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ORIGINAL ARTICLE

A novel step-down infusion method of barbiturate therapy: Its safety and effectiveness for intracranial pressure control

Yukako Yamakawa[1] | Motohiro Morioka[2] | Tetsuya Negoto[2] | Kimihiko Orito[2] | Munetake Yoshitomi[2] | Yukihiko Nakamura[2] | Nobuyuki Takeshige[2] | Masafumi Yamamoto[2] | Yasuharu Takeuchi[2] | Kazutaka Oda[1] | Hirofumi Jono[1] | Hideyuki Saito[1]

[1]Department of Pharmacy, Kumamoto University Hospital, Kumamoto, Japan

[2]Departments of Neurosurgery, Kurume University School of Medicine, Fukuoka, Japan

Correspondence
Hirofumi Jono, Department of Pharmacy, Kumamoto University Hospital, 1-1-1 Honjo, Chuo-ku, Kumamoto, 860-8556, Japan.
Email: hjono@kuh.kumamoto-u.ac.jp

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Abstract

Intracranial pressure (ICP) has to be maintained quite constant, because increased ICP caused by cerebrovascular disease and head trauma is fatal. Although controlling ICP is clinically critical, only few therapeutic methods are currently available. Barbiturates, a group of sedative-hypnotic drugs, are recognized as secondary treatment for controlling ICP. We proposed a novel "step-down infusion" method, administrating barbiturate (thiamylal) after different time point from the start of treatment under normothermia, at doses of 3.0 (0–24 h), 2.0 (24–48 h), 1.5 (48–72 h), and 1.0 mg/kg/h (72–96 h), and evaluated its safety and effectiveness in clinical. In 22 patients with severe traumatic brain injury or severe cerebrovascular disease (Glasgow coma scale ≤8), thiamylal concentrations and ICP were monitored. The step-down infusion method under normothermia maintained stable thiamylal concentrations (<26.1 μg/ml) without any abnormal accumulation/elevation, and could successfully keep ICP <20 mmHg (targeted management value: ICP <20 mmHg) in all patients. Moreover the mean value of cerebral perfusion pressure (CPP) was also maintained over 65 mmHg during all time course (targeted management value: CPP >65 mmHg), and no threatening changes in serum potassium or any hemodynamic instability were observed. Our novel "step-down infusion" method under normothermia enabled to maintain stable, safe thiamylal concentrations to ensure both ICP reduction and CPP maintenance without any serious side effects, may provide a novel and clinically effective treatment option for patients with increased ICP.

KEYWORDS
barbiturate, cerebral perfusion pressure, intracranial pressure, step-down infusion, traumatic brain injury

Abbreviations: CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; CVD, cerebral vascular disease; ICP, intracranial pressure; LC-MS/MS, liquid chromatography-tandem mass spectrometry; TBI, traumatic brain injury.

Yukako Yamakawa and Motohiro Morioka are contributed equally to this work.

1 | INTRODUCTION

Intracranial pressure (ICP), a pressure within intracranial space relative to atmospheric pressure, derives from cerebral blood and cerebrospinal fluid (CSF) circulatory dynamics. ICP reflects the dynamic relationship between increases or decreases in volume of the craniospinal axis and the ability to accommodate such changes. Although ICP has to be maintained quite constant by homeostasis, ICP is affected and increased by various pathological conditions, such as, brain injury, bleeding & swelling in the brain, and aneurysm. Because increased ICP caused by cerebrovascular disease and head trauma is fatal, appropriate monitoring and controlling ICP is clinically critical. Although guidelines recommend the evidence-based treatments, such as, decompressive craniectomy, prophylactic hypothermia, hyperosmolar therapy, cerebrospinal fluid drainage,[1–4] only few therapies for controlling increased ICP to maximize those standard medical and surgical treatment are currently available.

Barbiturate administration is one of evidence-based recommendation to control elevated ICP refractory to maximum standard medical and surgical treatment.[1–4] Barbiturates, a group of sedative-hypnotic drugs, are widely used for the treatment of seizure disorder, insomnia, general anesthesia, epilepsia, and increased ICP.[5] Barbiturate therapy is recognized as secondary treatment only when a dramatic increase in ICP occurs in patients with a severe traumatic brain injury (TBI) and severe cerebral vascular disease (CVD), with class II evidence of ICP reduction according to the guidelines for the management of TBI.[1–4] It is documented that barbiturates exert their cerebral protective and ICP reducing effects via several mechanisms, such as, alterations in vascular tone, suppression of metabolism, and inhibition of free radical mediated lipid peroxidation. The therapeutic effect of barbiturates may be associated with cerebral blood flow and regional metabolic demands, which in turn, lead to reduce the metabolic requirements.[6] The less the cerebral blood flow and related cerebral blood volume with subsequent beneficial effects on ICP and global cerebral perfusion. However, despite its reported therapeutic efficacy, the guidelines for the use of barbiturate therapy remain limited. It has been suggested that high-dose barbiturate therapy is considered only for hemodynamically stable patients, because it may be associated with worse outcomes compared with patients who have not been previously exposed to any secondary treatment. In addition, the barbiturate therapy may have some disadvantages, including but not limited to cardiac function depression and hypokalemia. Majdan et al. analyzed the effect of barbiturate therapy on TBI patients using data obtained from 13 centers across 5 European countries.[7] This study suggested that "high dose" barbiturate therapy (>2.0 g/24 h) had no significant effect on outcomes at any stage after injury; hemodynamic instability was proposed to be one of the important factors.[7] As of this moment, since the precise injection dose and treatment periods has yet to be determined, the pharmacokinetics of barbiturates and probable concentration-related clinical effects remain unknown.

