Sevoflurane Concentrations Required to Block Autonomic Hyperreflexia during Transurethral Litholapaxy in Patients with Complete Spinal Cord Injury

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Background: Autonomic hyperreflexia (AHR) is a potentially life-threatening hypertensive condition that occurs in patients with high spinal cord injury (SCI). The current study was aimed to determine sevoflurane concentrations that block AHR in SCI patients.

Methods: The study involved 28 patients with chronic, complete SCI scheduled to undergo transurethral litholapaxy during general anesthesia. Nine patients without SCI served as controls post hoc. Anesthesia was induced with thiopental, and sevoflurane concentrations in 50% nitrous oxide were adjusted to maintain a Bispectral Index of 40–50. When a patient developed AHR during bladder distension, the target sevoflurane concentration was maintained for at least 10 min, and then the procedure was resumed. Systolic blood pressure, heart rate, and Bispectral Index as well as plasma concentrations of catecholamines and arginine vasopressin were measured before and during the bladder distension. Each target concentration was determined by the up-and-down method based on changes (15% increase or more) of systolic blood pressure in response to bladder distension.

Results: In SCI, systolic pressure increased by 67 ± 33 mmHg, whereas heart rate decreased by 13 ± 8 beats/min during the first trial (P < 0.01). The hypertensive event was associated with increases of norepinephrine concentrations, but not of epinephrine or vasopressin concentrations. Systolic pressure, heart rate, and norepinephrine concentrations did not change significantly in the control patients. The end-tidal concentrations of sevoflurane to prevent AHR were EC50 of 3.12% and EC95 of 3.83%.

Conclusion: The EC95 for sevoflurane in 50% nitrous oxide to block AHR during transurethral litholapaxy in patients with SCI was 3.83%.

AUTONOMIC hyperreflexia (AHR) is a life-threatening emergency during which uncontrolled sympathetic hyperactivity occurs in patients with spinal cord injury (SCI) above the splanchnic outflow, usually at the level of T6.1,2 Various noxious and nonnoxious stimuli below the level of injury, such as distension of the bladder or bowel, uterine contractions during obstetric delivery, and surgery, may trigger the development of AHR.3,4 Of major concern is that the hypertension associated with AHR may lead to intracranial and retinal hemorrhage, seizures, myocardial infarction, coma, and death.5 Moreover, episodes of AHR are commonly associated with not only mild electrocardiographic changes, but also atrial fibrillation and cardiac arrest.6,7 Several pharmacologic agents, including intravenous ganglion blockers, hydralazine, α-adrenergic receptor blockers, calcium channel blockers, or nitrates, have been used in the prevention or control of AHR. Nevertheless, they are not always safe, convenient, or predictable.

The development of intraoperative AHR and hypertension may be prevented either by general anesthesia, which blunts autonomic reflexes, or regional anesthesia (spinal or epidural), which blocks afferent and autonomic efferent neural impulses.8–11 However, the depth of inhalation anesthesia required to block AHR has not been determined in SCI patients. The current study was undertaken to determine the end-tidal concentrations of sevoflurane needed to block AHR in SCI patients undergoing transurethral litholapaxy.

Materials and Methods

The protocol of the study was approved by the Chonnam National University Hospital Ethics Committee, Gwangju, Korea. Written informed consent was obtained from each patient. In patients who were unable to give consents because of injury, their consent was obtained from the next of kin. Twenty-eight patients with American Society of Anesthesiologists physical status II and with chronic, clinically complete traumatic high SCI scheduled to undergo transurethral litholapaxy with general anesthesia were studied. Nine age-matched, nondisabled patients undergoing cystoscopic procedures were enrolled post hoc to serve as controls. Patients receiving medication that would influence autonomic or cardiovascular responses to surgery were excluded, as were those whose time interval from injury to operation was less than 1 month. The level and completeness of SCI were assessed in accord with the 1996 American Spinal Injury Association standards.12

