

Does Epidural Anesthesia Have General Anesthetic Effects?

A Prospective, Randomized, Double-blind, Placebo-controlled Trial

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Background: Clinically, patients require surprisingly low end-tidal concentrations of volatile agents during combined epidural-general anesthesia. Neuraxial anesthesia exhibits sedative properties that may reduce requirements for general anesthesia. The authors tested whether epidural lidocaine reduces volatile anesthetic requirements as measured by the minimum alveolar concentration (MAC) of sevoflurane for noxious testing cephalad to the sensory block.

Methods: In a prospective, randomized, double-blind, placebo-controlled trial, 44 patients received 300 mg epidural lidocaine (group E), epidural saline control (group C), or epidural saline-intravenous lidocaine infusion (group I) after premedication with 0.02 mg/kg midazolam and 1 µg/kg fentanyl. Tracheal intubation followed standard induction with 4 mg/kg thiopental and succinylcholine 1 mg/kg. After 10 min or more of stable end-tidal sevoflurane, 10 s of 50 Hz, 60 mA tetanic electrical stimulation were applied to the fifth cervical dermatome. Predetermined end-tidal sevoflurane concentrations and the MAC for each group were determined by the up-and-down method and probit analysis based on patient movement.

Results: MAC of sevoflurane for group E, $0.52 \pm 0.18\%$ ($\pm 95\%$ confidence interval [CI]), differed significantly from group C, $1.18 \pm 0.18\%$ ($P < 0.0005$), and from group I, $1.04 \pm 0.18\%$ ($P < 0.001$). The plasma lidocaine levels in groups E and I were comparable (2.3 ± 1.0 vs. 3.0 ± 1.2 µg/ml \pm SD).

Conclusions: Lidocaine epidural anesthesia reduced the MAC of sevoflurane by approximately 50%. This MAC sparing is most likely caused by indirect central effects of spinal deafferentation and not to systemic effects of lidocaine or direct neural blockade. Thus, lower concentrations of volatile agents than those based on standard MAC values may be adequate during combined epidural-general anesthesia. (Key words: Anesthetic techniques; thoracic epidural anesthesia.)

IN our clinical practice, surprisingly low end-tidal concentrations of volatile agents appear to provide adequate anesthesia when a combined epidural-general technique is used. Epidural blockade will decrease general anesthetic requirements at the surgical site, but the presence of the endotracheal tube and positive-pressure ventilation would be expected to maintain a considerable need for general anesthesia.¹ Neuraxial anesthesia has been shown to markedly potentiate the sedative effects of midazolam in humans,²⁻⁴ which suggests that neural blockade may itself have sedative properties. Because sedative medications typically reduce general anesthetic requirements,⁵ we hypothesized that neuraxial blockade would reduce general anesthetic requirements as well. Minimum alveolar concentration (MAC) defines adequate general anesthesia to suppress purposeful movement in 50% of patients at incision, and it has, in practice, become a benchmark by which overall adequacy of anesthesia is clinically defined.⁵ We tested whether lidocaine epidural anesthesia reduces general anesthetic requirements as measured by the MAC of sevoflurane.

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Materials and Methods

This prospective, randomized, double-blind, placebo-controlled trial was approved by the Institutional Review Board at Virginia Mason Medical Center. Informed written consent was obtained from 44 patients, American Society of Anesthesiologists status I-III, ranging from 20-65 yr old. Exclusion criteria included weight less

