

Short-term Inhalation of Sevoflurane during Induction of General Anesthesia Can Inhibit the A-line ARX Index Response to Intubation: A Randomized Trial

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Background: Monitoring hypnotic depth is used to prevent awareness during general anesthesia. We used the A-line ARX index (AAI) to assess the effect of short-term inhalation of sevoflurane in the prevention of intubation-induced inadequate hypnotic depth during anesthetic induction.

Methods: Thirty patients were randomly divided into the sevoflurane and non-sevoflurane groups, both of which were given 3 $\mu\text{g kg}^{-1}$ fentanyl, 4 mg kg^{-1} thiamylal, and 0.2 mg kg^{-1} cis-atracurium intravenously to induce general anesthesia. The sevoflurane group then inhaled 6% sevoflurane and 4 L/min O_2 for 3 minutes, whereas the non-sevoflurane group was given 4 L/min O_2 alone. Both groups were intubated 3 minutes after induction. Measurements of the AAI, non-invasive blood pressure, and heart rate were performed every minute, starting 3 minutes prior to induction until 9 minutes after intubation.

Results: Intubation induced a significant AAI elevation in the non-sevoflurane group (47.13 ± 20.88 , 48.13 ± 20.05 , 40.87 ± 15.86 and 31.27 ± 15.26 at 1, 2, 3 and 4 minutes after intubation, respectively, vs. 17.67 ± 6.44 at 3 minutes after induction; $p < 0.05$), whereas the AAI remained unchanged for the sevoflurane group following intubation. Moreover, the non-sevoflurane group demonstrated higher AAI values after intubation compared with the sevoflurane group. There were no significant differences in blood pressure and heart rate between the two groups throughout the study.

Conclusion: Adding 6% sevoflurane with 4 L/min O_2 for 3 minutes during the induction period prevented inadequate hypnotic depth caused by intubation but was not sufficient to inhibit fluctuations in hemodynamics.
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Key words: A-line ARX index, hypnotic depth, awareness, intubation, sevoflurane

The incidence of awareness during general anesthesia has been reported to be 0.0068%,⁽¹⁾ 0.1 to 0.2%^(1,2) and as high as 0.4%⁽³⁾ in various studies. Despite its rarity, awareness may produce severe

postoperative psychological consequences.⁽⁴⁾ Hypnotic depth monitoring is valuable in the prevention of awareness in patients undergoing general anesthesia. To date, various technologies have been

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proven and used for hypnotic or anesthetic depth monitoring, including electroencephalography, bispectral index monitoring, the auditory evoked response (AEP), ocular microtremor,⁽⁵⁾ and the patient state analyzer index.⁽⁶⁾ In recent years, the A-line ARX index (AAI), extracted from the middle-latency auditory evoked potential (MLAEP) wave via autoregressive modeling with exogenous input (ARX), has been shown to effectively monitor hypnotic depth.⁽⁷⁾

Endotracheal intubation is a method of maintaining airway patency after the induction of general anesthesia. However, it is noxious and patient reactions can be strong enough to result in dramatic fluctuations in hypnotic depth and hemodynamic changes. Sevoflurane is one of the most popular general anesthetic agents, although it may cause cardiovascular inhibition.⁽⁸⁾ Here, we hypothesized that adding short-term sevoflurane inhalation during the intravenous induction of general anesthesia might prevent intubation-related inadequacy in hypnotic depth. We additionally hypothesized that this treatment might prevent fluctuations in hemodynamic status, as reflected by blood pressure and heart rate, following intubation. Therefore, we designed this study to investigate the effects of sevoflurane on hypnotic depth (assessed by AAI) and hemodynamic responses after intubation in orthopedic patients.

METHODS

This study was approved by the Human Studies Committee at Chang Gung Memorial Hospital. The required sample size was described using the following parameters: significance level = 0.05; difference in AAI between the two groups = 10; standard deviation = 5; statistical power = 0.95; $n = 15$ individuals per group. The experimental methods and procedures were well explained to the patients, and written consent was obtained prior to treatment. A total of 30 patients were enrolled in this study, all with American Society of Anesthesiologists physical status I or II. The patients underwent total hip replacement (THR) ($n = 20$), the Girdlestone procedure ($n = 2$), revision of a THR ($n = 6$), revision of a total knee replacement ($n = 1$), or knee arthroscopy ($n = 1$). Patients were excluded from the study if they had central nervous system disorders, cardiac disease, or hearing impairment, were under the legal age of con-

sent, had difficulty with mask ventilation or intubation, or required more than one attempt to intubate.

