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Relationship between Intracranial Pressure or Cerebral Perfusion Pressure and Prognosis in Patients with Severe Traumatic Brain Injury Treated with Mild Hypothermia

Koichi Hayakawa[1*], Osamu Tasaki[2], Hiromu Iwamura[1], Daiki Wada[1], Fukuki Saitou[1], Jiro Iba[3], Kazuhisa Yoshiya[3], Hitoshi Ikegawa[3], Tadahiko Shiozaki[3], Yasushi Nakamori[1], Satoshi Fujimi[4], Takeshi Shimazu[3] and Yasuyuki Kuwagata[1]

[1]*Department of Emergency and Critical Care Medicine, Kansai Medical University Takii Hospital, Osaka, Japan*

[2]*Nagasaki University Hospital Emergency Medical Center, Nagasaki, Japan*

[3]*Department of Traumatology and Acute Critical Medicine, Osaka University Graduate School of Medicine, Osaka, Japan*

[4]*Department of Emergency Medicine, Osaka General Medical Center, Osaka, Japan*

[*]**Corresponding author:** Koichi Hayakawa, Department of Emergency and Critical Care Medicine, Kansai Medical University General Medical Center, 10-15 Fumizono-Cho, Moriguchi, Osaka 5708507, Japan, Tel: +81669915779; Fax: +81669921001; E-mail: 11210329k@gmail.com

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Abstract

Aims: The purpose of this study was to predict the clinical course by intracranial pressure (ICP) or cerebral perfusion pressure (CPP) in the acute phase and prognosis in patients with severe head trauma who underwent therapeutic mild hypothermia (HT).

Methods: A consecutive 143 patients treated with HT for intracranial hypertension (ICH) in two trauma centers were included in this study. The pressure measured after computed tomography scanning was defined as the initial ICP or CPP. Outcome was assessed at 6 months according to the Glasgow Outcome Scale. ROC analysis was performed to clarify the threshold value of ICP/CPP predictive of ICP uncontrollable by HT.

Results: The cutoff value of ICP for uncontrollable ICP obtained from ROC analysis was 32.5 mmHg (sensitivity: 0.545, specificity: 0.875), and that for CPP was 56.5 mmHg (sensitivity: 0.813, specificity: 0.663). Fifty-three (96.4%) of 55 patients whose initial ICP was greater than 32.5 mmHg and 67 (95.7%) of 70 patients whose initial CPP was less than 56.5 mmHg had developed uncontrollable ICP.

Conclusion: The cutoff values predictive of ICP uncontrollable by HT from ROC analysis were 32.5 mmHg for ICP and 56.5 mmHg for CPP. For those patients with initial ICP greater than the cutoff value or an initial CPP less than the cutoff value, it may be harmful to prolong HT. The knowledge obtained from this study may be useful for considering the treatment strategy for severe traumatic brain injury.

Keywords: Cerebral perfusion pressure; Intracranial pressure; Prognosis; Severe traumatic brain injury

Introduction

Severe traumatic brain injury (TBI) is a main cause of death and severe disability after trauma [1]. Most patients with severe TBI suffer from intracranial hypertension (ICH), which is the main cause of death from TBI. Therefore, management of ICH is one of the most important factors in improving patient outcome.

ICH following TBI is intensively treated with a variety of measures. Although hypothermia can be used for ICH, it has not been proved to have beneficial effects on favorable neurological outcome [2-4]. We previously reported that mild hypothermia had no effects on patients with low ICP, [5] but it did have some beneficial effects in those with ICH [6]. Therefore, we have performed therapeutic mild hypothermia (HT) in patients with severe TBI with ICH. However, there are some patients with uncontrollable ICH even with HT, and in these patients, HT is frequently accompanied by a number of complications, such as pneumonia, meningitis, and thrombocytopenia. Recently, the optimal timing of decompressive craniectomy (DC) was discussed [7]. If a sophisticated treatment strategy can be used to control ICP and cerebral perfusion pressure (CPP) during the acute phase of injury, it may be helpful in improving the outcome from severe TBI. Therefore, the purpose of this study was to predict the clinical course by ICP or CPP in the acute phase of injury in patients with severe head trauma who underwent HT.

