

## Clinical Article

# Comparative Study of Brain Protection Effect between Thiopental and Etomidate Using Bispectral Index during Temporary Arterial Occlusion

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**Objective :** This study was conducted to compare the effect of etomidate with that of thiopental on brain protection during temporary vessel occlusion, which was measured by burst suppression rate (BSR) with the Bispectral Index (BIS) monitor.

**Methods :** Temporary parent artery occlusion was performed in forty one patients during cerebral aneurysm surgery. They were randomly assigned to one of two groups. General anesthesia was induced and maintained with 1.5-2.5 vol% sevoflurane and 50% N<sub>2</sub>O. The pharmacological burst suppression (BS) was induced by a bolus injection of thiopental (5 mg/kg, group T) or etomidate (0.3 mg/kg, group E) according to randomization prior to surgery. After administration of drugs, the hemodynamic variables, the onset time of BS, the numerical values of BIS and BSR were recorded at every minutes.

**Results :** There were no significant differences of the demographics, the BIS numbers and the hemodynamic variables prior to injection of drugs. The durations of burst suppression in group E (11.1±6.8 min) were not statistically different from that of group T (11.1±5.6 min) and nearly same pattern of burst suppression were shown in both groups. More phenylephrine was required to maintain normal blood pressure in the group T.

**Conclusion :** Thiopental and etomidate have same duration and a similar magnitude of burst suppression with conventional doses during temporary arterial occlusion. These findings suggest that additional administration of either drug is needed to ensure the BS when the temporary occlusion time exceed more than 11 minutes. Etomidate can be a safer substitute for thiopental in aneurysm surgery.

**Key Words :** Aneurysm · Barbiturate · Bispectral Index (BIS) Burst suppression · Etomidate · Temporary arterial occlusion.

## INTRODUCTION

Temporary arterial occlusion (TAO) is an established technique in the repair of intracranial aneurysms and facilitates the manipulation of the vessels in patients with fragile and giant aneurysm<sup>3</sup>. But, it carries the potential risks of ischemic injuries. Several measures have been suggested for the prevention of focal ischemia during TAO. They include mild hypothermia, maintenance of mean arterial pressure (MAP) to ensure collateral circulation, and the reduction of temporary occlusion time. In addition, pharmacological prevention with barbiturates or etomidates to improve the tolerance of the brain can be used<sup>7,13,16</sup>.

Barbiturates are used widely as the most effective agents for

intraoperative brain protection during aneurysm surgery<sup>22</sup>. The protective effect mainly comes from the suppression of cerebral metabolic requirement (CMR) and cerebral blood flow (CBF) redistribution and scavenging free radicals<sup>16</sup>. However, several studies<sup>9,15,18</sup> have shown that small bolus doses of barbiturate provide only a short duration of protection and incomplete burst suppression. Additionally, barbiturates at a protective concentration have the disadvantages of depressing the cardiovascular system and delaying neurological examinations due to prolonged awakening time<sup>16</sup>. Etomidate is also a potent cerebral metabolic depressant and it decreases the cerebral blood flow coupled with a reduction of CMR. Etomidate can be used as an induction agent in patients with hypotension or cardiac disease because it has the advantages of minimal cardiovascular depression<sup>19,20,22,24</sup>.

It maintains the cerebral perfusion pressure (CPP) and has a rapid elimination time compared with that of barbiturates. Although etomidate has been used during temporary vessel occlusion with good results<sup>3,21</sup>, this agent has not been as widely evaluated as barbiturates<sup>24</sup>.

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When these pharmacological CMR-reducing anesthetic agents are given for brain protection, their effects should be assessed with continuous electroencephalogram (EEG) monitoring<sup>2</sup>. However, most CMR-reducing anesthetic agents are administered without titration during emergency surgery because EEG monitoring needs a complex setting. The Bispectral Index (BIS) monitor has recently emerged as an alternative to EEG for documenting the effect of CMR-reducing agent including barbiturates<sup>2,12,25</sup>.

The present study was designed to compare the burst suppression effect of etomidate with that of barbiturates on brain protection measured by BIS monitor and to evaluate the usefulness of the BIS monitor during aneurysm surgery.