In this study, based on both experimental and clinical pharmacokinetic approaches, we assessed several patients with increased ICP by treatment of thiamylal, an approved and clinically-used barbiturate in Japan. Here, we proposed a novel "step-down infusion" method, administering thiamylal after different time point from the start of treatment under normothermia. Our novel step-down infusion method under normothermia allowed to maintain stable & safe thiamylal concentrations to ensure both ICP reduction and cerebral perfusion pressure (CPP) maintenance without any serious side effects.

2 | MATERIALS AND METHODS

2.1 | Ethics statement

The clinical study was reviewed and approved by the Institutional Ethical Committee of Kurume University (No. 12268). Written informed consent was obtained from all subjects for publication of this report and accompanying images.

2.2 | Drugs/chemicals and animals

Thiamylal and Thiamylal Sodium (Isozol; registered for trademark) were purchased from Nichi-Iko Pharmaceutical Co, Ltd. Thiamylal standard chemical was purchased from Pharmaceutical and Medical Device Regulatory Science Society of Japan. Pentobarbital (internal standard of thiamylal) was purchased from Kyoritsuseiyaku Corporation. Propofol standard chemical, eugenol (internal standard of propofol) and dansyl chloride (derivatization agent of propofol and eugenol) were purchased from Tokyo Chemical Industry. All other chemicals used in this study were of the highest purity grade available.

2.3 | Clinical study

From Dec 2013 to Feb 2016, 18 patients with severe TBI and 4 patients with cerebrovascular disease (CVD) with a Glasgow coma scale (GCS) value ≤8 were included in this clinical study (Table 1). Using the Guidelines for the Management of TBI,[3] emergent surgical operations including external decompression, hematoma evacuation, and aneurysmal clipping/coil embolization were performed and ICP was measured for a period of at least 7 days in all patients. Barbiturate (thiamylal) therapy was initiated as early as possible (about 4–5 h. after admission). If a patient's family refused the therapy or if any severe, complicated disease was found (especially a disease that affected a patient's vital signs), the patient was excluded from the study and a different suitable treatment was delivered. The following steps for the barbiturate (thiamylal) infusion protocol were performed for the "step-down infusion" of thiamylal: 3.0 mg/kg/h infusion at 0–24 h, 2 mg/kg/h infusion 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 treatment; (3.0-start; Figure 1A) under normothermia (36.0–37.0°C). In addition, in the latter half period of this study, we increased the dose of infusion by adding another 4.0 mg/kg/h at 24 h prior to

TABLE 1 Clinical characteristics of patients

Pt.	Age/ Sex	Diagnosis	GCS (admission)	Surgicaloperation	Treatment start timing (hours after admission)	Max. ICP (mmHg)	Max.conc. of thiamylal (μg/ml)	GOS (discharge)
Traumatic brain injury								
1	15/F	DAI	6	None	5.5	12	14.4	Good
2	49/M	ASDH/contusion	4	R-H/E-D	3.0	18	14.1	Good
3	49/M	ASDH	5	R-H	4.5	19	9.4	MD
4	57/M	ASDH	8	R-H	4.5	12	12.1	MD
5	60/M	ASDH/Contusion	4	R-H	3.0	17	14.7	SD
6	65/F	Contusion	3	R-H/E-D	4.0	15	11.4	VS
7	72/M	ASDH	7	R-H/ E-D	3.5	11	9.5	MD
8	75/F	ASDH bilateral	3	R-H/ E-D	3.5	11	8.1	VS
9	76/M	ASDH	3	R-H	5.5	15	8.2	VS
10	76/F	Contusion	5	none	4.0	14	5.7	VS
11	77/M	ASDH/contusion	8	R-H/ E-D	7.5	19	17.2	SD
12	78/F	ASDH/contusion	5	R-H/ E-D	7.0	21	10.2	MD
13	81/F	AEDH bilateral	3	R-H	4.5	9	10.0	MD
14	82/F	ASDH/contusion	8	R-H	5.0	10	12.3	SD
15	82/F	ASDH/AEDH	7	R-H	6.0	17	8.9	Dead
*High dose (4 mg/kg/hr) Thiamilal start								
16	38/M	ASDH/contusion	4	R-H/ E-D	5.0	20	26.1	MD
17	40/M	ASDH	6	R-H/ E-D	6.0	11	17.8	MD
18	63/M	ASDH	3	R-H/ E-D	4.5	13	15.6	SD
Cerebrovascular disease								
1	25/F	AVM/hematoma	5	R-H & AVM/ E-D	7.0	17	14.5	MD
2	36/M	SAH/hematoma	5	R-H/ Clipping/E-D	8.5	22	8.8	MD
3	59/M	SAH/hematoma	4	Embolization	8.0	11	12.6	MD
*High dose (4 mg/kg/hr) Thiamilal start								
4	67 M	SAHhematoma	5	Embolization/R-H/E-D	8.0	12	23.3	SD

Abbreviations: AEDH, acute epidural hematoma; ASDH, acute subdural hematoma; AVM, arterio-venous malformation; DAI, Diffuse axonal injury; E-D, external decompressive craniectomy; GCS, Glasgow Coma Scale; GOS, Glasgow outcome scale; MD, moderately disabled; R-H, removal of hematoma; SAH, subarachnoid hemorrhage; SD, severely disabled; VS, vegetative state.

