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Research Article

Can systemic lidocaine be used in controlled hypotension? A double-blinded randomized controlled study in patients undergoing functional endoscopic sinus surgery

Ahmed M. Omar *

King Fahd Military Hospital, Dhahran, Saudi Arabia

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KEYWORDS

Lidocaine;
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Abstract *Introduction:* Functional endoscopic sinus surgery (FESS) is one of the operations that need controlled hypotension. Many drugs were successfully used in this purpose, e.g., magnesium sulfate, esmolol, and volatile anesthetics. Hypotension was observed to occur after submucosal injection of lidocaine. Based on this observation, it was hypothesized in this double-blinded randomized controlled study that lidocaine may be effective in producing controlled hypotension.
Methods: Forty-eight ASA I–II adults planned to undergo FESS were given a standard general anesthetic after which they were divided into 2 equal groups to receive either lidocaine infusion in a dose of 1.5 mg/kg/h (group L, $n = 24$) or equal volumes of normal saline (group C, $n = 24$). Primary outcome was the surgical field rating score (0–5 points). Secondary outcomes included hemodynamic parameters, extubation time, end-tidal sevoflurane concentrations, fentanyl consumption, and postoperative visual analog pain scores (VASs).
Results: Both groups were similar regarding hemodynamic parameters. Surgical field scores were significantly lower in group L than in group C at all intraoperative time points ($P < 0.05$). Extubation time was significantly longer in group C than in group L [group C: 12.4(2.3) min and group L: 9.1(3) min, $P = 0.03$]. Intraoperative fentanyl dose was significantly higher in group C than in group L [group C: 172(37) mcg and group L: 149(34) mcg, $P = 0.03$]. End-tidal sevoflurane concentrations were significantly lower in group L than in group C at most intraoperative time points ($P < 0.05$). Postoperative VAS pain scores in the PACU were higher in group C than in group L ($P < 0.05$).

* Address: King Fahd Military Medical Complex, Dhahran, PO Box 946, Saudi Arabia. Tel.: +966 569527320; fax: +966 38440000.
E-mail address: ahmedmommer@yahoo.com
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Conclusion: This study showed the ability of intravenous lidocaine infusion of 1.5 mg/kg/h to produce controlled hypotension in patients undergoing FESS and the superiority of this technique over placebo to achieve favorable surgical field scoring.

1. Introduction

Controlled hypotension is one of the methods used by anesthesiologists to decrease intraoperative blood loss and provide a good surgical field in different types of surgery [1–4]. Functional endoscopic sinus surgery (FESS) is one of the operations that need controlled hypotension for this purpose [5,6].

Different types of drugs have been successfully used to provide deliberate hypotension such as inhalational volatile agents [7], clonidine [4], nitroglycerine [8], esmolol [9], remifentanil [10], dexmedetomidine [11], and magnesium sulfate [12–14].

Lidocaine is one of the most commonly used amide anesthetics. It can be safely given systemically to treat ventricular arrhythmias [15] and blunt the pressor response to endotracheal intubation [16]. Hypotension has been observed to occur after submucosal injection of lidocaine [17,18]. Based on this observation, I hypothesized that systemic lidocaine may be effective in producing controlled hypotension. No studies were found in the literature about the use of lidocaine in controlled hypotension.

The aim of this study is to compare the possible ability of lidocaine to produce controlled hypotension compared with placebo in patients undergoing FESS.

2. Methods

Forty-eight adult (aged 18–50 yr) ASA physical status I and II patients undergoing functional endoscopic sinus surgery (FESS) were included in this study. A written informed consent was obtained from all patients after approval by the Local Ethics Committee. The enrollment period lasted from October 2011 to December 2012 in King Fahd Military Hospital in Dhahran (KSA). Patients with hepatic, renal, cardiovascular, neuromuscular, or hematological disorders were excluded. Patients on anticoagulant, opioid, or sedative drugs were also excluded.

