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Research Article

Effect of intravenous lidocaine infusion on sevoflurane requirements as monitored by bispectral index: A randomized double-blinded controlled study

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KEYWOEDS

Lidocaine;
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Abstract *Introduction:* Systemic administration of lidocaine significantly decreased propofol requirements when compared to patients receiving placebo. Several studies conducted on animals have proved that systemic local anesthetics reduced minimum alveolar concentration (MAC) of inhalational anesthetics. The aim of this investigation is to study the effect of intravenous administration of lidocaine on the minimum alveolar concentration of sevoflurane required to keep BIS between 40 and 60 during maintenance of anesthesia in humans.

Methods: Twenty-eight ASA I–II adults planned to undergo laparoscopic procedures expected to last <2 h under general anesthesia were randomly assigned to 2 groups. After standardized induction of general anesthesia, patients were given IV lidocaine bolus (1.5 mg kg^{-1}) followed by 2 mg kg^{-1} h^{-1} infusion (group L, $n = 14$) or equal volumes of saline (group C, $n = 14$). Primary outcome of the study was end-tidal sevoflurane at bispectral index (BIS) values of 40–60. Secondary outcomes included doses of opioids, BIS values, and extubation time.

Results: The median doses of intraoperative fentanyl (range) in group C were similar to group L ($P = 0.08$). There were no significant differences between the 2 groups regarding BIS at any time point. End-tidal sevoflurane concentrations were significantly higher in group C than in group L at all intraoperative time points ($P < 0.05$). Extubation time was longer in group L than in group C ($P = 0.04$).

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Conclusion: In conclusion, intravenous lidocaine administration, during maintenance of general anesthesia, can decrease BIS-guided sevoflurane requirements.

1. Introduction

Several studies were conducted in humans to evaluate the effect of systemic lidocaine on anesthetic and opioid requirements. Systemic administration of local anesthetics significantly decreased propofol requirements when compared to patients in control group [1,2]. Perioperative requirements of opioids were reduced by 40% in patients who received intravenous lidocaine infusion during maintenance of anesthesia than those who received saline [3].

Several studies conducted on animals proved that systemic local anesthetics reduced minimum alveolar concentration (MAC) of inhalational anesthetics and analgesic requirements [4,5]. The mechanism of MAC reduction by lidocaine was not completely clarified. Sedative and analgesic effects of lidocaine might have a role.

We hypothesized that lidocaine may have a similar effect on MAC in humans. The aim of this investigation is to study the effect of intravenous administration of lidocaine on the minimum alveolar concentration of sevoflurane required to keep BIS between 40 and 60 during maintenance of anesthesia in humans.

2. Methods

This study was conducted in King Fahd Military Hospital, Dhahran, KSA from February 2012 to August 2012 after obtaining approval by its ethical committee. A written consent was obtained from a number of adult ASA I and II patients undergoing elective laparoscopic surgeries expected to last less than 2 h. Exclusion criteria included patients with BMI less than 20 or more than 35. Patients with history of reaction to lidocaine, patients with history of seizures or using sedatives, hypnotics or any other drugs that affect BIS, were also excluded.

Standard monitors were used including ECG, non-invasive arterial pressure, and pulse oximetry. Peripheral nerve stimulator was used to guide administration of muscle relaxant and its reversal at the end of surgery. BIS (Aspect Medical Systems Inc. BIS Vista®, USA) was also used to assess the depth of anesthesia.

After 6 h of fasting, anesthesia was induced using fentanyl 2 mcg kg^{-1} i.v. followed after 3 min by propofol 1.5–2.5 mg kg^{-1} iv. When BIS reached less than 50, atracurium 0.5 mg/kg iv was administered to allow tracheal intubation, which was performed when there was no response to train of four (TOF) stimulation. The lungs were ventilated with a tidal volume of 7–8 ml kg^{-1} and an oxygen fraction of 0.4 in air. The respiratory rate was adjusted to maintain an end tidal CO_2 between 30 and 35 mm Hg.

