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Efficacy of a Novel Prophylactic Barbiturate Therapy for Severe Traumatic Brain Injuries: Step-down Infusion of a Barbiturate with Normothermia

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Abstract

This study aimed to examine the beneficial effects of a novel prophylactic barbiturate therapy, step-down infusion of barbiturates, using thiamylal with normothermia (NOR+sdB), on the poor outcome in the patients with severe traumatic brain injuries (sTBI), in comparison with mild hypothermia (MD-HYPO). From January 2000 to March 2019, 4133 patients with TBI were admitted to our hospital. The inclusion criteria were: a Glasgow coma scale (GCS) score of ≤8 on admission, age between 20 and 80 years, intracranial hematoma requiring surgical evacuation of the hematoma with craniotomy and/or external decompression, and patients who underwent management of body temperature and assessed their outcome at 6–12 months. Finally, 43 patients were included in the MD-HYPO (n = 29) and NOR+sdB (n = 14) groups. sdB was initiated intraoperatively or immediately after the surgical treatment. There were no significant differences in patient characteristics, including age, sex, past medical history, GCS on admission, type of intracranial hematoma, and length of hospitalization between the two groups. Although NOR+sdB could not improve the patient's poor outcome either at discharge from the intensive care unit (ICU) or at 6–12 months after admission, the treatment inhibited composite death at discharge from the ICU. The mean value of the maximum intracranial pressure (ICP) in the NOR+sdB group was <20 mmHg throughout the first 120 h. NOR+sdB prevented composite death in the ICU in patients with sTBI, and we may obtain novel insights into the beneficial role of prophylactic barbiturate therapy from suppression of the elevated ICP during the first 120 h.

Keywords: barbiturate, step-down infusion, normothermia, severe traumatic brain injury, mortality

Introduction

Severe traumatic brain injuries (sTBI) are associated with high mortality and severe disability, and are also associated with unavoidable social, economic,

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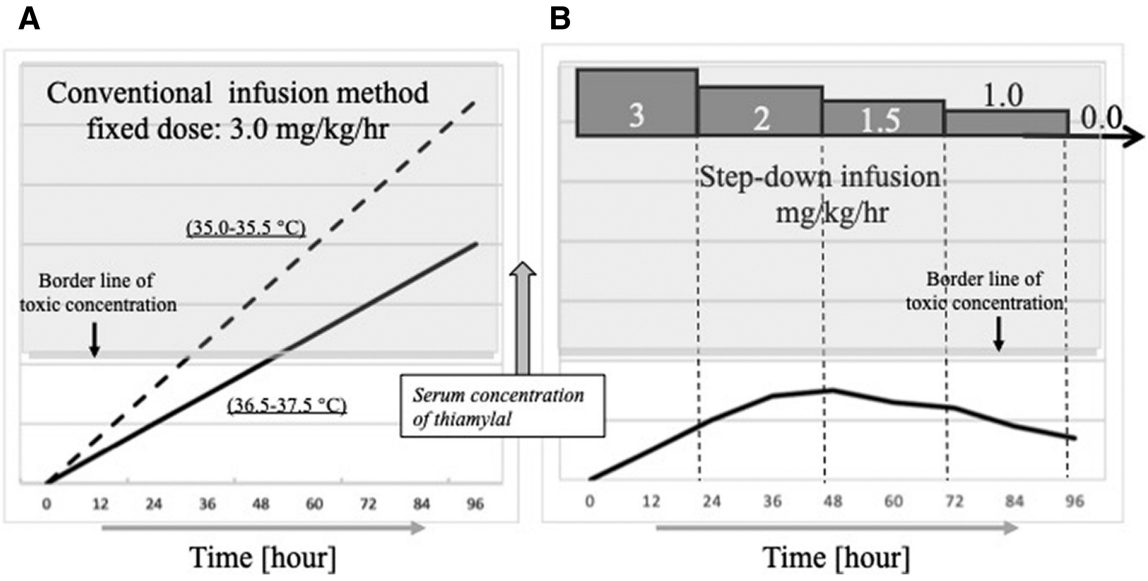

