Recent Advances and Future Directions of Hypothermia Therapy for Traumatic Brain Injury

Eiichi SUEHIRO,1 Hiroyasu KOIZUMI,1 Yuichi FUJIYAMA,1 and Michiyasu SUZUKI1

1Department of Neurosurgery, Yamaguchi University School of Medicine, Ube, Yamaguchi

Abstract

For severe traumatic brain injury (TBI) patients, no effective treatment method replacing hypothermia therapy has emerged, and hypothermia therapy still plays the major role. To increase its efficacy, first, early introduction is important. Since there are diverse pathologies of severe TBI, it is necessary to appropriately control the temperature in the hypothermia maintenance and rewarming phases by monitoring relative to the pathology. Currently, hypothermia is considered appropriate for severe TBI patients requiring craniotomy for removal of hematoma, while induced normothermia is appropriate for severe TBI patients with diffuse brain injury. Induced normothermia is expected to exhibit a cerebroprotective effect equivalent to hypothermia, as well as reduce the complexity of whole-body management and systemic complications. According to the Japan Neurotrauma Data Bank of the Japan Society of Neurotraumatology, the brain temperature was controlled in 43.9% of severe TBI patients (induced normothermia: 32.2%, hypothermia: 11.7%) in Japan. Brain temperature management was performed mainly in young patients, and the outcome on discharge was favorable in patients who received brain temperature management. Particularly, patients who need craniotomy for removal of hematoma were a good indication of therapeutic hypothermia. Improvement of therapeutic outcomes with widespread temperature management in TBI patients is expected.

Key words: traumatic brain injury, hypothermia, induced normothermia, intracranial pressure, evacuated mass lesion

Introduction

The main objective of treatment of traumatic brain injury (TBI) is to inhibit secondary brain injury as much as possible to improve the outcome of TBI patients. Secondary brain injuries can arise from space-occupying lesions, such as hematoma and cerebral edema, or abnormalities of cerebral blood flow and metabolism caused by systemic elements, such as respiratory and circulatory disorders.1,2) These injuries are closely associated with worsening outcomes of patients, and can be prevented during TBI by brain temperature management.

In the history of therapeutic hypothermia for TBI, clinical studies on the cerebroprotective effect on TBI were reported one after another in 1993 attracting attention worldwide.3–5) Surprisingly, in 2001 a multi-center randomized controlled study [the National Acute Brain Injury Study: Hypothermia (NABIS: H)] observed no significant effect of therapeutic hypothermia for TBI.6) Now, no such studies are actively performed, despite the lack of an effective treatment method for severe TBI to replace hypothermia. However, evidence over the following years regarding the indication and management methods of therapeutic hypothermia have suggested some improvement in the outcome for patients with TBI.7–9) In this article, basic and clinical studies on therapeutic hypothermia for TBI are reviewed by looking back at historical background of hypothermia, followed by a discussion on the current status and prospects of brain temperature management for TBI.
History of Therapeutic Hypothermia for TBI

The history of hypothermia therapy started during the Classical period of Greece when Hippocrates cooled the local skin surface as anesthesia before skin incision.\textsuperscript{10} In 1938, Fay et al.\textsuperscript{11} initially performed therapeutic hypothermia to inhibit aggravation of malignant tumor and to reduce pain by cooling the whole body. After World War II, hypothermia was sought as a new method in the heart surgery field. The first report of the cerebroprotective effect of therapeutic hypothermia was published in 1956, in which the cerebral infarct volume significantly decreased at 25°C in a dog middle cerebral artery ligation model.\textsuperscript{12} Over the 1960s to 1970s, favorable outcomes of resuscitation after drowning in a frozen river and pond were reported,\textsuperscript{13,14} through which the cerebroprotective action of hypothermia gradually attracted attention. However, at the same time frequent reports of clinical complications, such as circulatory disorder and infection, led to disfavor in therapeutic hypothermia for the brain injury. Then in 1987, hypothermia attracted attention again with the report of effective cerebroprotection with minimized systemic complications using moderate hypothermia for brain injury at 32°C in a cerebral ischemia model.\textsuperscript{15} Around the same time, favorable outcomes of severe acute subdural hematoma patients with incidental hypothermia were also reported,\textsuperscript{16} further attracting attention to therapeutic hypothermia for TBI. In 1991, the cerebroprotective effect of hypothermia in an experimental TBI model was reported,\textsuperscript{17} which promoted clinical application of hypothermia for TBI. In 1993, clinical studies which achieved favorable outcomes of therapeutic hypothermia for TBI were reported from the United States and Japan,\textsuperscript{3–5} bringing hypothermia back into the spotlight. Since then, the results of many basic and clinical studies on the cerebroprotective effect of hypothermia for the brain injury have been reported.

