cesarean deliv-

Table 2 Postoperative data.

Variable	Placebo group	Lidocaine group	*P* value
Postoperative fentanyl (μg/kg/d)			
1st day	14.4 ± 2.5	5.4 ± 2.9*	0.03
2nd day	12.6 ± 3.3		0.04
Postoperative sedation score			
1st day	1 (1–2)	4.1 ± 2.6*	0.33
2nd day	1 (1–1)	1 (1–2)	0.34
Length of hospital stay (days)	7 ± 2	5 ± 2*	0.03
Return of bowel function (h)	23 ± 3.6	19 ± 6.2*	0.05

Data values are presented as means ± SD or median (range).
* $P < 0.05$ significant compared with the placebo group.

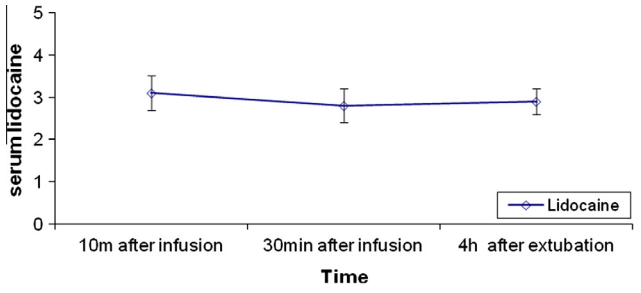

Figure 4 Perioperative serum lidocaine in group L (μg/ml).

ery concluded that lidocaine infusion was safe and associated with significant decrease in neuroendocrine response to surgical trauma [18].

We showed that lidocaine infusion was associated with earlier return of bowel sounds (23 ± 3.6 *vs.* 19 ± 6.2; $P = 0.05$).In their trial, Herroeder et al. [1] investigated the effect of intravenous perioperative lidocaine on gastrointestinal motility following colorectal surgery in adults. They concluded that lidocaine significantly improved gastrointestinal motility. Moreover, Groudine et al. [19] reported that intravenous lidocaine resulted in faster return of bowel function in patients undergoing radical prostatectomy. In a meta-analysis of 8 studies including 320 adult patients; lidocaine infusion was associated with significant decrease in duration of postoperative ileus [14].

Our patients in both groups showed a similar FLACC score; however, patients receiving lidocaine infusion showed marked decrease in opiate requirement (14.4 ± 2.5, 12.6 ± 3.3 *vs.* 5.4 ± 2.9, 4.1 ± 2.6 μg/kg/d on 1st and 2nd postoperative day, $P = 0.03, 0.04$ respectively), with no difference in sedation score between the groups. Koppert et al. [20]showed that perioperative lidocaine administration reduces pain during major abdominal surgery suggesting that IV lidocaine has a true preventive analgesic activity. Lauwick et al. [21] demonstrated that lidocaine infusion decreases postoperative fentanyl requirement in patients undergoing laparoscopic cholecystectomy. In another research on patients undergoing laparoscopic cholecystectomy, there was a significant improvement of post-operative analgesia and reduced intraoperative and post-operative opioid requirements in patients receiving lidocaine infusion [22].

The main interesting finding of our study is that lidocaine infusion is associated with significant shortening of hospital stay by almost 2 days (5 ± 2 *vs.* 7 ± 2; $P = 0.03$). We assume that shortening of hospital stay was due to effect of lidocaine infusion on neuroendocrine response to surgical trauma by inhibiting the sympathetic activation, and suppression of cortisol release. Furthermore, it was associated with decrease in opiate requirements, which is well known by its effect on prolongation of postoperative ileus. Opioid consumption in the lidocaine group was significantly less than that in the placebo group. This could be attributed to inhibition of chemonocireceptors by perioperative lidocaine infusion and hence decrease in sensory neural input which leads to central antihyperalgesic effect and decrease consumption of analgesics postoperatively. It is worth to note that effect of lidocaine is associated with surgeries accompanied with considerable tissue trauma such as laparotomies [20]. In a recent meta-analysis of 29 studies including 1752 patients, the authors demonstrated that lidocaine infusion was associated with a significant decrease in hospital stay with no effect on the hospital mortality [6].

One of the main limitations of this study is that, its power calculation was based on size effect gained from similar studies in adult population, which has different neuronal and hormonal responses to major abdominal surgery. We recommend further studies to evaluate the effect of lidocaine infusion in pediatrics, based on our study as a pilot one. Other limitations, is that we did not measure the cytokines' blood levels as a marker of inflammatory response due to financial issues.

6. Conclusion

Preoperative intravenous lidocaine infusion continued for 6 h postoperatively attenuates the stress response to elective major abdominal surgery in pediatrics. It is also associated with earlier return of bowel function, decrease in opiate requirements, and decrease in length of hospital stay.

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