Fig. 1 Schematic illustrations of the temporal thiamylal concentration, which also contains modified data from our previous study.[8] (A) Continuous infusion of a fixed dose of thiamylal (3.0 mg/kg/h) linearly increased the serum concentration to a critical level especially under hypothermia in the animal experience. (B) The serum concentration of thiamylal could be controlled within the safety concentration by the step-down infusion method.

and health problems. It has been reported that one of the main determinants of poor outcome in patients with sTBI is an increased intracranial pressure (ICP), which can result from intracranial hemorrhage, brain edema, and obstructive hydrocephalus, among others.[1] Therefore, several interventions to control ICP and improve the outcome, including management of body temperature and barbiturate therapy, have been widely studied.[2]

Barbiturates exert sedative and anesthetic effects by potentiating the action of γ-aminobutyric acid (GABA) at the $GABA_A$ receptor.[3] Barbiturates can decrease cerebral blood flow and volume, resulting in a reduction in the increased ICP.[4] However, according to the guidelines for the management of TBI, based on several clinical studies on barbiturates, high-dose barbiturate administration is only recommended (Level IIB) to control elevated ICP when hemodynamic stability is secured before and during barbiturate therapy.[5] On the other hand, thiamylal has been widely used for sedation in Japan[6,7] and could be used to control increased ICP if an appropriate protocol for thiamylal administration is established.

Recently, we focused on the therapeutic effect of thiamylal and examined its role in sTBI. In our preclinical pharmacokinetic analysis, continuous infusion of a fixed dose of thiamylal linearly increased the serum concentration to a critical level, especially under hypothermia (Fig. 1A). We successfully developed a novel infusion method called the "step-down infusion of barbiturate" (sdB), which helps to maintain a stable serum concentration of thiamylal within a safe margin for a prolonged duration (Fig. 1B).[8]

In our hospital, we have been treating patients with sTBI using mild hypothermia (MD-HYPO; 35–36°C through 5 days after TBI) from January 2000[9] and subsequently altered our therapeutic strategy to the combination therapy with normothermia (36–37°C for 5 days after TBI) and sdB (NOR+sdB) from December 2013 based on the newly established protocol.[8] The infusion methods allow good management of thiamylal concentrations to secure both ICP reduction and CPP maintenance without any severe complications. The favorable results of our previous study encouraged us to examine whether NOR+sdB was beneficial for patients with sTBI.

In the present study, we aimed to evaluate the beneficial effect of prophylactic barbiturate therapy on poor outcome in patients with sTBI, using thiamylal and by comparing the effects of NOR+sdB and MD-HYPO. The significant result of this study was that the former treatment significantly reduced mortality of the patients at discharge from the intensive care unit (ICU) with suppression of elevated ICP during the first 120 h.

Materials and Methods

Patient selection and characteristics

The study protocol was approved by the Ethics Committee of the Kurume University Hospital (No.