Methods

Patients

Included in this study were 143 consecutive patients treated with HT for ICH who were admitted to two trauma and critical care centers during 1997-2011. The overall trauma population was 5685 during the study period. The total population of patients with TBI and Abbreviated Injury Scale ≥ 3 was 1218 patients of whom 390 patients required evacuation of hematoma. All patients underwent the same initial standardized treatment protocol, which included appropriate resuscitation and stabilization in accordance with the Advanced Trauma Life Support Guidelines [8]. Patients were examined by computed tomography (CT) scan as soon after stabilization as possible.

If there was intracranial hematoma, we performed craniotomy or trepanation to reduce the effect of the mass and replaced the ICP monitor in accordance with Guideline for Surgical Treatment of Traumatic Brain Injury [9]. If brain swelling was severe during the surgery, DC was performed in conjunction with evacuation of the mass based on the judgment of the neurosurgeon.

In case of patients who did not require evacuation of the hematoma, if the Glasgow Coma Scale score was < 9 points and the CT scan was abnormal, an ICP monitor was inserted according to clinical guidelines [9]. A ventricular catheter was used if available; otherwise, a parenchymal or subdural monitoring system was used with a cranial burr hole.

Treatment of ICH

The therapeutic protocol for ICH is shown in Figure 1. When the ICP was > 25 mmHg even with the patient in a sedated condition and the head of the bed elevated to 30°, we performed the following therapy in sequence. Cerebrospinal fluid drainage was used first to treat ICP elevation.

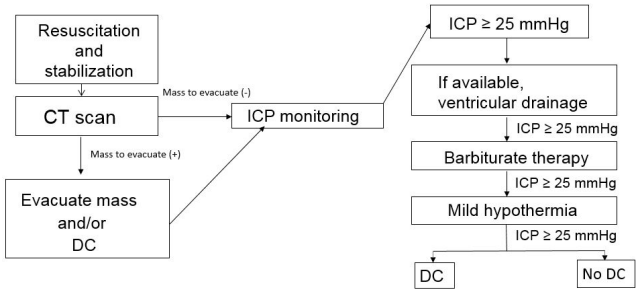

Figure 1: Therapeutic protocol for intracranial hypertension. CT, computed tomography; ICP, intracranial pressure; DC, decompressive craniectomy.

If this was ineffective in controlling ICP or was not available, barbiturate therapy and then HT were provided according to a published protocol [10]. First, a bolus of 4 mg/kg of barbiturate was injected followed by continuous administration at 4 mg/kg/h. If the ICP remained uncontrollable after administration of barbiturate, HT was started. HT was induced by core cooling with the injection of cold saline into the stomach and surface cooling with water-circulating blankets placed above and below the patient. If it was difficult to induce or maintain hypothermia due to shivering, we administered muscle relaxants. The core body temperature as measured in the bladder was lowered to between 33.5°C and 34.5°C. If the ICP was still uncontrollable after reaching the target temperature, DC was considered. HT was continued for as long as necessary to control ICP. If the patients suffered brain death or could not tolerate HT due to infection or pulmonary dysfunction, HT was discontinued. The rewarming speed was adjusted in consideration of the ICP and CPP, after starting at a rate of 1°C per day. DC was not performed routinely for refractory ICH that was not controllable with HT but was performed if the patient was likely to survive and the patient's family desired the treatment. Our clinical indications of DC were severe TBI patients with refractory ICP despite other treatments including HT, but who had no fatal brain damage as manifested by fixed and dilated bilateral pupils or brain herniation. No age limit was imposed, but we considered the patient's ability to carry out activities of daily living.

CPP (the difference between mean arterial pressure and ICP) was maintained at or above 50 mmHg by ICP control and the administration of intravenous fluids and vasopressors to increase blood pressure. Mannitol was not used routinely but only in patients with findings of impending herniation. Hypertonic saline was not used.

Data collection

Age, Glasgow Coma Scale score, light reflex, body temperature, and blood pressure were recorded at admission. Hypotension was defined as a systolic blood pressure < 90 mmHg. Base deficit, PaO_2, $PaCO_2$, and pH were also evaluated at admission by arterial blood gas analysis. Presence of a light reflex bilaterally or unilaterally was defined as a positive light reflex. The pressure measured after insertion of the ICP monitor was defined as the initial ICP or CPP. If an intracranial hematoma required evacuation, the pressure measured on ICU admission after the operation was defined as the initial ICP or CPP. The duration of HT was defined as the recorded time at which the patient was maintained at less than 35°C.