the first infusion at 3.0 mg/kg/h (4.0-start; Figure 1B) to the last 4 patients with severe ICP of the series, because we had already confirmed that no case showed serious complication treated by 3.0-start thiamylal at that moment. In addition to the barbiturate (thiamylal) infusion, propofol was also infused at 4.0–4.5 mg/kg/h to maintain anesthesia in all patients. Patients with a severe TBI were treated based on the guidelines for the management of severe TBI under normothermia (36.0–37.0°C) published by the Brain Trauma Foundation in 1996.[1] At the time of discharge, we evaluated clinical outcome according to the Glasgow Outcome Scale.[7]

2.4 | Sample preparation

The blood samples were collected at each time point (0, 6, 12, 24, 48, 72, 96, 108, 120, and 144 h) after the start of barbiturate therapy, centrifuged (4°C, 1,500 g, 10 min) for separating serum, and stored at −30°C until measurement. The frozen serum was thawed and centrifuged (4°C, 13,000 g, 10 min) and then dispensed. Thiamylal sample preparation; aliquot of 10-fold diluted serum samples (100 μl) were mixed with 50 μl of pentobarbital (internal standard of thiamylal) and 700 μl of acetonitrile. After centrifuging the mixture at 13,000*g* for 10 min at 4°C, 120 μl of the supernatant was added to 80 μl of ultra-pure water. The samples were placed in an autosampler which ran at 4°C. Propofol sample preparation; aliquots (50 μl) of serum samples were mixed with 50 μl of eugenol (internal standard of propofol) and 400 μl of acetonitrile. After centrifuging the mixture at 13,000*g* for 10 min at 4°C, 250 μl of the supernatant, 100 μl of dansyl chloride 1 mg/ml and 10 μl of NaOH were mixed, and the mixture was heated at 60°C for 10 min. The samples were placed in an autosampler which ran at 4°C.

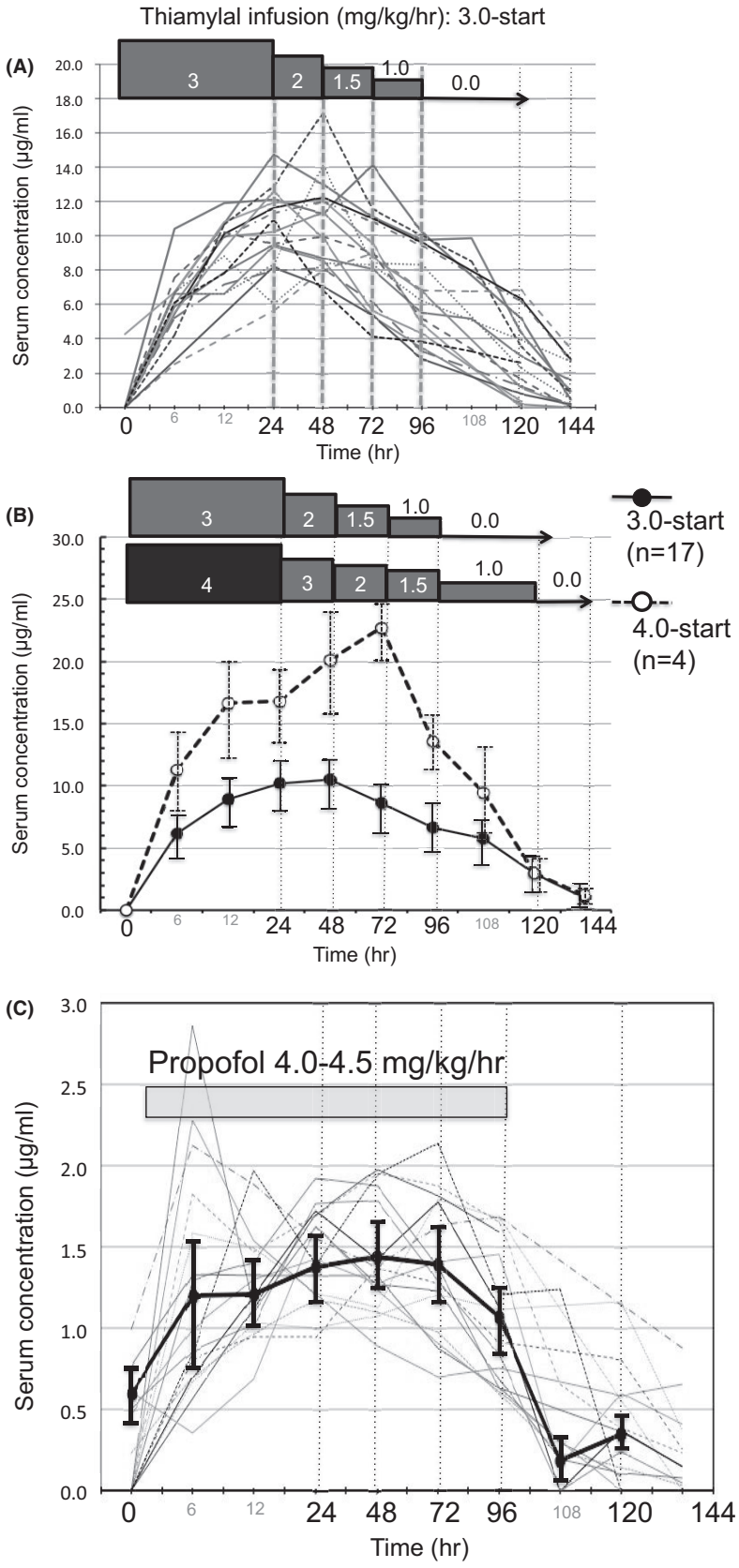

FIGURE 1 Thiamylal concentration in patients treated with step-down infusion method. (A) Serum thiamylal concentration in 17 patients (14 TBI, 3 CVD) treated with step-down infusion method started at 3.0 mg/kg/h (3.0-start), respectively. (B) Comparison of serum thiamylal concentration started at 3.0 mg/kg (3.0-start, solid line, Figure 1A) and started 4.0 mg/kg (4.0-start, dotted line) in 4 patients (3 patients with TBI; 1 patient with CVD). (C) Serum propofol concentration in those patients treated at 4.0–4.5 mg/kg/h over 96 h (gray box). Data are presented as mean ± SD