than 50 kg or more than 110 kg, history of musculoskeletal disorders, known allergy to amide local anesthetics, history of substance abuse, current prescription opioid use, and use of more than two alcoholic beverages on average per day in the past 5 yr. Patients received a standard premedication of 0.02 mg/kg midazolam and 1 μ g/kg fentanyl and a total of 10 ml/kg lactated Ringer's solution, administered intravenously before insertion of a 17-gauge Tuohy needle and placement of a 19-gauge epidural catheter 4 to 5 cm into the epidural space at a vertebral level between T9 and T12. Intravascular placement was ruled out with 3-ml test dose of saline with 1:200,000 epinephrine. Patients were then randomized to one of three groups. In the epidural lidocaine group (group E), patients immediately received a 15-ml plain 2% lidocaine epidural bolus (300 mg) *via* epidural catheter in divided doses; patients in the epidural saline control group (group C) and the intravenous lidocaine group (group I) received 15 ml saline *via* epidural catheter. Cephalad limit of sensory block to cold sensation with an alcohol swab and lower extremity motor strength using a modified Bromage scale were checked bilaterally 15 min after injection of epidural solution without the blinded observer present. After evaluating epidural blockade and after preoxygenation, general anesthesia was induced with 4 mg/kg thiopental, 1 mg/kg succinylcholine and sevoflurane in 100% oxygen, followed by direct laryngoscopy and tracheal intubation. After induction, groups E and C received an intravenous saline bolus (5 ml) and infusion (6 ml/h), whereas group I received a lidocaine intravenous bolus (1 mg/kg) and infusion (25 μ g \cdot kg⁻¹ \cdot min⁻¹). Intravenous administration of lidocaine in group I was intended to simulate systemic levels of lidocaine caused by absorption after epidural injection.^{6,7} An esophageal stethoscope with temperature monitoring capability was placed per routine. Mean arterial blood pressure was maintained at more than 60 mmHg with an ephedrine (5–10 mg) or phenylephrine (50–100 μ g) bolus. End-tidal carbon dioxide was kept between 32–42 mmHg and fresh oxygen flow was kept at 10 l/min. A predetermined target sevoflurane end-tidal concentration was maintained for at least 10 min. After assurance of recovery of a strong single twitch in response to ulnar nerve stimulation, two electrodes were placed just lateral and 5 cm distal to the left acromion process in the fifth cervical (C5) dermatomal sensory distribution. Patients were tested for the presence or absence of gross, purposeful movement of the head or the extremities during or within 60 s of a 10-s burst of 50 Hz, 60 mA tetanic electrical stimulation

with a nerve stimulator (Neurotechnology, Digistim 2 Plus, Kerville, TX). Breath holding, bucking, or grimacing was not considered movement.⁸ Isolated movement of the left arm as a result of direct muscle stimulation during tetanic electrical stimulation also was classified as a negative response.

Each group initially was tested at 2.2% end-tidal sevoflurane, which estimates the reported ED₉₅ of sevoflurane (2.07%) necessary to prevent purposeful movement in response to incision in healthy patients.⁹ Subsequent corrections of 0.2% end-tidal sevoflurane were made per the up-and-down method based on previously reported standard deviations of MAC values.^{9,10} If a particular patient did not move, the sevoflurane concentration was reduced by 0.2% in the subsequent patient randomized to the same group, whereas if a particular patient did move, the sevoflurane concentration was increased by 0.2% in the subsequent patient in the same group. Serum lidocaine levels were drawn from patients in group E and group I just after the completed assessment of movement at a site other than the arm receiving the intravenous infusion. Plasma samples were tested using the TDx/FLx Lidocaine Assay System; Abbott Laboratories (Abbott Park, IL; coefficient of variation of less than 5% with controls of 1.5, 3.0, and 7.5 μ g/ml). All patients were assessed postoperatively during their hospital stay.

Statistical Analysis

Prospective power analysis with up-and-down methodology indicated that seven patients per group were needed after the first crossover to achieve a 95% CI of less than 0.2% for a calculated MAC of sevoflurane.¹⁰ Thus, in groups E, C, and I a total of 17, 13, and 14 patients were enrolled, respectively. Demographic data were compared among groups using analysis of variance. The ED₅₀ (MAC) of sevoflurane with a 95% CI was determined by the up-and-down method and by probit analysis. Two-tailed Student *t* tests were used to test for significance between group E and control groups C and I. A *P* value less than 0.05 was considered significant.

