Efficacy of Low Dose Barbiturate Coma Therapy for the Patients with Intractable Intracranial Hypertension Using the Bispectral™ Index Monitoring

Hung-Shik An, M.D., Byung-Moon Cho, M.D., Jeong-Han Kang, M.D., Moon-Kyu Kim, M.D., Sae-Moon Oh, M.D., Se-Hyuck Park, M.D.
Department of Neurosurgery, Kangdong Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Korea

Objective: Barbiturate coma therapy (BCT) is a useful method to control increased intracranial pressure (IICP) patients. However, the complications such as hypotension and hypokalemia have caused conditions that stopped BCT early. The complications of low dose BCT with Bispectral™ index (BIS) monitoring and those of high dose BCT without BIS monitoring have been compared to evaluate the efficacy of low dose BCT with BIS monitoring.

Methods: We analyzed 39 patients with high dose BCT group (21 patients) and low dose BCT group (18 patients). Because BIS value of 40-60 is general anesthesia score, we have adjusted the target dose of thiopental to maintain the BIS score of 40-60. Therefore, dose of thiopental was kept 1.3 to 2.6 mg/kg/hour during low dose BCT. However, high dose BCT consisted of 5 mg/kg/hour without BIS monitoring.

Results: The protocol of BCT was successful in 72.2% and 38.1% of low dose and high dose BCT groups, respectively. The complications such as QT prolongation, hypotension and cardiac arrest have caused conditions that stopped BCT early. Hypokalemia showed the highest incidence rate in complications of both BCT. The descent in potassium level were 0.63 ± 0.26 in low dose group, and 1.31 ± 0.48 in high dose group. The treatment durations were 4.89 ± 1.68 days and 3.38 ± 1.24 days in low dose BCT and high dose BCT, respectively.

Conclusion: It was proved that low dose BCT showed less severe complications than high dose BCT. Low dose BCT with BIS monitoring provided enough duration of BCT possible to control ICP.

KEY WORDS: Barbiturate coma therapy · Bispectral™ index (BIS) · Thiopental.
MATERIALS AND METHODS

Patient population

Total number of patients who were treated with BCT was 63 from 2003 to 2008. Twenty-one patients with high dose BCT from 2003 to 2006 (Table 1) and 18 patients with low dose BCT from 2006 to 2008 (Table 2) were chosen in this study. We selected these patients who had severe IICP.

Table 1. Cases of high dose BCT without BIS monitoring

| Case | Age | Sex | Initial ICP* | Initial GCS score | Brain insult | Operation | Duration (days) | Success of BCT | Cause of BCT stopped |
|------|-----|-----|--------------|-------------------|--------------|-----------|----------------|-----------------|---------------------|
| 1    | 55  | M   | Mild         | 7                 | SDH          | Craniectomy| 5              | O               | QT prolongation     |
| 2    | 59  | M   | Moderate     | 4                 | Aneurysm     | EVD       | 3              | X               | Hypotension         |
| 3    | 49  | M   | Mild         | 8                 | SDH          | ICP monitor| 4              | O               | QT prolongation     |
| 4    | 46  | M   | Mild         | 4                 | SDH          | Craniectomy| 2              | X               | Hypotension         |
| 5    | 66  | M   | Mild         | 7                 | SDH          | Craniectomy| 5              | O               | QT prolongation     |
| 6    | 61  | M   | Moderate     | 4                 | Aneurysm     | Craniectomy| 3              | X               | Hypotension         |
| 7    | 54  | F   | Moderate     | 3                 | ICH          | EVD       | 3              | X               | QT prolongation     |
| 8    | 53  | M   | Mild         | 4                 | SDH          | Craniectomy| 4              | O               | QT prolongation     |
| 9    | 49  | F   | Mild         | 8                 | SDH          | Craniectomy| 4              | O               | QT prolongation     |
| 10   | 57  | F   | Mild         | 7                 | Aneurysm     | EVD       | 4              | O               | QT prolongation     |
| 11   | 56  | F   | Moderate     | 4                 | SDH          | Craniectomy| 5              | O               | QT prolongation     |
| 12   | 43  | M   | Mild         | 3                 | Aneurysm     | EVD       | 3              | X               | Cardiac arrest      |
| 13   | 59  | M   | Mild         | 7                 | ICH          | EVD       | 3              | X               | Hypotension         |
| 14   | 39  | M   | Mild         | 6                 | Aneurysm     | ICP monitor| 4              | X               | Hypotension         |
| 15   | 55  | M   | Mild         | 6                 | SDH          | Craniectomy| 1              | X               | QT prolongation     |
| 16   | 48  | F   | Mild         | 8                 | Aneurysm     | Craniectomy| 1              | X               | Hypotension         |
| 17   | 68  | M   | Mild         | 7                 | Infarction   | ICP monitor| 4              | X               | Hypotension         |
| 18   | 53  | M   | Mild         | 8                 | Aneurysm     | EVD       | 5              | X               | Hypotension         |
| 19   | 46  | F   | Mild         | 8                 | SDH          | Craniectomy| 2              | X               | QT prolongation     |
| 20   | 51  | F   | Moderate     | 4                 | T-ICH        | EVD       | 2              | X               | Hypotension         |
| 21   | 55  | M   | Mild         | 7                 | T-ICH        | ICP monitor| 4              | O               | QT prolongation     |