2.5 | Liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis

Thiamylal and propofol concentrations were measured as described previously.[8,9] We performed LC–MS/MS analysis using the API 3200™ LC/MS/MS system (AB SCIEX, Foster City) with a triple quadruple mass spectrometer in the negative ion mode with the following: thiamylal, *m/z* 253; thiamylal d3, *m/z* 58, and pentobarbital, *m/z* 225; pentobarbital d3, *m/z* 182. The relevant MS/MS settings were: charged aerosol detection gas at 3.0 psig; curtain at 10 psig; Ion Source Gas (GS) 1 at 30 psig; GS2 at 30 psig; IS at −4500 V and temperature at 600°C. Chromatographic separation was performed using the Atlantis C18 3 μm 2.1 × 50 mm column (Waters Corp). Mobile phase A consisted of 10 mM ammonium acetate and mobile phase B consisted of 10 mM ammonium acetate in acetonitrile. The gradient conditions (% of Mobile phase B) were: 0–3 min, 60%; 3–8 min, 60 → 95%; 8–10 min, 95%; 10–10.1 min, 95 → 60%; and 10.1–15 min, 60%. propofol, *m/z* 412; propofol d3, *m/z* 171, and eugenol, *m/z* 398; eugenol d3, *m/z* 171. The relevant MS/MS settings were: charged aerosol detection gas at 3.0 psig; curtain at 20 psig; Ion Source Gas (GS) 1 at 70 psig; GS2 at 60 psig; IS at 5500 V and temperature at 300°C. Chromatographic separation was performed using the Atlantis C18 3 μm 2.1 × 50 mm column (Waters Corp). Mobile phase A consisted of 0.1% formic acid and mobile phase B consisted of 0.1% formic acid in acetonitrile. The gradient conditions (% of Mobile phase B) were: 0–0.1 min 30%, 0.1–3 min 30 → 90%, 3–7 min 90%, 7–8 min 90 → 30%, 8–10 min 30%. Consequently, LC–MS/MS analysis was performed with the calibration range (thiamylal: 0.03125–4 μg/ml; propofol: 0.03125–4 μg/ml) and the lower detection limit (thiamylal: 2 ng/ml; propofol: 10 ng/ml) in this study.

2.6 | Statistical analysis

Relationship between ICP and thiamylal/propofol concentrations or between serum potassium and thiamylal concentrations in patients were analyzed by Pearson's correlation coefficient. The *p* value less than .05 was considered statistically significant. Statistical processing was performed using R (ver.3.2.2, R Foundation for Statistical Computing).

3 | RESULTS

3.1 | A novel "step-down infusion" method of barbiturate therapy

We sought to determine the appropriate administration method of barbiturate thiamylal for controlling increased ICP, based on the experimental pharmacokinetic analysis and previous clinical experience of fixed dose infusion barbiturate therapy.[1–4] We first performed experimental pharmacokinetic approaches to gain insight into the appropriate administration method for thiamylal. Our pharmacokinetic analysis using dogs administrated with thiamylal, suggested that the hypothermia increased the serum concentration of thiamylal, and also that the fixed dose long-time infusion of thiamylal, induced accumulation of thiamylal in both hypothermic and normothermic condition (Figure S1). Based on those results and previous clinical experience of fixed dose infusion barbiturate therapy,[1–4] we proposed a novel infusion method termed "step-down infusion" for thiamylal (3.0-start, Figure 1A): 3.0 mg/kg/h infusion at 0–24 h, 2 mg/kg/h infusion at 24–48 h, 1.5 mg/kg/h at 48–72 h, and 1.0 mg/kg/h at 72–96 h from start of treatment under normothermia (36.0°C–37.0°C).

3.2 | Thiamylal concentration in patients treated with "step-down infusion" method

A total of 22 patients (18 patients with TBI; 4 patients with CVD) were enrolled in this study (Table 1). The mean age of patients was 59.3 ± 19.4 years (mean ± SD). Surgical procedures included 12 external decompressions and 19 hematoma removals (Table 1). Of those patients, as shown in Figure 1A, 17 patients (14 patients with TBI; 3 patients with CVD) were treated with "step-down infusion" of thiamylal (3.0-start), and the time course of thiamylal serum concentration was monitored, respectively. The peak serum thiamylal concentration (mean ± SD, 10.52 ± 2.76 μg/ml) was observed at 48 h when the drug dose was not at its maximum (2 mg/kg/h), and the thiamylal concentration was gradually decreased (Figure 1B). In those patients, it should be noted that the blood pressure of patients was relatively stable, and there was no evidence of hemodynamic instability during their clinical course. In addition to the step-down infusion (3.0-start), 4 patients (3 patients with TBI; 1 patient with CVD) were treated with the increased step-down infusion with 4.0 mg/kg/h at 24 h infusion prior to the first 3.0 mg/kg/h infusion (4.0-start) (Figure 1B). Although the increased step-down infusion (4.0-start) exhibited that the peak concentration was increased (22.7 ± 2.58 μg/ml, mean ± SD) and shifted to 72 h (Figure 1B), no hemodynamic instability was found in the clinical course. In addition to the thiamylal infusion, propofol was also infused at 4.0–4.5 mg/kg/h to maintain anesthesia in all patients, and the time course of serum propofol concentration was also monitored. As shown in Figure 1C, the serum propofol concentration showed no obvious change in all patients treated with the step-down infusion methods.