Subjects were assigned to either the sevoflurane or non-sevoflurane group, according to designations randomly selected by the researcher from a pool that contained 15 assignments to the sevoflurane group and 15 to the non-sevoflurane group. All study procedures were prepared and performed by an anesthesiologist and an anesthetic nurse. The same doctor administered anesthesia for all surgical procedures. The other researcher was responsible for recording the study results for each patient and monitoring vital signs. No premedication was given. Monitoring with an A-line™ AEP monitor (Danmeter, Odense, Denmark), noninvasive blood pressure system, and electrocardiograph was instituted before the study commenced.

Before the induction of general anesthesia, the AAI, mean blood pressure (MBP), and heart rate (HR) were recorded once per minute for 3 minutes, and these data were used as the baseline control values. After the third baseline control value was obtained, general anesthesia induction was performed. Anesthetic medication was given intravenously in the following order: $3 \mu\text{g kg}^{-1}$ fentanyl, 4 mg kg^{-1} thiamylal, and 0.2 mg kg^{-1} cis-atracurium. Immediately after intravenous drug administration, the sevoflurane group was given 6% sevoflurane and 4 L/min O_2 for 3 minutes by inhalation via face mask. The non-sevoflurane group was given 4 L/min O_2 alone for 3 minutes. The MBP, HR, and AAI were recorded each minute for both groups. Three minutes after intravenous drug administration, intubation was performed, after which anesthesia was maintained in both groups with 2.5% sevoflurane and 4 L/min O_2 . The MBP, HR and AAI were recorded each minute after intubation for 9 minutes. Afterward, anesthesia care was transferred to the responsible attending anesthesiologist.

Upon completion of the surgery when the patients were fully conscious, each patient was interviewed in the postoperative care unit to determine whether they had been aware of the intubation and operative procedures. The results of these interviews were documented.

Data analysis

Where appropriate, an independent t-test, Wilcoxon rank-sum test, chi-squared test, and

Fisher's exact test were used to compare data between the two study groups. Two-way repeated measures analysis of variance (ANOVA) was used to examine differences in BP, HR, and AAI during intubation between groups. First, the interaction between time and study group was examined. Multiple comparisons were made to compare differences at the same time point across the two study groups. The mean square error used for the multiple comparisons was based on an ANOVA test with interaction according to Hines's suggestion.⁽⁹⁾ The significance level (α) used in this study was 0.05. To compensate for multiple comparisons, Bonferroni correction of the significance level was used.

RESULTS

Twenty subjects in our study were men and 10 were women. The mean age (mean \pm SD) was 56.6 ± 15.1 years old, and the mean weight was 68.8 ± 12.4 kilograms. Patients were randomly assigned to the sevoflurane ($n = 15$) or non-sevoflurane ($n = 15$) groups. Both groups included 10 men and 5 women. The mean age of the sevoflurane group was 51.4 ± 14.9 years, and the non-sevoflurane group 61.8 ± 13.7 years. The mean weight in the sevoflurane group was 71 ± 14.3 kg, and the non-sevoflurane

group 66.7 ± 10.1 kg. There were no significant differences in age ($p = 0.057$) or weight ($p = 0.346$) between groups.

Before anesthetic induction, the mean baseline MBP for the sevoflurane group was 102.38 ± 17.23 mmHg, and mean baseline HR was 72.84 ± 9.36 beats per minute. For the non-sevoflurane group, the respective values were 101.27 ± 8.91 mmHg, and 71.36 ± 12.24 bpm. There were no significant differences in the baseline mean MBP ($p = 0.827$) or HR ($p = 0.711$) between groups.

The AAI was measured from 3 minutes before induction until 9 minutes after intubation. There were no difficulties obtaining a clear signal for any of the patients. Prior to induction, the baseline mean AAI was 75.69 ± 13.08 in the sevoflurane group and 76.20 ± 6.88 in the non-sevoflurane group, with no significant difference between groups ($p = 0.894$).

