The Effect of Chronic Opioid Use on End-Tidal Concentration of Sevoflurane Necessary to Maintain a Bispectral Index Below 50: A Prospective, Single-Blind Study

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BACKGROUND: Opioid analgesics decrease the minimum alveolar concentration of inhalation agents during the acute phase response. However, the effect of chronic opioid exposure on minimum alveolar concentration of inhalation agents remains unknown. This study aimed to determine the concentration of sevoflurane necessary to maintain a bispectral index (BIS) <50 ($SEVO_{BIS50}$) in patients with chronic opioid use compared with those naïve to opioid use.

METHODS: We included chronic opioid users who received a stable dose of oral morphine of at least 60 mg/d according to the morphine equivalent daily dose for at least 4 weeks and opioid-naïve patients. General anesthesia that included thiopental, vecuronium, and sevoflurane in oxygen was administered to all patients. Anesthesia was maintained using predetermined end-tidal sevoflurane concentrations. Fifteen minutes after achieving the determined end-tidal sevoflurane concentration through closed circuit anesthesia, BIS was measured for 1 minute in both groups. $SEVO_{BIS50}$ was determined using Dixon's up–down method and probit analysis.

RESULTS: Nineteen and 18 patients from the chronic opioid and control groups, respectively, were included in the final analysis. $SEVO_{BIS50}$values for the chronic opioid and control patients were 0.84 (95% confidence interval, 0.58–1.11) and 1.18 (95% confidence interval, 0.96–1.40), respectively (P = .0346).

CONCLUSIONS: Our results suggest that the end-tidal concentration of sevoflurane necessary to maintain a BIS <50 is lower for chronic opioid users than for opioid-naïve patients. (Anesth Analg 2017;125:156–61)

Currently, opioids are the most powerful analgesics available for pain control used in medicine. They are widely used not only to control both cancer-related and unrelated pain, but are also used for anesthesia and sedation.[1] As the survival rate of patients with cancer has increased, use of opioids to relieve pain for cancer survivors has also escalated. The number of patients who use opioids to control pain unrelated to cancer has also increased. Therefore, the likelihood of encountering chronic opioid users in clinical anesthetic practice is intensified, and it will continue to grow along with the increase in prescriptions of opioid analgesics.[2]

When opioid analgesics are used in general anesthesia, they lower the minimum alveolar concentration (MAC) of inhalation agents.[3] In addition, anesthesiologists commonly use balanced anesthesia, which utilizes both opioids and inhalation agents for general anesthesia, in recent years.[4] Therefore, the impact of opioids on MAC of inhalation agents during surgery has been well studied. However, the impact of chronic opioid use on MAC has not been studied to date. Accordingly, there are no guidelines or helpful information regarding general anesthesia with inhalation agents for chronic opioid users.

The bispectral index (BIS) is often used to determine the level of consciousness under anesthesia, and a previous study revealed an inverse correlation between BIS and the end-tidal concentration of sevoflurane (sevoET).[5] In addition, with regard to patients who receive general anesthesia, an appropriate BIS target is at or <50.[6] In a previous study, the concentration of sevoflurane needed to maintain BIS <50 ($SEVO_{BIS50}$) was 0.97% (95% confidence interval [CI], 0.89–1.05) in patients between 41 and 59 years old.[7]

On the basis of this information, we conducted this study to assess $SEVO_{BIS50}$ in chronic opioid users and opioid-naïve patients and determine the differences in demand during general anesthesia using inhalation agents. We hypothesized that the $SEVO_{BIS50}$ values are significantly different between chronic opioid users and opioid-naïve patients.

METHODS

This study was conducted with approval from the institutional review board of the National Cancer Center Korea (NCC2015-0147) and is registered at ClinicalTrials.gov (October 16, 2015; registration number: NCT02582437; principal investigator, D. H. Kim). All patients provided written informed consent before enrollment. Patients aged 41 to 69 years who were classified as American Society

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of Anesthesiologists class I or II, who were scheduled to undergo elective surgery under general anesthesia at the National Cancer Center in Korea from October 17, 2015, to December 31, 2015, were included.