## MATERIALS AND METHODS

This study received Institutional Review Board approval, and informed consent was obtained from each patient. A total of 41 patients who underwent temporary vessel occlusions during elective and emergency cerebral aneurysm surgery were selected for this study. Patients were excluded if they had focal neurologic deficits, intraoperative rupture with massive bleeding, or unstable vital signs during operation. The patients who had a history of allergic reaction to any of the study medications, seizure disorder, poorly controlled asthma, diabetes, hypertension, or had been treated with opioids or sedatives were also excluded in this study.

The patients were randomly assigned to two groups according to the drugs used to induce the pharmacological burst suppression: group T was given pentothal sodium (Chungwae Pharmaceuticals, Suwon, Korea) and group E was given Etomidate-Lipuro (B. Braun Melsungen, Berlin, Germany). When the patients arrived on the operating room, they were monitored with electrocardiography, pulse oximetry, non-invasive and invasive blood pressure measurement and capnography to assess the carbon dioxide end tidal concentration, and we measured the temperature and urine output. For detecting the burst suppression during surgery, the BIS sensor™ (BIS XP sensor; Aspect Medical Systems, Newton, MA, USA) was applied on forehead according to the manufacturer instruction. The EEG was continuously displayed, monitored and recorded using a BIS XP monitor (BIS™ monitor, Model A-2000™, Aspect Medical System, Newton, MA, USA; software version 3.12). For anesthetic induction, thiopental 4-5 mg/kg was intravenously (IV) administered to both groups, and then tracheal intubation was facilitated with IV rocuronium bromide (0.6 mg/kg) (Esmeron, Hanwha Pharmaceuticals, Chuncheon, Korea).

After intubation, anesthesia was maintained with 1.5-2.5 vol% sevoflurane (Abbott Laboratories Ltd., Wueenbrough, Kent, UK) in 50% O<sub>2</sub> and N<sub>2</sub>O. The lungs were ventilated with a mixture of oxygen and nitrous oxide (FiO<sub>2</sub> of 0.5) and the ventilation was continuously adjusted to maintain a carbon dioxide arterial pressure (PaCO<sub>2</sub>) of 30-35 mm Hg. The depth of anesthesia was

maintained in both groups by using a BIS monitor in the range of BIS 40-55 throughout the operation and there was less than 10% variation in the BIS value.

The hemodynamic variables were maintained within 20% of the preoperative values by adjusting the maintenance anesthetics accordingly. When clinically indicated, a continuous, low-dose infusion of dopamine was administered via a syringe pump to maintain blood pressure in both groups. Thirty minutes prior to temporary arterial occlusion, the nitrous oxide was turned off and changed into air. Arterial blood gas (ABG) analysis was done before and after TAO to ensure that the PaCO<sub>2</sub> stayed within 30-35 mm Hg. Burst suppression of the EEG was induced prior to TAO by bolus injection of thiopental (5 mg/kg) or etomidate (0.3 mg/kg) according to the groups. After thiopental or etomidate injection, 50-100 mcg of phenylephrine (Hana Pharmaceuticals, Hawchung, Korea) was intermittently injected as needed to maintain the mean arterial blood pressure (MAP) at a level greater than 70 mm Hg. After thiopental or etomidate administration, the onset time (the time taken from thiopental injection to the first appearance of burst suppression) and the duration of burst suppression (the time taken from the first appearance of burst suppression to the complete fade of it) were recorded. The BIS number, the burst suppression ratio (BSR) values, the systolic and diastolic blood pressure, and the heart rate were recorded every minute. After appearance of burst suppression, TAO was carried out for aneurysm neck clipping. Surgical procedures and recording of the BIS monitor were carried out simultaneously.

## Statistical analysis

The sample size for this study was predicated on detecting a mean difference in the duration 10.0±10.0 minutes between the groups through a pilot study. On the basis of a statistical power of 80%, a significance level of 5% and a 1 : 1 randomization, we calculated that a minimum sample size of 15 subjects per each group would be needed to detect a significant difference. Allowing for a 10% dropout rate, a total of 34 subjects (17 subjects per each group) would be needed for the two groups. To compare the two groups, we first performed a normality test using the Kolmogorov-Smirnov test. Differences in the baseline characteristics between the groups of patients who received thiopental and etomidate were compared using the t-test, and the results were presented as mean±SD. The chi-square test was used for the categorical variables, as appropriate.

