Section Editor: **Peter S. A. Glass**

The Effect of a Bolus Dose of Intravenous Lidocaine on the Minimum Alveolar Concentration of Sevoflurane: A Prospective, Randomized, Double-Blinded, Placebo-Controlled Trial

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BACKGROUND: The anesthetic effect of volatile anesthetics can be quantified by the minimum alveolar concentration (MAC) of the drug that prevents movement in response to a noxious stimulus in 50% of patients. The underlying mechanism regarding how immobilization is achieved by volatile anesthetics is not thoroughly understood, but several drugs affect MAC. In this study, we investigated the effect of a single IV bolus dose of lidocaine on the MAC of sevoflurane in humans.
METHODS: We determined the MAC for sevoflurane using the Dixon "up-and-down" method in 3 groups of patients, aged 30 to 65 years, who underwent elective surgery (30 patients per group). Study medication (placebo, 0.75 mg·kg^{-1} lidocaine or 1.5 mg·kg^{-1} lidocaine) was administered 3 minutes before skin incision after a 15-minute equilibration period and the response to skin incision was recorded (movement versus no movement).
RESULTS: MAC was 1.86% ± 0.40% in the placebo and 1.87% ± 0.45% in the 0.75 mg·kg^{-1} lidocaine group (P = 1.00). MAC was 1.63% ± 0.24% in the 1.5 mg·kg^{-1} lidocaine group, which was significantly lower than that of the placebo group (mean difference of 0.23% sevoflurane [95% adjusted confidence interval {CI}, 0.03–0.43]; P = 0.022). No significant difference was observed between the 0.75 mg·kg^{-1} lidocaine and the placebo groups (mean difference of −0.01% sevoflurane [95% adjusted CI, −0.27 to 0.25]; P = 1).
CONCLUSIONS: IV 1.5 mg·kg^{-1} lidocaine decreased the MAC by at least 0.03% sevoflurane (mean difference 0.23% sevoflurane [95% adjusted CI, 0.03–0.43]). We did not observe a significant reduction in the MAC of sevoflurane with the IV administration of 0.75 mg·kg^{-1} lidocaine. (Anesth Analg 2013;117:323-8)

The induction of immobility in response to surgical stimulation is an essential feature of general anesthesia. The capability of volatile anesthetics to immobilize patients who are exposed to noxious stimulation is measured using the MAC, which is defined as "the minimum alveolar concentration of anesthetic that prevents movement in 50% of subjects in response to a noxious stimulus."[1] The MAC is influenced by several drugs, including fentanyl,[2] midazolam,[3] propofol,[4] and clonidine.[5] IV lidocaine is used for various reasons in clinical practice (e.g., to decrease the consumption of intraoperative anesthetics,[6] to positively influence recovery after surgery,[7] and to attenuate the hemodynamic response after tracheal intubation),[8,9] and the bolus application of lidocaine is common practice.[8–15] IV infusion of 200 to 400 μg·kg^{-1}·min^{-1} lidocaine decreases the MAC of halothane, isoflurane, and sevoflurane in animals by 28%,[16] 43%,[17] and 39%,[18] respectively. Therefore, lidocaine may also decrease the MAC of sevoflurane in humans. However, the effect of lidocaine on the MAC of sevoflurane has not been fully elucidated. This study quantified the effect of 2 bolus doses of lidocaine on the MAC of sevoflurane in humans. Our hypothesis was that the administration of an IV bolus of 1.5 mg·kg^{-1} lidocaine would decrease the MAC of sevoflurane by 20%.

METHODS

Institutional ethics committee approval, registration at EudraCT (Ethics Committee of the Medical University of Vienna, ref. no. 3/2010, EudraCT ref. no. 2010-018276-25), and written informed consent were obtained before patient enrollment in our study.

The MAC of sevoflurane in adults varies between 1.71% ± 0.17% (SE)[19] and 2.05% ± 0.08% (SE).[20] Therefore, we estimated that 11 crossovers (responses/nonresponses) per group would be necessary to detect a 20% difference in the MAC between the groups with a power of 80% and a type 1 error of 5%.[21] Patients were included until this number was reached. The total number of included patients was limited to 30 per group for feasibility.