*ICP: < 20 mmHg (normal), 20-30 mmHg (mild), 30-40 mmHg (moderate), > 40 mmHg (severe). BCT: barbiturate coma therapy, DAI: diffuse axonal injury, EVD: external ventricular drainage, ICH: intracerebral hemorrhage, ICP: intracranial pressure, SDH: subdural hemorrhage, T-ICH: traumatic intracerebral hemorrhage

Table 2. Cases of low dose BCT with BIS monitoring

| Case | Age | Sex | Initial ICP* | Initial GCS score | Brain insult | Operation | Duration (days) | Success of BCT | Cause of BCT stopped |
|------|-----|-----|--------------|-------------------|--------------|-----------|----------------|-----------------|---------------------|
| 1    | 43  | M   | Moderate     | 4                 | SDH          | Craniectomy| 4              | X               | Hypotension         |
| 2    | 37  | M   | Mild         | 4                 | SDH          | Craniectomy| 4              | O               | QT prolongation     |
| 3    | 55  | M   | Mild         | 7                 | T-ICH        | ICP monitor| 10             | O               | QT prolongation     |
| 4    | 61  | M   | Mild         | 7                 | SDH          | Craniectomy| 4              | X               | QT prolongation     |
| 5    | 74  | M   | Mild         | 7                 | Aneurysm     | ICP monitor| 6              | O               | QT prolongation     |
| 6    | 40  | M   | Moderate     | 3                 | Aneurysm     | EVD       | 6              | O               | QT prolongation     |
| 7    | 37  | M   | Mild         | 4                 | Aneurysm     | EVD       | 6              | O               | QT prolongation     |
| 8    | 44  | M   | Moderate     | 4                 | SDH          | Craniectomy| 3              | O               | QT prolongation     |
| 9    | 65  | M   | Mild         | 6                 | Infarction   | Craniectomy| 3              | O               | QT prolongation     |
| 10   | 30  | M   | Mild         | 4                 | DAI          | ICP monitor| 4              | O               | QT prolongation     |
| 11   | 52  | F   | Moderate     | 4                 | SDH          | Craniectomy| 6              | O               | QT prolongation     |
| 12   | 47  | F   | Moderate     | 4                 | SDH          | Craniectomy| 3              | X               | Hypotension         |
| 13   | 63  | M   | Moderate     | 3                 | SDH          | Craniectomy| 4              | O               | Hypotension         |
| 14   | 56  | M   | Mild         | 4                 | Aneurysm     | EVD       | 5              | O               | QT prolongation     |
| 15   | 52  | F   | Mild         | 7                 | DAI          | ICP monitor| 5              | O               | QT prolongation     |
| 16   | 55  | F   | Mild         | 7                 | SDH          | Craniectomy| 5              | O               | QT prolongation     |
| 17   | 45  | M   | Mild         | 6                 | ICH          | EVD       | 6              | O               | QT prolongation     |
| 18   | 47  | F   | Mild         | 4                 | Aneurysm     | EVD       | 4              | X               | QT prolongation     |