Patients were randomly allocated into 2 groups using computer-produced randomization tables. Patients in group L received 1.5 mg kg^{-1} bolus of 1% lidocaine i.v. followed by 2 mg kg^{-1} h^{-1} infusion while those in group C received equal volumes of saline. The study medications were prepared by a hospital pharmacist who was not involved in the study. Each drug syringe was given a code which remained blinded until statistical analysis has been completed. The anesthesiologist who was blinded to group allocation injected the bolus over a period of 1 min, and then started the infusion 5 min after tracheal intubation.

During maintenance of anesthesia, sevoflurane concentration was adjusted to keep BIS between 40 and 60. Sevoflurane was increased or decreased by 0.5% if BIS goes outside this range. Boluses of fentanyl (20–50 μg i.v.) were injected to maintain arterial pressure within 20% of the baseline mean arterial pressure. BIS values and end-tidal sevoflurane concentration were also recorded every 10 min.

After the end of surgery, sevoflurane and the study infusions were discontinued. Neuromuscular block was reversed by atropine (10–15 mcg kg^{-1}) and neostigmine (40–50 mcg kg^{-1}) and the patients were extubated awake.

The primary outcome of the study was the end-tidal sevoflurane at BIS 40–60. Based on a previous article [6], the mean (±SD) minimum alveolar concentrations of sevoflurane in adults is 1.9 (0.24)%. We assumed that a 20% difference in end-tidal sevoflurane at BIS 40–60 between the groups would be clinically significant. A sample size was calculated to be 12 at an alpha error of 0.01 and beta error of 0.1. Fourteen cases were enrolled in each group to compensate for dropouts. Secondary outcomes included doses of opioids used intraoperatively, BIS values recorded every 5 min, cumulative dose of lidocaine, extubation time (defined as time from sevoflurane discontinuation to tracheal extubation), and intraoperative recall.

Statistical analyses were performed using the SPSS for Windows, version 15 (SPSS Inc., Chicago, IL). Data were first tested for normality by Klomogorov–Smirnov test. Normally distributed continuous data were analyzed by using student *t*-test. Non-normally distributed continuous and ordinal data were analyzed using Mann–Whitey U test. Categorical data was analyzed by chi square or Fisher's exact test as appropriate. The results are presented as mean ± SD, median (range), or number of patients as appropriate. A P value < 0.05 was considered statistically significant.

3. Results

Forty-three patients were found eligible for the study. Five patients refused participation and 10 patients met our exclusion criteria. Twenty-eight patients were randomized into 2 groups: Control (C) group ($n = 14$) and Lidocaine (L) group P ($n = 14$). No patient was excluded from the study.

The 2 study groups were found to be similar regarding to demographic and surgical data except for anesthesia time which was longer in group L (Table 1). The median doses of intraoperative fentanyl (range) in group C [200(200–300)] were similar to group L [150(120–300)] ($P = 0.08$). The mean (±SD) cumulative dose of lidocaine given to patients in group L was 301(29) mg.

Table 1 Patient and surgical characteristics.

	Group C (n = 14)	Group L (n = 14)	P value
Age (yr)	39(11)	37(10)	NS
Sex (M/F)	6/8	7/7	NS
BMI (kg m^{-2})	26.7(2.2)	24.5(1.8)	NS
ASA (I/II)	5/9	6/8	NS
Surgery			
Cholecystectomy	5	6	NS
Hernial repair	4	4	NS
Appendectomy	5	4	NS
Duration of surgery (min)	51(18)	47(20)	NS
Duration of anesthesia (min)	60(17)	77(23)	0.04

Data are mean (±SD) or number. Group C: control; group L: lidocaine; BMI: body mass index; NS: non-significant.

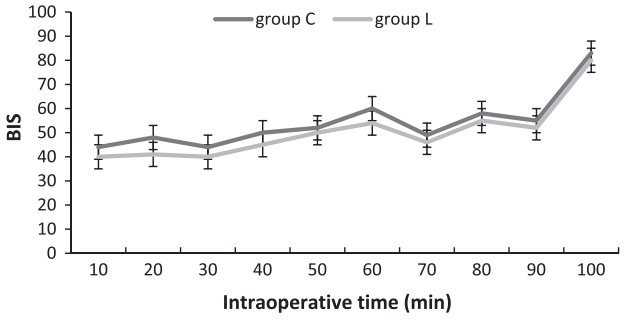

Figure 1 Mean (±SD) intraoperative bispectral index (BIS). Group C: control; group L: lidocaine. $P > 0.05$ at all time points.