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Accepted for publication March 11, 2013.

Funding: This study was solely financed by the Medical University of Vienna, Vienna, Austria. There was no external financial support for this study.

The authors declare no conflict of interest.

Reprints will not be available from the authors.

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DOI: 10.1213/ANE.0b013e318294820f

We enrolled 90 adult patients of ASA physical status I and II scheduled for elective surgery under general anesthesia requiring a skin incision of at least 3 cm on the trunk[22] and in whom airway protection with a laryngeal mask was feasible. Patient age was restricted to 30 to 65 years because the MAC is uniform in this range.[23]

Exclusion criteria included cardiac arrhythmias, seizures, analgesic or sedative medications before surgery, a history of chronic pain, existing contraindications for inhaled induction, and a known allergy to the study medication.

Patients were randomly assigned to 1 of 3 groups. Randomization was performed using block randomization with a predefined randomization list. The corresponding envelopes, which included the study medication data (0.9% saline for placebo, 1.5 mg·kg^{-1} lidocaine in saline or 0.75 mg·kg^{-1} lidocaine in saline), were opened by the study nurse who prepared the study medication. All other investigators were blinded to the study medication. Patients did not receive any preoperative medication. Routine anesthetic monitors were applied, and the Bispectral Index (BIS) was monitored (BIS monitor Model A-2000, software version 3.3 with an averaging Window of 15 seconds by Aspect Medical Systems, Norwood, MA). Anesthesia was induced by "multiple deep inhalation breaths" of 8% sevoflurane in pure oxygen.[24] The end-tidal (ET) concentration of sevoflurane was measured using a Draeger Primus monitor with an accuracy of 0.1% (Draeger Primus, Draeger Medical Austria GmbH, Vienna, Austria). Once the BIS decreased <40,[25] a laryngeal mask airway was inserted, and the patients' lungs were ventilated with a 35% oxygen-in-air mixture at a fresh-gas flow of 6 L·min^{-1}. The ET sevoflurane concentration was later increased/decreased to the predefined level and held constant for at least 15 minutes before skin incision.[1] Tidal volumes of 6 to 8 mL·kg^{-1} at a frequency of 10 to 16 per minute were used to achieve normocapnia ($ETCO_2$ 30–40 mm Hg). MAC decreases 4% to 5% per degree centigrade decrease in core temperature.[23] Therefore, forced air was applied to the lower limbs to maintain normothermia; body temperature was measured using a probe in the nasopharynx.

The ET sevoflurane concentration of the first patient in each group was 2.0%. The ET sevoflurane concentration in the subsequent patient of this group was increased by 0.2% if the first patient moved in response to the skin incision. The ET sevoflurane concentration in the subsequent patient was decreased by 0.2% if the first patient did not move in response to the skin incision. The "up-and-down" adjustment of the ET sevoflurane concentration was continued in all subsequent patients in each group. This procedure is referred to as the "Dixon up-and-down method."[21]

The study medication was administered as a single bolus over 30 seconds 3 minutes before the skin incision. The responses to the skin incision (movement or no movement) were observed by investigators, who were positioned at the patient's head and arms and at the patient's legs and who were blinded to the study group and the ET sevoflurane concentration.[22] The response to the skin incision was deemed "movement" if a gross, purposeful movement of the head or at least 1 extremity was observed within 1 minute after the skin incision.[26] Coughing, bucking, and straining were not considered movement.

Values of noninvasive arterial blood pressure, heart rate (HR), and BIS were recorded every 2 minutes throughout the study period, before the administration of the study medication, immediately before the skin incision, and 1 minute after the skin incision.

The MAC of sevoflurane (mean and standard deviation of each group) was estimated using the Dixon up-and-down method.[21] These estimates for the mean and standard deviations were used to calculate the *t* test statistics, confidence intervals (CIs), and *P*-values. *P*-values were adjusted for multiplicity due to the 3 tests using Bonferroni correction (–min [3 × unadjusted *P*-value, 1]). To check validity of these test statistics and estimates, we calculated 1000 bootstrap samples and calculated bootstrap estimates, which produced the same results.