To identify the changes of the BIS and SR between the groups, we analyzed using repeated-measures analysis of variance at 5 minutes intervals for 15 minutes. Within-subjects analysis evaluated the statistically significant changes from baseline in an individual group whereas between-subject factor analysis examined the anesthetic technique over time. The data in the figures was represented as mean±SD. All *p*-values were 2-tailed, and *p*-values <0.05 were considered significant. All the analyses were performed using a Statistical Analysis software package (SAS version 9.1, SAS Institute, Cary, NC, USA).

**RESULTS**

Forty-one patients (15 males and 26 females) were studied. To induce burst suppression on the BIS monitor, twenty-one patients received thiopental (5 mg/kg) and twenty patients received etomidate (0.3 mg/kg). There were no significant differences of the demographic variables between the groups (Table 1). The incidence of ruptured aneurysms was 57.1% (12/21) in group T and 35% (7/21) in group E. There was also no significant difference between the groups for the BIS numbers and the hemodynamic variables prior to thiopental or etomidate administration. The duration of TAO time was 8.8±5.3 min in group T and 7.7±4.1 min in group E, respectively but no significant difference was noticed between groups. The onset time was 59.2±29.7 sec in group T and 68.0±39.1 sec in group E (p=0.434). The duration of burst suppression as measured by the BSR on the BIS monitor was 11.1±6.8 min in group T and 11.1±5.6 min in group E, which meant no significant difference between the groups (p=0.979) (Table 1). More phenylephrine was required in group T (67%) compared to group E (20%) to maintain blood pressure. There were no significant differences between the ABG analysis in both groups (Table 2). Table 3 shows the locations of the aneurysms in both groups, and one patient in group E had two aneurysms.

Fig. 1 illustrates the changes of the BIS after thiopental or etomidate administration. The BIS number over time after drug administration showed similar changes in both groups. The BIS number was decreased rapidly for the first 5 min, and there was a trend toward the basal level of BIS in both groups. The magnitude of BIS number change in group E was compared with that of group T, but there was no significant difference between the groups (p=0.878). The changes of the BSR values increased rapidly during the first 5 minutes in both groups after thiopental or etomidate administration (Fig. 2). Then, the BSR changes returned to the basal level in both groups which showed a nearly identical pattern of changes between the groups. None of the patients suffered from neurologic deficits immediately after the operation.

**DISCUSSION**

A variety of intravenous anesthetic agents have a profound ef-

**Table 1.** Patients' demographic characteristics and physiologic variables prior to thiopental or etomidate administration

| Variables                       | Group P (n=21) | Group E (n=20) | p-value |       |
|---------------------------------|----------------|----------------|---------|-------|
| Age (years)                     | 59.5±11.4      | 57.5±12.5      | 0.582   |       |
| Sex (M)                         | Male           | 5              | 10      | 0.082 |
|                                 | Female         | 16             | 10      |       |
| Weight (kg)                     | 59.2±9.3       | 62.5±12.4      | 0.346   |       |
| Height (cm)                     | 158.9±7.9      | 161.7±8.2      | 0.265   |       |
| Dosage (mg)                     | 294.5±45.4     | 18.1±2.7       |         |       |
| Onset (sec)                     | 59.5±29.7      | 68±39.1        | 0.434   |       |
| Duration (min)                  | 11.1±6.8       | 11.1±5.6       | 0.997   |       |
| BIS value (prior to TAO)        | 42.9±9.9       | 45.1±7.1       | 0.412   |       |
| Phenylephrine (No. of patients) | No             | 7              | 16      | 0.003 |
|                                 | Yes            | 14             | 4       |       |
| Aneurysm status                 | Unruptured     | 9              | 13      | 0.155 |
|                                 | Ruptured       | 12             | 7       |       |
| MAP (mm Hg)                     | 67.4±9.8       | 72.3±10.4      | 0.131   |       |
| HR (rates/min)                  | 72.7±12.4      | 71.2±11.1      | 0.805   |       |
| Temp (°C)                       | 36.0±0.3       | 35.8±0.5       | 0.313   |       |
| TAO time (min)                  | 8.8±5.3        | 7.7±4.1        | 0.456   |       |
| Hemoglobin (gm%)                | 12.2±1.7       | 1.8±1.5        | 0.726   |       |

