Epidural Lidocaine Decreases Sevoflurane Requirement for Adequate Depth of Anesthesia as Measured by the Bispectral Index® Monitor

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Background: Epidural anesthesia potentiates sedative drug effects and decreases minimum alveolar concentration (MAC). The authors hypothesized that epidural anesthesia also decreases the general anesthetic requirements for adequate depth of anesthesia as measured by Bispectral Index (BIS).

Methods: After premedication with 0.02 mg/kg midazolam and 1 μg/kg fentanyl, 30 patients aged 20–65 yr were randomized in a double-blinded fashion to receive general anesthesia with either intravenous saline placebo or intravenous lidocaine control (1 mg/kg bolus dose; 25 μg · kg⁻¹ · min⁻¹). A matched group was prospectively assigned to receive epidural lidocaine (15 ml; 2%) with intravenous saline placebo. All patients received 4 mg/kg thiopental and 1 mg/kg rocuronium for tracheal intubation. After 10 min of a predetermined end-tidal sevoflurane concentration, BIS was measured. The ED₅₀ of sevoflurane for each group was determined by up-down methodology based on BIS less than 50 (MAC₅₀). Plasma lidocaine concentrations were measured.

Results: The MAC₅₀ of sevoflurane (0.59% end tidal) was significantly decreased with lidocaine epidural anesthesia compared with general anesthesia alone (0.92%) or with intravenous lidocaine control (1% control; P < 0.0001). Plasma lidocaine concentrations in the intravenous lidocaine group (1.9 μg/ml) were similar to those in the epidural lidocaine group (2.0 μg/ml).

Conclusions: Epidural anesthesia reduced by 34% the sevoflurane required for adequate depth of anesthesia. This effect was not a result of systemic lidocaine absorption, but may have been caused by deafferentation by epidural anesthesia or direct rostral spread of local anesthetic within the cerebrospinal fluid. Lower-than-expected concentrations of volatile agents may be sufficient during combined epidural–general anesthesia.

NEURAXIAL anesthesia has been shown to have direct sedative effects¹ and to markedly reduce the amount of hypnotic agents required for sedation.²,³ Epidural lidocaine also reduced by 50% the sevoflurane minimum alveolar concentration (MAC) required to suppress movement in response to a noxious electrical stimulus applied above the level of sensory block.⁴ Based on these findings, we hypothesized that epidural local anesthetic decreases the amount of sevoflurane required for adequate depth of anesthesia.

The Bispectral Index® (BIS®) monitor is a proprietary algorithm that translates electroencephalographic data from a forehead montage into a nominal scale of 100 (awake) to 0 (isoelectric electroencephalogram).⁵ Glass et al.⁶ concluded that for a variety of clinically used anesthetic agents, BIS values less than 50 indicated an adequate depth of anesthesia. In studies specifically relating BIS to sevoflurane, values less than 50 also reliably indicated adequate depth of anesthesia.⁵,⁷ Therefore, we determined the ED₅₀ of sevoflurane to produce a BIS value of less than 50 (MAC₅₀) in the presence and absence of epidural lidocaine to measure effects of epidural anesthesia on depth of anesthesia.

Materials and Methods

This prospective trial was approved by the Institutional Review Board at Virginia Mason Medical Center. Informed written consent was obtained from patients aged 20–65 yr (American Society of Anesthesiologists classification I–II). Patients scheduled for general anesthesia were randomized in a double-blind fashion to receive intravenous saline placebo or intravenous lidocaine control. Patients scheduled for combined epidural–general anesthesia were prospectively assigned to epidural lidocaine with intravenous saline placebo. Exclusion criteria for all groups included weight less than 50 kg or more than 110 kg, cerebrovascular disease, seizure disorder, developmental delay or organic brain syndrome, known allergy to amide local anesthetics, history of substance abuse, current prescription opioid or benzodiazepine use, and consumption of more than two alcoholic beverages per day for the past year.

All subjects received a standard premedication of 0.02 mg/kg midazolam and 1 μg/kg fentanyl approximately 30 min before induction of general anesthesia. Patients scheduled for combined epidural–general anesthesia received 10 ml/kg of lactated Ringer’s solution intravenously before insertion of a 17-gauge Tuohy needle and placement of a 19-gauge epidural catheter 4–5 cm into the epidural space at a vertebral level between T9 and T12. Fifteen milliliters of plain 2% lidocaine (300 mg) was injected via the epidural catheter after a negative test dose of 15 μg epinephrine in 3 ml saline. Sensory block to cold with an alcohol swab was tested bilaterally 15 min after injection of epidural solution. In all study patients, a standard BIS® monitor strip (BIS Sensor®, Aspect Medical Systems, Newton, MA) was placed on the forehead before induction of general anesthesia.