Secondary analyses of demographic data, the time before the skin incision, and baseline values between the study groups were analyzed using a Fisher exact test or a 1-way analysis of variance. Repeated analysis of variance measurements were performed in each group to investigate the time course of blood pressure, HR, and BIS. Bonferroni correction was performed because of the 3 subgroups. All adjusted *P*-values < 0.05 were considered statistically significant. Analyses of the calculation and comparisons of the MAC of sevoflurane were performed using R (R, release 2.12, The R Foundation for Statistical Computing, Vienna, Austria). Secondary analyses were performed using SPSS 19.0 (IBM SPSS Statistics, IBM Corp., Armonk, NY). Data are presented as the means ± SD (95% CI).

RESULTS

Ninety-one patients were recruited for our study. One patient did not complete the study protocol because laryngeal mask placement was not possible. This patient was replaced, and the data from 90 patients were used in the calculations (Fig. 1). Demographic and morphometric characteristics were comparable among the groups (Table 1).

The time from the insertion of the laryngeal mask to skin incision was at least 19 minutes in all patients. Therefore, the maintenance of steady-state ET sevoflurane concentrations for >15 minutes was possible. Body temperatures at the time of skin incision were similar in all groups.

The MAC of sevoflurane was 1.63% ± 0.24% (95% CI, 1.54–1.71) in the 1.5 mg·kg^{-1} lidocaine group, 1.87% ± 0.45% (95% CI, 1.73–2.01) in the 0.75 mg·kg^{-1} lidocaine group, and 1.86% ± 0.40% (95% CI, 1.72–2.00) in the placebo group (Fig. 2).

The mean difference between the MAC of sevoflurane in the 1.5 mg·kg^{-1} lidocaine group and in the placebo group was 0.23% sevoflurane (95% adjusted CI, 0.03–0.43), which is a relative reduction of MAC of approximately 12%. The mean difference between the MAC of sevoflurane in the 1.5 mg·kg^{-1} lidocaine group and in the 0.75 mg·kg^{-1} lidocaine group was 0.24 % sevoflurane (95% adjusted CI, 0.02–0.46). The MAC in the 1.5 mg·kg^{-1} lidocaine group was therefore significantly lower than in the placebo group (adjusted *P* = 0.022) and in the 0.75 mg·kg^{-1} lidocaine group (adjusted *P* = 0.034). No significant difference in the MAC was noted between the lidocaine 0.75 mg·kg^{-1} and the placebo group (mean difference of −0.01% sevoflurane [95% adjusted CI, −0.27 to 0.25]; adjusted *P* = 1).