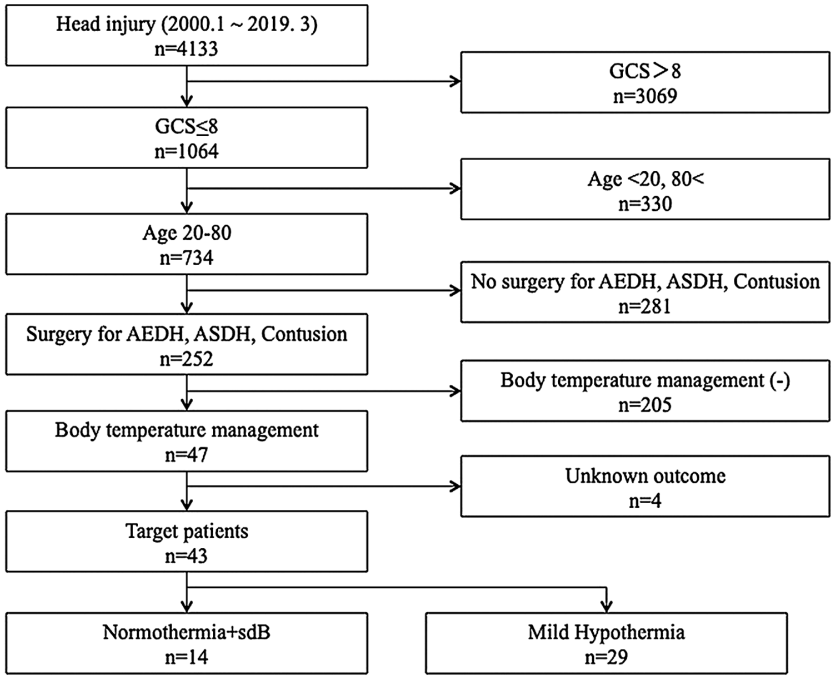

Fig. 2 Flow chart outlining the inclusion and exclusion criteria of this study. AEDH: acute epidural hematoma, ASDH: acute subdural hematoma, GCS: Glasgow coma scale, sdB: step-down infusion of barbiturate (thiamylal).

12268). A retrospective review of consecutive patients who were admitted to the Kurume University Hospital Advanced Critical Care Center was conducted from January 2000 to March 2019. Data collected included age, sex, Glasgow coma scale (GCS) score on admission, past medical history, primary diagnosis of TBI, length of ICU stay, Glasgow outcome scale (GOS) scores at discharge from the ICU and at 6–12 months after admission, and complications observed in the NOR+sdB group. In addition, the maximum ICP was measured every 1 h for 120 h in the NOR+sdB group. sTBI was defined as a GCS score of ≤8.

Outcome measurements were collected through telephone calls, outpatient follow-up records, and records from the hospital the patients had transferred from. We evaluated the poor outcome (GOS 1–2) at discharge from the ICU and at 6–12 months after admission as a primary endpoint, and our secondary objective was to explore composite death (GOS 1) at the same time points.

Inclusion criteria

The flow chart of the study design is shown in Fig. 2, and the inclusion criteria were as follows: GCS of ≤8 on admission; age between 20 and 80 years; conditions like intracranial hematoma including acute epidural hematoma (AEDH), acute subdural hematoma (ASDH), or contusion that needed surgical evacuation of the hematoma with craniotomy and/or external decompression; patients who underwent management of body temperature; and patients who could assess their outcome at 6–12 months. Finally, 43 patients were included in the MD-HYPO (n = 29) and NOR+sdB (n = 14) groups.

Management of body temperature

From January 2000 to December 2013, we treated patients with MD-HYPO, which was induced by surface cooling with water-circulating blankets. MD-HYPO was induced after the patient was admitted to the ICU and continued for 48–72 h, and then the patients were slowly rewarmed when the ICP was <20 mmHg.[9] If the ICP of the patients was >20 mmHg or increased again during rewarming, we continued MD-HYPO for an additional 48 h. The body temperature of the patients was maintained between 35°C and 36°C for 120 h after the start of hypothermia. From January 2014 to March 2019, the body temperature of patients with sTBI was maintained between 36°C and 37°C for 120 h using a Cool Line IVTM catheter (Asahi Kasei ZOLL Medical Co., Ltd, Tokyo, Japan).

Step-down infusion method of barbiturate using thiamylal

Prophylactic barbiturate using thiamylal was initiated intraoperatively or immediately after surgical treatment. The sdB method was performed as previously described,[8] and the novel treatment method

Table 1 Summary of the patient's characteristics between MD-HYPO and NOR+sdB groups

Characteristics	MD+HYP (n = 29)	NOR+sdB (n = 14)	p value
No. of cases	29	14	
Age (years)	51.8 ± 14.8	60.1 ± 13.6	p = 0.09
Sex ratio (M:F)	19:10	9:5	p = 1.0
Medical history			
Hypertension	5	4	p = 0.44
Diabetes mellitus	2	1	p = 1.0
Hyperlipidemia	1	0	p = 1.0
Oral antithrombotic drug	2	0	p = 1.0
Ischemic heart disease	1	0	p = 1.0
Tumor	2	4	p = 0.08
GCS on admission (mean)	4.7 ± 1.6	4.6 ± 2.1	p = 0.56
3	8	7	
4	9	2	
5	3	0	
6	3	6	
7	4	2	
8	2	2	
Type of intracranial hematoma			p = 0.45
ASDH	21	12	
AEDH	4	0	
Contusion	4	2	
Length of hospitalization	31.4 ± 24.2	37.8 ± 12.1	p = 0.12

