Applying Cerebral Hypothermia and Brain Oxygen Monitoring in Treating Severe Traumatic Brain Injury

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Key words
- Brain tissue oxygen
- Cerebral perfusion pressure
- Glasgow Outcome Scale
- Hypothermia
- Intracranial pressure
- Traumatic brain injury
- Treatment process capability

Abbreviations and Acronyms
Cpk: Treatment process capability
CPP: Cerebral perfusion pressure
GOS: Glasgow Outcome Scale
ICP: Intracranial pressure
ICT: Intracranial temperature
ICU: Intensive care unit
$P_{ti}O_2$: Brain tissue oxygen
TBI: Traumatic brain injury

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BACKGROUND: **Severe traumatic brain injury (TBI) was to be one of the major health problems encountered in modern medicine and had an incalculable socioeconomic impact. The initial cerebral damage after acute brain injury is often exacerbated by postischemic hyperthermia and worsens the outcome. Hypothermia is one of the current therapies designed to combat this deleterious effect. The brain tissue oxygen ($P_{ti}O_2$)-guided cerebral perfusion pressure (CPP) management was successfully reduced because of cerebral hypoxic episodes following TBI.**

MATERIALS AND METHODS: **Forty-five patients with severe TBI whose Glasgow Coma Scale (GCS) score ranged between 4 and 8 during September 2006 and August 2007 were enrolled in China Medical University Hospital, Taichung, Taiwan. One patient with a GCS score of 3 was excluded for poor outcome. These patients were randomized into three groups. Group A (16 patients) was intracranial pressure/cerebral perfusion pressure (ICP/CPP)–guided management only, Group B (15 patients) was ICP/CPP guided with mild hypothermia, and Group C (14 patients) was combined mild hypothermia and $P_{ti}O_2$ guided with CPP management on patients with severe TBI. All patients were treated with ICP/CPP management (ICP <20 mm Hg, CPP >60 mm Hg). However, the group with $P_{ti}O_2$ monitoring was required to raise the $P_{ti}O_2$ above 20 mm Hg. Length of intensive care unit stay, ICP, $P_{ti}O_2$, Glasgow Outcome Scale (GOS) score, mortality, and complications were analyzed.**

RESULTS: **The ICP values progressively increased in the first 3 days but showed smaller changes in hypothermia groups (Groups B and C) and were significantly lower than those of the normothermia group (Group A) at the same time point. We also found out that the averaged ICP were significantly related to days and the daily variations [measured as (daily observation − daily group mean)^2] of ICP were shown to the significantly different among three treatment groups after the third posttraumatic day. The values of $P_{ti}O_2$ in Group C tended to rise when the ICP decreased were also observed. A favorable outcome is divided by the result of GOS scores. The percentage of favorable neurologic outcome was 50% in the normothermia group, 60% in the hypothermia-only group, and 71.4% in the $P_{ti}O_2$ group, with statistical significance. The percentage of mortality was 12.5% in the normothermia group, 6.7% in the hypothermia-only group, and 8.5% in the $P_{ti}O_2$ group, without statistical significance in three groups. Complications included pulmonary infections, peptic ulcer, and leukocytopenia (43.8% in the normothermia group, 55.6% in the hypothermia-only group, and 50% in the $P_{ti}O_2$ group).**

CONCLUSIONS: **Therapeutic mild hypothermia combined with $P_{ti}O_2$-guided CPP/ICP management allows reducing elevated ICP before 24 hours after injury, and daily variations of ICP were shown to be significantly different among the three treatment groups after the third posttraumatic day. It means that the hypothermia groups may reduce the ICP earlier and inhibit the elicitation of acute inflammation after cerebral contusion. Our data also provided evidence that early treatment that lowers $P_{ti}O_2$ may improve the outcome and seems the best medical treatment method in these three groups. We concluded that therapeutic mild hypothermia combined with $P_{ti}O_2$-guided CPP/ICP management provides beneficial effects when treating TBI, and a multicenter randomized trial needs to be undertaken.**