3.3 | Clinical effects of step-down infusion of thiamylal on controlling increased ICP

We next sought to determine the clinical effects of step-down infusion of thiamylal on controlling increased ICP in patients. In 18 traumatic brain injury cases, 1 case died as a result of a severe general infection caused by a whole-body open injury received at first accident, the relationship between infection and barbiturate therapy was unclear (Table 1). At discharge, 4 cases (22.2%) were in a vegetative state, 4 cases (22.2%) were severely disabled, 7 cases (38.9%) were moderately disabled, and 2 cases (11.1%) had positive outcomes (Table 1). For

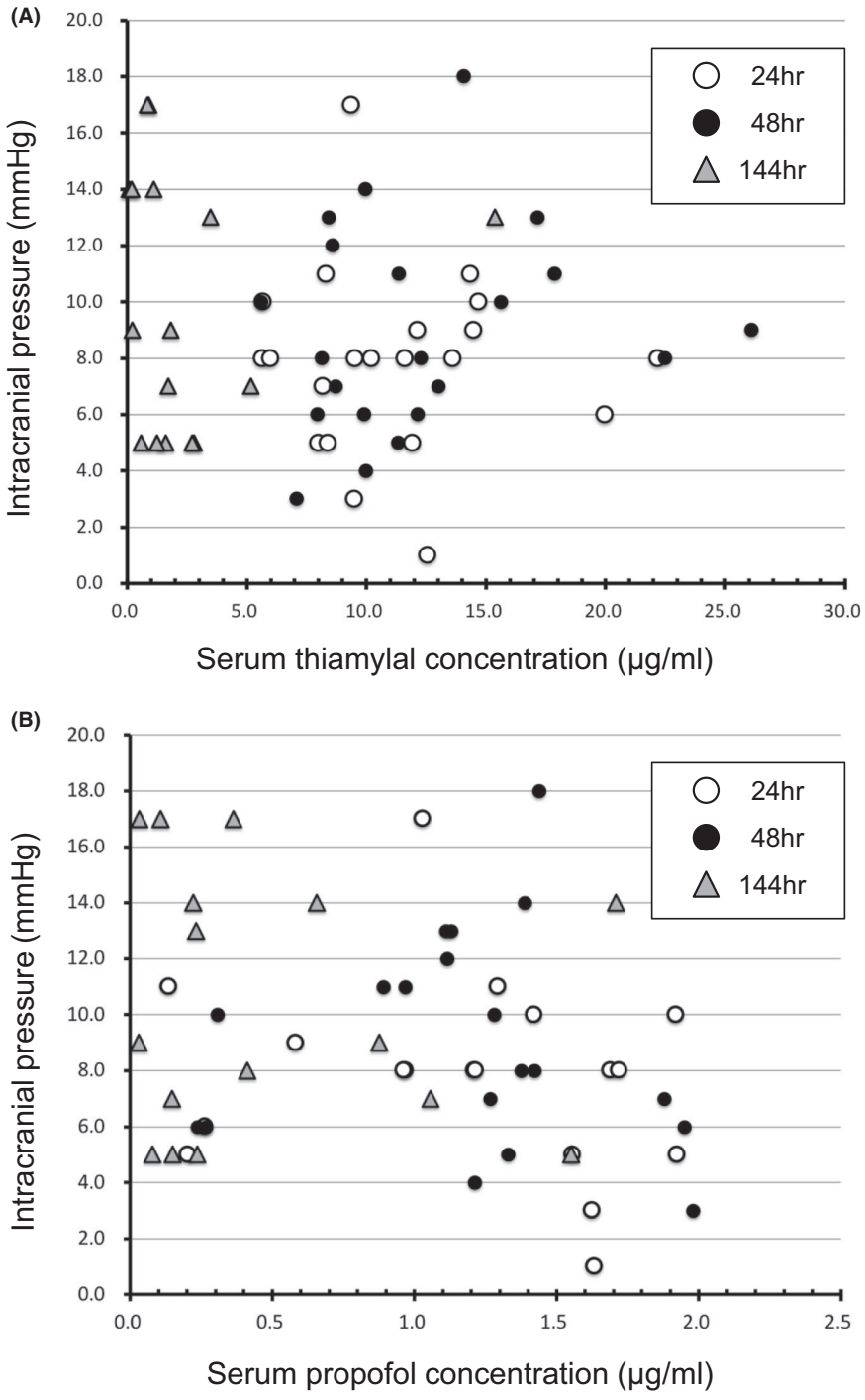

FIGURE 2 Relationship between ICP and thiamylal/propofol in patients treated with step-down infusion of thiamylal. Relationship between ICP and thiamylal (A) or propofol (B) concentration at 24 h, 48 h and 144 h from the start of the step-down infusion. White circles: 24 h, black circles: 48 h, and gray triangles: 144 h, indicated ICP after the start of step-down infusion. (A: $r = -0.06$, $p = 0.63$; B: $r = -0.22$, $p = 0.11$)

those patients, we investigated the correlation between ICP and thiamylal/propofol concentration, by evaluating the ICP and thiamylal or propofol concentration at 24, 48, and 144 h from the start of the step-down infusion (Figure 2). The step-down infusion of thiamylal could successfully keep ICP <20 mmHg (targeted management value: ICP <20 mmHg) in all patients (Figure 2A and B). The most patients with low concentrations of thiamylal (<15.0 μg/ml) exhibited the ICP within normal range (<15 mmHg, Figure 2A).[10] Even in patients with high concentrations of thiamylal (>15.0 μg/ml), the ICP of all patients was also within normal range (<15 mmHg) without any abnormal reaction.