Values are mean ± SD. AEDH: acute epidural hematoma; ASDH: acute subdural hematoma; F: female; GCS: Glasgow coma scale; GOS: Glasgow outcome scale; M: male; MD-HYPO: mild hypothermia; NOR: normothermia; sdB: step-down infusion of barbiturate with thiamylal

could help maintain a stable concentration of thiamylal under normothermia (Fig. 1B). Briefly, the infusion protocol was as follows: 3.0 mg/kg/h at 0–24 h, 2.0 mg/kg/h at 24–48 h, 1.5 mg/kg/h at 48–72 h, and 1.0 mg/kg/h at 72–96 h from the start of the treatment in the first six patients (3-0 start). For the rest (eight patients, 4-0 start), the dose of the thiamylal therapy was increased by adding another 4.0 mg/kg/h at 24 h prior to the first infusion at 3.0 mg/kg/h. If possible, a 5 mg/kg intravenous bolus injection of thiamylal was administered at the start of the treatment. We explained the advantages and disadvantages of this treatment to the patient's family and obtained their consent.

Sedative drug and ICP control

All patients were intubated and mechanically ventilated with administration of drugs such as midazolam, propofol, fentanyl, vacuronium, and/or rocuronium, and this was continued during the term for management of body temperature. Continuous ICP monitoring was performed using the ICP sensor (Johnson and Johnson, Raynham, MA, USA) at the same time as craniotomy or external decompression. Refractory increased ICP was defined as that >20 mmHg and subsequently lasting for more than 1 h. When refractory increased ICP was observed, osmotic diuretics such as mannitol or glyceol were administered to control the value within 20 mmHg. In the NOR+sdB group, changes in the maximum ICP values were extracted every 6 h for the first 24 h and then every 24 h for 120 h during the treatment.

Complication

Hypotension was defined as the need to administer a vasopressor. Hypokalemia was defined as a serum concentration less than 3.5 mEq/L. Pneumonia was diagnosed based on the presence of an infiltration shadow on chest X-ray. Arrhythmia was defined when patients were treated with antiarrhythmic drugs.

Table 2 Clinical outcome

Variable	MD-HYPO (n = 29)	NOR+sdB (n = 14)	p value
GOS at discharge			
1	9	0	
2	5	4	
3	11	5	
4	2	5	
5	2	0	
Dichotomous (poor outcome)			p = 0.33
1–2	14	4	
3–5	15	10	
Dichotomous (composite death)			p = 0.02
1	9	0	
2–5	20	14	
GOS at 6–12 months			
1	9	2	
2	4	1	
3	6	3	
4	6	5	
5	4	3	
Dichotomous (poor outcome)			p = 0.19
1–2	13	3	
3–5	16	11	
Dichotomous (composite death)			p = 0.29
1	9	2	
2–5	20	12	

GOS: Glasgow outcome scale; MD-HYPO: mild hypothermia; NOR: normothermia; sdB: step-down infusion of barbiturate using thiamylal

Statistical analysis

Age, GCS on admission, and length of hospitalization were expressed as the mean ± standard deviation. To analyze the poor outcome of our patients using a dichotomy, we set the threshold as follows: poor (GOS 1–2) and good (GOS 3–5). Age, GCS on admission, and length of hospitalization were analyzed by Mann–Whitney *U*-test between two groups, and other evaluations were performed by Fisher's exact test using GraphPad Prism version 6 for Windows (GraphPad Software, San Diego, CA, USA). Statistical significance was set at $p < 0.05$.