Patients who fulfilled the inclusion criteria were divided into groups. Those who had received a stable daily dose of over 60 mg of oral morphine according to the standard morphine equivalent daily dose for at least 4 weeks were classified as the chronic opioid group, and those with no history of opioid use were classified as the control group. The standard for opioid tolerance in previous studies was 25 μg/h transdermal fentanyl, 30 mg/day oxycodone, 8 mg/day hydromorphone, or an equivalent, stable daily dose of another opioid.[8] The exclusion criteria were as follows: use of drugs that may affect MAC of sevoflurane (barbiturates, benzodiazepines, chlorpromazine, hydroxyzine, verapamil, or marijuana) within the 4 weeks before surgery, acute alcohol abuse, chronic alcohol abuse, contraindications for sevoflurane use, obesity (body mass index >30 kg/m^2), craniotomy, body temperature >37.2°C, or anticipation of difficult intubation. In addition, patients with ≥25% changes in heart rate or mean blood pressure, those whose oxygen saturation decreased to <95%, and those who required drugs other than sevoflurane during anesthesia were excluded from the final analysis.

All patients were admitted to the operating room without prior medication. Noninvasive blood pressure, electrocardiograms, pulse, oxygen saturation, and skin temperature were monitored. For BIS monitoring (BIS; Covidien, Mansfield, MA), a single-use, disposable BIS sensor was applied to the forehead after the skin was wiped with alcohol swabs. All patients were preoxygenated with 100% oxygen for 5 minutes. Anesthesia was induced with 5 mg/kg thiopental. After confirming loss of consciousness, neuromuscular block was achieved with 0.15 mg/kg vecuronium. Subsequently, the trachea was intubated with a cuffed endotracheal tube, and induction was completed using the semiclosed circuit Zeus anesthesia machine (Dräger, Lübeck, Germany) with a total oxygen gas flow of 6 L/min and a sevoflurane concentration of 5%. The end-tidal carbon dioxide concentration and sevoET were measured using the Zeus gas analyzer. After endotracheal intubation, we waited because of a change in the mode of the automated Zeus closed circuit anesthesia (CCA) machine until the predetermined sevoflurane concentration was achieved. To minimize bias, the clinicians who performed the induction were asked to leave the operating room after intubation. Then, another anesthesiologist who was blinded to group allocation monitored BIS and continued the clinical trial.

The predetermined consistent sevoET was confirmed and maintained for 15 minutes to ensure equilibrium cerebral anesthetic partial pressure by the automated Zeus CCA system. Subsequently, BIS values were obtained for 1 minute at 10-second intervals. If the average of the 5 values was <50, we decreased the value by 0.2% for the next patient, and if the average was >50, we increased the value by 0.2% for the next patient. The starting point for both groups was in accordance with the results of a previous study, in which MAC_{BIS50} was 0.97% for patients aged 41 to 69 years with a sevoET set to 1.0%.[7] The maximum decrease in sevoET was maintained at 0.3% to avoid waking the patient during the measurement period. During the measurement period, end-tidal carbon dioxide concentration was maintained at 30 to 35 mm Hg.

Furthermore, volume-controlled ventilation was administered through the CCA system. The fraction of inspired oxygen was set at 0.5. To prevent hypotension, 10 mL·kg^{-1}·hour^{-1} of lactated Ringer's solution was infused throughout the measurement period. In this clinical trial, all measurements were recorded before surgical stimulation.

Data sampling was continued until approximately 10 changes in direction and 6 midpoints of concentration pairs were obtained (19 and 18 patients in each group), which are known requirements to achieve reliable MAC values using Dixon's up-and-down method.[9,10]

Statistical Analysis

Patient characteristics were compared between the 2 groups by Wilcoxon rank-sum test and 2-sample *t* test for continuous variables and by Fisher exact test and χ^2 test for categorical variables as appropriate.

The values for $SEVO_{BIS50}$ of sevoflurane were derived by calculating the midpoint concentration of consecutive patients manifesting a crossover pair from BIS <50 to BIS >50 according to Dixon's up-and-down technique.[7,9,11] A crossover pair is 2 consecutive patients who have concentrations of BIS <50 and BIS >50. The calculated $SEVO_{BIS50}$ values for sevoflurane between the 2 groups were compared using the Wilcoxon rank-sum test.