After applying the routine monitors (electrocardiogram, pulse oximetry, noninvasive blood pressure, and peripheral nerve stimulator over the ulnar nerve proximal to the wrist crease to monitor the depth of neuromuscular blockade), all patients were given a standardized general anesthetic and IV fluids (5–7 ml/kg/h of lactated Ringer). General anesthesia was induced by 2–2.5 mg/kg propofol and 1–1.5 mcg/kg fentanyl. Muscle relaxation was accomplished by rocuronium 0.6 mg/kg and tracheal intubation was done when train-of-four (TOF) count reached zero.

Immediately after endotracheal intubation, patients were randomly assigned to 2 equal groups using computerized randomization tables (in closed envelopes): Control group (C, $n = 24$) and group lidocaine (L, $n = 24$). The hospital pharmacists who were not involved in the study prepared the study medications in 4 different coded syringes (two 10-ml syringes for boluses and two 50-ml syringes for infusion) and gave them to the attendant anesthesiologist who was blinded to group allocation. The 10-ml syringes for boluses contained either 1.5 mg/kg lidocaine (1% solution) for group L or equal volume of normal saline for group C. The 50-ml infusion syringes contained either 1% lidocaine (10 mg/ml) in group L to be given in a rate of 1.5 mg/kg/h (0.15 ml/kg/h) or equal volumes of normal saline in control group. Lungs were mechanically ventilated to normocarbia (monitored with end-tidal CO_2) with 40% oxygen in medical air. Sevoflurane was used in 1–1.5 MAC (approximately 2–3%) to keep mean arterial pressure (MAP) from 60 to 70 mmHg. Rocuronium boluses (5–10 mg) were given to train-of-four (TOF) count less than 2. An oropharyngeal pack was inserted after intubation, and then, the patient was positioned in a slight head-up position. The surgeon was allowed to inject submucosal epinephrine in saline (1:100,000) without lidocaine. If MAP was resistant to reach the target or if heart rate increased more than 20% from baseline, fentanyl 1 mcg/kg was given (every 30 min). If MAP was still resistant after 5 min of every fentanyl bolus, a nitroglycerine or esmolol infusion was titrated to effect on the discretion of the attending anesthesiologist. Bradycardia (< 48 bpm) was treated by atropine 0.5 mg and hypotension (MAP < 60 mmHg) was treated by phenylephrine boluses (50–100 mcg) or infusion (50–100 mcg/min). The surgeons who were blinded to group allocation were asked to assess the surgical field every 15 min according to this 6-point scale [19]: (**0** = no bleeding, **1** = slight bleeding–blood evacuation not necessary, **2** = slight bleeding-sometimes blood has to be evacuated, **3** = low bleeding-blood has to be often evacuated. Operative field is visible for some seconds after evacuation, **4** = average bleeding-blood has to be often evacuated. Operative field is visible only right after evacuation, **5** = high bleeding-constant blood evacuation is needed. Sometimes bleeding exceeds evacuation. Surgery is hardly possible).

On conclusion of surgery, the study medications and sevoflurane were discontinued. The effect of muscle relaxant was antagonized by neostigmine 40–60 mcg/kg with glycopyrrolate 5–8 mcg/kg when TOF count was 3 or 4. Patients were extubated while awake after removal of the oropharyngeal pack and transferred to postanesthesia care unit (PACU). Pain was assessed in PACU by a nurse who was blinded to group allocation every 15 min by visual analog score (VAS) starting from 0 (no pain) to 10 (worst imaginable pain). If pain VAS score was 1–4, 30 mg of IV ketorolac was given. If pain score > 4 or if the pain was not relieved by ketorolac, fentanyl 0.5 mcg/kg was given. Ondansetron 4 mg IV was given as a rescue antiemetic in case of postoperative nausea and vomiting (PONV). Phenylephrine was used in PACU with the same doses used intraoperatively to treat hypotension.