Results

Demographics were similar among groups (table 1). The MAC of sevoflurane that suppressed movement in response to tetanic stimulation in 50% of subjects (95% CI) was 0.52% (0.34–0.70%) for epidural lidocaine–general anesthesia (group E) compared to 1.18% (1.00–

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Table 1. Demographic Data, Intraoperative Measurements, and MAC Values

	Group E	Group C	Group I
n	17	13	14
Female/male	13/4	9/4	11/3
Age (yr)	53 ± 10	47 ± 13	45 ± 12
Body weight (kg)	76 ± 15	71 ± 11	82 ± 14
Height (cm)	168 ± 8	168 ± 12	168 ± 8
Body temperature (°C)	35.8 ± 0.3	36.0 ± 0.4	36.1 ± 0.4
Sensory block-cephalad limit			
Mode (range)	T2 (T5-T1)	None	None
Motor block (Bromage scale)			
Mode (range)	0 (0-2)	None	None
Plasma lidocaine (µg/ml)	2.3 ± 1.0	—	3.0 ± 1.2
Minimum alveolar concentration (MAC)—end-tidal % (95% CI)			
Up-down methodology	0.52% (0.34-0.70)*	1.18% (1.00-1.36)	1.04% (0.86-1.22)
Probit backup analysis	0.56% (0.43-0.68)*	1.17% (0.98-1.29)	1.12% (1.01-1.30)

All values reported as mean ± SD unless otherwise indicated; Bromage modified scale: 0 = no motor block; 1 = barely able to flex knees; 2 = move feet only; 3 = complete motor block.

Group E = epidural lidocaine-general anesthesia; Group C = epidural saline-general anesthesia; Group I = intravenous lidocaine + epidural saline-general anesthesia. *End-tidal sevoflurane of group E differed significantly from group C ($P < 0.0005$) and from group I ($P < 0.001$).

1.36%) for the epidural saline-general anesthesia control (group C; $P < 0.0005$) and compared to 1.04% (0.86-1.22%) for the epidural saline-general anesthesia control with an added intravenous lidocaine infusion (group I; $P < 0.001$; table 1; figs. 1-3). The average plasma lidocaine levels in the epidural lidocaine group E and in the intravenous lidocaine group I were comparable (table

1). Ephedrine (5 mg) was used in one patient and phenylephrine (50-150 µg) was used in four patients in group E, whereas no vasopressors were necessary in the control groups C and I to maintain a mean arterial pressure of more than 60 mmHg before testing. No patients reported intraoperative awareness during follow-up while in the hospital.

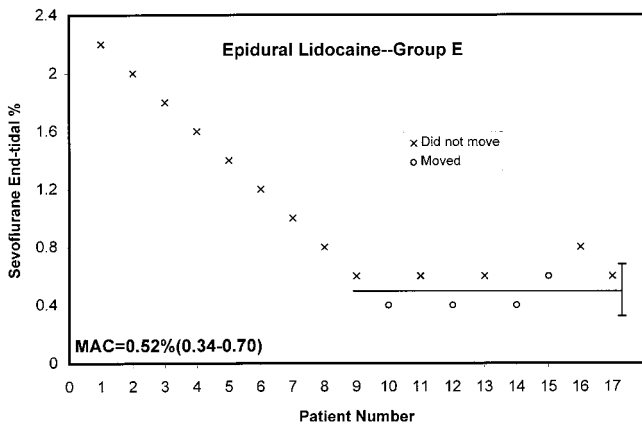


Fig. 1. Patients in group E (epidural lidocaine-intravenous saline) moving or not moving in response to tetanic electrical stimulation at predetermined end-tidal sevoflurane concentrations. When a patient did not move in response to tetanic electrical stimulation, an “x” was recorded and the sevoflurane concentration was decreased by 0.2% in the following patient. When the patient did move in response to tetanic electrical stimulation, an “o” was recorded, and the sevoflurane concentration was increased by 0.2% in the following patient. Minimum alveolar concentration (MAC) values are calculated by the up-and-down method and are reported with 95% CI.