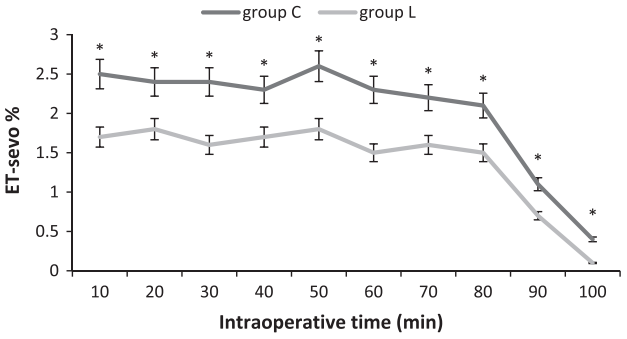

Figure 2 Mean (±SD) end-tidal sevoflurane (ET-sevo) concentrations. Group C: control; group L: lidocaine $^{*}P < 0.05$.

There were no significant differences between the 2 groups regarding BIS at any time point (fig 1). End-tidal sevoflurane concentrations were significantly higher in group C than in group L at all intraoperative time points (fig 2). No significant differences were detected between the 2 groups regarding the hemodynamic parameters (fig 3 and 4).

No patient in the 2 groups reported intraoperative awareness when asked about it the day following surgery.

4. Discussion

This study shows that i.v. lidocaine at a dose of 1.5 mg kg^{-1} bolus followed by 2 mg kg h^{-1}, reduces sevoflurane requirement while maintaining BIS score between 40 and 60, during

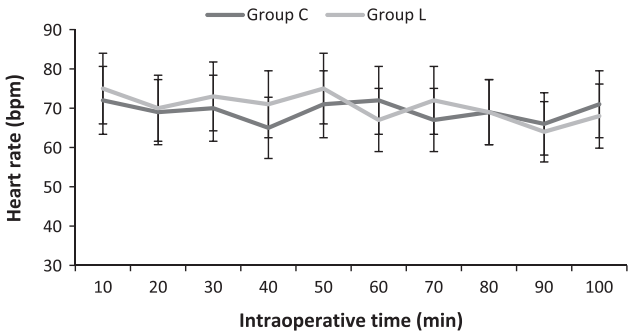

Figure 3 Mean (±SD) heart rate. Group C: control; group L: lidocaine; bpm: beat per minute. $P > 0.05$ at all time points.

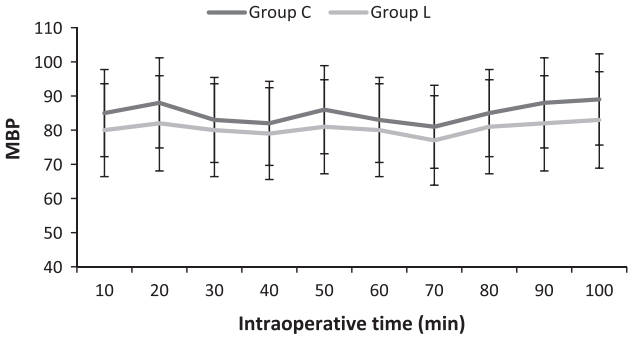

Figure 4 Mean (±SD) mean blood pressure (MBP). Group C: control; group L: lidocaine. $P > 0.05$ at all time points.

maintenance of anesthesia in patients undergoing laparoscopic surgeries.

Systemic lidocaine infusion has been used in several studies to evaluate its benefits on the outcome of anesthesia. Having inflammation-modulatory properties [7], it significantly reduced pain and allowed more rapid discharge [8]. In a meta-analysis of 8 randomized, controlled, clinical trials, patients who underwent abdominal surgeries while receiving continuous perioperative i.v. lidocaine, showed less duration of postoperative ileus, less pain, nausea, and vomiting and shorter hospital stay [9]. McKay et al. proved that patients who received perioperative lidocaine infusion, required less opioid and had shorter length of PACU stay [3]. Groudine et al. also observed that i.v. lidocaine infusion was associated with significant decrease in postoperative pain and duration of hospitalization [10]. Despite the higher doses of fentanyl used in the control group compared to the lidocaine group in our study, they did not reach a statistical significance. The study was perhaps not powered enough to detect this difference (fentanyl dose was not our primary outcome). In one animal study published in 2012 by Columbano et al., it was found that there was no reduction in sevoflurane requirements when fentanyl was used contrary to buprenorphine. They concluded that the type of opioid used is the factor that may affect sevoflurane requirements [11].