$SEVO_{BIS50}$ values were also calculated using back-up probit analysis. Probit analysis was performed using SAS version 9.4 software (SAS Institute, Cary, NC). The calculated $SEVO_{BIS50}$ values for sevoflurane from both groups were compared using the 2-sample *t* test. *P* values <.05 were considered statistically significant.

Although our sample size was determined on the basis of the results of previous studies (approximately 10 changes in direction and 6 midpoints of concentration pairs),[9,10] we performed additional analyses to confirm the statistical power of our sample size. Power analysis on the assumption of a type I error of 0.05 and a power of 0.80 to detect a difference of 0.2% in $SEVO_{BIS50}$ showed that 21 patients were required for each of the 2 groups. The same power analysis to detect a difference of 0.3% in $SEVO_{BIS50}$ showed that 10 patients were required for each of the 2 groups.

RESULTS

Among patients who provided written informed consent, 20 chronic opioid users and 19 opioid-naïve patients who met the inclusion criteria were sequentially selected. Subsequently, 1 patient who developed severe bradycardia and ventricular premature complexes during the measurement period was excluded from the chronic opioid group. Another patient was excluded from the control group because of a decrease in the mean blood pressure by more than 25% before the induction of anesthesia despite appropriate crystalloid hydration, which necessitated the use of a vasopressor.

In total, 37 patients were included in the final analysis, including 19 in the chronic opioid group and 18 in the control group. Table 1 shows the baseline characteristics of the

Table 1. Patient Characteristics

	Chronic Opioid (N = 19)	Control (N = 18)	
	Mean ± SD (minimum, maximum)	Mean ± SD (minimum, maximum)	*P*
Age (y)	57.4 ± 7.2 (48, 69)	57.3 ± 7.9 (45, 69)	.96[a]
BMI (kg/m^2)	22.4 ± 2.1 (18.6, 25.9)	23.7 ± 2.8 (17.9, 28.7)	.12[b]
Height (cm)	167.8 ± 5.2 (158.5, 176.4)	166.3 ± 7.1 (149.5, 177.7)	.48[b]
Sex (%)			.69[c]
Male	16 (84.21)	14 (77.78)	…
Female	3 (15.79)	4 (22.22)	…
ASA class			.64[d]
1	6 (31.58)	7 (38.89)	…
2	13 (68.42)	11 (61.11)	…
$Etco_2$ (15 min)	31.9 ± 1.5 (29, 34)	32.2 ± 2.0 (29, 36)	.64[b]
MEDD (mg)	100 ± 58.7 (60, 300)	…	…
Time from last opioid use to anesthesia (min)	507.3 ± 342.8 (65, 1170)	…	…
Time from last opioid use to anesthesia (min) (exclusion 5 patients who use last opioid 4 h before anesthesia)	651.4 ± 277.7 (250, 1170)	…	…

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; $Etco_2$, end-tidal carbon dioxide; MEDD, morphine equivalent daily dose; SD, standard deviation.

[a]Wilcoxon rank-sum test.

[b]Two-sample *t* test.

[c]Fisher exact test.

[d]χ^2 test.

patients. There were no statistically significant differences between groups in baseline characteristics.

Because the number of participants in each group was relatively small, patients with similar age, sex, and body mass index were selected in the 2 groups. Therefore, there were no clinically significant differences between the groups commensurate with the *P* values. The individual patients who underwent $SEVO_{BIS50}$ measurements according to Dixon's up-and-down method are presented in Figure 1.