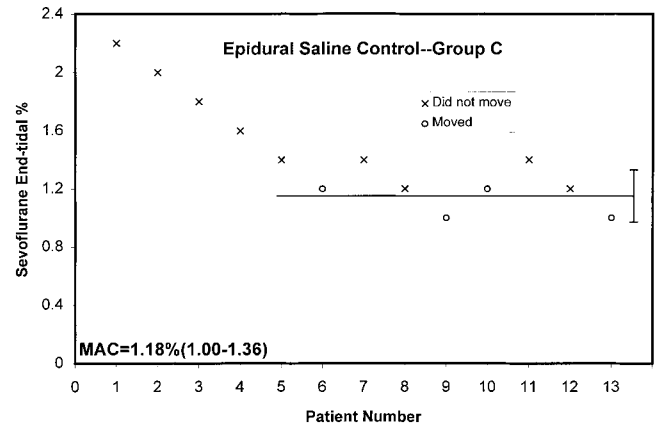


Fig. 2. Patients in group C (epidural saline-intravenous saline) moving or not moving in response to tetanic electrical stimulation at predetermined end-tidal sevoflurane concentrations. When a patient did not move in response to tetanic electrical stimulation, an “x” was recorded and the sevoflurane concentration was decreased by 0.2% in the following patient. When the patient did move in response to tetanic electrical stimulation, an “o” was recorded, and the sevoflurane concentration was increased by 0.2% in the following patient. Minimum alveolar concentration (MAC) values are calculated by the up-and-down method and are reported with 95% CI.

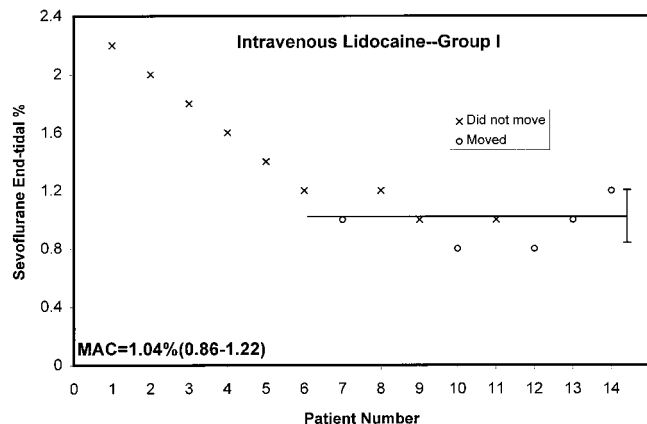


Fig. 3. Patients in group I (epidural saline–intravenous lidocaine) moving or not moving in response to tetanic electrical stimulation at predetermined end-tidal sevoflurane concentrations. When a patient did not move in response to tetanic electrical stimulation, an “x” was recorded, and the sevoflurane concentration was decreased by 0.2% in the following patient. When the patient did move in response to tetanic electrical stimulation, an “o” was recorded and the sevoflurane concentration was increased by 0.2% in the following patient. Minimum alveolar concentration (MAC) values are calculated by the up-and-down method and are reported with 95% CI.

Discussion

Lidocaine epidural anesthesia reduced the MAC of sevoflurane from 1.18 to 0.52%, or by approximately one half. This substantial MAC-sparing effect may have clinical relevance. Use of combined epidural–general anesthesia may initiate preemptive analgesia, provide a smooth transition to postoperative epidural analgesia, and improve clinical outcome^{11,12}; however, the technique is possibly underused for fear of superimposing the cardiovascular depressant effects of general anesthesia on epidural anesthesia. Our findings imply that a markedly lesser amount of volatile agent provides adequate anesthesia during combined epidural–general anesthesia than predicted by standard MAC values. The effects on suppression of consciousness were not assessed directly. As volatile agents produce dose-dependent cardiovascular depression,¹³ the use of reduced concentrations of volatile anesthetics could improve hemodynamic stability during combined epidural–general anesthesia. Conversely, adherence to traditional minimum end-tidal concentrations of volatile anesthetics during combined epidural–general anesthesia may provoke unnecessary hypotension and fluid overload and prolong emergence and recovery.