We next focused on the correlation between the time course of thiamylal concentration and ICP/CPP in patients treated with the step-down infusion of thiamylal. As shown in Figure 3, the increased ICP was maintained stable within the targeted management value (ICP <20 mmHg) by the increased thiamylal concentration. The mean value of CPP was also maintained over 65 mmHg during the all time course (targeted management

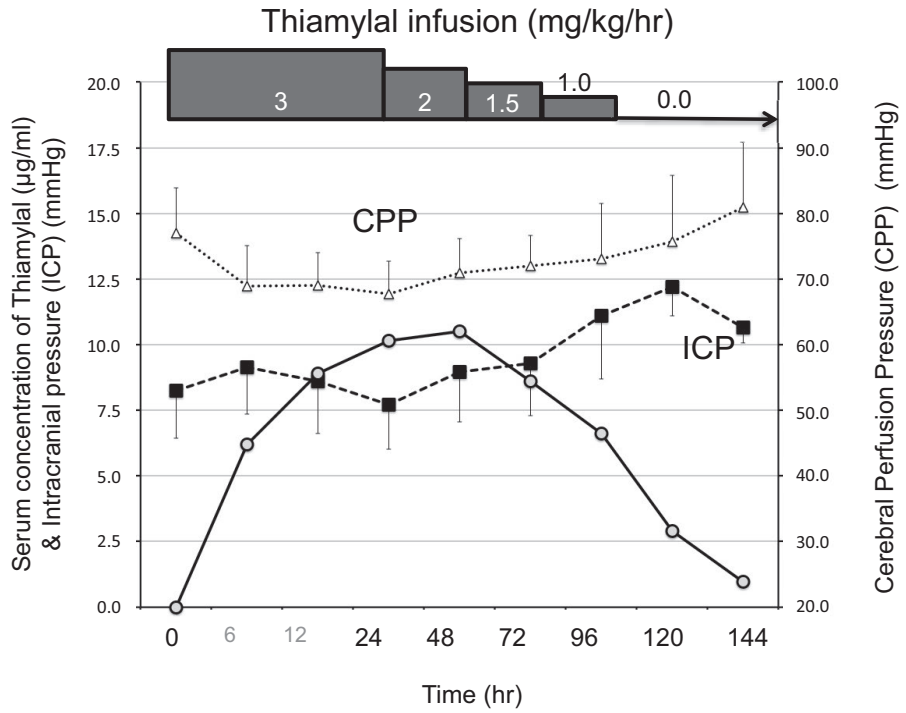

FIGURE 3 Correlation between the time course of thiamylal concentration and ICP/CPP in patients. The time course for the mean values of ICP (black Squares), CPP (white triangles), and the thiamylal concentration (white circles) were monitored in patients treated with step-down infusion of thiamylal. Data are presented as mean ± SD

value: CPP >65 mmHg). Moreover, we monitored and controlled the serum potassium in the intensive care unit (ICU), and also determined the correlation between thiamylal concentration and serum potassium. As shown in Figure 4, our results indicated that no threatening changes in potassium were observed in patients treated with the step-down infusion of thiamylal, even at high thiamylal concentration (26.1 μg/ml).

3.4 | Clinical course and thiamylal concentration in a representative patient case

We finally introduced the representative case of 60-year-old male patient with acute subdural hematoma. After receiving the emergency operation to remove hematoma & underwent an external decompressive craniotomy, this patient started ICP monitoring and step-down infusion of thiamylal. As shown in the clinical course and thiamylal concentration transition (Figure 5), thiamylal concentrations were increased appropriately and maintained stably (ranging from 10.0 to 15.0 μg/ml for 4 days), which in turn, led to maintain the stable ICP and CPP within both targeted management values, respectively.

4 | DISCUSSION

4.1 | Barbiturate therapy

According to the current guidelines, in some cases, high-dose barbiturate therapy for patients with severely increased ICP has been administered for treatment.[1–4,6,11] However, the therapy resulted in some serious complications and its effect on outcomes remains controversial.[12] To address those issues, we have examined the pharmacological characteristics of infused barbiturates and developed a novel infusion method termed as "step-down infusion" method by analyzing the time course of drug concentrations in this study.

Barbiturates such as pentobarbital, methohexital, thiopental and thiamylal, have been reportedly used in a barbiturate therapy. Their fundamental pharmacological parameters are slightly different,[12] For instance, thiopental was recently described to be more effective than pentobarbital in controlling refractory intracranial hypertension and in its neuroprotective effects.[13] Thiopental and thiamylal, possess a sulfa moiety and hence are known as thiobarbiturates, are pharmacologically similar. In this study, we focused on thiamylal, an approved and clinically-used barbiturate in Japan, and evaluated its administration as barbiturate therapy. Previous studies in 1980 s reported that the serum concentration of barbiturates measured at single time point were the following; approximately 30–200,[14] 30–60,[15] and 5–40[16] μg/ml during barbiturate therapy, not including the detailed time course of the serum concentrations, and also described side effects of barbiturates such as hypotension. To date, the appearance of burst and suppression by electroencephalography has been used to determine barbiturate doses; however, severe hypotension and increased infection rates have also been reported.[17,18] Using the conventional infusion methods, fixed dose of barbiturates was maintained over several days, and the exact serum concentration of barbiturate was unknown. We considered that the previous administration methods may cause