INTRODUCTION

Severe traumatic brain injury (TBI) is a leading cause of death and permanent disability among young people in Taiwan (2). The pathophysiology of TBI has increased remarkably during the past two decades, and four overlapping phases have been described by Reilly (20). They are primary injury, evolution of the primary injury, secondary or additional injury, and recovery. Secondary brain damage, including impaired autoregulation, systemic hypotension, cerebral ischemia, and intracranial hypertension, is a major factor determining a patient's outcome following traumatic brain injury. However, even when a cerebral perfusion pressure of >60 mm Hg is maintained following craniotomy, cerebral ischemia and hypoxia may still occur (4, 14), worsening the patient's chances of a satis-

factory outcome. As a result, prevention of cerebral hypoxia should result in an improved outcome in patients with TBI (1, 7). Hypothermia is one of the current therapies designed to combat such deleterious effects (12, 16). The brain tissue oxygen ($P_{ti}O_2$)–guided cerebral perfusion pressure (CPP) management was successful in reducing cerebral hypoxic episodes following TBI (6, 10, 15, 22). In this paper, we investigated the efficacy of therapeutic mild hypothermia combined with cerebral oxygen monitoring on patients with severe TBI.

MATERIALS AND METHODS

Of 512 patients with nonpenetrating TBI during September 2006 and August 2007 who were enrolled in the China Medical University Hospital, Taichung, Taiwan, 45 patients with severe TBI after craniotomy were included in the study. Inclusion criteria included the following: 1) a history of TBI; 2) Glasgow Coma Scale (GCS) scores of 4–8; and 3) brain damage confirmed by sequential computed tomography (CT) scanning within 6 hours after trauma. Exclusion criteria included 1) pregnant women; 2) patients younger than age 12 years or older than age 70 years; 3) a GCS score of 3; 4) multiply injured patients; and 5) those with any previous disabling neurologic disease.

This clinical study was designed as a randomized, controlled trial and patients were assigned to one of the following three groups after craniotomy. Group A (16 patients) was intracranial pressure/cerebral perfusion pressure (ICP/CPP)–guided management only, Group B (15 patients) was combined mild hypothermia and ICP/CPP-guided management, and Group C (14 patients) was combined mild hypothermia and $P_{ti}O_2$ guided with ICP/CPP management on patients with severe TBI.

Management

Patients with severe TBI were managed according to the guidelines of the American Association of Neurologic Surgeons, based on prompt evacuation of hematoma if necessary and the prevention of secondary insults to the brain. All patients were intubated and placed on volume-controlled ventilation under sedation to maintain a partial pressure of oxygen in arterial blood (PaO_2) of at least 100 mm Hg and arterial carbon dioxide pressure or tension ($PaCO_2$) of approximately 35–40 mm Hg. Sedation of the patients was induced by administering midazolam in Group A, with vecuronium in hypothermia groups (Groups B and C) to prevent shivering. The ICP should be maintained lower than 20 mm Hg, and the CPP showed to be maintained at greater than 60 mm Hg. Intracranial hypertension was treated by elevating the head end of the bed, sedation, paralysis, and mannitol. External ventricular drainage was not performed routinely, but it was used in patients with intraventricular hemorrhage and/or ventricular dilatation. Nutritional support was started as soon as possible and maintained by administering adequate parenteral or enteral solutions.

Hypothermia was started immediately after surgery for patients with evacuated mass lesions and after arrival in the intensive care unit (ICU). Hypothermia was induced by surface cooling with the use of water-circulating blankets, and ice pillows were placed around the head and neck. In this way, the brain temperature could be reduced to 33°–35°C within 2 hours and can be maintained at this temperature thereafter. Patients were sedated, paralyzed, and ventilated and were slowly rewarmed after the tendency of the ICP decreased.