After preoxygenation, general anesthesia was induced...
in all patients with 4 mg/kg thiopental, 1 mg/kg rocuronium, and 5% sevoflurane in oxygen followed by direct laryngoscopy and tracheal intubation. Controlled ventilation was instituted at tidal volumes of 8-12 ml/kg at a rate necessary to maintain end-tidal carbon dioxide between 32 and 36 mmHg with fresh 100% oxygen flow at 10 l/min. Esophageal temperature was maintained near 36°C. After induction, designated patients in the general anesthesia group received a lidocaine intravenous bolus dose (1 mg/kg in 5 ml) and infusion (25 µg·kg⁻¹·min⁻¹), whereas all other patients received a placebo intravenous saline bolus dose (5 ml) and infusion (6 ml/h). Intravenous administration of lidocaine was intended to simulate systemic concentrations of lidocaine caused by absorption after epidural injection. Mean arterial blood pressure was maintained at greater than 60 mmHg with intravenous lactated Ringer’s solution and ephedrine (5-10 mg) or phenylephrine (50–100 µg) bolus doses if required; use of these agents was recorded. A predetermined target sevoflurane end-tidal concentration was maintained for 10 min, followed immediately by a 1-min assessment of the BIS (Spacelabs, Redmond, WA, incorporating BIS version 3.2, Aspect Medical Systems) consisting of six readings taken at 10-s intervals by an observer blinded to the patient’s treatment protocol. The first patient in each group was tested at 1.0% end-tidal sevoflurane and evaluated for a BIS value less than 50, the sevoflurane concentration was reduced by 0.2% in the subsequent patient randomized to the same group, whereas if a given patient had a BIS greater than or equal to 50, the sevoflurane concentration was increased by 0.2% in the subsequent patient in the same group until a MACBIS50 was determined. Venous plasma lidocaine concentrations were drawn from patients receiving epidural or intravenous lidocaine after the completed assessment at a site other than the arm receiving the intravenous infusion.

### Statistical Analysis

Prospective power analysis with up-down methodology indicated that seven patients would be required after the first treatment crossover in each group to achieve 95% confidence intervals (CIs) of less than 0.2% for a MACBIS50 of sevoflurane based on previously published SDs. Randomization to general anesthesia with intravenous lidocaine versus saline placebo was accomplished prospectively using a sealed envelope technique after completion of informed consent. Demographic data were compared among groups with analysis of variance or chi-square analysis. The MACBIS50 of sevoflurane with 95% CIs for each group of patients was determined by up-down methodology with back-up probit analysis. Linear regression was performed to determine the relation of measured BIS values to end-tidal concentrations of sevoflurane for epidural–general versus general anesthesia. Two-tailed unpaired Student t tests were used to test for significance between groups. A P value < 0.05 was considered significant.

### Results

Demographics were similar among groups (table 1). The times from premedication to induction of general anesthesia and from induction to BIS testing did not differ significantly among the groups (table 1). Epidural lidocaine decreased the MACBIS50 of sevoflurane (end-tidal % [95% CIs]) compared with general anesthesia.

**Table 1. Demographic Data and Intraoperative Measurements**

<table>
<thead>
<tr>
<th></th>
<th>Group E</th>
<th>Group G</th>
<th>Group I</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>11</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>49 (11)</td>
<td>48 (11)</td>
<td>43 (8)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>78 (12)</td>
<td>90 (15)</td>
<td>82 (18)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>178 (8)</td>
<td>168 (10)</td>
<td>175 (13)</td>
</tr>
<tr>
<td>Female/male</td>
<td>4:7</td>
<td>8:1</td>
<td>5:5</td>
</tr>
<tr>
<td>Body temperature (°C)</td>
<td>35.8 (0.4)</td>
<td>36.1 (0.4)</td>
<td>36.1 (0.5)</td>
</tr>
<tr>
<td>End-tidal CO₂ (mmHg)</td>
<td>35 (1)</td>
<td>35 (1)</td>
<td>34 (1)</td>
</tr>
<tr>
<td>Sensory block to cold-cephalad limit mode (25–75%)</td>
<td>T3 (T6–T2)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Plasma lidocaine (µg/ml)</td>
<td>2.0 (0.4)</td>
<td>—</td>
<td>1.9 (0.8)</td>
</tr>
<tr>
<td>Assessment intervals (min)</td>
<td>30 (6)</td>
<td>29 (7)</td>
<td>35 (14)</td>
</tr>
<tr>
<td>Sedation to induction</td>
<td>19 (4)</td>
<td>17 (4)</td>
<td>18 (3)</td>
</tr>
<tr>
<td>Induction to BIS testing</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

All values reported as mean (SD) unless otherwise indicated. Group E: epidural lidocaine–general anesthesia–intravenous saline placebo; group G: general anesthesia–intravenous saline placebo; group I: general anesthesia–intravenous lidocaine control.