Values are expressed mean (SD). Calculated by t-test and chi-square test. p-value<0.05. Group T : group thiopental, Group E : group etomidate, BIS : Bispectral Index, MAP : mean arterial pressure, HR : heart rate, Temp : temperature, TAO : temporary arterial occlusion

**Table 2.** The comparison of arterial blood gas analysis

| Variables                 | Group P (n=21) | Group E (n=20) | p-value |
|---------------------------|----------------|----------------|---------|
| pH                        | 7.4±0.1        | 7.4±0.8        | 0.119   |
| PaCO <sub>2</sub> (mm Hg) | 30.8±2.2       | 31.2±2.6       | 0.652   |
| PaO <sub>2</sub> (mm Hg)  | 214.7±55.8     | 216.8±44.1     | 0.896   |
| Bicarbonate (mmol/L)      | 24.2±2.9       | 24.6±2.0       | 0.620   |
| Base excess (mmol/L)      | 0.5±3.3        | 0.5±2.3        | 0.271   |
| Lactate (mmol/L)          | 2.6±1.1        | 2.0±1.1        | 0.089   |

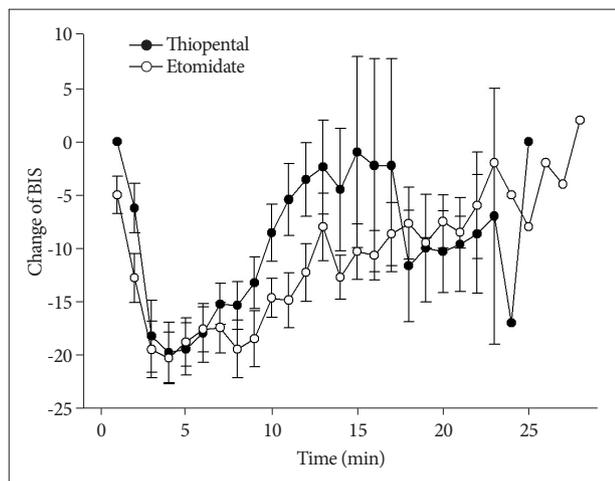
Values are expressed mean (SD). Calculated by t-test and chi-square test. p-value<0.05. Group T : group thiopental, Group E : group etomidate, PaCO<sub>2</sub> : partial pressure of arterial blood CO<sub>2</sub> tension, PaO<sub>2</sub> : partial pressure of O<sub>2</sub> tension

**Table 3.** The location of aneurysms

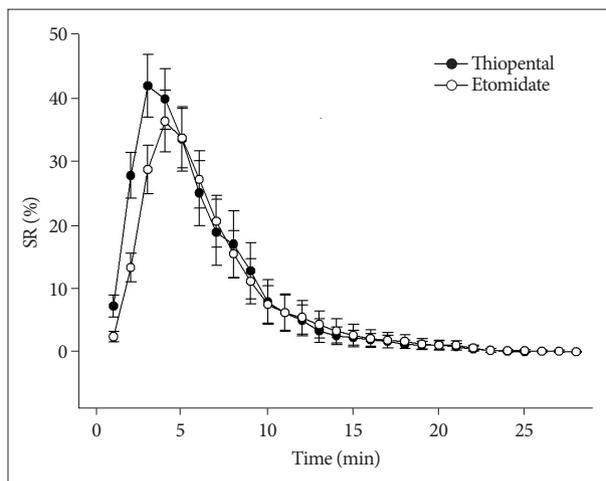
| Location          | Group T (n=21) | Group E (n=20) |
|-------------------|----------------|----------------|
| A-comm a.         | 10 (47.6%)     | 9 (42.8%)      |
| MCA               | 8 (38.1%)      | 6 (21.4%)      |
| P-comm a.         | 2 (9.5%)       | 4 (19%)        |
| Ant. choroidal a. | 1 (4.8%)       | 2 (9.5%)       |