For the patients of Group C, the treatment targets were the same as Group B (hypothermia combined ICP/CPP-guided group) but in addition, the avoidance of hypoxic $P_{ti}O_2$ levels of less than 20 mm Hg was attempted. Hypoxic episodes were counteracted by further increasing the cerebral perfusion pressure to the point where $P_{ti}O_2$ values reached 20 mm Hg. This goal was accomplished by increasing vasopressor and fluid intake as individually required. We would like to emphasize that increasing the fraction of inspired oxygen (FiO_2) did not raise the $P_{ti}O_2$.

Statistical Analysis

Student's t test for unpaired results and, whenever necessary, the χ^2 test, one-way ANOVA, Fisher's exact test, repeated measures ANOVA, and Kruskal–Wallis test were used to compare measurements. Data were expressed as means ± standard deviations. The squared deviations [measured as (daily observation − daily group mean)^2] were used to compare the daily variation of ICP. Statistical significance was set at $P < 0.05$ and the Glasgow Outcome Scale (GOS) score was analyzed by measuring process capability (Cpk).

MONITORING

Each patient in Groups A and B was monitored using an ICP monitor (Camino;

Table 1. Clinical Characteristics of the Three Treatment Groups

Variable	Group A	Group B	Group C	*P*-value
Number of patients	16	15	14	0.9355*
Sex (male : female)	10:6	9:6	8:6	0.9563*
Mean age (years)	43.5 ± 16.4	44.0 ± 15.1	38.8 ± 18.0	0.6475†
GCS score	6.4 ± 1.3	6.3 ± 1.2	6.5 ± 1.2	0.8793†
ICP at admission (mm Hg)	18.2 ± 14.6	16.8 ± 5.3	14.1 ± 6.0	0.5124†
Major findings on CT scans, *n* (%)				
Intracranial hematoma	8 (50)	7 (46.67)	7 (50)	0.6124†
Diffuse brain injury	5 (31.25)	4 (26.67)	3 (21.43)	0.6352†
Contusions and others	3 (18.75)	4 (26.67)	4 (28.57)	0.4156†
Craniotomy	11 (68.75)	11 (73.33)	10 (71.43)	0.7251†

Note: Group A: treated with intracranial pressure / cerebral perfusion pressure (ICP/CPP)–guided management only; Group B: ICP/CPP guided with mild hypothermia; Group C: combination of mild hypothermia and $P_{ti}O_2$-guided with CPP management; CT, computed tomography; GCS, Glasgow Coma Scale; ICP, intracranial pressure.
*χ^2 test.
†One-way ANOVA.

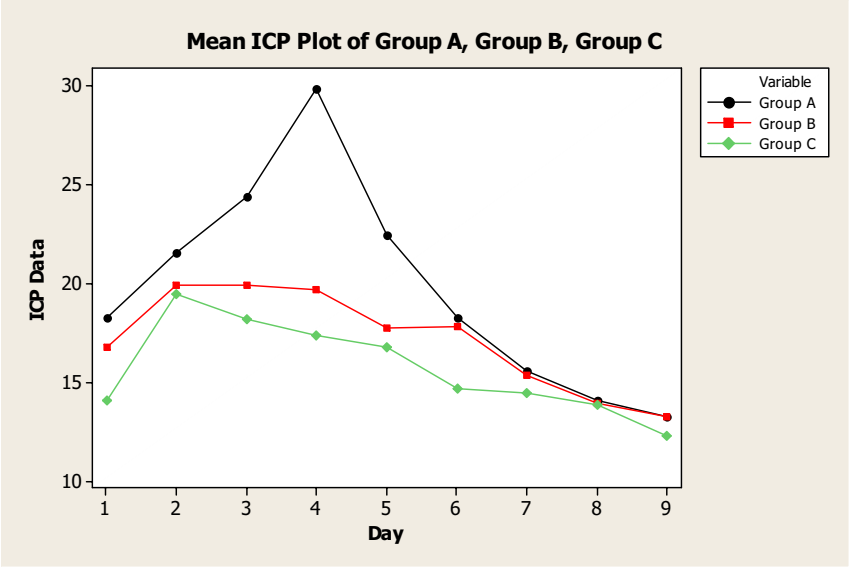

Figure 1. Shows the intracranial pressure (ICP) values progressively increased in first 3 days. However, hypothermia groups (Group B and C) have relatively smaller changes and significantly lower value than those of the normothermia group (Group A).