Systemic lidocaine has proved to reduce MAC in animals. Wilson et al. observed in a study that lidocaine with or without ketamine significantly reduced the MAC of sevoflurane in dogs [12]. Matsubara et al. also found that intravenous lidocaine decreased MAC of sevoflurane in anesthetized dogs without affecting blood pressure or heart rate [13]. Pypendop and Ilkiw

also showed in another study that lidocaine dose dependently reduced the MAC of isoflurane in cats [14].

The effect of i.v. lidocaine on MAC was suggested to be due to its action at the spinal level by decreasing the motor response [15]. However, it was observed that intravenous lidocaine infusion reduced bispectral index-guided propofol requirement during TIVA [16,17]. These studies supported that the mechanism by which intravenous lidocaine decreased anesthetic requirements was due to its inhibitory effect at the central nervous system. In a case report, lidocaine was inadvertently administered at a dose of 100 mg per min for 7–8 min and BIS read zero [18]. This incidence supported that brain activity was decreased by systemic lidocaine administration.

The only study conducted on humans to explore the effect of lidocaine on MAC was done by Hodgson and Liu [19]. They found that epidural lidocaine reduced the end-tidal sevoflurane required for BIS less than 50 compared with sole general anesthesia by 34% explaining this by rostral migration of lidocaine to the brain cerebrospinal fluid. Moreover, they did not find a MAC-reducing effect of systemic lidocaine when given in doses that reach plasma levels comparable to epidural lidocaine (about 2 mcg ml^{-1}). There are some differences between their study and ours that can explain the different findings. The doses of systemic lidocaine used are different. We used 1.5 mg kg^{-1} as a bolus dose then 2 mg kg^{-1} h^{-1} as an infusion while they used 1 mg kg^{-1} as a bolus then 1.5 mg kg^{-1} h^{-1} as an infusion. Our higher doses might have resulted in the MAC-reducing effect of systemic lidocaine. Unfortunately we did not measure the plasma levels of lidocaine (not available in our hospital) but definitely they were higher than those levels attained in their study (2 mcg ml^{-1}). Future studies are needed to compare the MAC-reducing effect of lidocaine when infused in different doses and exactly determine the required plasma levels which can produce that effect.

The second difference is the design of the two studies. They divided their study patients into 3 groups: general-epidural group who received lidocaine in their epidurals, general anesthesia group who received systemic lidocaine and control general anesthesia group. We divided our study patients into 2 groups only. Moreover, they changed the concentrations of sevoflurane according to recorded BIS values above or below 50. When we examined their results we found some patients who attained very low BIS (<30) and others with very high values (>70). We manipulated sevoflurane concentrations to strictly keep BIS values in our patients between 40 and 60. Blinding was not complete in their study (epidural and general anesthesia group) and randomization was not perfect either because they directly assigned epidural-general patients to receive intravenous saline. On the contrary our study was fully randomized and double blinded. The doses of intraoperative opioids used in their study were not measured while in our study they were not significantly different between the 2 study groups. There might have been differences in their opioid doses that cause confounding in interpreting the results. Lastly our study may be more powerful than theirs. We calculated our power analysis with 0.01 alpha error and 0.1 beta error. Unfortunately they did not mention the values they used in their power analysis.

The dose of bolus and the rate of infusion of lidocaine used in this study were based on previous studies that proved that this dose did not result in plasma concentration more than 4 mcg ml^{-1} [20–22], which is below the toxic levels [23].

Since sevoflurane concentration was adjusted according to BIS values, there was no difference between the 2 groups as regard to BIS scores. However, no patient in the study could recall intraoperative events. There was also no difference between the 2 groups as regard to fentanyl consumption. Extubation time was longer in the lidocaine group which can be explained by blunting of the cough reflex by lidocaine [24].

In conclusion, intravenous lidocaine administration, during maintenance of general anesthesia, can decrease BIS-guided sevoflurane requirements.

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