All patients were premedicated with midazolam (0.1 mg/kg, orally) 60 min before induction of anesthesia. Upon arrival in the operating room, a 20-gauge catheter was inserted into a radial artery connected to a pressure transducer (Deltran; Utah Medical Products, Midvale, UT) to continuously monitor blood pressure and to take blood samples. The Bispectral Index (BIS) was displayed...
continuously using an Aspect A-2000 BIS® monitor (BIS® XP, software version 3.31; Aspect Medical Systems, Natick, MA) using standard BIS forehead strips. Each patient received 500 ml colloid solution (6% hydroxyethyl starch) over 15–20 min to prevent hypotension before the procedure, and approximately 10 ml · kg⁻¹ · h⁻¹ Ringer’s lactate solution throughout the study. Anesthesia was induced with 5–7 mg/kg intravenous thiopental, followed by 0.12 mg/kg intravenous vecuronium after full preoxygenation. Direct laryngoscopy and tracheal intubation were performed when neuromuscular block had been achieved. The anesthesia was maintained with 2% sevoflurane (inspired) and 50% nitrous oxide in oxygen for up to 5 min. The inspired concentration of sevoflurane was then adjusted to achieve an initial BIS reading of 40–50. All patients were mechanically ventilated to maintain the end-tidal carbon dioxide tension between 35 and 40 mmHg. Neuromuscular blockade was carefully controlled by train-of-four monitoring, and additional boluses of vecuronium were administered to maintain one response at the orbicularis oculi during the procedure. Routine monitoring included invasive measurement of arterial pressure, heart rate (HR), and rhythm using a five-lead electrocardiogram, and oxygen saturation by pulse oximetry. The end-tidal concentrations of carbon dioxide, sevoflurane, and nitrous oxide were measured using a gas analyzer (Capnomac Ultima; Datex, Helsinki, Finland).

When the BIS and end-tidal sevoflurane concentration were stable for at least 20 min, the procedure (pretest) was started in which a cystoscope was inserted into the bladder and a 1.5% glycine solution was slowly infused. In patients in whom signs of AHR were evident during first trials, the bladder filling was immediately terminated. When the systolic blood pressure (SBP) exceeded 180 mmHg, the inspired sevoflurane concentration was increased to control the autonomic response. AHR was defined as an increase of SBP 20–40 mmHg greater than the value measured 1 min before the procedure in response to bladder distension during the first trial.¹³ After a rest period of 10–20 min during which the hemodynamics returned to baseline, the target end-tidal concentration of sevoflurane was maintained for at least 10 min, and then the procedure was resumed (second trial). The target sevoflurane concentrations were determined by the response of the preceding patient using an up-and-down sequential-allocation technique.¹⁴ The first patient received 2.0% end-tidal concentration of sevoflurane (corresponding to 1.62 minimum alveolar concentration [MAC] including 50% nitrous oxide when adjusted for age¹⁵). When the patient response was positive (an increase in SBP of ≥ 15% above the value measured 1 min before the procedure), the end-tidal concentration for the next patient was increased by 0.3%. If the response was negative (SBP increased by < 15%), the end-tidal concentration of sevoflurane for the next patient was decreased by 0.3%. The positive response was defined as an increase in SBP of 15% or greater,¹⁶,¹⁷ and subsequent corrections of 0.3% end-tidal concentration of sevoflurane were made per the up-and-down method, which was based on SDs of anesthetic concentrations for blockade of AHR in our preliminary study.

If hypotension occurred (mean arterial pressure < 65 mmHg), blood pressure was restored by increasing the intravenous fluid rate. If the patient did not respond to fluid therapy (mean arterial pressure decreased less than 45 mmHg even after a fluid challenge of 300 ml lactated Ringer’s solution), the patient was withdrawn from the study, and the same concentration of sevoflurane was administered to the next patient enrolled. At the completion of surgery, the inhaled anesthetic was discontinued, and residual neuromuscular block was antagonized with atropine and neostigmine. All anesthetic procedures were conducted by an anesthesiologist, and data were assessed by a person unaware of the anesthetic concentrations used.