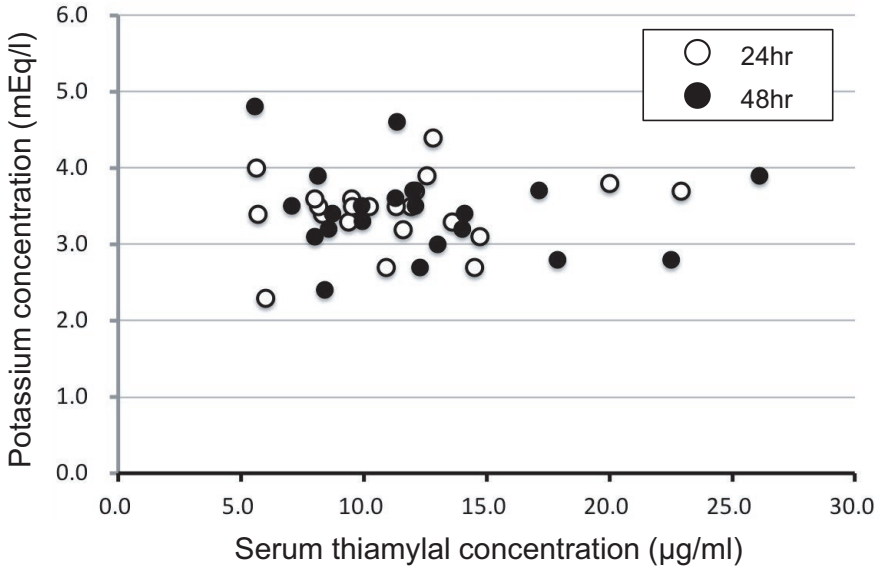

FIGURE 4 Correlation between serum potassium and thiamylal concentrations in patients. The serum potassium after 24 h (white circles) and 48 h (black circles) from the start of the step-down infusion revealed no threatening changes even at a high thiamylal concentration (26.1 μg/ml). (r = −0.01, p = 0.97)

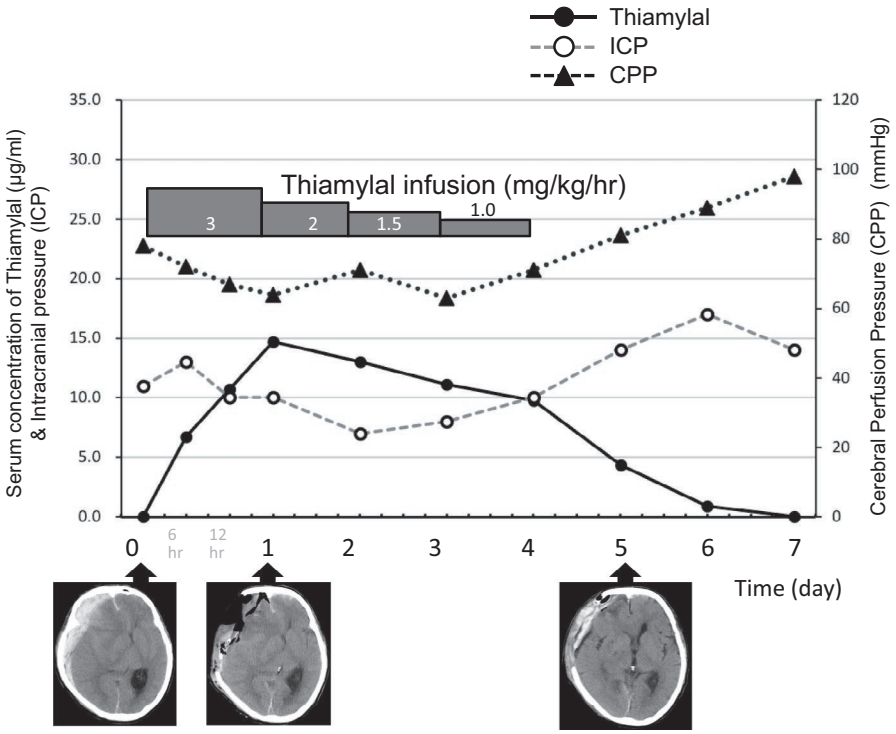

FIGURE 5 Clinical course and thiamylal concentration in a representative patient case. The 60-year-old male patient (patient 5) with acute subdural hematoma, received the emergent operation for hematoma removal & external decompressive craniotomy. Step-down infusion of thiamylal began on day 0, with stable concentration ranging from 10.0 to 15.0 μg/ml over 4 days (black Circle). The CPP (black triangle) and ICP (white circle) were maintained appropriately and stably

severe side effects by barbiturates accumulation. Indeed, therapeutic hypothermia has been frequently observed together with barbiturate therapy. Current studies revealed that in patients with ICP >20 mmHg after TBI, therapeutic hypothermia did not result in any outcomes, and serious adverse events were more often reported in the hypothermia group.[19,20] Moreover our experimental pharmacokinetic analysis showed that body temperature was important factor, and the combination of barbiturates and hypothermia is not recommended (Figure S1). Thus, in this study, we proposed a novel "step-down infusion" method, administering thiamylal after different amounts of time from the start of treatment under normothermia.