Outcome was assessed at 6 months according to the Glasgow Outcome Scale. Good recovery and moderate disability were considered favorable outcomes, whereas severe disability, persistent vegetative state, and death were considered unfavorable.

The subjects were divided into four groups according to clinical course (Figure 2). In Group A, HT was applied first and ICP was controllable. In Group B, HT was applied first but ICP remained uncontrollable and then DC was performed. In Group C, HT was applied first but ICP remained uncontrollable, but DC was not performed. In Group D, DC with evacuation of the mass was performed first, followed by HT.

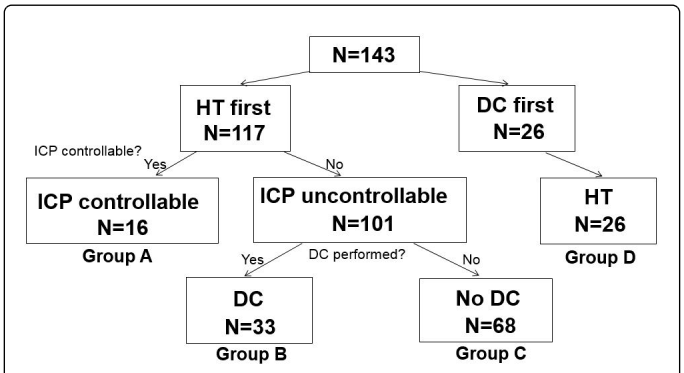

Figure 2: Clinical course of the 143 patients. The patients were divided into groups A, B, C, and D. ICP, intracranial pressure; DC, decompressive craniectomy; HT, therapeutic mild hypothermia.

Receiver operating characteristic (ROC) analysis was performed to clarify the threshold values of ICP and CPP to predict ICP uncontrollable by HT. In the analysis, the objects were Groups A, B and C, the dependent variable was whether ICP was controllable, and the independent variables were the initial ICP and CPP values.

ROC analysis was also performed to clarify the relationship between initial ICP or CPP and prognosis. The dependent variable was outcome

at 6 months after injury, and the independent variables were the initial ICP and CPP values.

The present study was a retrospective analysis of prospectively collected data. This study was carried out according to the principles of the Declaration of Helsinki and approved by the institutional review board of Osaka University Medical Hospital (approval number: 14177). The board waived the need for informed consent because this was a retrospective study using clinical data.

Statistical analysis

Continuous variables are presented as the median value with interquartile range, and categorical variables are presented as a percentage of the total. The Kruskal-Wallis test was used for comparisons among groups with continuous variables, and the $\chi 2$ test was used for categorical variables. All p-values were two-sided, and $p<0.05$ was considered to be statistically significant. All analyses were done with SPSS for Windows Ver. 21.0 (SPSS, Inc., Chicago, IL).

Results

The clinical course of the 143 patients is shown in Figure 2. Of these patients, 117 underwent HT first, and the remaining 26 underwent DC accompanied by evacuation of the mass first, followed by HT (Group D). Among the patients undergoing HT first, the number of patients with controllable ICP was 16 (14%) (Group A), whereas that with uncontrollable ICP was 101 (86%). Among those with uncontrollable ICP, DC was performed in 33 patients (Group B) and not performed in 68 (Group C).

Patient outcomes at 6 months after injury are shown in Table 1. Seventeen (12%) of the 143 patients had a favorable outcome, and 126 (88%) had an unfavorable outcome because all of these patients had severe ICH.

Outcome	n (%)
Death	88 (61.5)
Persistent vegetative state	17 (11.9)
Severe disability	21 (14.7)
Moderate disability	9 (6.3)
Good recovery	8 (5.6)

Table 1: Glasgow outcome scale 6 months after injury.

Patient characteristics in each group are shown in Table 2. In Group C, the Glasgow Coma Scale score was worse, the percentage of patients with positive light reflex was lower, the initial ICP was higher, and the initial CPP was lower compared with those values in the other 3 groups.