Systolic blood pressure, HR, and BIS values were recorded before induction of anesthesia, at 1 min before commencement of bladder filling and at 1-min intervals thereafter for up to 5 min after the end of bladder emptying. During bladder distension, these parameters were defined as their values measured at the time of peak pressure response throughout the period of bladder filling. Arterial blood was sampled before induction of anesthesia, at 1 min before, and at the end of the bladder distension when SBP reached maximum during the first trial. The samples were collected into prechilled tubes containing EDTA–Na and were immediately centrifuged at 3,000 rpm for 10 min at 4°C. The plasma was stored at −70°C until assayed. Concentrations of norepinephrine and epinephrine were measured in duplicates using high-pressure liquid chromatography. The assay sensitivity for each catecholamine was 10 pg/ml, and the within-run precision coefficients of variation were 13.5% and 14.2% for norepinephrine and epinephrine, respectively.¹⁸ Concentrations of arginine vasopressin were determined by radioimmunoassay (DSL-2000 SP Aktive® Cortisol; Diagnostic System Laboratories, Sinsheim, Germany).

Statistical Analysis
All results are presented as mean ± SD. Sex was analyzed using the Fisher exact test. The other demographic data were compared using an unpaired Student t test. Serial changes in hemodynamic, hormonal, and BIS data during the first trials were analyzed using a two-way analysis of variance with repeated measures, with time as within factor, group (SCI/control) as between factor, and an interaction between time and group. A Scheffé test was used when a significant difference was indicated with analysis of variance. EC₅₀ values (50% effec-
Table 1. Demographic Data in Spinal Cord–injured and Control Patients

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 9)</th>
<th>SCI (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F</td>
<td>8/1</td>
<td>26/2</td>
</tr>
<tr>
<td>Age, yr</td>
<td>46 ± 5</td>
<td>43 ± 9</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>65 ± 17</td>
<td>61 ± 13</td>
</tr>
<tr>
<td>Height, cm</td>
<td>171 ± 5</td>
<td>172 ± 4</td>
</tr>
<tr>
<td>Postinjury, months</td>
<td>—</td>
<td>95 ± 55</td>
</tr>
<tr>
<td>Hemoglobin, g/dl</td>
<td>14.6 ± 1.4</td>
<td>12.6 ± 1.8*</td>
</tr>
<tr>
<td>Duration of procedure, min</td>
<td>59 ± 12</td>
<td>64 ± 26</td>
</tr>
</tbody>
</table>

Values are mean ± SD or number of patients.
* P < 0.001 vs. uninjured patients; † P < 0.001 vs. control group.
Control = uninjured patients; SCI = spinal cord–injured patients.

Results

Demographic data and duration of procedure were comparable between the SCI and control groups (table 1). In the SCI group, hemoglobin levels (12.6 ± 1.8 vs. 14.6 ± 1.4 g/dl; P < 0.01) and end-tidal sevoflurane concentrations (1.02 ± 0.33 vs. 1.38 ± 0.29%; P < 0.01) required to maintain BIS at 40–50 during the first trial were less than in the control group. Twenty-eight of the 32 SCI patients initially enrolled completed the investigation. Three patients were excluded because they did not develop AHR in response to bladder distension, and a fourth was excluded because his mean arterial pressure during the administration of target concentration of anesthetics decreased to less than 45 mmHg despite fluid therapy. Of the 28 patients, the level of lesion was between C4 and T6, with 22 above T1.

Table 2 shows SBP, HR, BIS, and plasma hormone concentrations in the first trial. Before anesthesia induction, norepinephrine and epinephrine concentrations were significantly less in the SCI group than in the control group (P < 0.05), whereas SBP, HR, and BIS did not differ between the groups. SBP and BIS decreased after induction (P < 0.01) in both groups, although the between-group differences were not statistically significant. HR and plasma concentrations of norepinephrine and vasopressin did not change in either group. In response to bladder distension, SBP increased significantly by 73 ± 4% (67 ± 33 mmHg), whereas HR decreased by 18 ± 10% (13 ± 8 beats/min) during the first episode of AHR in the SCI group. The hemodynamic response was associated with an increase of plasma norepinephrine concentrations from 86 ± 71 to 158 ± 133 pg/ml (P < 0.01; fig. 1). Of the 28 SCI patients, SBP was greater than 160 mmHg in 11 (39%) during the first trial, being even greater than 200 mmHg in 6. Nine patients (32%) whose SBP was greater than 180 mmHg received additional sevoflurane to treat hypertension. SBP and HR returned to approximately pre-AHR levels after bladder emptying. In the control group, SBP, HR, and plasma concentrations of norepinephrine did not change during bladder distension. Repeated-measures analysis of variance showed a significant interaction between groups over time for SBP, HR, and norepinephrine and epinephrine concentrations. During bladder distension, SBP was significantly less, HR greater, and norepinephrine concentrations similar when compared with those in the SCI group. Plasma epinephrine and vasopressin concentrations did not change significantly during bladder distension in either group.