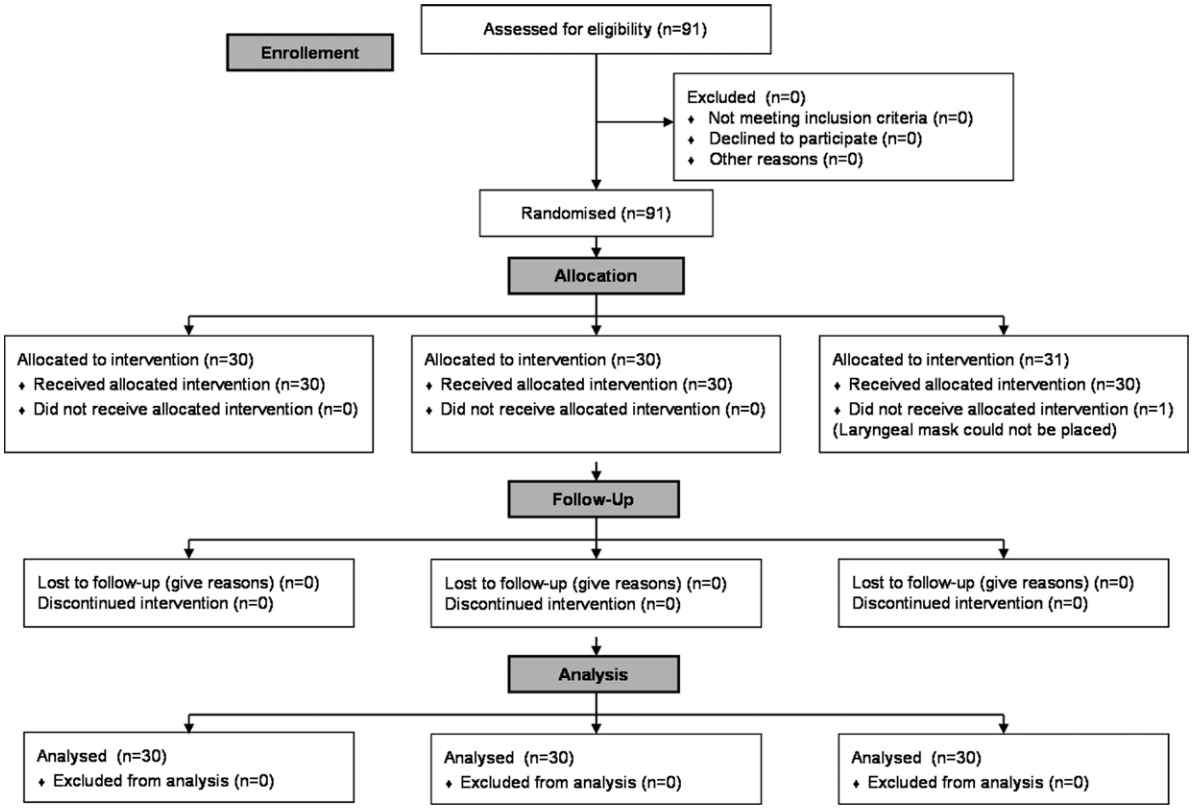

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) 2010 flow diagram. Prospective randomized clinical trial for the comparison of the effects of IV lidocaine on the minimum alveolar concentration of sevoflurane.

Table 1. Patient Characteristics and Potential Confounding Factors

	1.75 mg·kg^{-1} Lidocaine	0.75 mg·kg^{-1} Lidocaine	Placebo	*P*[a]
Age, y	47.0 ± 9.3	47.0 ± 7.9	51.0 ± 9.7	0.184
Height, cm	166.9 ± 7.8	165.4 ± 8.4	164.3 ± 7.0	0.447
Weight, kg	69.8 ± 10.9	68.0 ± 13.1	70.0 ± 10.8	0.759
Female/male	29/1 (97/3)	28/2 (93/7)	29/1 (97/3)	1.000
Time from LMA insertion to incision, min	22.2 ± 6.3	22.0 ± 2.8	22.3 ± 4.6	0.980
Body temperature, °C[b]	36.5 ± 0.3	36.3 ± 0.2	36.4 ± 0.3	0.625

Data are presented as the mean ± SD or absolute numbers (proportion).
LMA = laryngeal mask airway.
[a]All *P*-values were obtained from analysis of variance *f* test except gender, which used Fisher exact test.
[b]Values obtained at the time of skin incision.

Systolic arterial blood pressure (SAP) and BIS decreased significantly in the 1.5 mg·kg^{-1} lidocaine group after injection (prestudy medication until preincision), but HR was not significantly affected. SAP also decreased significantly in the 0.75 mg·kg^{-1} lidocaine group after injection, but BIS and HR were not significantly affected. No significant changes were observed in SAP, BIS, or HR after injection in the placebo group. In Table 2, a detailed time course is provided of SAP, HR, and BIS in the 3 groups from the administration of study medication until after skin incision.