Variables	Group A	Group B	Group C	Group D	p value
	(n=16)	(n=33)	(n=68)	(n=26)	
Age, years	44.5 (22.5-65.0)	54 (23.0-65.0)	43 (26.5-69.0)	56 (39.0-64.0)	0.862
Sex, male (%)	50	60.6	63.2	65.4	0.76
GCS score	6 (4.0-8.0)	7 (4.0-9.0)	4.5 (3.0-6.5)	7 (5.0-11.0)	<0.001
Light reflex (%)	81.3	75.8	32.4	69.2	<0.001
sBP (mmHg)	146.5 (115.0-178.0)	139 (116.0-172.0)	154.5 (115.0-200.0)	149 (128.0-180.0)	0.808
BT (°C)	36.2 (35.4-36.5)	35.7 (35.5-36.5)	35.9 (35.2-36.6)	36.2 (35.1-36.4)	0.999
pH	7.41 (7.36-7.45)	7.35 (7.31-7.42)	7.39 (7.33-7.43)	7.41 (7.37-7.42)	0.302
$PaCO_2$ (mmHg)	40.7 (29.1-44.8)	38.9 (31.3-43.4)	34.3 (30.8-40.5)	36.7 (34.6-39.8)	0.442
PaO_2 (mmHg)	170 (91.5-334)	171 (96-298)	146 (77-310)	102 (72.9-226)	0.502
Base deficit (mmol/L)	1.6 (-0.5-3.2)	2.8 (2.3-4.8)	3.8 (1.4-5.6)	1.7 (0.4-4.1)	0.006
MAP (mmHg)	91 (85.0-100)	92 (72.0-106)	90.5 (67.5-108)	87.5 (75.0-100)	0.95
ICP (mmHg)	24.5 (11.5-29.5)	23	46.5	14	<0.001

		(16.0-40.0)	(25.5-66.5)	(9.0-33.0)	
CPP (mmHg)	67.5 (58.5-77.5)	53 (46.0-75.0)	38 (18.0-61.0)	67 (50.0-82.0)	<0.001
Midline shift (mm)	5.4 (0.8-8.6)	9.2 (3.0-14.5)	7.1 (2.6-10.6)	10.4 (4.8-15.0)	0.071
HT duration (hours)	49 (18.0-77.0)	50 (24.0-89.0)	40.5 (21.0-63.8)	61 (39.0-124.0)	0.063
Favorable outcome	Jul-16	Jul-33	0/68	Mar-26	<0.001
TCDB classification, no. (%)					
Diffuse injury I	0 (0)	0 (0)	0 (0)	0 (0)	0.998
Diffuse injury II	3 (18.8)	1 (3.0)	1 (1.5)	0 (0)	0.054
Diffuse injury III	3 (18.8)	6 (18.2)	16 (23.5)	0 (0)	0.125
Diffuse injury IV	2 (12.5)	5 (15.2)	18 (26.5)	0 (0)	0.054
Evacuated mass lesion	6 (37.5)	19 (57.6)	23 (33.8)	26 (100)	<0.001
Non-evacuated mass lesion	2 (12.5)	2 (6.1)	10 (14.7)	0 (0)	0.34

Kruskal-Wallis test was used for comparisons between groups with continuous variables and $\chi 2$ test for categorical variables.
BT, body temperature; CPP, cerebral perfusion pressure; GCS, Glasgow Coma Scale; HT duration, duration of hypothermia therapy; ICP, intracranial pressure; MAP, mean arterial pressure; sBP, systolic blood pressure; TCDB, Traumatic Coma Data Bank.

Table 2: Patient characteristics.

There was no significant difference in HT duration between the 4 groups, although the median HT duration was shortest in Group C and longest in Group D. DC was not performed in Group C, despite the patients having uncontrollable ICP treated with HT, either because the patient's family did not desire DC or the patient did not have a clinical indication for it.

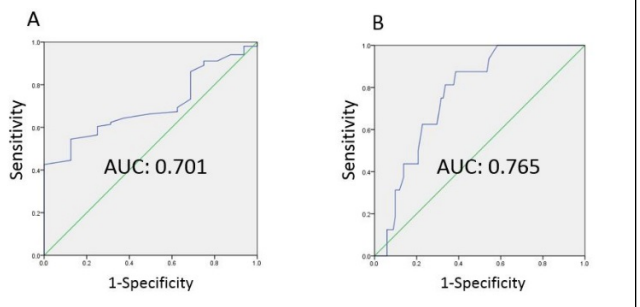

Figure 3: ROC analysis to clarify the threshold value of ICP/CPP for uncontrollable ICP by therapeutic mild hypothermia. The ROC analysis with corresponding AUC is shown for ICP in A and CPP in B. AUC, area under the curve; CPP, cerebral perfusion pressure; ICP, intracranial pressure; ROC, receiver operating characteristic.