*ICP: < 20 mmHg (normal), 20-30 mmHg (mild), 30-40 mmHg (moderate), > 40 mmHg (severe). BCT: barbiturate coma therapy, DAI: diffuse axonal injury, EVD: external ventricular drainage, ICH: intracerebral hemorrhage, ICP: intracranial pressure, SDH: subdural hemorrhage, T-ICH: traumatic intracerebral hemorrhage
due to cerebral edema following parenchymal damage not respective of their causative pathologic conditions, either head trauma or stroke. Patients were comatose with GCS score of 8 or less at admission. They underwent various surgical managements such as decompressive craniectomy, external ventricular drainage (EVD) insertion and intracranial pressure (ICP) monitor insertion prior to BCT. During the decompressive craniectomy, subdural type ICP monitor was inserted. Ventricular type ICP monitor was inserted during the EVD insertion while epidural type ICP monitor insertion was performed without any other procedure. Patients who expired immediately after starting BCT and who were not on ICP monitoring were excluded.

Protocols of BCT

We monitored ICP at the beginning of BCT. ICP values of 20 mmHg or less were set as normal ICP, 20 to 30 mmHg as mild, 30 to 40 as moderate, and higher than 40 as severe\(^\text{13}\). If ICP was kept less than 20 mmHg for more than 48 hours, the protocol of BCT was stopped. This was set as a success of BCT. When life-threatening or uncontrollable complications were evident (i.e., QT prolongation, hypotension, cardiac arrest), BCT was stopped. This was set as a failure of BCT.

We followed the BCT protocol from the study of Eisenberg et al.\(^\text{4}\). High dose BCT was induced with thiopental with a loading of 10 mg/kg over 30 minutes, and then the continuous infusion of 5 mg/kg/hour was maintained for following 3 days\(^\text{13}\). On the fourth day, the dose of thiopental was reduced by half.

Low dose BCT was monitored by BIS monitor. In low dose BCT protocol, the dose of thiopental was ranged between 1.3 and 2.6 mg/kg/hour.

Hypotension (systolic blood pressure < 90 mmHg) during BCT was managed with volume replacement and dopamine. However, if hypotension persisted, we ceased BCT. Hypokalemia was managed with potassium chloride (KCl). If changes in electrocardiography (ECG) occurred, such as prolonged QT interval, BCT was stopped immediately. BCT was continued when other controllable complications (i.e., hypernatremia, hyperkalemia) were corrected with an appropriate measures.

**BIS monitor**

Continuous electroencephalogram (EEG) monitoring is not available in all intensive care unit (ICU). Therefore, portable EEG-based monitors like the BIS monitor are now used in ICU to monitor the depth of anesthesia and sedation. The BIS monitor has been used in our study since 2006. We used an A-2000 BIS index monitor (version 3.01; Aspect Medical Systems), with commercially available BIS sensor strips with three electrodes. One electrode was placed on the center of the forehead, one directly above and parallel to eyebrow, and one in the temple area (Fig. 1). The monitor uses Fourier transformation and bispectral analysis to compute a number (BIS score) ranging from 0 (isoelectric) to 100 (fully awake)\(^\text{2}\). The BIS scores of 0 to 40, 40 to 60, 60 to 70, and 70 to 100 are deep hypnotic state, general anesthesia state, deep sedation state, and light sedation state, respectively\(^\text{2}\).

**Statistics**

SPSS v11.0 software (SPSS Inc., Chicago, IL, USA) running on a Windows XP platform was used for analysis. All summary data are expressed as mean ± standard deviation. The paired t-test was performed if the normal distribution assumption was satisfied. Variables were compared between subgroups. Statistical significance was set at \(p < 0.05\).