Integra NeuroSciences, Plainsboro, New Jersey, USA) inserted through a frontal burr hole. Patients in Group C were monitored using ICP and brain tissue P_{O_2} and temperature probes inserted through a triple-lumen bolt (LICOX CMP Triple Lumen Monitoring System; Integra NeuroSciences) via a frontal burr hole. The ICP catheters were inserted into the brain as soon as possible after the episode of trauma. They are usually placed in the frontal region of the more severely injured side after evacuating hematoma. The ICT/$P_{ti}O_2$ catheters were inserted into normal tissue near the traumatic brain at a depth of 22–27 mm in the parenchyma as described in Meixensberger (15).

The brain temperature was measured continuously by using an ICT catheter in Group C, and the acoustic meatus temperature was checked every hour in Groups B and C.

The data were collected from the start of the ICU admission through the period of intracranial hypertension. At the end of each hour, the mean ICP, temperature, $P_{ti}O_2$, and mean arterial pressure (MAP) were recorded. Cerebral perfusion pressure (CPP) was calculated as MAP − ICP. Further, ICP, ICT, MAP, CPP, and $P_{ti}O_2$ values were recorded for all the patients.

GOS scores (from 1 to 5) according to death, vegetative state, severe disability, moderate disability, and mild or no disability were evaluated for at least 6 months after injury. Neurologic outcomes were further classified as favorable outcome (GOS scores, 5 and 4), unfavorable outcome (GOS scores, 3 and 2), and death (GOS score, 1).

All parametric measurements were compared between the different methods of treatment. The relationship between ICP, ICT, $P_{ti}O_2$, and GOS were analyzed and the days of ICU and hospital stay were compared.

HOSPITAL COST

The total hospital cost, including the costs of ICU and ward stays, was analyzed as described previously (3). The ICU stay/day cost US$365/day. The ward costs were US$85/day. The ICU cost = cost of ICU/day × ICU days, and the ward stay cost = cost of ward/day × ward stay days.

RESULTS

Of the 45 patients enrolled in this study, 16 were in Group A [intracranial pressure/cerebral perfusion pressure (ICP/CPP)–

Table 2. ICP Mean: Based on Squared Deviations $(y_{ij} - y_{gj})^2$

	Group A	Group B	Group C	*P*-value*
Day 1	39.7 (4.9, 104.4)	5.1 (1.5, 22.7)	26.9 (6.6, 50.0)	0.0913
Day 2	26.6 (2.9, 112.6)	8.4 (2.0, 37.2)	12.5 (3.9, 56.8)	0.3157
Day 3	92.1 (20.3, 140.5)	11.6 (3.6, 57.8)	10.1 (1.3, 58.4)	0.0155
Day 4	70.6 (41.0, 102.0)	10.0 (2.8, 75.1)	9.1 (2.7, 47.0)	0.0044
Day 5	70.4 (40.9, 118.7)	13.7 (5.3, 67.2)	12.3 (7.4, 22.2)	0.0009

Note: Values are median (25th percentile, 75th percentile). Sample size: Group A is 16 in days 1–3; 15 in day 4; and 14 in day 5. Group B is 15 in days 1–5. Group C is 14 in days 1–5. ICP, intracranial pressure.
*Kruskal-Wallis test.