Response to anesthetic induction

After induction, the AAI for both groups decreased significantly compared with baseline ($p < 0.001$, Fig. 1); no significant differences in AAI were observed between groups ($p > 0.05$). For both groups, the mean MBP at the third minute after induction was significantly lower than baseline ($p < 0.001$). No differences were observed in post-induc-

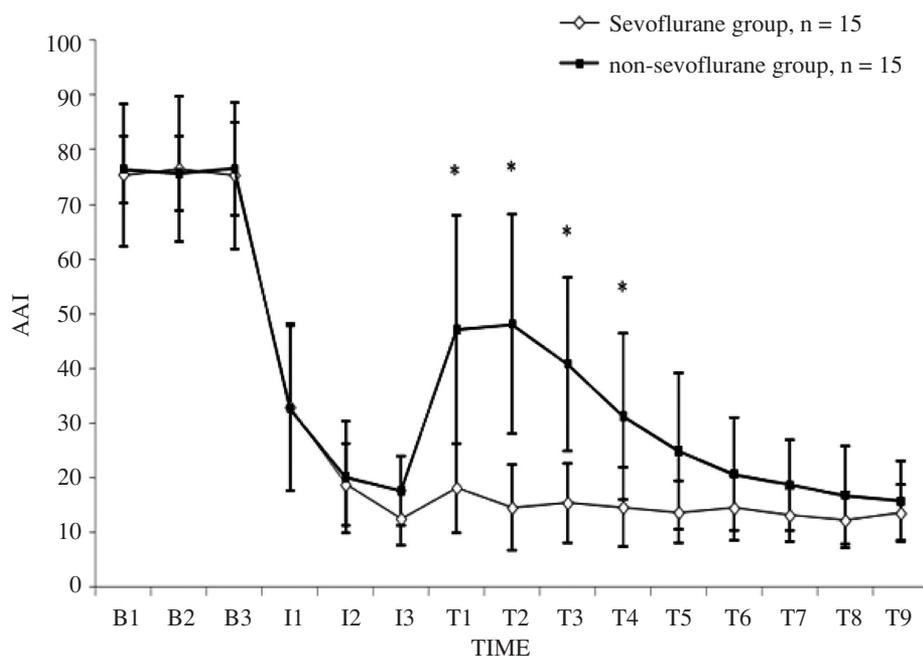


Fig. 1 A-line ARX index (AAI) before and after thiethylal induction with and without sevoflurane inhalation, and after intubation. B1, B2 and B3 indicate three, two and one minutes before drug administration (baseline). I1, I2 and I3 indicate one, two and three minutes after drug administration. Intubation was performed at the end of I3. T1 to T9 indicate one to nine minutes after intubation. An asterisk (*) indicates that during T1 to T4, the AAI values for the non-sevoflurane group were significantly higher compared with the sevoflurane group and were also higher than the value at I3 ($p < 0.05$).

tion HR compared with baseline values for either group ($p > 0.05$). Finally, there were no significant differences between the groups in terms of post-intubation MBP and HR ($p > 0.05$, Fig. 2, 3).

Response to intubation

The sevoflurane group exhibited no significant changes in the AAI after endotracheal intubation, whereas the AAI values for the non-sevoflurane group from the first to the fourth minute after intubation were significantly higher compared with the value 3 minutes after induction (47.13 ± 20.88 , 48.13 ± 20.05 , 40.87 ± 15.86 and 31.27 ± 15.26 at 1, 2, 3 and 4 minutes after intubation, respectively, vs. 17.67 ± 6.44 at 3 minutes after induction; $p < 0.001$ at 1, 2 and 3 minutes, and $p = 0.002$ at 4 minutes after intubation, Fig. 1). Afterward, a gradual decline in the AAI was observed in the non-sevoflurane group. When the AAI was compared between groups, the non-sevoflurane group scored markedly higher during the first to the fourth minute after intubation (47.13 ± 20.88 , 48.13 ± 20.05 , 40.87 ± 15.86 and 31.27 ± 15.26 for the non-sevoflurane group vs. 18.2 ± 8.15 , 14.6 ± 7.77 , 15.47 ± 7.23 , and 14.67 ± 7.19 for the sevoflurane group at 1, 2, 3 and 4 minutes after intubation, respectively, $p < 0.001$, Fig. 1).