CO₂ = carbon dioxide; BIS = Bispectral Index.
control (0.59% [0.41–0.77] vs. 0.92% [0.74–1.10]; P < 0.0001) (fig. 1), whereas the addition of intravenous lidocaine did not decrease the MAC\textsubscript{BIS50} compared with control (1.00% [0.82–1.18] vs. 0.92% [0.74–1.10]; P = 0.83) (table 2). MAC\textsubscript{BIS50} values calculated with probit backup analysis were similar to those derived by up–down methodology (table 2). Because there were no differences in MAC\textsubscript{BIS50} between general anesthesia groups with or without low-concentration intravenous lidocaine, data for all patients receiving general anesthesia were compared with the epidural–general anesthesia group for analysis of BIS values \textit{versus} sevoflurane concentration. The slope of the linear relation of BIS to end-tidal sevoflurane is preserved while the x-intercept is decreased in the presence of epidural anesthesia (fig. 2). The average plasma lidocaine concentrations in the epidural lidocaine group (2.0 ± 0.4 μg/ml) and in the intravenous lidocaine group (1.9 ± 0.8 μg/ml) were comparable (table 1). One patient required epidrhrine (10 mg) and one patient required phenylephrine (50 μg) to maintain a mean arterial pressure above 60 mmHg in the epidural group. One patient randomized to the intravenous lidocaine group was removed from the study before BIS testing because of protocol violations stemming from a difficult and prolonged intubation. A new patient was randomized to this group. No patients reported intraoperative awareness on follow-up while in the hospital.

### Discussion

Lidocaine epidural anesthesia reduced by 34% the end-tidal sevoflurane required for BIS less than 50 compared with general anesthesia alone. Intravenous lidocaine resulting in systemic concentrations comparable to those measured during epidural anesthesia did not alter the relation between sevoflurane and BIS, demonstrating that absorbed epidural lidocaine did not account for the reduction in MAC\textsubscript{BIS50}. Our findings support the hypothesis that epidural anesthesia markedly reduces the amount of volatile general anesthetic required for adequate depth of anesthesia and suggest that the use of volatile agents during combined epidural–general anesthesia techniques can be reduced accordingly.

Neuralxial anesthesia has known sedative properties. Sedation has been reported with spinal anesthesia in unpremedicated patients with an association between level of sensory block and degree of sedation.\textsuperscript{1} A number of studies demonstrate a 40–50% reduction in the doses of midazolam, thiopental, and propofol required to induce hypnosis in human subjects with intrathecal or epidural blockade with local anesthetics.\textsuperscript{2,3,12,13} Because agents that cause sedation generally decrease general anesthetic requirements, it is reasonable that the sedative effects of epidural anesthesia should reduce general anesthetic requirements as well.

We speculate that the observed decrease in level of consciousness during general anesthesia observed with

### Table 2. Minimum Alveolar Concentration of Sevoflurane for BIS < 50 (MAC\textsubscript{BIS50})

<table>
<thead>
<tr>
<th>Method</th>
<th>Group E</th>
<th>Group G</th>
<th>Group I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up–down method</td>
<td>0.59* [0.41–0.77]</td>
<td>0.92 [0.74–1.10]</td>
<td>1.00† [0.82–1.18]</td>
</tr>
<tr>
<td>Probit analysis</td>
<td>0.59</td>
<td>0.90</td>
<td>1.02</td>
</tr>
</tbody>
</table>

All values reported as end-tidal % sevoflurane (95% confidence interval). Group E: epidural lidocaine–general anesthesia–intravenous saline placebo; group G: general anesthesia–intravenous saline placebo; group I: general anesthesia–intravenous lidocaine control.

* MAC\textsubscript{BIS50} group E differed significantly from group G (P < 0.0001). † MAC\textsubscript{BIS50} group I did not differ significantly from group G (P = 0.83).