Table 3. ICP High: Based on Squared Deviations $(y_{ij} - y_{gj})^2$

	Group A	Group B	Group C	*P*-value*
Day 1	39.3 (6.3, 203.3)	20.6 (2.4, 55.8)	39.6 (10.3, 95.8)	0.5946
Day 2	46.7 (10.4, 164.4)	11.6 (2.6, 92.2)	16.5 (1.7, 59.5)	0.3112
Day 3	107.9 (56.6, 192.5)	9.8 (3.5, 66.2)	13.3 (2.3, 42.3)	0.0006
Day 4	119.5 (48.1, 167.3)	14.4 (0.6, 116.6)	16.7 (1.3, 61.7)	0.0014
Day 5	100.0 (79.7, 170.9)	16.0 (4.0, 81.0)	10.8 (7.4, 53.1)	0.0007

Note: Values are median (25th percentile, 75th percentile). Sample size: Group A is 16 in days 1–3; 15 in day 4; and 14 in day 5. Group B is 15 in days 1–5. Group C is 14 in days 1–5. ICP, intracranial pressure.
*Kruskal-Wallis test.

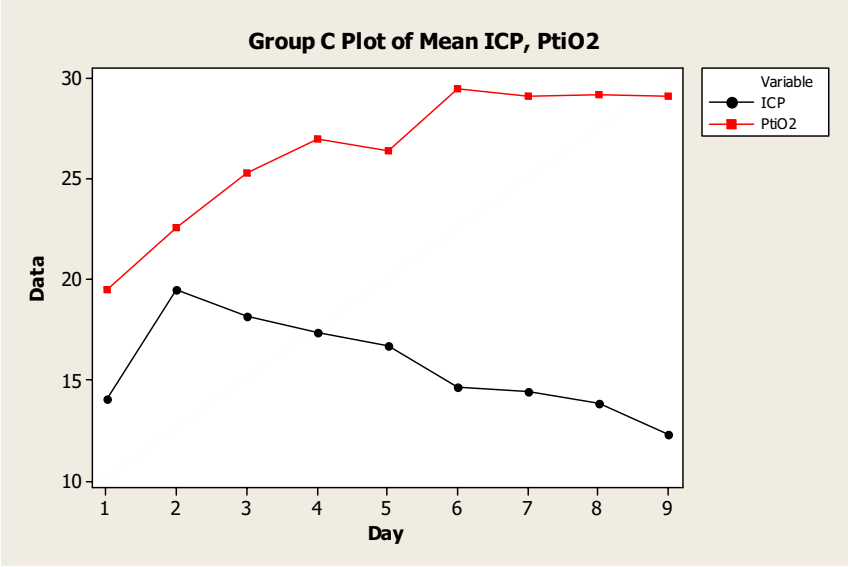

Figure 2. Shows the mean intracranial pressure values in Group B and C were much lower than Group A, and the values of $P_{ti}O_2$ tend to increase when the ICP decreases.

guided management only], 15 in Group B (combined mild hypothermia and ICP/CPP-guided management), and 14 in Group C (combined mild hypothermia and $P_{ti}O_2$ guided with ICP/CPP management). The characteristics of the patients are shown in **Table 1**; there was no statistical significance in these three groups.

ICP and $P_{ti}O_2$ Comparison

The ICP values progressively increased in the first 3 days but showed smaller changes in the hypothermia groups (Groups B and C) and were significantly lower than those of the normothermia group (Group A) at the same time point. Accordingly, the highest ICP was observed 72 hours after injury in Group A and 24–48 hours in Groups B and C. And the values in Groups B and C were much lower than those for Group A (**Figure 1**). Using repeated measures ANOVA in SAS software, we found out that the averaged ICP were significantly related to days. In addition, daily variations [measured as (daily observation − daily group mean)^2] of ICP were found to the significantly different among the three treatment groups after the third posttraumatic day (**Tables 2** and **3**). The values of $P_{ti}O_2$ in Group C tended to rise when the decreased ICP values were also observed (**Figure 2**).

Length of Hospital Stay and Total Hospital Cost

The mean ICU stay was significantly longer in the hypothermia groups; they were 9 days in Group A, 11.33 days in Group B, and 11.6 days in Group C ($P < 0.05$). But the total hospital stay was much shorter in Group C (**Table 4**).

The total hospital costs, including the costs of ICU and ward days, were US$5257 in Group A, US$5915.35 in Group B, and US$5815 in Group C on average.