The MBP after intubation showed no significant

differences when compared with baseline in either group ($p > 0.05$, Fig. 2). MBP values after intubation were also not significantly different between groups ($p > 0.05$, Fig. 2). One to two minutes after intubation, both groups demonstrated higher HR values than at baseline (sevoflurane group, 88.4 ± 18.50 and 80.73 ± 19.92 vs. 72.84 ± 9.36 at 1 and 2 minutes after intubation, $p = 0.005$ and 0.023 , respectively; non-sevoflurane group, 84.67 ± 20.02 and 80.53 ± 16.01 vs. 71.36 ± 12.24 at 1 and 2 minutes after intubation, $p = 0.012$ and 0.020 , respectively; Fig. 3). Afterwards, the post-intubation HR decreased to near baseline values. We found that HR values after intubation were not significantly different between groups ($p > 0.05$, Fig. 3).

Post-operative period

Following the operation when patients were fully conscious in the postoperative care unit, they were interviewed to determine their state of awareness during the intubation and operative procedures. No patients in either group were aware of these events.

DISCUSSION

Because our experimental design called for short-term inhalation of a volatile anesthetic during

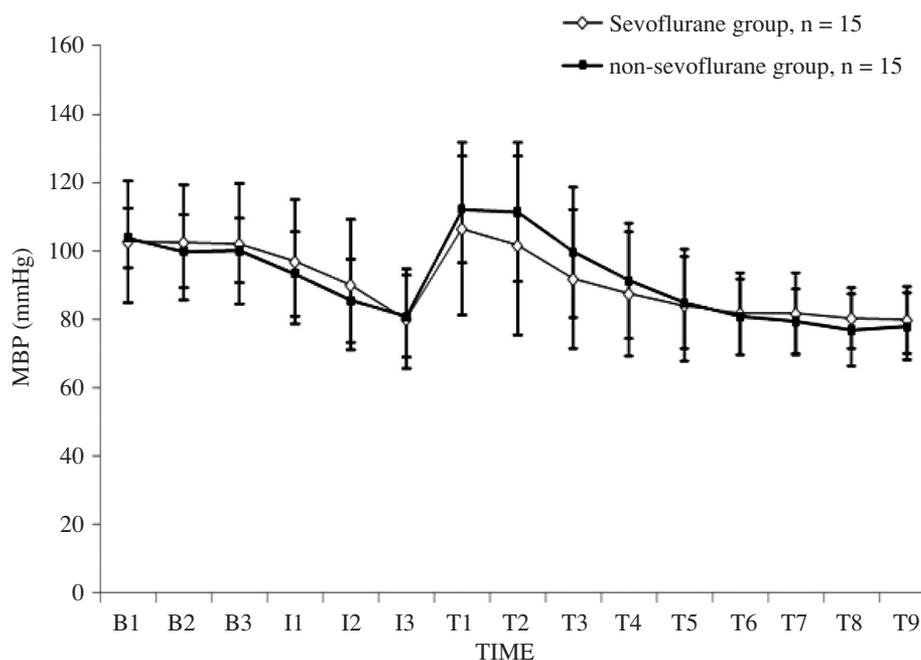


Fig. 2 Mean blood pressure (MBP) before and after thi-amylal induction with and without sevoflurane inhalation, and after intubation. B1, B2 and B3 indicate three, two and one minutes before drug administration (baseline). I1, I2 and I3 indicate one, two and three minutes after drug administration. Intubation was performed at the end of I3. T1 to T9 indicate one to nine minutes after intubation. There were no significant differences in MBP between groups. For both groups, MBP values after intubation were not significantly higher than baseline values.