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**Fig. 1.** A 42-years-old woman visited emergency care unit with acute altered mentality. She was comatose with pupil dilatation. After EVD insertion, she had been treated with low dose BCT with BIS monitoring. A : CT image shows diffuse SAH on both sylvian fissure and massive ICH on the left frontal area with IVH. B : BIS leads are being placed on her forehead. C : BIS monitoring was started after BCT. BCT : barbiturate coma therapy, BIS : Bispectral\(^\text{TM}\), index, CT : computed tomography, EVD : external ventricular drainage, ICH : intracerebral hemorrhage, SAH : subarachnoid hemorrhage.
RESULTS

The demographic data is presented in Table 3. Mean ages, male to female ratios were 50.17 ± 11.25 and 53.43 ± 7.14, 13 : 5 and 14 : 7 in low dose and high dose BCT group, respectively. The initial ICP are presented in Table 3. The initial ICP was mild (66.7%) and moderate (33.3%) in low dose BCT group. In high dose BCT group, the initial ICP was mild in 76.2% and moderate in 23.8% (Table 3). The types of brain insult are listed in Table 3. The ratios of spontaneous insult to traumatic insult were 7 : 11 and 10 : 11 in low dose and high dose BCT group, respectively (Table 4). The percentages of surgical managements that low dose BCT groups received were EVD insertion (27.8%), ICP monitor insertion (22.2%), and decompressive craniectomy (50%), while high dose BCT groups received EVD insertion (33.3%), ICP monitor insertion (19.1%), and decompressive craniectomy (52.6%) (Table 5).

Outcome of BCT

The protocol of BCT was successful in 72.2% and 38.1% of low dose and high dose BCT groups when ICP was kept under 20 mmHg more than 48 hours (Table 6). The complications such as QT prolongation, hypotension and cardiac arrest have caused conditions that stopped BCT early. QT prolongation was seen in 2 and 8 patients in low dose and high dose BCT group. Cardiac arrest occurred in 1 patient in high dose BCT group. Hypotension was observed in 3 and 4 patients in low dose and high dose BCT group. Cardiac arrest was found only in high dose BCT group. Also patients showed hypotension were 16.7% of low dose BCT group and 19.1% of high dose BCT group (Table 7).

There were various complications in both groups, such as hypotension, azotemia, pneumonia, and electrolyte imbalance (hypernatremia, hypokalemia, hyperkalemia) (Table 8). Electrolyte imbalance was the most common complication in both BCT. Hypokalemia showed the highest incidence rate among three types of electrolyte imbalance which was found in both groups. The initial values of potassium measured at the beginning of the study were 3.73 ± 0.28 mEq/L and 3.82 ± 0.31 mEq/L in two groups, respectively ($p = 0.350$). When hypokalemia occurred as a complication of BCT, the average values of potassium level were 3.11 ± 0.28 mEq/L and 2.51 ± 0.48 mEq/L in low dose BCT and high dose BCT groups, respectively ($p < 0.005$). The descent in potassium level were 0.63 ± 0.26 in low dose group, and 1.31 ± 0.48 in high dose group ($p < 0.005$) (Table 9).

### Table 3. Demographic data

|                      | Low dose BCT | High dose BCT | p-value |
|----------------------|--------------|---------------|---------|
| No. of cases         | 18           | 21            |         |
| Age (years)          | 50.17 ± 11.25(30-74) | 53.43 ± 7.14 (39-68) | 0.280   |
| Sex (M : F)          | 13 : 5       | 14 : 7        |         |
| Initial GCS score    |              |               |         |
| 3-4                  | 11 (68.9%)   | 8 (38.1%)     |         |
| 5-8                  | 7 (31.1%)    | 13 (61.9%)    |         |
| Initial ICP          |              |               |         |
| Normal (< 20 mmHg)   | 0            | 0             |         |
| Mild (20-30 mmHg)    | 12 (66.7%)   | 16 (76.2%)    |         |
| Moderate (30-40 mmHg)| 6 (33.3%)    | 5 (23.8%)     |         |
| Severe (> 40 mmHg)   | 0            | 0             |         |

BCT: barbiturate coma therapy, ICP : intracranial pressure

### Table 4. Types of brain insult

| Mode of brain insult | Low dose BCT (%) | High dose BCT (%) |
|----------------------|------------------|-------------------|
| Spontaneous          | 7 (38.9)         | 11 (52.4)         |
| Trauma               | 11 (61.1)        | 10 (47.6)         |

### Table 5. Surgical managements prior to BCT

| Operation                        | Low dose BCT (%) | High dose BCT (%) | p-value |
|----------------------------------|------------------|-------------------|---------|
| EVD                              | 5 (27.8)         | 7 (33.3)          |         |
| ICP monitor                      | 4 (22.2)         | 4 (19.1)          | > 0.5   |
| Decompressive craniectomy        | 9 (50.0)         | 10 (52.6)         |         |