NEUROLOGIC OUTCOME

The Cpk values (medical treatment process capability) of Group C (Cpk = 0.50) were of the greatest among them. The Cpk values of Group A and B were 0.35 and 0.46, respectively (**Figure 3**). Currently, combined mild hypothermia and $P_{ti}O_2$-guided CPP management on patients is the best medical treatment method.

A favorable outcome is divided by the GOS score. The percentage of favorable neurologic outcome was 50% in the normothermia group, 60% in the hypothermia only group, and 71.4% in the $P_{ti}O_2$ group, respectively, with statistical significance. The percentage of mortality was 12.5% in the normothermia group, 6.7% in the hypothermia only group, and 8.5% in $P_{ti}O_2$ group, respectively, without statistical significance in these three groups. The main characteristics of the results are shown in **Table 4**.

COMPLICATIONS

The proportion of patients with complications is shown in **Table 5**. Complications include pulmonary infections, peptic ulcer, and leukocytopenia (43.8% in the normothermia group, 55.6% in the hypothermia only group, and 50% in the $P_{ti}O_2$ group). There was no evidence of severe complications related to hypothermia compared to the normothermia group.

Table 4. Main Characteristics of the Results in the Three Groups

	Group A	Group B	Group C	*P*-value
Mean GOS	3.3 ± 1.3	3.5 ± 1.2	3.9 ± 1.2	0.0426*
Mean ICP	20.4 ± 17.7	17.7 ± 8.6	16.0 ± 4.9	0.0459*
Mean ICU stay	9.0 ± 4.7	11.3 ± 3.1	11.6 ± 4.5	0.0167*
Mean total stay	32.2 ± 23.9	32.3 ± 18.4	30.2 ± 19.7	0.0956*
Favorable outcome (≥4), *n* (%)	8 (50)	9 (60)	10 (71.4)	0.0395† 0.0437‡
Favorable outcome (≥3), *n* (%)	11 (31.4)	12 (34.2)	12 (34.2)	0.0201† 0.257‡
Mortality, *n* (%)	2 (12.5)	1 (6.7)	1 (7.1)	0.8180† 1.0000

GOS, Glasgow Outcome Scale; ICU, intensive care unit; ICP, intracranial pressure.
*One-way ANOVA.
†χ^2 test.
‡Fisher's exact test.