DISCUSSION

The important finding of this study was that that a single IV bolus of 1.5 mg·kg^{-1} lidocaine decreased the MAC by at least 0.03% sevoflurane (mean difference 0.23% sevoflurane [95% adjusted CI, 0.03–0.43]). We did not observe a significant reduction in the MAC of sevoflurane with the IV administration of 0.75 mg·kg^{-1} lidocaine. Systemic administration of lidocaine dose dependently decreases the MAC of sevoflurane in rats,[27] horses,[28] and dogs[18,29] by up to 39%. However, a reduction in the MAC of sevoflurane by systemic lidocaine could not be demonstrated in humans.[30] These apparently contrary results may be explained by the fact that we determined the MAC reduction after a bolus at a single time point. Because of differing pharmacokinetics and pharmacodynamics among patients, we may have missed the peak effect of the lidocaine dose. In addition, there was most likely considerable variability in the effect site plasma concentration at the time we determined the MAC. The MAC in the animal studies was determined under steady-state conditions using a real skin incision as the noxious stimulus. The larger reduction in the MAC of sevoflurane in these studies was most likely due to the higher concentrations of lidocaine (initial loading dose of 2 mg·kg^{-1} followed by an infusion of 12 mg·kg^{-1}·h^{-1})[18] at the time that the MAC

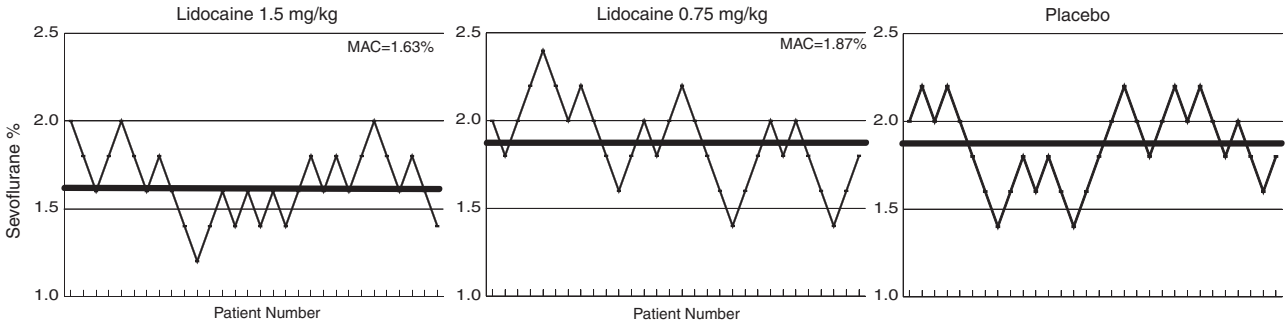

Figure 2. The minimum alveolar concentration (MAC) of sevoflurane in the study groups.

Table 2. Evolution of Bispectral Index, Systolic Arterial Blood Pressure, and Heart Rate from the Prestudy Medication Administration to the Postskin Incision in the Study Groups

	Placebo	0.75 mg·kg^{-1} Lidocaine	1.5 mg·kg^{-1} Lidocaine
BIS prestudy medication	36.8 ± 9.8 (33.1–40.5)	38.0 ± 11.2 (33.8–42.1)	41.8 ± 9.6 (38.2–45.4)
BIS preincision	35.4 ± 9.4 (31.8–38.9)	34.6 ± 9.1 (31.2–37.9)	37.0 ± 6.5 (34.6–39.5)
BIS postincision	42.9 ± 17.1 (36.6–49.3)	40.2 ± 15.8 (34.3–46.1)	44.4 ± 10.8 (40.4–48.5)
P	0.43[a]; **0.043**[b]; 0.153[c]	0.096[a]; **0.033**[b]; 0.954[c]	**0.02**[a]; **0.004**[b]; 0.659[c]
SAP prestudy medication	98.3 ± 14.3 (92.9–103.6)	100.6 ± 13.5 (95.6–105.6)	105.6 ± 15.2 (99.9–111.3)
SAP preincision	97.0 ± 12.5 (92.4–101.7)	95.2 ± 11.6 (90.9–99.5)	101.6 ± 13.1 (96.7–106.5)
SAP postincision	114.0 ± 15.8 (108.1–119.9)	111.5 ± 25.4 (102.0–120.9)	111.2 ± 16.7 (104.9–117.4)
P	0.42[a]; **<0.001**[b]; **<0.001**[c]	**<0.001**[a]; **<0.001**[b]; **0.032**[c]	**0.001**[a]; **0.003**[b]; 0.084[c]
HR prestudy medication	65.4 ± 10.4 (61.5–69.3)	65.1 ± 14.5 (59.7–70.5)	62.7 ± 9.1 (59.3–66.1)
HR preincision	63.4 ± 7.1 (60.7–66.0)	63.4 ± 13.2 (58.5–68.3)	61.7 ± 8.7 (58.5–65.0)
HR postincision	80.8 ± 14.1 (75.6–86.1)	76.0 ± 19.1 (68.8–83.1)	76.2 ± 17.8 (69.6–82.8)
P	0.217[a]; **<0.001**[b]; **<0.001**[c]	0.156[a]; **<0.001**[b]; **0.001**[c]	0.309[a]; **<0.001**[b]; **<0.001**[c]