Primary outcome was the surgical field quality. Based on a pilot study conducted on 13 patients undergoing FESS in this hospital (not published) and a previous study [20], median surgical field quality with sevoflurane was found to be 3.5(range 1–4). Difference of 1 grade in surgical field quality was assumed to be clinically significant. Based on these data and assumption, a sample size of 21 in each group was calculated

when alpha error is 0.05 and beta error is 0.1. Twenty-four patients were enrolled in each group to accommodate for drop-outs and the ordinal nature of the primary outcome. Secondary outcomes included HR and MAP recorded every 15 min intraoperatively, end-tidal sevoflurane every 15 min, total doses of fentanyl intra- and postoperatively, extubation times (defined as time from discontinuing sevoflurane till tracheal extubation), estimated total blood loss in the suction canister (after subtracting the volume of saline used in irrigation), number of patients who needed treatment with atropine, phenylephrine and nitroglycerine, pain VAS at 15, 30, and 60 min postoperatively in PACU, and incidence of PONV or hypotension in the recovery room.

Data were statistically described in terms of mean (±SD), median (range), frequencies (number of cases), and percentages when appropriate. Data were tested first for normal distribution by Kolmogorov–Smirnov test. Comparison of quantitative variables between the study groups was done using Student t test for independent samples if normally distributed. Mann–Whitney U test was used for non-normally distributed quantitative and ordinal data. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

3. Results

Seventy-seven patients were found eligible for the study. Nine patients refused participation and 20 patients met the exclusion criteria. Forty-eight patients were randomly allocated to 2 equal groups: control group (group C, $n = 24$) and lidocaine group (group L, $n = 24$). Both groups were found to be similar regarding demographic and surgical data except for anesthesia time which was significantly longer in group C than in group L (Table 1). Surgical field scores were significantly lower in group L than in group C at all intraoperative time points (Table 2). Extubation time was significantly longer in group C than in group L [group C: 12.4(2.3) min and group L: 9.1(3) min, $P = 0.03$].

Intraoperative fentanyl dose was significantly higher in group C than in group L [group C: 172(37) mcg and group L: 149(34) mcg, $P = 0.03$].

Table 2 Intraoperative quality of surgical field (0–5 points). Data are median (range).

	Group C ($n = 24$)	Group L ($n = 24$)	P value
15 min	4(1–5)	2(1–4)	0.01*
30 min	4(1–4)	2(1–3)	0.02*
45 min	4(1–4)	2(1–3)	0.01*
60 min	3(1–4)	3(0–4)	0.02*
75 min	4(1–3)	2(0–3)	0.008*
90 min	4(1–4)	2(1–3)	0.02*
105 min	4(1–4)	3(1–3)	0.04*

Group C: control; group L: lidocaine.
* $P < 0.05$.

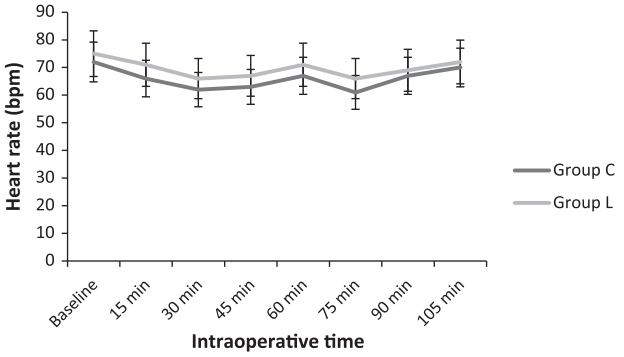

Figure 1 Mean (SD) heart rate in beats per min recorded at different time points. No significant differences. Group C: control; group L: lidocaine.

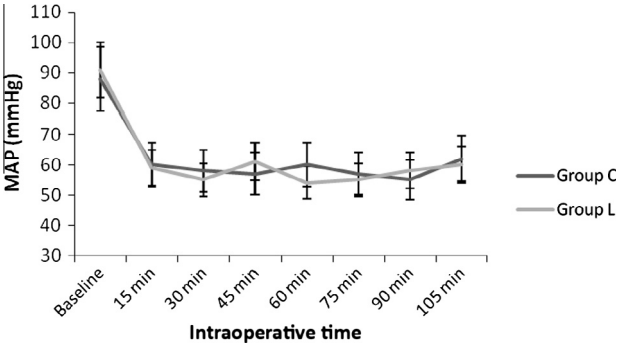

Figure 2 Mean (SD) mean arterial pressure (MAP) recorded at different time points. No significant differences. Group C: control; group L: lidocaine.