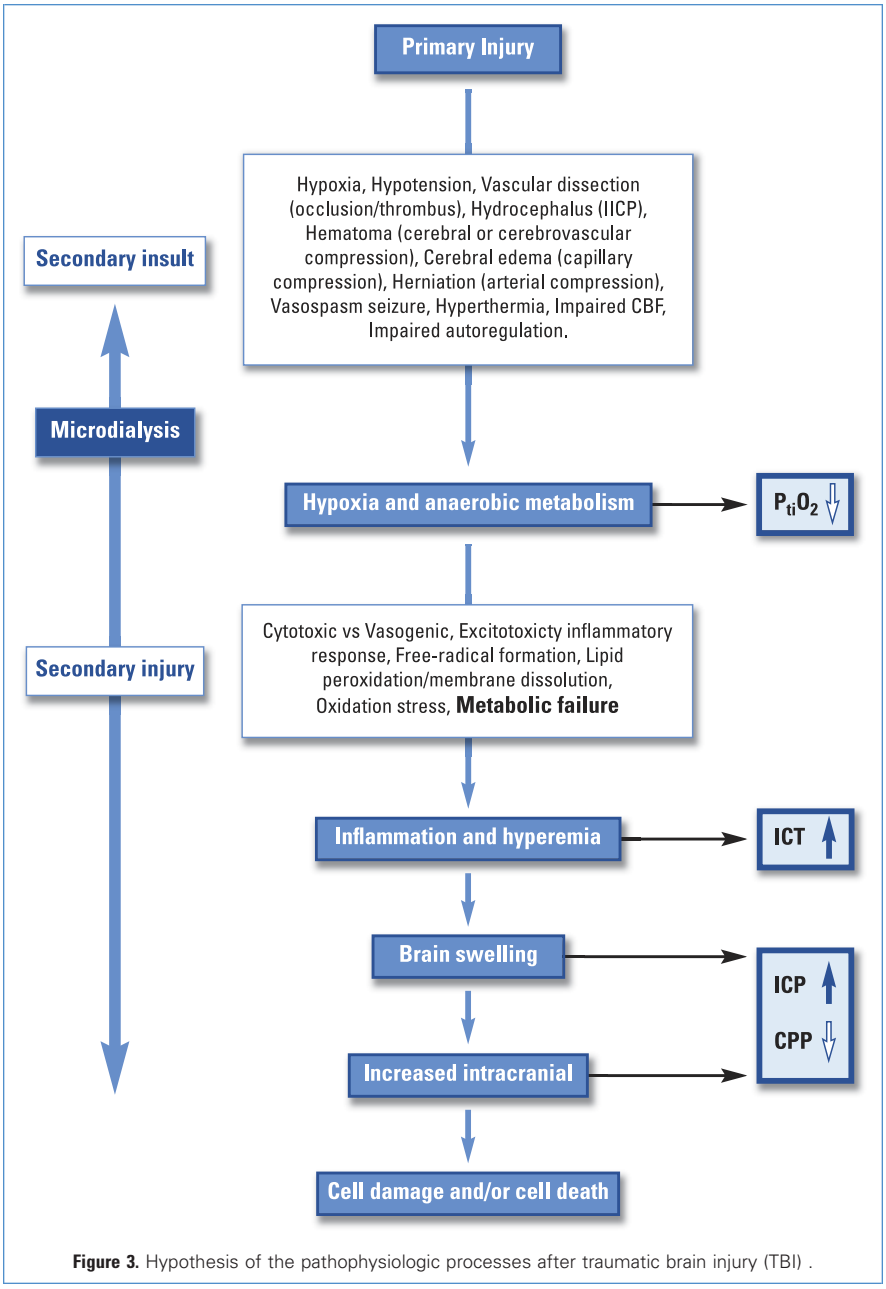

Figure 3. Hypothesis of the pathophysiologic processes after traumatic brain injury (TBI) .

DISCUSSION

Targets for postoperative care practice in patients with severe TBI have been widely debated. CPP management has been advocated by Rosner et al. (21) based on a concept called vasodilatory cascade. This method may reduce the incidence of secondary ischemic events; however, it may also increase the incidence of systemic complications (5, 19). Huang et al. (9) compared the three methods of ICP-targeted therapy, CPP-targeted therapy (maintained the CPP at >70 mm Hg), and modified CPP-targeted therapy (maintained the CPP >60 mm Hg). They concluded that modified CPP-targeted therapy with CPP >60 mm Hg has fewer complications and similar clinical outcomes. However, even when a cerebral perfusion pressure of >60 mm Hg is maintained following craniotomy, cerebral ischemia and hypoxia may still occur (4, 14), worsening the patient's chances of a satisfactory outcome.

Cerebral ischemia may be caused by impaired autoregulation, systemic hypotension, hypoxia, and intracranial hypertension and has been identified as a principal cause of secondary brain damage, including intracranial hypertension and impaired CPP (**Figure 3**). Under this hypothesis, the $P_{ti}O_2$ may present earlier than ICP. The prevention of cerebral hypoxia should result in an improved outcome in patients with traumatic brain injury (1, 7).

Recent clinical trials have confirmed that mild and moderate hypothermia may alleviate secondary brain injury after TBI, mainly through reducing ICP and improving CPP. The possible mechanisms include facilitating restoration of membrane function, attenuating cytoskeletal damage, ameliorating axonal damage, and reducing apoptosis (11, 13, 17, 24). But the indications for therapeutic hypothermia must be determined in severe TBI for its higher incidence of side effects, especially moderate hypothermia (17, 28). Rapidly achieving the target temperature and slowly rewarming over a period of 24 hours optimizes neuroprotection, mainly preventing the acute deterioration of intracranial hypertension in the first 72 hours after TBI (17, 18). Takashi et al. (25) tried to find the optimal temperature for the management of severe TBI. They concluded that a 35°–35.5°C body temperature is sufficient to control intracranial hypertension without inducing cardiac dysfunction and oxygen debt.