Values are expressed frequency (%). Group T : group thiopental, Group E : group etomidate, A-comm a. : anterior communicating artery, MCA : middle cerebral artery, P-comm a. : posterior communicating artery, Ant. choroidal a. : anterior choroidal artery

fect on cerebral metabolism. Etomidate, potent and nonbarbiturate hypnotics with anticonvulsant properties, produce a reversible dose-dependent reduction in the cerebral metabolic rate<sup>14,19</sup>. Etomidate, like that of barbiturates, can produce a burst suppression pattern on an EEG and a marked depression of the CMRO<sub>2</sub> up to 50% with little cardiac depression and minimal effect on the hemodynamic variables, although the exact mechanism of action is unknown<sup>19,20,24</sup>. In the present study, we compared the effect of etomidate on burst suppression with that of



**Fig. 1.** Changes of Bispectral Index (BIS) values after thiopental or etomidate administration in patients who underwent temporary arterial occlusion during aneurysm surgery. Changes of BIS present the difference from the time of drug injection shows similar changes according to the time in both groups. The magnitude of BIS number change in group E was compared with that of group T, but there was no significant difference between the groups ( $p=0.878$ ).



**Fig. 2.** Changes of burst suppression ratio (BSR) after thiopental or etomidate administration during temporary arterial occlusion on aneurysm surgery. The SR (%) means BSR. The first appearance time of BSR are  $59.2 \pm 29.7$  sec in group thiopental (T) and  $68.0 \pm 39.1$  sec in group etomidate (E) ( $p=0.434$ ). The duration of burst suppression as measured by the BSR on the Bispectral Index monitor is  $11.1 \pm 6.8$  min in group T and  $11.1 \pm 5.6$  min in group E, which indicates no significant difference between the groups ( $p=0.979$ ).

thiopental as measured by the BIS monitor. The main findings were that the durations of burst suppression by etomidate were not statistically different from that of thiopental and etomidate showed a nearly identical pattern of burst suppression as that of barbiturate.

Several authors<sup>10,13</sup> have described use of pharmacological brain protection with CMR-reducing agents during intracranial vascular occlusion in humans. Hoff et al.<sup>10</sup> reported improved neurological outcomes after treatment with a neuroprotectant like barbiturates than without medications. Lavine et al.<sup>13</sup> also reported significant advantages of intravenous brain protections using barbiturates, etomidate and propofol as compared to not using protective agents. Barbiturates are commonly used and have long been considered to be the most effective cerebral protectant among several anesthetics<sup>16,22</sup>.

However, several studies suggested that small single bolus doses of thiopental might have very little value for providing significant metabolic suppression required for intracerebral protection. Moffat et al.<sup>15</sup> reported that bolus therapy of barbiturates (4 mg/kg) was inadequate for brain protection as thiopental achieved a very short duration of burst suppression on EEG during carotid occlusion with carotid endarterectomy. Gelb et al.<sup>9</sup> reported that a single dose of barbiturates would not protect against prolonged focal cerebral infarction. Ramesh and Umamaheswara Rao<sup>18</sup> recently suggested that a single bolus of barbiturate provide a limited values and incomplete protection. In addition, barbiturates have the potential disadvantages of hemodynamic instability and decreased cardiac contractility. Both of these factors result in significant drops in systemic blood pressure and it jeopardizes collateral circulation flow to the ischemic area<sup>17</sup>. These reports and potential risks led us to search for

other agents with longer protection time during TAO with few side effects.

In the present study, barbiturates and etomidate produced substantial duration of burst suppression, approximately 11 minutes of BSR measured by the BIS monitor. This finding suggests that additional and/or continuous barbiturates administration is needed to ensure burst suppression on EEG when the duration of TOA exceeds 11 min.