BIS = Bispectral Index.
epidural anesthesia occurs via inhibition of tonic afferent spinal signaling to the brain. Afferentation theory as delineated by Lanier et al.\textsuperscript{14} proposes that tonic sensory and muscle-spindle activity maintains a state of wakefulness, thought to be integrated via the spinal cord in the reticular activating system. Accordingly, an acute decrease in tonic afferent input would be predicted to decrease the level of consciousness and thereby increase susceptibility to anesthetic agents.\textsuperscript{15} In support of this theory, epidural lidocaine anesthesia has been shown to delay arousal from general anesthesia.\textsuperscript{15} Decreased MAC of volatile agents with both neuromuscular blockade of tonic muscle-spindle activity\textsuperscript{16} and epidural anesthesia\textsuperscript{4} also provided indirect evidence that deafferentation decreases general anesthetic requirements for adequate depth of anesthesia. Our results provide direct evidence for potentiating effects of epidural anesthesia on loss of consciousness as we used BIS rather than suppression of movement, which may be more of an indicator of spinal cord reflex function.\textsuperscript{4}

It is also possible that the apparent general anesthetic effect of epidural anesthesia is caused by rostral spread of subanesthetic concentrations of lidocaine within the cerebrospinal fluid rather than to indirect effects of deafferentation. Epidural local anesthetics are known to readily diffuse into the cerebrospinal fluid and to result in concentrations comparable to those associated with intrathecal injection for spinal anesthesia.\textsuperscript{17,18} Although we found that sensory block reached, on average, the third thoracic dermatome 15 min after dosing, and other research suggests that cephalad spread of sensory blockade with epidural local anesthetics is largely established within this time frame,\textsuperscript{19} it cannot be ruled out that concentrations of local anesthetic below those required to produce perceptible sensory block may have diffused into the cerebrospinal fluid to influence the electrical activity of higher neural centers and thereby decrease the measured BIS value.

We used the BIS\textsuperscript{9} monitor with BIS less than 50 as a standard indicator of adequate depth of anesthesia. The BIS integrates electroencephalographic data via a proprietary algorithm based on empirical data into a nominal 100 to 0 scale, where 100 represents the awake state and 0 represents the isoelectric electroencephalogram.\textsuperscript{5} In a recent review of depth of anesthesia, Kissin\textsuperscript{20} concluded that among current technologies, the BIS in particular shows promise as a monitor of unconsciousness. The BIS demonstrated a high predictive performance for depth of sedation, and the probability of responsiveness became vanishingly small at a BIS value of 50 or less in studies of sevoflurane.\textsuperscript{5,7} Glass et al.\textsuperscript{6} also concluded that for propofol, midazolam, and isoflurane, BIS values less than 50 indicate a low probability of consciousness. In aggregate, these findings suggest that BIS less than 50 may serve as a clinically relevant predictor of the unconscious state and adequate depth of anesthesia.

There are several limitations to our study. First, although patients receiving general anesthesia were randomized in a double-blinded fashion to intravenous lidocaine versus saline placebo, patients scheduled to receive combined epidural–general anesthesia for surgery were assigned directly to the lidocaine epidural–sevoflurane general anesthesia-intravenous saline protocol. However, the same inclusion and exclusion criteria were used for all patients, and assessments were made by an observer blinded to the treatment arm of each patient. Second, it is possible that epidural anesthesia affected the metabolism of midazolam, fentanyl, and thiopental used in this study. Because these agents are known to produce sedation, systematic differences in plasma concentrations of these agents could differentially affect BIS values. On the other hand, the small doses and large volume of distribution of these agents make it unlikely that differential metabolism underlies our results. In support of this, the end-tidal sevoflurane associated with a BIS value of 50 during general anesthesia (1.0%; fig. 2A) was comparable to values from published studies using sevoflurane exclusively (1.2%).\textsuperscript{5,7}

In summary, epidural anesthesia reduced by 34% the sevoflurane required to achieve adequate depth of anes-
EPIDURAL ANESTHESIA DECREASES BIS DURING GENERAL ANESTHESIA

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thasia as measured by BIS during general anesthesia. Whereas other studies have suggested a decrease in sedative or general anesthetic requirement with epidural anesthesia, this study provides direct evidence of a supraspinal effect of epidural neuraxial blockade and suggests that the level of consciousness is suppressed. Reduced concentrations of volatile agents may thereby produce adequate depth of anesthesia during combined epidural–general anesthesia.

References

5. Olofsen E, Dahan A: The dynamic relationship between end-tidal sevoflurane and isoflurane concentrations and bispectral index and spectral edge frequency of the electroencephalogram. Anesthesiology 1999; 90:1345–53