Consequently, no patients in Group C had a favorable outcome. Favorable outcomes were experienced by 7 (44%) of 16 patients in Group A and in 7 (21%) of 33 patients in Group B. In Group D treated by DC and then HT, 3 (12%) of the 26 patients had a favorable outcome. The ROC analysis to clarify the threshold values of ICP and CPP for predicting ICP uncontrollable by HT is shown in Figure 3.

The cutoff value of ICP obtained from ROC analysis was 32.5 mmHg (sensitivity: 0.545, specificity: 0.875), and that for CPP was 56.5 mmHg (sensitivity: 0.813, specificity: 0.663). Fifty-three (96.4%) of 55 patients whose initial ICP was greater than 32.5 mmHg and 67 (95.7%) of 70 patients whose initial CPP was less than 56.5 mmHg had developed uncontrollable ICP. The ROC analysis performed to determine initial ICP and CPP values predictive of favorable outcome are shown in Figure 4.

The cutoff value of ICP obtained from ROC analysis was 28.5 mmHg (sensitivity: 0.612, specificity: 0.857), and that for CPP was 65.5 mmHg (sensitivity: 0.714, specificity: 0.777). Sixty-three (96.9%) of 65 patients whose initial ICP was greater than 28.5 mmHg and 80 (95.2%) of 84 patients whose initial CPP was less than 65.5 mmHg had a poor prognosis.

The time from the induction of HT to DC in Group B is shown in Figure 5. The median time was 17 hours. Of the 7 patients with favorable outcome, DC was performed within 24 hours in 5 patients and between 48 and 72 hours in the other two patients.

Discussion

Current clinical guidelines recommend monitoring of ICP in all patients with TBI who have Glasgow Coma Scale scores ≤ 8 and abnormality on the CT scan, although the usefulness of ICP monitoring has been debated in recent years [11]. We have performed ICP-oriented therapy to avoid secondary brain damage for more than a decade [12].

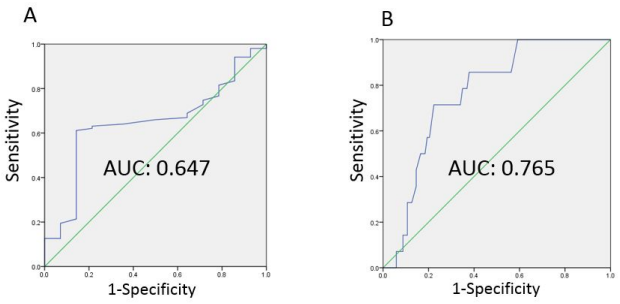

Figure 4: ROC analysis to clarify the threshold for outcomes. The dependent variable was outcome at 6 months after injury, and the independent variables were the initial ICP and CPP. The ROC analysis with corresponding AUC value is shown for ICP in A and for CPP in B. AUC, area under the curve; CPP, cerebral perfusion pressure; ICP, intracranial pressure; ROC, receiver operating characteristic.

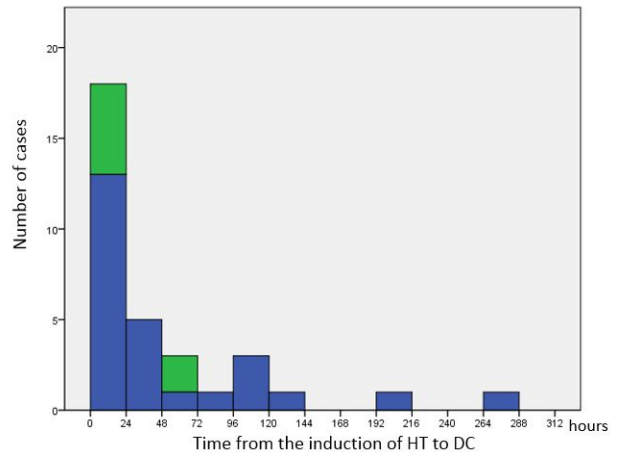

Figure 5: The time from the induction of HT to DC in group B. The vertical axis shows the number of cases, and the horizontal axis shows the time from the induction of HT to DC. Blue bars indicate unfavorable outcome, and green bars indicate favorable outcome. DC, decompressive craniectomy; HT, therapeutic mild hypothermia.