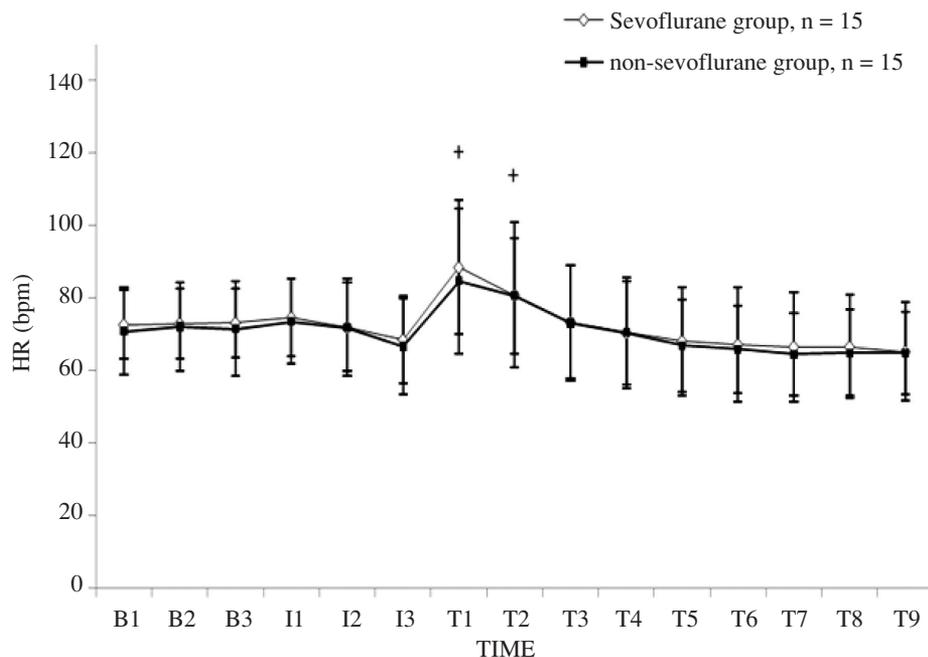


Fig. 3 Heart rate (HR) before and after thiamylal induction with and without sevoflurane inhalation, and after intubation. B1, B2 and B3 indicate three, two and one minutes before drug administration (baseline). I1, I2 and I3 indicate one, two and three minutes after drug administration. Intubation was performed at the end of I3. T1 to T9 indicate one to nine minutes after intubation. A plus sign (+) indicates that the HR values for both groups were significantly higher at T1 and T2 compared with baseline values ($p < 0.05$). There were no significant differences in HR between groups.

the anesthesia induction period, we administered a high concentration of sevoflurane (6%) with high-flow oxygen delivery (4 L/min) for the combined anesthetic induction in the sevoflurane group. We used AEP monitoring to assess the status of hypnotic depth.^(10,11) A lower AAI corresponded to a deeper level of unconsciousness. Our results indicated no significant differences in AAI between groups directly following induction. However, following intubation, a marked difference in the AAI was observed between groups. After intubation, the sevoflurane group was able to maintain an AAI below 20, while AAI values were significantly elevated in the non-sevoflurane group.

According to investigations by Kalkman et al. and Ujani et al., the MLAEP is suppressed after loss of consciousness during the induction of anesthesia.^(12,13) Consistent with these studies, we found AAI values below 25 at 3 minutes after the induction of general anesthesia in the majority of our subjects. This suggests that an induction dose of 4 mg kg⁻¹ thiamylal is adequate to produce unconsciousness. Theoretically, awareness does not occur at this AAI. However, stimulation by endotracheal intubation causes an elevated AAI, a phenomenon that we reported in a previous study.⁽¹⁴⁾ In the current work, the group of patients who received thiamylal but not

sevoflurane experienced increased AAI as a result of intubation. One to two minutes after intubation, the group who did not receive sevoflurane had AAI values approaching 50, which approaches the AAI value at consciousness. Under these circumstances, we are concerned about the consequences of inadequate hypnotic depth, such as awareness.^(2,15,16) When sevoflurane was given after thiamylal administration, this light hypnotic status was not observed after intubation. The mean AAI for all patients in the sevoflurane group was consistent with unconsciousness. Although it is difficult to prove that awareness does not occur at these low AAI levels, keeping patients in a deeper hypnotic state after intubation is preferable.