Table 2 presents the $SEVO_{BIS50}$ values calculated according to Dixon's up-and-down method and probit analysis. $SEVO_{BIS50}$ values were significantly different between the chronic opioid and control groups (0.84% vs 1.18%, P = .0346). Similar results were obtained using probit analysis with values of 0.83% (95% CI, 0.54–1.18) and 1.19% (95% CI, 0.86–1.51), respectively. The difference in $SEVO_{BIS50}$values between the 2 groups was 0.36% (95% CI, 0.14–0.58%) by probit analysis. In addition, with the exclusion of 5 chronic opioid users who used opioids within 4 hours before induction, $SEVO_{BIS50}$ values for the chronic opioid and control groups were 0.76% vs 1.18% (P = .0397). Similar results were obtained using probit analysis with values of 0.84% (95% CI, 0.57–1.23) and 1.19 (95% CI, 0.92–1.46), respectively. The difference in $SEVO_{BIS50}$ values between the 2 groups was 0.32% (95% CI, 0.10%–0.54%) by probit analysis (Table 3). The dose–response curves of probit analysis of individual sevoET values and the probability of BIS <50 are shown in Figure 2.

DISCUSSION

Our results confirm that the $SEVO_{BIS50}$ values are lower in chronic opioid users than in opioid-naïve patients. $SEVO_{BIS50}$ is different from the classic MAC, which requires a standard stimulus-like surgical incision. BIS assesses suppression of brain activity underlying awareness and (perhaps) recall during anesthesia. Classic MAC assesses responsiveness to painful stimuli, which encompasses hypnosis, analgesia, and immobilization. Both phenomena use different but overlapping anatomic and neurophysiological pathways. For example, immobilization, the phenomenon measured by classic MAC, is actually mediated in large part by anesthetic actions in the spinal cord, whereas BIS is associated only with brain activity. The BIS50 titration end point has been studied previously.[6,12] BIS <50 is needed for loss of consciousness and recall[6] and can be used as a predictor for movement during surgical incision.[12] In previous studies, $SEVO_{BIS50}$ was approximately 60% of the classic MAC in all age groups, whereas MAC_{awake} was approximately one-third of the classic MAC.[7,13]

Because our result required measuring BIS without surgical stimulation, the impairment of neurocognitive function in chronic opioid users must be considered a possible reason for this outcome.[14] Although the effects of chronic opioid use are not well known, it has been reported to affect some neurologic receptors. In a rat study by Taylor et al,[15] GABAergic activity in the ventral tegmental area of opioid-tolerant rats changed through brain-derived neurotrophic factors and activated microglia. The authors concluded that chronic opioid exposure leads to augmentation of GABA-A receptors that mediate the GABAergic tone through the ventral tegmental area. In our experiments, we used sevoflurane, which mediates many of its effects in the brain through engagement of GABA-A receptors.[16] Therefore, there is a possibility that lower sevoflurane amounts are required in the chronic opioid group to achieve the same degree of unconsciousness as those in the control group.

In addition, our results differed from classic MAC studies because anesthetic action of sevoflurane on the spinal cord was not determined in this study. Some studies reported that chronic opioids cause neuromodulation in the spinal cord and development of opioid-induced hyperalgesia.[17,18] Furthermore, 2 studies in rats showed that opioid-induced hyperalgesia can increase the MAC of sevoflurane.[19,20] As a result, chronic opioid use appears to differentially affect the level of consciousness and spinal cord responses to surgical stimulation.