Results

A total of 43 patients were included in this study and their baseline characteristics are shown in Table 1. According to the MD-HYPO group, the mean age of the patients was 51.8 years and 65.5% were male. The medical history of the patients included hypertension (17.2%), diabetes mellitus (6.9%), hyperlipidemia (3.4%), intake of oral antithrombotic drugs (6.9%), ischemic heart disease (3.4%), and tumors (6.9%). The mean initial GCS of the patients was 4.7, the type of intracranial hematoma was ASDH (72.4%), AEDH (13.8%), and contusion (13.8%), and the mean length of stay in the ICU was 31.8 days. In the NOR+sdB group, the mean age of the patients was 60.1 years and 64.3% were male. The medical history of the patients included hypertension (28.6%), diabetes mellitus (7.1%), and tumor (28.6%).The mean initial GCS score of the patients was 4.6, type of intracranial hematoma was ASDH (85.7%) and contusion (14.3%), and the mean length of stay in the ICU was 37.8 days. Overall, there were no significant differences in the patient characteristics between both groups.

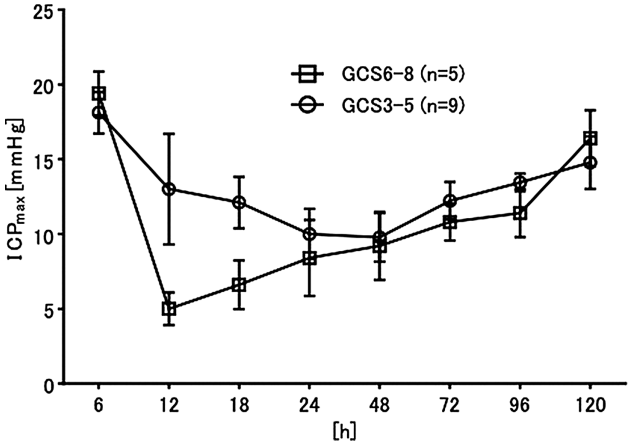

Fig. 3 Temporal changes of the maximum ICP value through 120 h after initiating NOR+sdB. Values are presented as the mean ± SEM. GCS: Glasgow coma scale; h: hour; ICP: intracranial pressure; max: maximum; NOR: normothermia; sdB: step-down infusion of barbiturate (thiamylal)

As shown in Table 2, the poor outcome (GOS 1–2) at discharge from ICU (48.3% vs. 28.6%, p = 0.33) and at 6–12 months after admission (44.8% vs. 21.4%, p = 0.19) did not differ between the MD-HYPO and NOR+sdB groups. However, results from the secondary endpoint at discharge from the ICU revealed a significant reduction in composite death in the NOR+sdB group (0%) in comparison with that in the MD-HYPO group (31%, p = 0.02).

To address the effect of NOR+sdB on composite death, we evaluated the temporal maximum ICP values over 120 h during the treatment. As shown in Fig. 3, the mean value of the maximum ICP was consistently controlled below 20 mmHg, especially less than 15 mmHg from 6 to 120 h after initiating the management of body temperature even for patients in the more severe group (GOS 3–5) on admission, while the mean ICP value of the patients with GOS 3–5 in our previous report did not completely suppress less than 20 mmHg.[9]

The patients in the NOR+sdB group underwent the following complications during hospitalization: hypotension (2 patients, 14.3%), hypokalemia (10 patients; 71.4%), pneumonia (8 patients; 57.1%), arrhythmia (1 patient; 7.1%), and gastrointestinal bleeding (0%). All the patients were treated with standard therapies.

Discussion

In this study, we could not meet the primary endpoint, which was a significant improvement in the outcomes of the patients. However, our novel treatment approach reduced mortality among patients with sTBI at the time of discharge from the ICU. Moreover, the maximum ICP during the first 120 h after the treatment was consistently controlled to <20 mmHg, especially <15 mmHg from 12 to 120 h, even if the condition of the patients was more severe with GOS 3–5. According to our previous study, MD-HYPO had decreased the mean value of ICP to <20 mmHg, while the incidence of elevated ICP >20 mmHg was 18.2%–34.8% during the first 5 days in the ICU.[9] The response to the ICP-lowering treatment was a key factor for the lowered risk of death in an early stage after sTBI, and barbiturate could also improve the survival of the patients with neurosurgical trauma if ICP was controlled.[10,11] These findings suggest that NOR+sdB was more potent in suppressing elevated ICP than MD-HYPO and contributed to the prevention of ICU death.