In this context, we used mild therapeutic hypothermia combined with $P_{ti}O_2$-guided CPP management to control the intracranial hypertension earlier and reduce unnecessarily high CPP by limiting the perfusion pressure to that necessary to ensure adequate oxygenation.

Our results indicate that the normothermia group (Group A) is associated with higher ICP, and the highest ICP was observed 72 hours after injury. But the hypothermia groups (Groups B and C) have less elevated ICP within 24 hours after injury. Using repeated measures ANOVA in SAS software, we found out that the average ICPs were significantly related to days. In addition, daily variations [measured as (daily observation − daily group mean)^2] of ICP were shown to the significantly different among the three treatment groups after third posttraumatic day (**Tables 2** and **3**). It means that the hypothermia group may

Table 5. Main Complications of Three Groups of Patients with Severe TBI

Main Complications	Group A	Group B	Group C
Pulmonary infection	4	4	5
Urinary tract infection	4	3	5
Thrombocytopenia	0	1	1
Hemorrhage in gastrointestinal tract	2	3	2
Sepsis	1	1	0
Renal failure	0	1	0
Arrhythmia	3	4	3

TBI, traumatic brain injury.

control the intracranial hypertension earlier and achieve optimum neuroprotection.

Recent reports indicate that the long-term outcome in patients suffering from severe TBI is mainly determined by cerebral protection. Evidence also associates ICP reduction with attenuation of free radical production or inhibited acute inflammatory response in hypothermia. The posttraumatic increase in oxygen radicals plays a role in the genesis of damage to the microvasculature and the subsequent breakdown of the blood–brain barrier (8, 23). This clinical study showed that the hypothermia groups may reduce the ICP earlier and inhibit the elicitation of acute inflammation after cerebral contusion. Our data also provide evidence of time course of $P_{ti}O_2$ values over the various posttraumatic days. As described by other investigators, $P_{ti}O_2$ values are lowest in the first 24 hours, indicating a high risk of ongoing brain damage (26, 27). However, treatment of low $P_{ti}O_2$ values by decreasing ICP use hypothermia and raising CPP is highly successful in reducing early hypoxic episodes (**Figure 2**).

Results of this study demonstrate that brain tissue $P_{ti}O_2$–guided treatment is associated with a significant increased in favorite outcome following TBI. We also analyzed using measuring process capability (Cpk). The capability measure is preferred in most industries because it indicates whether it is capable and how well-entered the process is. A larger value of Cpk was considered as better clinical effect. Out data showed combined mild hypothermia, and $P_{ti}O_2$-guided CPP management on patients is the best medical treatment method in these three groups.

For cost analysis, in our study, the length of ICU stay and direct costs were higher in hypothermia groups compared with the normothermia group. It was caused by a longer monitoring in hypothermia groups because of the totally and rewarming course of paralysis. It was also the reason of higher insurance pay in recent years. But the better favorite outcome in group C may compensate the social cost in future.

CONCLUSION

Our results indicate that the hypothermia groups reduce elevated ICP earlier than 24 hours after injury, and daily variations of ICP were significantly different among the three treatment groups after the third posttraumatic day. It means that in the hypothermia groups the ICP may be reduced earlier and elicitation of acute inflammation after cerebral contusion may be inhibited.

Our data also provide evidence of early treatment; the lower $P_{ti}O_2$ may improve the outcome and seems to be the best medical treatment method in these three groups. We concluded that therapeutic mild hypothermia combined with $P_{ti}O_2$-guided CPP/ICP management provides beneficial effects when treating TBI, and a multicenter randomized trial needs to be undertaken.

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