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Clinical Article

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

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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 monitoing.

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.

INTRODUCTION

Barbiturate coma therapy (BCT) for the treatment of increased intracranial pressure (IICP) has been studied since 1970s with varying outcomes[11,15,16]. In 1988, investigators reported the results of a five-center randomized controlled trial of high-dose barbiturate therapy for intractable IICP in patients with Glasgow coma scale (GCS) of 4 to 8[4]. Kim et al.[9] found that the patients in the barbiturate therapy group had shown improvement in ICP control. Due to drug availability and experience of use described in the literature, thiopental is most common barbiturate used for lowering IICP[7]. However, BCT has serious adverse effects such as hypotension, azotemia, pneumonia, and electrolyte imbalance (hypernatremia, hypokalemia, hyperkalemia)[6,8,17]. The BCT is mostly interrupted by these complications.

There have been rare domestic reports about the adverse effects of BCT for IICP patients and Bispectral™ index (BIS) monitoring in BCT in Korea. In this study, we summarized and analyzed the results of BCT with BIS monitoring used for IICP patients. We hypothesized that low dose BCT with BIS monitoring would show less severe complications comparing high dose BCT without BIS monitoring. The complications of low dose BCT with 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.

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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	
2	59	M	Moderate	4	Aneurysm	EVD	3	X	QT prolongation
3	49	M	Mild	8	DAI	ICP monitor	4	O	
4	46	M	Mild	4	SDH	Craniectomy	2	X	Hypotension
5	66	M	Mild	7	SDH	Craniectomy	5	O	
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	
9	49	F	Mild	8	SDH	Craniectomy	4	O	
10	57	F	Mild	7	Aneurysm	EVD	4	O	
11	56	F	Moderate	4	SDH	Craniectomy	5	O	
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	

*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	
3	55	M	Mild	7	T-ICH	ICP monitor	10	O	
4	61	M	Mild	7	SDH	Craniectomy	4	X	QT prolongation
5	74	M	Mild	7	Aneurysm	ICP monitor	6	O	
6	40	M	Moderate	3	Aneurysm	EVD	6	O	
7	37	M	Mild	4	Aneurysm	EVD	6	O	
8	44	M	Moderate	4	SDH	Craniectomy	3	O	
9	65	M	Mild	6	Infarction	Craniectomy	3	O	
10	30	M	Mild	4	DAI	ICP monitor	4	O	
11	52	F	Moderate	4	SDH	Craniectomy	6	O	
12	47	F	Moderate	4	SDH	Craniectomy	3	X	Hypotension
13	63	M	Moderate	3	SDH	Craniectomy	4	X	Hypotension
14	56	M	Mild	4	Aneurysm	EVD	5	O	
15	52	F	Mild	7	DAI	ICP monitor	5	O	
16	55	F	Mild	7	SDH	Craniectomy	5	O	
17	45	M	Mild	6	ICH	EVD	6	O	
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[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.[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[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)[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[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 $p < 0.05$.

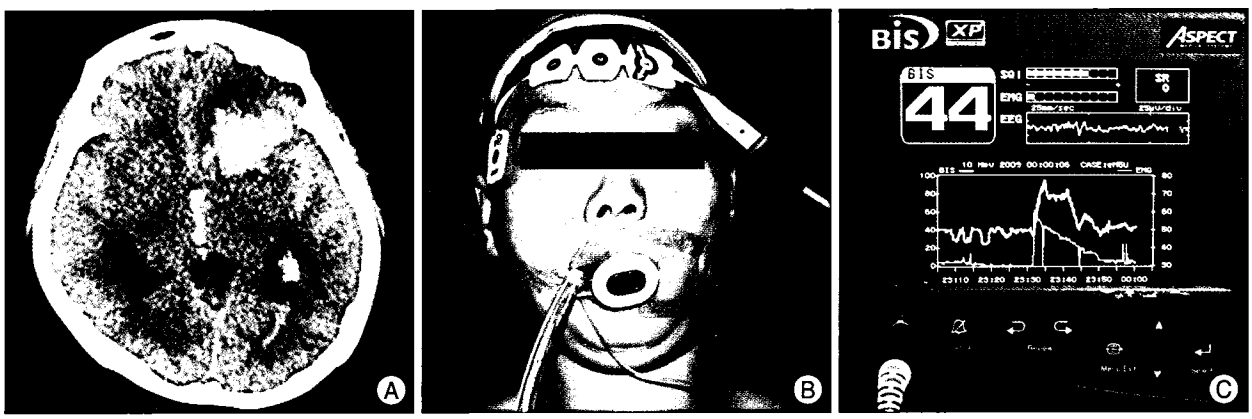

Fig. 1. A 42-years-old woman visited emergency care unit with acute altered mentality. She was comatose with pupil dilatation. After EVD insertion, she had been treated with low dose BCT with BIS monitoring. A : CT image shows diffuse SAH on both sylvian fissure and massive ICH on the left frontal area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