We speculate that the observed decrease in MAC seen with epidural anesthesia occurs *via* inhibition of the

tonic afferent spinal nerve signaling to the brain and to the spinal cord above the level of neural blockade. Afferent theory proposes that tonic sensory and muscle-spindle activity maintains a state of wakefulness.¹⁴ Accordingly, a decrease in tonic afferent input would decrease the level of consciousness. For example, neuromuscular blockade with pancuronium decreased the MAC of halothane by 25%, presumably *via* the abolition of muscle-spindle activity and thereby the reduction of tonic afferent signaling to the brain.¹⁵ In addition, as proposed by Eappen *et al.*,¹⁶ decreased afferent input to the brain could lessen excitatory descending modulation of spinal cord motoneurons and suppress motor function. Thus, the combination of decreased input from sensory and motor afferents seen with epidural anesthesia would be a reasonable mechanism for a general anesthetic effect and for a decreased MAC of volatile agents.

Indirect support for deafferentation from neuraxial blockade leading to decreased MAC comes from a number of studies that showed that approximately 50% lower doses of midazolam and thiopental induce hypnosis in human subjects after intrathecal or epidural blockade, implying a sedative effect of neuraxial anesthesia.^{2–4} Sedative effects of intrathecal bupivacaine in humans have also been shown that were directly related to cephalad height of sensory blockade.¹⁷ Furthermore, laboratory studies in the rat indicate a reduced thiopental requirement to prevent movement in response to noxious stimuli at the cornea or upper limb after intrathecal bupivacaine injection.¹⁶ Although the suppression of level of consciousness and of movement may represent different effects, agents that cause sedation generally also reduce the MAC of volatile agents. Therefore, these data support deafferentation from epidural anesthesia as a cause for the reduction of volatile anesthetic MAC.

Three alternative mechanisms for the reduction of MAC with epidural anesthesia include (1) systemic general anesthetic effects of absorbed epidural lidocaine, (2) direct epidural sensory blockade of the noxious stimulus at C5, and (3) subanesthetic levels of epidural lidocaine depressing spinal cord motor function.

Epidural administration of lidocaine typically results in measurable plasma levels, which peak at 5 min and then remain stable for at least 1 h.¹⁸ Intravenous lidocaine infusions have been shown in animals and humans to have a MAC-sparing effect of 10–28% at plasma concentrations between 3–6 $\mu\text{g}/\text{ml}$.¹⁹ Thus, systemic absorption of epidural lidocaine could have contributed to the

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decreased MAC of sevoflurane we observed in the epidural lidocaine-intravenous saline group. However, we included an intravenous lidocaine control group to simulate the anticipated systemic levels of lidocaine after epidural dosing. In the intravenous lidocaine group, the MAC of sevoflurane was significantly higher than in the epidural lidocaine group and comparable to the MAC of the general anesthesia control group (figs. 1-3), whereas the mean lidocaine levels measured at the time of MAC determination were comparable in the intravenous and the epidural lidocaine groups ($3.0 \mu\text{g/ml}$ vs. $2.3 \mu\text{g/ml}$; table 1). Thus, it is unlikely that a systemic general anesthetic effect of absorbed epidural lidocaine was the primary mechanism for the decreased MAC of sevoflurane in the epidural lidocaine group.