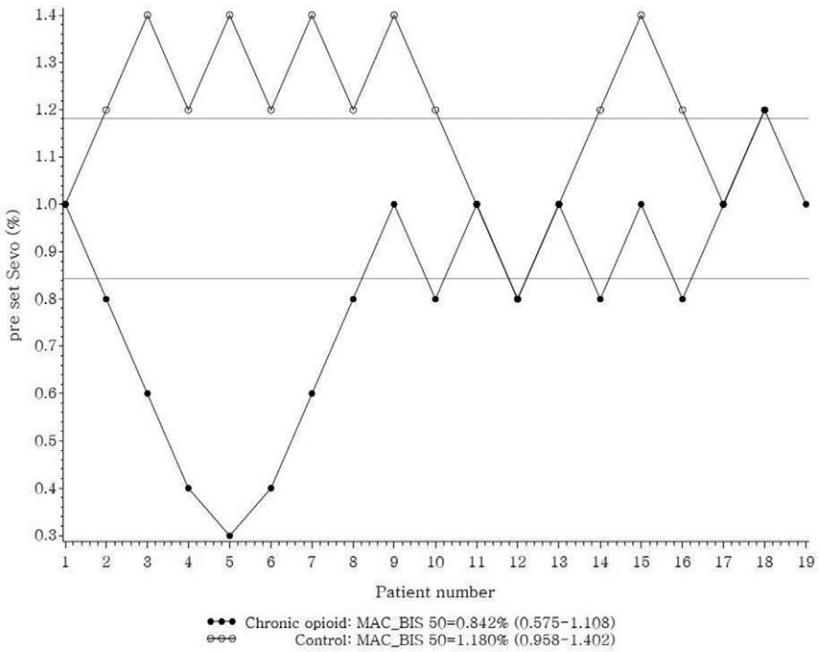

Figure 1. Sequence of individual patients in chronic opioid and control groups receiving sevoflurane at predetermined end-tidal concentrations. End-tidal sevoflurane concentration in chronic opioid and control groups for maintaining BIS <50 were calculated by the up-and-down method and shown as horizontal bars. BIS indicates bispectral index.

Table 2. End-Tidal Sevoflurane Concentration for Maintaining BIS <50 ($SEVO_{BIS50}$)

Method	Chronic Opioid (N = 19)	Control (N = 18)	Difference	*P*
Up-and-down method	0.84	1.18		.0346[a]
Probit analysis (95% CI)	0.83 (0.54–1.18)	1.19 (0.86–1.51)	0.36 (0.14–0.58)	.0017[b]

All values are expressed as end-tidal percentage of sevoflurane.
Abbreviations: BIS, bispectral index; CI, confidence interval; $SEVO_{BIS50}$, sevoflurane needed to maintain BIS <50.
[a]Wilcoxon rank-sum test.
[b]Two-sample *t* test.

Table 3. End-Tidal Sevoflurane Concentration for Maintaining BIS <50 ($SEVO_{BIS50}$) for Patients Having At Least 4 h After Opioid Use Until Anesthesia

Method	Chronic Opioid (N = 14)	Control (N = 18)	Difference	*P*
Up-and-down method	0.76	1.18		.0397[a]
Probit analysis (95% CI)	0.84 (0.57–1.23)	1.19 (0.92–1.46)	0.32 (0.10–0.54)	.0053[b]

All values are expressed as end-tidal percentage of sevoflurane.
Abbreviations: BIS, bispectral index; CI, confidence interval; $SEVO_{BIS50}$, sevoflurane needed to maintain BIS <50.
[a]Wilcoxon rank-sum test.
[b]Two-sample *t* test.

Another important potential limitation for our study is the duration between the last opioid administration and anesthesia induction in the chronic opioid group. Ideally, we would have prohibited all opioid ingestion before induction, but ethical considerations did not allow for this. We had to permit the last opioid use to prevent withdrawal symptoms even if subclinical. Table 1 displays the time from last opioid administration to induction of anesthesia (mean ± standard deviation: 507 ± 342.8 minutes). To exclude the effect of opioids in the acute phase, additional subgroup analysis was performed in this study. Five patients who used opioids less than 4 hours before induction were excluded in additional analysis. After exclusion of the 5 patients, time from last opioid use to anesthesia administration was 651.4 ± 277.7 minutes (mean ± standard deviation; minimum–maximum: 250–1170 minutes). The result was similar to our main outcome, and the $SEVO_{BIS50}$ value of the chronic use group was still lower than that of the opioid-naïve group.

In addition, statistical analysis using small sample sizes to obtain more correct $SEVO_{BIS50}$ values is an important issue in our study. As a result of the relatively small number of participants in each group, the 95% CIs for estimation of the sevoflurane concentration for maintaining a BIS <50 were rather wide (0.54–1.12 for chronic opioid and 0.86–1.51 for control patients). The true sevoflurane concentration for maintaining a BIS <50 for each group would be expected to fall within these intervals with approximate 95% probability. Likewise, by definition, there is a 95% chance that the true difference in $SEVO_{BIS50}$ values between the 2 groups would be expected to fall within 0.14% to 0.58% by probit analysis.