BCT: barbiturate coma therapy, EVD: external ventricular drainage, ICP: intracranial pressure

### Table 6. Correlation ICP control with thiopental dose

| Success* of BCT | Low dose BCT (%) | High dose BCT (%) | p-value |
|-----------------|------------------|-------------------|---------|
|                 | 13 (72.2)        | 8 (38.1)          | 0.070   |

*ICP controlled (success) : ICP < 20 mmHg for 2days. BCT: barbiturate coma therapy, ICP: intracranial pressure

### Table 7. Correlation ICP control with thiopental dose

| Failure of BCT | Low dose BCT (%) | High dose BCT (%) | p-value |
|---------------|------------------|-------------------|---------|
|               | 5 (27.8)         | 13 (61.9)         |         |
Patients showed QT prolongation on ECG were 11.1% of low dose BCT group and 38.1% of high dose BCT group.

**Duration of BCT**

We compared the duration of coma therapy of the two groups. Low dose group had longer duration than high dose group for coma therapy. The durations were 4.89 ± 1.68 days and 3.38 ± 1.24 days in low dose BCT group and high dose BCT group, respectively (p = 0.003) (Table 10).

**DISCUSSION**

It has been recognized for many years that barbiturate has many pharmacological effects, which is beneficial for the management of IICP patients. However, BCT also has serious side effects. Dosing of barbiturates is guided by the extent of induced burst-suppression pattern on the electroencephalogram (EEG). Dosing beyond the point of burst suppression may increase the risk of complications without further therapeutic benefit. For this reason, careful monitoring of EEG parameters is mandatory.

The BIS monitor potentially aids monitoring barbiturate induced coma because it provides continuous data on EEG suppression. We have been monitoring BIS to value sedative status for BCT since 2006. Because ICP is controlled by deep sedation, we adjusted the target does of thiopental to maintain the BIS score of 40-60 which is the same value that shows when a patient is under general anesthesia.

Therefore, dose of thiopental was maintained 1.3 to 2.6 mg/ kg/hour during low dose BCT. However, high dose BCT used 5 mg/kg/ hour for initial 3 days without BIS monitor. On the fourth day, the dose of thiopental was reduced by half. A bolus intravenous injection of thiopental (100 or 200 mg) was used when ICP increased more than 20 mmHg during low dose and high dose BCT.

Various complications were associated during BCT. The complications occurred during the treatment with BCT included hypotension, azotemia, pneumonia, and electrolyte imbalance (hypernatremia, hypokalemia, hyperkalemia). Complications of BCT were mostly transient and could be adequately resolved in the ICU setting. However, hypotension and electrolyte imbalance were exceptions which often presented in severe forms. Hypotension during BCT was due to the depressive effect of thiopental on cardiac contractility. Electrolyte imbalance was the most common complication in both BCT groups. Hypokalmeia was found in both BCT groups and showed the highest incidence rate. There are several reasons why the administration of thiopental may cause hypokalemia. Thiopental inhibits the neuronal current of voltage-dependant potassium. This would lead to a decrease in extracellular potassium, which would resolve on cessation of the thiopental. Another possible mechanism is its reduction of intracellular production of pyruvate and lactate through the inhibition of phosphofructokinase and an increase in intracellular pH. Hypokalmeia is a well-known cause for a prolonged QT interval on ECG. It is known that action potential prolongation under hypokalemic conditions has recently been attributed to reductions in the repolarizing K+ currents, which sets the ground for arrhythmia thus increasing the risk of ventricular tachycardia and sudden death.
The duration of low dose BCT (4.89 ± 1.68 days) compared to the one of high dose BCT (3.38 ± 1.24 days) was longer by 2 days. It was because the treatment was not ceased during low dose BCT since complications like hypotension and hypokalemia were less severe. The protocol of BCT was successful in 72.2% and 38.1% of low dose and high dose BCT groups, respectively. Consequently, the less severe complications of low dose BCT resulted in the longer duration of treatment. There was enough duration of treatment to control ICP.