Figure 2 shows individual responses to bladder distension according to the up-and-down sequence during the second trial. The sevoflurane concentration required to block AHR in 50% patients was 3.12 ± 0.29% (95%
confidence interval, 2.89–3.34%), where BIS decreased to 20

EC50 and EC95 values of sevoflurane for the blockade of AHR by logistic analyses were 3.09% (95% confidence interval, 2.79–3.60%) and 3.83% (3.44–7.26%), respectively, in the presence of 50% nitrous oxide. Based on the MAC of sevoflurane described in the age range of the study population16 and the concomitant use of 50% nitrous oxide, the combined EC50 and EC95 of sevoflurane for AHR blockade expressed as a multiple of the MAC were 2.24 and 2.66, respectively. EC50 values calculated by logistic analysis were comparable with those determined by up-and-down methodology.

**Discussion**

Our study demonstrated that the end-tidal concentrations of sevoflurane to block AHR in SCI patients undergoing transurethral litholapaxy were EC50 of 3.12% and EC95 of 3.83%, where BIS decreased to 20 ± 18. The blockade of AHR in patients with complete SCI support the previous notion that subcortical structures, including the spinal cord, are major sites of action of inhaled anesthetics to suppress cardiovascular responses to noxious stimuli.19,20

The end-tidal concentrations of sevoflurane that block adrenergic responses to surgical incision have been determined in patients undergoing surgery as 1.32 MAC with the contribution of 0.55 MAC nitrous oxide in one study,16 and 1.90 MAC with the contribution of 0.70 MAC nitrous oxide in another.17 In the current study, the sevoflurane concentration that blocked AHR was 1.77 MAC in 0.49 MAC nitrous oxide. These findings indicate that a deep level of anesthesia is required to block AHR, although the conditions and criteria determining anesthetic requirements differed among the studies. In contrast, sevoflurane concentrations required to maintain BIS at 40–50 in the SCI patients were significantly less than in the control group (1.02% vs. 1.38%; P < 0.01), but consistent with published data.21 Although the influence of SCI on MAC values remains controversial in animal studies,22,23 our study suggests that the anesthetic requirement to produce BIS less than 50 may be reduced, whereas the requirement to block AHR remains high in SCI patients.

The level of sevoflurane anesthesia required to block AHR decreased mean arterial blood pressure to 56 ± 8 mmHg despite the fluid therapy in every patient of SCI. Because its low blood gas partition coefficient allows rapid adjustment of depth, sevoflurane might be used to acutely increase the concentration immediately before the bladder distension to block AHR in SCI patients. Alternatively, combinations of sevoflurane with other adjuncts (nitrous oxide or opioids) may be better propositions, because they may synergistically decrease the concentrations of inhaled anesthetics required to produce immobility or to prevent autonomic responses in the face of noxious stimulation.16,17,24,25

During the first trial, 11 (39%) of 28 SCI patients developed hypertension (SBP ≥ 160 mmHg). SBP was greater than 200 mmHg in 6 patients (21%), in which the blood pressure increase was occasionally alarming despite the general anesthesia. For example, SBP was 217 mmHg and the pressure response persisted for more than 10 min in a 43-yr-old man with quadriplegia caused by a traumatic fracture dislocation at the C5–C6 level when he was aged 41 years. Hypertension, albeit tran-
sient, may be hazardous, particularly in those with limited coronary or myocardial reserve, hypertension, or cerebrovascular diseases. Individuals with SCI are particularly at an increased cardiovascular risk. Caution should be exercised when inhaled anesthetics are used to prevent or treat AHR in patients with a high SCI.