It is theoretically plausible that the epidural lidocaine group tolerated the same tetanic electrical stimulation at lower concentrations of sevoflurane because of direct sensory blockade at C5. This is unlikely for two reasons. First, sensory block to cold perception reached T2 (mode; range T1-T5) at 15 min after epidural injection, and it has been previously shown that the cephalad spread of sensory anesthesia after thoracic epidural dosing of 15 ml mepivacaine, 2%, was largely fixed by 15 min.²⁰ More importantly, we further explored this possibility by enrolling an additional group of 10 nonrandomized patients with lumbar epidural catheters (L1-L3). All methodology was as described for the thoracic epidural lidocaine group, starting the up-down run with an end-tidal sevoflurane concentration of 0.6%. The demographics were comparable to the randomized patients (height, 176 ± 9 cm; weight, 89 ± 10 kg; ratio of men:women, 6:4; temperature, 35.8°C), as were the plasma lidocaine levels ($2.2 \pm 0.4 \mu\text{g/ml}$). The cephalad level of sensory block to cold was lower than in the thoracic epidural lidocaine group (mode T6; range T3-T9), minimizing the possibility of sensory blockade at C5. The MAC of sevoflurane in this group was calculated by up-down methodology to be 0.70% (95% CI, 0.52-0.88%), which overlaps that of the thoracic epidural lidocaine group but does not overlap that of the general anesthesia control group. This reduction in the MAC of sevoflurane in the additional lumbar epidural anesthesia group supports the conclusion that the reduction in MAC seen with epidural anesthesia did not result from direct neural blockade at C5.

Finally, it is conceivable that subanesthetic levels of epidural lidocaine could potentiate the effects of volatile agents on spinal cord motor function above the level of sensory blockade, thereby decreasing MAC. In rats, the

MAC of isoflurane after exclusion of higher brain function *via* hypothermic transection of the cervical spinal cord was the same as the MAC in intact animals.²¹ This finding suggests that the spinal cord contains the necessary components of the circuitry that produces unconscious, purposeful movement. Further evidence for the importance of spinal cord motor function in determining MAC is the finding that volatile anesthetics directly depress spinal cord motor function. Electrical stimulation of a peripheral nerve produces two late waves on the electromyogram designated as the H reflex and the F wave. The amplitudes of these waves reflect excitability of spinal cord motoneurons.²² In volunteers undergoing isoflurane anesthesia, attenuation of H-reflex and F-wave amplitudes correlated with the suppression of unconscious, purposeful movement. These findings support the theory that isoflurane's depression of spinal cord motoneurons plays a significant role in defining MAC,²² and this effect may have been potentiated by subanesthetic levels of lidocaine above the level of clinically appreciable neural block.

The MAC of sevoflurane in the general anesthesia control group (1.18%) is lower than the published MAC of sevoflurane (1.58%; 1.71%) in two studies of patients with similar demographics to ours.^{9,23} Two explanations are likely. First, MAC values defined by tetanic electrical stimulation typically are somewhat lower than those based on response to skin incision.^{1,22} Second, we used premedication during epidural catheter placement and administration of thiopental for induction of general anesthesia, which are factors known to reduce MAC.^{5,8} However, the tetanic electrical stimulus and the doses of premedication and induction agent were standardized for all patients; therefore, the ratios of the MAC values should remain unchanged. It is additionally possible that the pharmacokinetics or pharmacodynamics of midazolam, fentanyl, or thiopental were different among the groups and that the MAC values in this study were thereby disproportionately reduced.

In summary, lidocaine epidural anesthesia reduced the MAC of sevoflurane by approximately 50%. This MAC sparing is most likely caused by central effects of spinal deafferentation, not to the systemic effects of lidocaine nor to direct neural blockade of cervical spinal nerves. Although the effects on suppression of awareness will necessitate further investigation, the apparent general anesthetic effects of epidural anesthesia should permit decreased use of volatile agents during combined epidural-general anesthesia, which may minimize hemody-

namic instability and decrease side effects of volatile anesthetics.

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