DC or craniotomy performed in the super-acute phase of head trauma carries a greater risk because of a tendency toward bleeding that arises due to abnormalities of coagulation and fibrinolysis [13]. Therefore, we perform HT first rather than surgery for refractory ICH if possible. HT has the effects of lowering the ICP and increasing the CPP by decreasing cerebral blood flow, the arterio-jugular venous oxygen difference, and the cerebral metabolic rate of oxygen [6]. However, HT is sometimes complicated by problems such as infection, electrolyte abnormality, and thrombocytopenia. The EUROTHERM trial has shown that HT does not improve recovery or disability in patients with TBI when compared with standard care [14].

Presently, the effectiveness of HT on improving prognosis has been questioned, but HT is one of the options to reduce ICP and is likely to be considered if the ICP cannot be controlled with standard care until DC can be performed. In our management protocol, with the family's informed consent, we perform DC if HT is not effective and there is a clinical indication for its use. There are prediction model which used age, Glasgow Coma Scale, pupil reactivity, CT findings, cardiac rhythm alternations etc. of traumatic brain injury for mortality or disability [15-18], but not for whether ICP can be controlled by HT alone. We hypothesized that we could use the initial ICP or CPP to predict the clinical course as to whether patients could be managed by HT alone or required DC due to uncontrollable ICP despite the use of HT.

It was difficult to control ICP by HT alone in the patients with an initial ICP >32.5 mmHg or an initial CPP<56.5 mmHg in Groups A and B, and most of these patients eventually required DC. These findings indicated that DC may need to be considered first rather than HT in such patients. Although DC has been reported in a small number of studies the DECRA Trial reported in 2011 found that DC was associated with more unfavorable outcomes although it decreased ICP and the length of stay in the ICU [7,19,20]. A number of problems with this trial were pointed out that related to inclusion limited to a small subset of patients, choice of operative technique, differences in study groups, minimal mean elevations in ICP before randomization, and quick-trigger criterion for the use of DC (an increase in ICP>20 mmHg only for >15 minutes).

In the present study, because 7 (21%) of 33 patients with uncontrollable ICP with HT underwent DC and experienced favorable outcomes, we believe that DC has beneficial effects on some types of patients with TBI. The RESCUEicp study (Randomized Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of intracranial pressure) to assess the effectiveness of DC as last-tier intervention in patients with TBI and refractory ICH has been published last year [21]. DC resulted in lower mortality and higher rates of vegetative state, severe disability than medical care. The rates of moderate disability and good recovery with DC were similar to those with medical management.

It seems to be important to use properly the option of the treatment for ICH corresponding to ICP and CPP.

Limitations

We acknowledge several limitations of this study. First, this is the retrospective clinical study performed at just two facilities. Although both facilities treat patients with TBI using the same clinical protocol and there is no difference between the facilities, a larger sample size is needed to confirm the findings of the present study. We also included some patients in Group C who did not have DC because of the desire of the patient's family, which might have some effects on the outcome.

Second, the time from injury to the measurement of ICP varied in this study. Although most patients were transferred directly from the scene and the time from emergency call to arrival at hospital was about 30 minutes, evacuation of the mass was performed first in some patients so that ICP or CPP was measured after the procedure in those patients. Thus, the significance of ICP or CPP may be different between pressures measured before and after surgery. Separate analysis of TBI patients with or without space-occupying lesion may be necessary.

Third, hyperosmolar agents were not routinely used in this study. Although hyperosmolar agents have been reported to decrease ICP and increase CPP, [22-24] the effectiveness of repeated administration

of hyperosmolar agents is not established. We use mannitol only temporarily to decrease ICP and do not use routinely because of its effects of a rebound increase in ICP and hypernatremia. However, the threshold for ICP or CPP might have changed if the treatment protocol were combined with the use of mannitol or hypertonic saline.

Conclusion

We clarified the relationship between ICP or CPP and prognosis in patients with severe TBI who underwent therapeutic HT. The cutoff values obtained from ROC analysis to clarify the threshold values of ICP and CPP indicative of ICP uncontrollable by HT were 32.5 mmHg for ICP and 56.5 mmHg for CPP. For those patients with initial ICP greater than the cutoff value or an initial CPP less than the cutoff value, it may be harmful to prolong HT. The knowledge obtained from this study may be useful for considering the treatment strategy for severe TBI.

Acknowledgment

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