The hypertensive response to bladder distension was associated with a significant increase of plasma concentrations of norepinephrine, indicating an enhanced sympathetic activity. This finding is consistent with that in a previous case report that demonstrated a paroxysmal neurogenic hypertension in a quadriplegic man, and that of Maizorov et al., who found a marked increase in renal sympathetic activity in a rat T5 spinal injury model. Moreover, disruption of descending spinal pathways may result in functional and morphologic changes of the sympathetic nervous system caudal to SCI. In fact, postinjury dendrite degradation of sympathetic preganglionic neurons, followed by signs of sprouting and new synapse formation in the injured medulla, has been demonstrated in SCI rats. Such spinal remodeling may underlie a marked capacity for peripheral afferent stimulation of sympathetic nervous system arising after SCI.

However, the peak norepinephrine concentration reached during the episode of AHR in the SCI did not exceed that in the control group. An exogenous infusion of norepinephrine to produce similar blood pressure changes in quadriplegic subjects required many times greater plasma levels of norepinephrine than those associated with AHR. The augmented norepinephrine response may be attributed to the loss of descending inhibitory control, peripheral α-adrenoceptor hyperresponsiveness, or decreased reuptake of catecholamines. On the other hand, plasma epinephrine and vasopressin concentrations were not changed, being consistent with a previous study. These hormones may have a minimal role in mediating cardiovascular changes during AHR.

Although one previous study demonstrated that AHR may occur as early as the fourth postinjury day in patients with severe cervical SCI, it generally occurs in chronic stages of SCI. It takes at least 1 month to develop the malignant hypertention of AHR. Therefore, we excluded those patients whose time interval from injury to operation was less than 1 month. Nevertheless, 3 of 32 SCI patients did not develop AHR during the first trial where the anesthetic concentration was adjusted to maintain BIS at 40–50. It is unlikely that this anesthetic concentration prevented the occurrence of AHR, although it may avert a severe crisis, because the EC50 (3.12%) of sevoflurane was much greater than the anesthetic concentration (1.02 ± 0.33%) used during the first trial. It is also true that not all patients with lesions at T6 or above exhibit AHR in response to stimulation below that level.

Our study has a few limitations. First, an inhaled anesthetic requirement is generally quantified by either a lack of response in terms of movement (MAC) or by a lack of hemodynamic responses (MAC needed to block adrenergic response). However, in patients with SCI, both of these responses are altered, i.e., a paralyzed patient does not move even in the absence of adequate anesthe sia, and abnormal spinal reflexes dominate the cardiovascular control. A BIS value less than 50 indicates an adequate depth of hypnosis to prevent recall for a variety of clinically used anesthetic agents. Therefore, we used the amount of sevoflurane required to maintain a BIS of 40–50 irrespective of the adequateness of anesthesia during the first trial. Second, the up-and-down method of Dixon assumes that each measurement in a subject is independent and not correlated with any other measurements. A noxious stimulus (bladder distension) was applied twice to the same subject, so that errors into the results may occur due to intrasubject correlations and tolerance or sensitization. However, the preliminary study using two patients showed persistent AHR (i.e., not self-extinguished) despite repeated bladder distensions during the procedure that lasted more than 1 h. Third, we did not measure plasma concentrations of catecholamine and vasopressin during the second trial. Had the measurements been repeated, it would have reinforced our results. We did measure the concentrations at the beginning of the second trial; however, the norepinephrine concentrations just before bladder distension were greater compared with those at baseline of the first trial, so we could not distinguish the small changes of norepinephrine elicited by AHR. The greater norepinephrine concentrations may be related to the use of high concentrations of sevoflurane or a prolonged norepinephrine response.

In conclusion, transurethral litholapaxy can be accomplished without development of AHR at end-tidal sevoflurane concentrations of 3.12% and 3.83% in 50% and 95% of SCI patients, respectively, when administered with 50% nitrous oxide.

References

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