Data are mean ± SD (95% confidence interval). Bonferroni-adjusted *P*-values <0.05 are bolded. Comparisons were performed using analysis of variance with no interaction and the corresponding post hoc contrast tests. Corrections for multiplicity for the post hoc analysis were made using Bonferroni adjustment.
BIS = Bispectral Index; SAP = systolic arterial blood pressure (mm Hg); HR = heart rate (bpm).
Differences within each study group: [a]prestudy medication versus preincision; [b]preincision versus postincision; [c]prestudy medication versus postincision.

was determined. These doses are higher than commonly used in clinical practice (e.g., initial loading dose of 1.5–2.0 mg·kg^{-1} followed by an infusion of 1.5–3.0 mg·kg^{-1}·h^{-1}).[31–33] The study by Hodgson et al.[30] was not a true MAC reduction study of lidocaine in that patients received midazolam, fentanyl, and thiopental for induction. It is likely that these drugs affected the MAC that was measured after a bolus injection of 1 mg·kg^{-1} lidocaine followed by continuous infusion of 1.5 mg·kg^{-1}·h^{-1} lidocaine. The MAC of sevoflurane in the control group in the study by Hodgson et al.[30] was 1.18%, which is lower than that observed in our study and what is commonly reported.[34] In our study, the ET sevoflurane concentration remained constant for at least 15 minutes, which provided steady-state conditions. However, lidocaine was administered as a single bolus 3 minutes before skin incision, which may be considered a limitation of our study. As previously reported, lidocaine enters the central nervous system within 2.5 minutes after an IV bolus injection and exerts its effects on the central nervous system within 3 minutes after the injection.[35–38] Although its effect on the central nervous system may outlast the rapidly decreasing plasma concentrations after a single bolus,[39,40] we decided to determine MAC 3 minutes after bolus administration when the lidocaine concentration and its effect on the central nervous system seem to be noticeably high. Ideally, for a MAC reduction study the drug under investigation should be administered to obtain various steady-state concentrations that have obtained equilibrium with their effect site. The effect of lidocaine 3 minutes after a single bolus may not reflect the maximum effect on the MAC of sevoflurane (e.g., under steady-state conditions at the higher doses used in the animal studies). Further studies to fully elucidate this issue are required. We, however, wished to determine the MAC reduction of lidocaine in situations similar to the clinical use of lidocaine in the operating room.[8–15] IV lidocaine has several uses in the operating room, and possible effects of IV lidocaine on MAC have been reported (e.g., modification of signal transduction in dorsal horn neurons).[41–43] However, a significant decrease in the MAC of sevoflurane by IV bolus administration of lidocaine was observed in our study. This effect was smaller than expected and may be of questionable clinical value.

DISCLOSURES

Name: Thomas Hamp, MD.
Contribution: This author helped design the study, analyze the data, and prepare the manuscript.
Attestation: Thomas Hamp approved the final manuscript. Thomas Hamp attests to the integrity of the original data and the analysis reported in this manuscript. Thomas Hamp is the archival author.
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Contribution: This author helped to conduct the study, collect the data, and prepare the manuscript.
Attestation: Mario Krammel approved the final manuscript.

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Attestation: Walter Plöchl approved the final manuscript and attests to the integrity of the original data and the analysis reported in this manuscript.
This manuscript was handled by: Peter S. A. Glass, MB, ChB.

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