There are some limitations which could affect the reliability of the results of our study. The patient groups included heterogeneous conditions, which were head trauma and stroke. The group also had various types of surgical management. In addition, the sample size was small. We need homogeneous comparison groups with large sample sizes.

CONCLUSION

The BCT is a useful method to control IICP. However, the complications such as hypotension and hypokalemia have caused conditions that stopped BCT early. We have compared the complications of low dose BCT with BIS monitoring and those of high dose BCT without BIS monitoring to prove that the low dose BCT with BIS monitoring caused less severe complications. It has shown that low dose BCT had less severe complications than high dose BCT. Low dose BCT with BIS monitoring provided enough duration of BCT possible to control ICP.

References

1. Adelson PD, Bratton SL, Carney NA, Chesnut RM, du Coudray HE, Goldstein B, et al.: Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents. Chapter 13. The use of barbiturates in the control of intracranial hypertension in severe pediatric traumatic brain injury. Pediatr Crit Care Med 4: S49-S52, 2003
2. Bard JW: The BIS monitor: a review and technology assessment. AANA J 69: 477-483, 2001
3. Carlsson C, Nordstrom CH, Sjesjo BK: Metabolic change in the cerebral cortex of the rat induced by intravenous pentothal sodium. Acta Anaesthesiol Scand 57: 7-17, 1975
4. Eisenberg HM, Frankowski RF, Contant CF, Marshall LF, Walker MD: High dose barbiturate control of elevated intracranial pressure in patients with severe head injury. J Neurosurg 69: 15-23, 1988
5. Finfer SR, Cohen J: Severe traumatic brain injury. Resuscitation 48: 77-90, 2001
6. Friederich P, Urban BW: Interaction of intravenous anesthetics with human neuronal potassium currents in relation to clinical concentrations. Anesthesiology 91: 1853-1860, 1999
7. Heo DH, Hu C, Cho SM, Whang K, Pyen S, Kim HJ: Barbiturate coma therapy in severe and refractory vasospasm following subarachnoid hemorrhage. J Korean Neurosurg Soc 33: 142-148, 2003
8. Huynh F, Mahasa VH, Ensom MH: A critical review: does thioental continuous infusion warrant therapeutic drug monitoring in the critical care population? Ther Drug Monit 31: 153-169, 2009
9. Kim YI, Park SW, Nam TK, Park YS, Min BK, Hwang SN: The effect of barbiturate coma therapy for the patients with severe intracranial hypertension: a 10-year experience. J Korean Neurosurg Soc 44: 141-145, 2008
10. Macias-Robles MD, Perez-Clemente AM, Macia-Bobes C, Alvarez-Rueda MA, Pozo-Nuevo S: Prolonged QT interval in a man with anorexia nervosa. Int Arc Med 2: 23, 2009
11. Marshall LF, Smith RW, Shapiro HM: The outcome with aggressive treatment in severe head injuries. Part II: acute and chronic barbiturate administration in the management of head injury. J Neurosurg 50: 26-30, 1979
12. Prins SA, de Hoog M, Blok JH, Tibboel D, Visser GH: Continuous noninvasive monitoring of barbiturate coma in critically ill children using the Bispectral index monitor. Crit Care 11: R108, 2007
13. Rangel-Castilla L, Gopinath S, Robertson CS: Management of intracranial hypertension. Neurol Clin 26: 521-541, 2008
14. Sahir IN, Killeen MJ, Goddard CA, Thomas G, Gray S, Grace AA, et al.: Transient alterations in transmural repolarization gradients and arrhythmogenicity in hypokalaemic Langendorff-perfused murine hearts. J Physiol 581: 277-289, 2007
15. Schwartz ML, Tator CH, Roved DW, Reid SR, Meguro K, Andrews DF: The University of Toronto head injury treatment study: a prospective, randomized comparison of pentobarbital and mannitol. Can J Neurol Sci 11: 434-440, 1984
16. Ward JD, Becker DP, Miller JD, Choi SC, Marmarou A, Wood C, et al.: Failure of prophylactic barbiturate coma in the treatment of severe head injury. J Neurosurg 62: 383-388, 1985
17. Yanay O, Brogan TV, Martin LD: Continuous pentobarbital infusion in children is associated with high rates of complications. J Crit Care 19: 174-178, 2004