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

	Low dose BCT (%)	High dose BCT (%)
Mode of brain insult		
Spontaneous	7 (38.9)	11 (52.4)
Trauma	11 (61.1)	10 (47.6)
Types of brain insult		
ICH	1 (5.6)	2 (9.4)
Aneurysm	5 (27.8)	7 (33.3)
Cerebral infarction	1 (5.6)	1 (4.8)
Tumor	0	1 (4.8)
DAI	2 (11.0)	1 (4.8)
SDH	8 (44.4)	8 (38.0)
T-ICH	1 (5.6)	2 (9.4)

BCT : barbiturate coma therapy, DAI : diffuse axonal injury, ICH : intracerebral hemorrhage, SDH : subdural hemorrhage, T-ICH : traumatic intracerebral hemorrhage

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

	Low dose BCT (%)	High dose BCT (%)	*p*-value
Success* of BCT	13 (72.2)	8 (38.1)	0.070
Failure of BCT	5 (27.8)	13 (61.9)	

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

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 7. Cause of BCT stopped

	Low dose BCT (%)	High dose BCT (%)	*p*-value
QT prolongation	2 (11.1)	8 (38.1)	0.125
Cardiac arrest	0	1 (4.8)	
Hypotension	3 (16.7)	4 (19.1)	

BCT : barbiturate coma therapy, BCT : barbiturate coma therapy, ICP : intracranial pressure

Table 8. Complications

	Low dose BCT (%)	High dose BCT (%)
Hypernatremia	11 (61.1)	16 (76.2)
Hyperkalemia	7 (38.9)	11 (52.4)
Hypokalemia	15 (83.3)	18 (85.7)
Azotemia	1 (5.6)	1 (4.8)
Hypotension	4 (22.2)	5 (23.8)
Pneumonia	2 (11.1)	0
Arrest	0	1 (4.8)

BCT : barbiturate coma therapy

Table 9. Correlation serum potassium level with thiopental dose

	Low dose BCT (mean)	High dose BCT (mean)	*p*-value
K level (mEq/L, before BCT)	3.73 ± 0.28 (3.60-4.20)	3.82 ± 0.31 (3.50-4.70)	0.350
K level (mEq/L, after BCT)	3.11 ± 0.28 (2.60-3.70)	2.51 ± 0.48 (1.90-3.60)	< 0.005
K reduction level (mEq/L)	0.63 ± 0.26	1.31 ± 0.48	< 0.005

BCT : barbiturate coma therapy

Table 10. Duration of BCT

	Low dose BCT (mean)	High dose BCT (mean)	*p*-value
Duration (days)	4.89 ± 1.68 (3-10)	3.38 ± 1.24 (1-5)	0.003

BCT : barbiturate coma therapy

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[4]. However, BCT also has serious side effects[6,17]. Dosing of barbiturates is guided by the extent of induced burst-suppression pattern on the electroencephalogram (EEG)[1]. Dosing beyond the point of burst suppression may increase the risk of complications without further therapeutic benefit[9]. For this reason, careful monitoring of EEG parameters is mandatory[12].

The BIS monitor potentially aids monitoring barbiturate induced coma because it provides continuous data on EEG suppression[12]. 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[13]. 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[3]. 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[5]. Another possible mechanism is its reduction of intracellular production of pyruvate and lactate through the inhibition of phosphofructokinase and an increase in intracellular pH[3]. Hypokalemia is a well-known cause for a prolonged QT interval on ECG. It is known that action potential prolongation under hypokalemia conditions has recently been attributed to reductions in the repolarizing K+ currents, with studies on the murine heart[10]. Prolonged QT interval represents a local difference in myocardial excitability which sets the ground for arrhythmia thus increasing the risk of ventricular tachycardia and sudden death[11].

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.

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