Table 1 Demographic and surgical data. Data are mean (SD) or number.

	Group C ($n = 24$)	Group L ($n = 24$)	P value
Age (yr)	36.3(8.1)	36.7(7.7)	0.72
Gender (M/F)	14/10	13/11	0.81
BMI (kg/m^2)	26.7(3.6)	27.9(3.2)	0.69
ASA (I/II)	17/7	15/9	0.61
Surgical time (min)	59(9)	62(8)	0.74
Anesthesia time (min)	99(13)	87(14)	0.02*
Estimated blood loss (ml)	106(29)	91(33)	0.13

M: male; F: female; BMI: body mass index; group C: control; group L: lidocaine.
* $P < 0.05$.

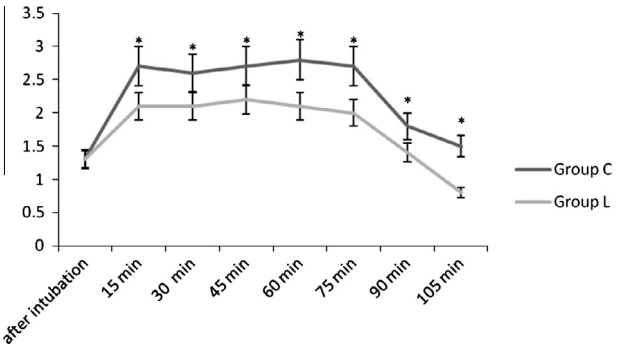

Figure 3 Mean (SD) end-tidal sevoflurane (ET sevo) concentrations at different time points. Group C: control; group L: lidocaine. $^{*}P < 0.05$.

Table 3 Visual analog score (VAS) of pain in the PACU.

	Group C ($n = 24$)	Group L ($n = 24$)	P value
VAS at 15 min	3(1–6)	2(1–5)	0.001*
VAS at 30 min	4(1–5)	3(1–4)	0.03*
VAS at 60 min	4(1–4)	3(1–4)	0.009*

Data are median (range group C: control; group L: lidocaine.
* $P < 0.05$.

Both groups were found to be similar regarding intraoperative hemodynamics (Figs. 1 and 2). End-tidal sevoflurane concentrations were significantly lower in group L than in group C at most intraoperative time points (Fig. 3).

One patient in group C and 2 patients in group L needed atropine for intraoperative bradycardia ($P = 0.61$). Two patients in group C and 3 patients in group L needed intraoperative use of phenylephrine ($P = 0.66$). Two patients in each group needed rescue use of esmolol infusion ($P = 1.0$).

Postoperative VAS pain scores in the PACU were higher in group C than in group L (Table 3). Nineteen patients in group C and 13 patients in group L needed ketorolac ($P = 0.13$), while seven patients in group C and only 3 patients in group L needed fentanyl in PACU ($P = 0.3$). No patient in the study had PACU hypotension.

Sixteen patients in group C and 11 patients in group L complained of PONV in the PACU ($P = 0.12$).

4. Discussion

The main finding of this study is that intravenous lidocaine infusion is an effective method in producing controlled hypotension in patients undergoing FESS surgery, and it is more superior to placebo in producing favorable surgical field.

Deliberate hypotension is still widely used by anesthesiologists to decrease intraoperative blood loss and produce good surgical fields in different types of surgery [1–4]. However, the risk of organ hypoperfusion is a concern in this technique [21]. Targeting a mean blood pressure of 60–70 mmHg was considered safe as evidenced by normal metabolic and hormonal profiles in the form of serum lactate, pyruvate kinase, and glucose [22,23]. Since then the target MAP of 60–70 mmHg was used in most academic and clinical grounds.