4.2 | Clinical effectiveness and the safety of the step-down infusion method

Our novel "step-down infusion" method under normothermia allowed to maintain stable & safe thiamylal concentrations to ensure both ICP reduction and CPP maintenance. When we aggressively performed cranial external decompression and hematoma removal, ICP was reduced with increasing concentrations of thiamylal (Figure 3). The step-down infusion of thiamylal could successfully keep ICP <20 mmHg (targeted management value: ICP <20 mmHg) in all patients (Figure 2). Even in patients with high concentrations of thiamylal (>15.0 μg/ml), ICP of all patients was within normal range (<15 mmHg, Figure 2A).[10] A maximum concentration of 26.1 μg/ml was considered safe, at least using our step-down infusion method in patients (Figure 2A). Thus, our barbiturate injection method may be effective at controlling ICP without any side effects. Previously, Nordby et al. reported that young adult patients (under 40-years-old), treated with barbiturate therapy (3–5 mg/kg/hr of thiopental) and hypothermia, exhibited better outcome in barbiturate therapy group (the highest serum concentration: 35–210 μg/ml), while the patients showed higher rate of cardiac depression, pulmonary complication and electrolyte abnormality.[14] Pittman et al. showed that 7 severely head-injured children treated with barbiturate therapy (1–2 mg/kg/hr of Pentobarbital, the highest serum concentration: 30–60 μg/ml), exhibited hypotension as complication.[15] In addition, Kasoff et al. reported that 25 young patients (under 17-year-old), treated with pentobarbital infusion (1–4 mg/kg/hr), exhibited the hypotension, cardiovascular depression, and arrythmias in high concentration group (40–50 μg/ml).[16] Although the evidence is limited, previous studies suggest that the maximum concentrations of thiamylal (8.1–26.1 μg/ml) in our study may be considered as in safety range. Moreover in addition to the ICP control in TBI patients, CPP-targeted therapy has recently become the most recommended therapeutic protocol. The recent guideline outlining the management of patients with severe TBI, recommends the CPP monitoring to decrease the mortality by 2 weeks, and suggests the recommended target CPP value for survival and favorable outcomes is between 60 and 70 mmHg.[4,21–23] Previously, despite its strong ICP reducing effect of barbiturate, the severe side effects of hypotension or cardiac inhibition decreased mean blood pressure and would offset any ICP lowering effects on CPP.[12] Chang et al. reported that hypoxic episodes were common after severe TBI when CPP values were below 60 mmHg,[24] suggesting the maintaining CPP is crucial. As shown in Figure 3, our novel step-down thiamylal infusion method enabled to reduce ICP while maintaining the mean CPP above 65 mmHg at all time, owing to the stable mean arterial pressure. In addition to hypotension, it has been reported that barbiturate therapy sometimes induces hypokalemia at rates exceeding 80%, and serious hypokalemia (<2.0 mmol/L) in approximately 25% of patients may be lethal.[25,26] In our study, although there were a few hypokalemia cases, the potassium concentrations were under control even at a high thiamylal concentration (26.1 μg/ml), indicating the thiamylal level was safe for potassium balance and cardiac function. With regards to other side effects, there were no other serious complications observed in all patients, except for the case with severe general infection caused by acquired whole-body open injury previously.

4.3 | Timing of barbiturate therapy

In 1985, Ward et al. performed a prophylactic barbiturate therapy, delivered right after following head injury in a number of randomly assigned patients, while the other patients received the same therapy without barbiturates.[27] This randomized study did not reveal the advantage of barbiturate therapy, and there were higher rates of serious hypotension and infectious complications. This study showed that barbiturate group showed significant hypothermia and half of the patients showed high pentobarbital concentrations (over 30 μg/ml), suggesting that high-dose barbiturate therapy should not be recommended due to the high rate of complications, including but not limited to severe hypotension and infections.[27] In this study, our step-down infusion of thiamylal was started as early as possible (about 4–5 h. after admission, Table 1), and successfully managed ICP/CPP levels. Those results proposed that the control of barbiturate concentrations must be important for preventing serious complications, and that prophylactic barbiturate therapy could be safe and effective in the treatment of severe TBI. We encountered a few cases with extremely high ICP levels because of delay in the transfer to our institution. Based on our experience, controlling ICP may be quite challenging even with barbiturates in case ICP levels are elevated higher. Thus, we suggest that it may be important for barbiturate therapy to be initiated as soon as possible, prior to a rapid increase in ICP.

4.4 | Limitations

Although we have examined the detailed time course of barbiturate concentrations and confirmed the safety of our novel step-down infusion therapy and, the sample size was still small and the types of barbiturates are limited. Since the step-down infusion method (4.0-start) was only used for few patients with severe ICP in this study, we think the safety and effectiveness of step-down infusion (4.0-start) need to be further evaluated in the future study. In addition, since we have aggressively, surgically removed a hematoma and performed external decompressive craniotomy with prophylactic barbiturate therapy, ICP values were relatively lower than in previous studies. Moreover considering a good and safer combination, we administrated propofol simultaneously in order to induce sedation. Propofol is metabolized in the liver [28,29] and continuous injection of propofol yielded stable concentrations and no obvious adverse events (Figures 1C and 2B). Additionally, we also need to consider the drug-drug interaction of the combined drugs (Table S1). Therefore, the present study could not exclude the possibility that there were some other important factors for controlling ICP in addition to the clinical effects of our step-down infusion therapy. Further investigation will be definitely needed to elucidate more

detailed mechanism, safety and effectiveness of step-down infusion of barbiturate therapy for controlling ICP.

5 | CONCLUSIONS

The novel "step-down infusion" method of barbiturate therapy was proposed and evaluated in this study, and could maintain a stable concentration of thiamylal in normothermic patients, achieving both ICP reduction and CPP maintenance without any serious side effects such as hypotension or hypokalemia. These findings provide novel insights into controlling the increased ICP to maximize the standard medical and surgical treatment.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Y.Y. and M.M. designed and performed Research. Y.Y., K.O., and H.J. analyzed data. T.N., K.O., M.Y., Y.N., N.T., M.Y., and Y.T. collected the data. Y.Y., M.M., T.N., and H.J. wrote manuscript.

DATA AVAILABILITY STATEMENT

The data are not publicly available due to privacy or ethical restrictions.

ORCID

Hirofumi Jono https://orcid.org/0000-0002-7977-7597

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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