After induction, patients in both groups achieved the same AAI level, but following intubation, the non-sevoflurane group showed significant elevation compared with the sevoflurane group. Work by Ujani et al. and Alpiger et al. demonstrated that the AAI is an appropriate index with which to differentiate the conscious and unconscious states.^(13,17) However, because the AAI rapidly declines and reaches a plateau once the patient is asleep, differences in the plane of unconsciousness are difficult to gauge with confidence. The lack of sensitivity of the AAI once patients have reached this

plateau suggests that even though patients in both groups in our study were unconscious and had the same AAI values after induction, there may still have been differences in anesthetic depth and sedation level.

After induction and intubation, there were no significant differences in HR and MBP between groups. The application of short-term inhalation of sevoflurane during the induction of general anesthesia exerted minimal effects on hemodynamic responses. We found that the HRs of both groups were significantly elevated one to two minutes after intubation compared with baseline values. This elevation might have been due to the noxious stimulus of the intubation process. Although MBP elevation was also observed after intubation, the elevation did not reach statistical significance. These phenomena suggest that changes in these two hemodynamic variables are not parallel.

Many studies have indicated that hemodynamic variables correlate poorly with the hypnotic status of the patient.⁽¹⁸⁻²⁰⁾ Mi et al. suggested that the consciousness level is related to the cortical brain, whereas the body's motor and hemodynamic responses to noxious stimuli are mediated by subcortical structures in different locations in the brain.⁽²¹⁾ In our study, the non-sevoflurane group had higher AAI values after intubation compared with the sevoflurane group. However, the MBP and HR showed no significant differences between groups after intubation. Therefore, our results indicate that hypnotic depth and post-intubation hemodynamic responses are not directly correlated.

In summary, this study demonstrated that the addition of inhaled 6% sevoflurane and 4 L/min O₂ for 3 minutes during anesthetic induction may prevent intubation-related inadequacy in hypnotic depth compared with use of 4 mg kg⁻¹ thiamylal alone. This technique may help minimize the side effects of intubation. We additionally demonstrated that the MBP and HR were ineffective in monitoring the hypnotic depth.

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隨機性試驗：全身麻醉誘導期短暫吸入七氟烷 (Sevoflurane) 能夠抑制 A-line ARX 參數對於插管的反應

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- 背景：**意識深度的監測，是防止進行全身麻醉時，發生知覺的一種方法。在此次試驗中，我們採用 A-line ARX 參數 (A-line ARX index, AAI) 來評估，在麻醉誘導期短暫吸入七氟烷 (Sevoflurane)，是否能有效抑制因氣管內插管所引起的意識深度不足的現象。
- 方法：**我們選取了 30 位病患，隨機分成 sevoflurane 組及 non-sevoflurane 組。兩組病患在麻醉誘導時，均給予靜脈注射 fentanyl $3 \mu\text{g kg}^{-1}$ 、thiamylal 4mg kg^{-1} 、以及 cis-atracurium 0.2mg kg^{-1} 。靜脈注射誘導後，給予 sevoflurane 組的病患吸入 3 分鐘的 6% sevoflurane 加上 O_2 4 L/min，而 non-sevoflurane 組的病患則僅吸入 3 分鐘的 O_2 4 L/min，之後進行氣管內插管。我們從麻醉誘導前 3 分鐘開始，以間隔一分鐘的頻率，來測量並記錄病患的 AAI、血壓以及心跳的數值，直到插管後第 9 分鐘。
- 結果：**在 non-sevoflurane 組的病患，AAI 數值在插管後第一至第四分鐘，比起插管前有明顯上升的現象。而在 sevoflurane 組，插管後的 AAI 數值，則較插管前沒有明顯變化。此外，插管後 non-sevoflurane 組的 AAI 數值，亦較 sevoflurane 組為高。比較兩組病患的血壓及心跳，在整個試驗過程中並沒有差異存在。
- 結論：**此次試驗顯示，在麻醉誘導期讓病患合併吸入 3 分鐘的 6% sevoflurane 加上 O_2 4 L/min，可以有效防止之後因插管所引起的意識深度不足的現象，但是並不能進一步抑制血壓及心跳的變動。
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關鍵詞：A-line ARX 參數，意識深度，知覺，插管，七氟烷

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