Several years after introduction of deliberate hypotension in surgical practice, the consensus has been changed from achieving a predefined MAP to producing favorable surgical fields [6,24,25]. Surgical field scoring systems have been adopted in clinical studies to compare between different techniques of controlled hypotension and were found to be more practical than achieving predefined mean arterial pressures [2,5,6,13,14,19,24,25]. Poor correlation was found between the degree of hypotension and the quality of surgical field and consequently moderate hypotension did not necessarily produce favorable surgical fields [6,25]. The investigators in these 2 studies postulated that nitroprusside could not produce good surgical field rating because of its vasodilator effect. Vasodilation might actually increase the vascularity of the mucosa of the nasal sinuses and make the procedure more difficult. This hypothesis may be supported by the poorer results of volatile anesthetics in comparison to other drugs used in controlled hypotension [13,20]. Higher sevoflurane concentrations in group C in this study may have resulted in more mucosal congestion than group L and consequently poorer surgical field. Moreover, there is some evidence that lidocaine can produce some degree of vasoconstriction in human. Jorfeldt et al. [26] found that total systemic vascular resistance increased at plasma lidocaine concentrations of 3–6 mcg/kg, and they postulated that vasoconstriction in some parts of the peripheral circulation should have happened. The doses used in this study were used in previous studies and resulted in serum lidocaine levels less than 4 mcg/ml [27,28]. These relatively low plasma lidocaine concentrations could have caused some degree of mucosal vasoconstriction in the nasal sinuses and consequently produced favorable surgical fields.

When given to awake patients, lidocaine did not cause hypotension [29]. However, Enlund et al. noticed that submucosal injection of lidocaine in the oral cavity resulted in a dose-dependent decrease in MAP of anesthetized patients [17]. They included a group of patients who received lidocaine without epinephrine and found that this group also had a period of post-infiltration hypotension. This observation might indicate that hypotension did not result only from the probable β2-receptor stimulation by epinephrine but also from a non-understood mechanism of lidocaine. The authors postulated that deep general anesthesia is a mandatory prerequisite of hypotensive effects of lidocaine. The results of the current investigation may support their notion. Despite of using lower concentrations of sevoflurane in group L than in group C, the achieved MAPs were similar.

There are 2 probable mechanisms of hypotensive ability of lidocaine. The first mechanism is the ability of all local anesthetics to exert dose-dependent negative inotropic action on the heart by affecting calcium influx [30]. This negative inotropic effect of lidocaine may be aggravated by a similar effect of volatile anesthetics. Inability of lidocaine to cause hypotension in awake patients may suggest that its negative inotropic action is weak. The second mechanism is the ability of lidocaine to blunt the airway's reflexes to endotracheal tube [31]. Lidocaine infusion may have resulted in abolishing the patients' sensation to endotracheal tubes, thus eliminating an important mechanism of intraoperative sympathetic stimulation.

In spite of producing more favorable surgical field scoring in group L, the amount of blood loss in this group did not reach a statistical significance when compared to control group. This may be explained by the underpowering of the

study in detecting this difference and the inaccurate method of blood loss estimation.

The decreased doses of fentanyl needed intraoperatively in group L can be explained be the analgesic effect of lidocaine which was previously demonstrated [32]. This may also resulted in better postoperative analgesia and decreased need to analgesics in PACU. This opioid-sparing effect of lidocaine and the lowered sevoflurane concentrations might probably resulted in shorter extubation time in group L.

The dose of lidocaine infusion in this study was used imperatively. No previous studies were found in the literature regarding this use. However, this dose was safely used in studies of other purposes [27,28,32]. Future studies are needed to compare the effects of different doses of lidocaine on the conduct of controlled hypotensive anesthesia.

In conclusion, this study showed the ability of intravenous lidocaine infusion of 1.5 mg/kg/h to produce controlled hypotension in patients undergoing FESS and the superiority of this technique over placebo to achieve favorable surgical field scoring.

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