Although it has not been nearly as extensively studied as the barbiturate, etomidate produced dose-dependent burst suppression with an approximately a 50% reduction in the  $CMRO_2$ <sup>19</sup>. Etomidate has been advocated by several studies as a neuroprotectant in intracranial aneurysm surgery, although its effect in this regard is controversial<sup>6,8,11,23</sup>. Batjer et al.<sup>3</sup> reported successful management with etomidate during temporary vascular occlusion in patients with large and giant cerebral aneurysms. Samson et al.<sup>21</sup> also reported on the use of etomidate as a cerebral protectant with minimal cardiac suppression. Unlike barbiturates, etomidate can be used as an induction agent in hypovolemic patients and it offers the two major advantages of minimal cardiovascular depression and maintaining the CPP. During TAO, hypotension may worsen the microcirculation and collateral circulations. This will increase cerebral ischemic damage and carries the risk of ischemia in the territory distal to the occlusion<sup>17</sup>. Therefore, it is of considerable importance to maintain an adequate CPP during TAO. In this respect, etomidate seems to be a suitable drug for a patient with hypovolemia or cardiac disease in whom TAO is performed. But, several studies suggested that etomidate is associated with the potential risks of adrenal insufficiency<sup>26</sup>, increasing cerebral ischemic injuries<sup>6</sup> and developing brain tissue acidosis in patient with existing

lower PO<sub>2</sub> values<sup>11</sup>). The present study also showed that more phenylephrine was required to maintain blood pressure in patients with a thiopental group compared to that of patients in the etomidate group.

It is recommended to assess burst suppression with continuous EEG monitoring when cerebral protection is performed with pharmacological agents such as barbiturates or etomidate. However, not all the hospitals are available for intraoperative EEG monitoring systems and it is a bulky apparatus requiring specialized training to interpret. BIS monitoring has recently emerged as an alternative to conventional EEG machine for monitoring brain metabolic activity<sup>2</sup>).

BIS is a complex EEG parameter which integrates several disparate descriptors of the EEG into a single variable<sup>4</sup>). It is scaled from 100 to 0, with 100 representing an awake EEG and zero representing complete electrical silence (cortical suppression). One of the subparameters incorporated in the BIS is the suppression ratio, quantifying the percentage of suppression during burst suppression pattern. BSR represents the percentage of the previous 63-second epochs of the EEG that is recognized as being isoelectric by voltage criteria on BIS. BIS number represents depth of anesthesia and BSR does brain protection effect<sup>4</sup>).

In the present study, we assessed the values of BSR on the BIS monitor instead of the burst suppression on EEG to compare the burst suppression of both drugs. Etomidate showed a nearly identical magnitude of BSR changes as that of barbiturates.

In many studies, it is often assumed that burst suppression has been equated with maximal cerebral suppression as that of isoelectric EEG, irrespective to its magnitude<sup>1</sup>). Doyle and Matta<sup>5</sup>) investigated the effect of different degree of EEG suppression on the CBF and oxygen difference in patients undergoing general anesthesia for resection of acoustic neuroma. However, they concluded that cerebral metabolism during 50% EEG burst suppression is not equivalent to isoelectric EEG. That is, the degree of BSR inversely correlates with the reduction in the CMRO<sub>2</sub>. Based on the present study results, it is expected that single bolus administration of etomidate would provide a similar magnitude (degree) of cerebral metabolism reduction and cerebral protection.

Several studies<sup>12,25</sup>) have reported significant correlation between conventional EEG and BIS values and have used the values of BSR as a guide in barbiturate infusion therapy. Therefore, it is considered that the BIS monitoring can be substituted for conventional EEG monitoring to confirm burst suppression with CMR-reducing agents in patients undergoing ischemic procedures such as extracranial to intracranial bypass procedures, carotid endarterectomy or temporary clipping during aneurysm surgery.

In this study, we have only investigated the BIS values and BSR patterns with the injection of both drugs which were known as brain protectant. Further imaging study will be helpful to confirm the brain protection effect. Also, only one dosage of drug was used for this study and thus various doses of drugs

should be tried for exact estimation of action duration.

## CONCLUSION

It appears that the etomidate and barbiturates provide approximately 11 minute duration of burst suppression and a similar magnitude of burst suppression (the same potential for brain protection) during temporary artery occlusion. Therefore, additional and/or continuous administration of barbiturates is needed to ensure the burst suppression on EEG when prolonged arterial occlusion is inevitable. Using the BIS monitor with the values of BSR is clinically useful to demonstrate the burst suppression pattern on EEG with the CMR-acting agents during aneurysm surgery in which temporary arterial occlusion is expected. Based on our study, etomidate can be a substitute for barbiturate during aneurysm surgery with minimal cardiac suppression.

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