In comparison to previous studies involving $SEVO_{BIS50}$, our study has an advantage. We utilized the Zeus CCA system, which does not allow fresh gas flow to increase, as observed in semiclosed circuit systems. Furthermore, it delivers sevoflurane through a pure vapor injection. In

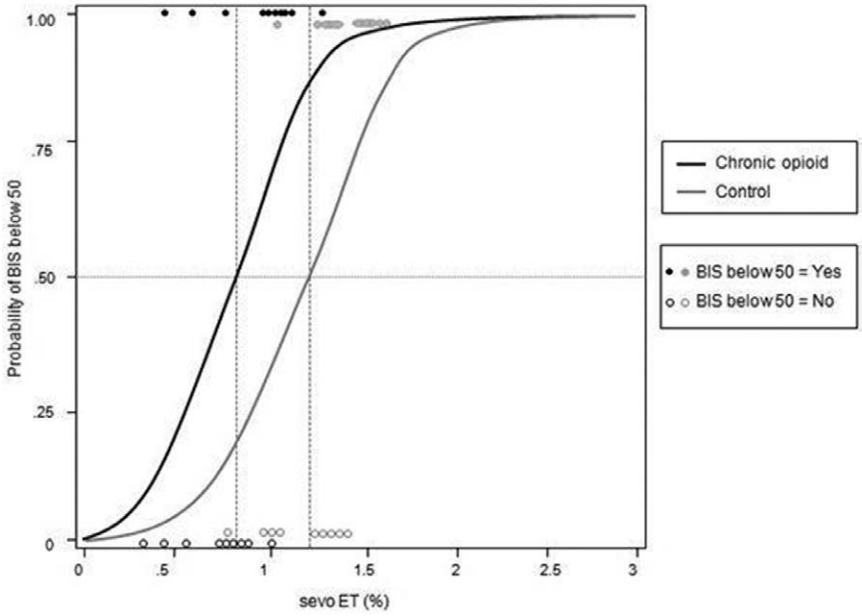

Figure 2. Dose–response curves for sevoflurane plotted from probit analysis of individual end-tidal concentrations and the probability of a BIS value <50. $SEVO_{BIS50}$s in chronic opioid and control groups estimated with probit analysis were 0.83% (95% confidence interval, 0.54%–1.18%) and 1.19% (95% confidence interval, 0.86%–1.51%). BIS indicates bispectral index; $SEVO_{BIS50}$, sevoflurane needed to maintain BIS <50.

addition, the delivered sevoflurane is calibrated according to a predetermined sevoET value by considering the base of pharmacokinetics using the patient's weight and height to calculate the functional residual capacity in less than 3 minutes.[21] Therefore, the CCA system gave us more reliable and accurate results compared with those obtained in previous studies using semiclosed circuit systems with regard to reaching and maintaining a consistent sevoET.[7,22]

There were some limitations to our study. First, as we discussed, the last opioid administration was not prohibited for 12 hours before the start of the clinical trial. Second, accurate assessment of $SEVO_{BIS50}$ requires volatile induction and maintenance of anesthesia. However, because excessive opioid use by patients in the chronic opioid group could increase the risk of aspiration,[23] we used thiopental as the induction agent. In addition, the measurement period was more than 18 minutes after the addition of thiopental, but considering the short half-life of thiopental in the brain, we considered its impact on $SEVO_{BIS50}$ to be minor or insignificant. Third, vecuronium, a neuromuscular-blocking agent, was used for endotracheal intubation. According to a recent study by Ekman et al,[24] BIS is not affected by neuromuscular-blocking drugs. Therefore, our use of vecuronium should not have affected our determination of BIS values. Finally, differences in $SEVO_{BIS50}$ values after application of noxious stimuli such as skin incisions were simply not part of our protocol because we did not intend to determine classic MAC. However, to the best of our knowledge, our study is the first to investigate differences in the demand for inhalation agents during general anesthesia between chronic opioid users, specifically those with opioid tolerance, and opioid-naïve patients.

In conclusion, our results suggest that $SEVO_{BIS50}$ values are significantly lower for chronic opioid users than for opioid-naïve patients. Additional studies should be performed to determine whether these differences also translate to classic MAC values obtained during actual surgical stimulation.

DISCLOSURES

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