We recently focused on prophylactic barbiturate therapy because it has been reported to decrease elevated ICP. In addition, high-dose barbiturate therapy is recommended for the control of elevated ICP based on the guidelines for the management of TBI.[5] However, the treatment did not provide favorable outcomes with negligible complications.[12] A previous randomized study demonstrated that higher complications were seen in the group receiving prophylactic barbiturate therapy, which decreased body temperature and increased serum concentration of pentobarbital.[13] These findings indicate that prophylactic barbiturate treatment might be a good candidate if a suitable infusion method for the maintenance of body temperature and serum concentration can be developed safely.

Among barbiturates, there have been some clinical studies on thiopental and pentobarbital, while there are few studies on thiamylal, to our knowledge. Recently, we have paid attention to thiamylal because the drug was reported to be ultra-short-acting, has fewer cardiovascular side effects, and has more potent than thiopental.[14] Moreover, thiamylal is widely used for sedation in children in Japan.[6,7,15] Therefore, we believe that thiamylal is a good candidate drug to provide novel protective findings of prophylactic barbiturate in patients with sTBI. Indeed, our novel sdB could control the serum concentration within the safety margin (Fig. 1B), and we recently introduced the favorable effect of NOR+sdB.[8] In addition, the novel treatment could control elevated ICP, maintain CPP over 65 mmHg, and maintain a stable serum concentration of thiamylal without serious complications.

On the other hand, animal and clinical studies have demonstrated that hypothermia is neuroprotective and improves the outcome of TBI.[16,17] One of the protective mechanisms of hypothermia is the

persistent reduction of high ICP value after TBI.[18] However, larger randomized clinical trials and meta-analyses did not reveal significant effects of the therapy,[16,17] and it is still controversial whether therapeutic hypothermia improves the poor outcome of the patients considering its several negative effects.[19] Moreover, hypothermia increases complications, such as pneumonia, and induces unfavorable conditions in comparison with normothermia.[20,21] Based on this, NOR+sdB was thought to be reasonable to decrease complications and provide favorable results to patients with sTBI.

Although prophylactic barbiturate therapy provided favorable effects in relation to early death after sTBI, there were some adverse effects, such as hypotension, hypokalemia, pneumonia, and arrhythmia in the NOR+sdB group. The rate of complications seemed to be higher in comparison with our previous study.[9] However, an earlier study excluded 8 patients out of 38 because of severe hypotension or death. In addition, three patients in the MD-HYPO group in the present study, who were included in our study, died within the first 5 days during the management of body temperature. Complications in the NOR+sdB group were treatable with standard therapies and did not influence the lethal prognosis, as no patients died at the time of discharge from the ICU.

Although we demonstrated significant beneficial effects of NOR+sdB, some limitations of the study must be acknowledged. First, the direct neuroprotective effect of thiamylal, apart from ICP lowering, should be considered in our patients. Further preclinical and clinical studies are needed to clarify the central protective effect of NOR+sdB in brain injuries. Next, we included the age group between 20 and 80 years, and the effects of thiamylal in other generations, such as young and very elderly patients, should be further evaluated. Third, the management method of body temperature was updated from January 2014, which might be a confounding factor for the outcome of our patients. However, previous methods using water-circulating blankets could reach 36°C within the first several hours. Therefore, we thought that the different methods for the management of body temperature had little influence on their outcome.

Conclusion

We revealed that treatment with NOR+sdB prevented ICU deaths in patients with sTBI, and the beneficial role of the therapy might be observed when the ICP is maintained <20 mmHg during the first 120 h. The novel prophylactic barbiturate with normothermia is thought to be promising, and further randomized clinical studies using larger populations are needed to confirm the beneficial results of the current preliminary findings of this study.

Conflicts of Interest Disclosure

There are no conflicts of interest.

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