There have been various proposals of the mechanisms of action for brain hypothermia, including the inhibition of glutamic acid release. These mechanisms require cooling from before injury or early after injury, but the cerebroprotective effect could be obtained several hours after injury by extending the duration of cooling or devising a warming method in some basic experiments,\textsuperscript{18–20} which strongly promoted clinical application. A large-scale clinical study was initiated in 1994 to obtain evidence of the effect of hypothermia for TBI. Favorable results were expected, but no effect was observed in the study reported by Clifton et al.\textsuperscript{6} in 2001, and popularity for hypothermia for TBI declined again. Therefore, clinicians started to make minor adjustments to improve the brain temperature management method and indication of hypothermia for TBI. Their efforts have increased the degree of perfection of hypothermia as a treatment method, for which improvement of the therapeutic outcome is expected.

Protective Mechanism and Complication of Hypothermia for TBI (Table 1)

The protective mechanism of hypothermia for TBI includes many mechanisms involved in inhibition of secondary brain injury: inhibitions of glutamic acid release,\textsuperscript{21} calcium-dependent cascade,\textsuperscript{22} cerebral metabolism,\textsuperscript{23} reactive oxygen species and NO production,\textsuperscript{24,25} apoptosis,\textsuperscript{26} and the blood-brain barrier disturbance.\textsuperscript{27} Consequently, many complications have been reported to be induced by the introduction of hypothermia. Some of these include infection (reduced immune function), electrolyte abnormality (hypokalemia), and thrombocytopenia. Frequent complications associated with the circulatory system include arrhythmia and reduction of the cardiac output as the body temperature decreases accompanied by metabolic acidosis. Moreover, liver, renal, and gastrointestinal dysfunctions and hyperglycemia develop. In consideration of the risks of these complications, appropriate centralized management is warranted.

Table 1 Protective mechanism point and complication of hypothermia therapy

| Point of protective mechanism                  | Complication                                   |
|-----------------------------------------------|------------------------------------------------|
| Glutamate acid release                        | Infection                                      |
| Calcium-dependent cascade                     | Electrolyte abnormality                        |
| Cerebral metabolism                           | Thrombocytopenia                               |
| Reactive oxygen species and NO production     | Arrhythmia                                     |
| Apoptosis                                      | Reduction of the cardiac output                |
| The blood-brain barrier disturbance            | Liver dysfunction                              |
|                                               | Renal dysfunction                              |
|                                               | Gastrointestinal dysfunction                   |
|                                               | Hyperglycemia                                  |
Brain Temperature Management in Therapeutic Hypothermia for TBI

I. Introduction

It is desirable to introduce hypothermia as early as possible after injury. Since the mechanisms of therapeutic hypothermia stem from inhibition of various cascades induced early after injury, a marked protective effect cannot be expected when cooling is not immediately initiated. Clinically, no significant protective effect was observed in NABIS: H performed by Clifton et al.6) On secondary analysis of their study, the favorable outcome rate was 48% in the hypothermia group, being significantly higher than that (24%) in the normothermia group in 45-year-old or younger patients who were incidentally hypothermic from arrival,28) suggesting that early introduction is the factor that brings out the cerebroprotective effect of hypothermia. Based on these findings, Clifton et al.29) initiated a new clinical study in 2005 (NABIS: H II). The subjects were limited to young patients aged 16–45 years for whom cooling can be initiated within 2.5 hours after injury.29) The patients could be cooled to 33°C within a mean of 4.4 hours.29) However, the final favorable outcome rate was 44% in the normothermia group and 40% in the hypothermia group, showing no significant difference.29) Although many basic studies reported positive data on the protective effect of hypothermia, no evidence was obtained in clinical studies, most likely due to the difficulty in introducing hypothermia very early after injury. Earlier introduction of hypothermia can be achieved in the future by improving the emergency medical system, such as the use of air ambulance, and developing body temperature-lowering devices.

II. Maintenance phase

In the initial report showing the effect of hypothermia, the experimental head injury model was cooled at 32°C for one hour.17) In later reports, the cerebroprotective effect of hypothermia improved when hypothermia was maintained even longer (3–6 hours).18,30,31) Clinically, hypothermia for the brain injury was normally maintained for 24 hours or 48 hours.6,32) However, Jiang et al.33) achieved favorable therapeutic outcomes by applying long-term hypothermia for a maximum of 14 days. They compared the outcome at 6 months after injury between patients treated with short-term (2 days) and long-term (5 days) hypothermia.7) Favorable outcome rates were 29.0% and 43.5% in the short- and long-term hypothermia groups, respectively, showing a significant improvement by long-term hypothermia.7) These findings suggest that the cerebroprotective effect of hypothermia is increased as the maintenance of hypothermia prolongs, although an increase in complications is a concern.

The appropriate duration for exhibiting the cerebroprotective effect while inhibiting complications is the most important issue in hypothermia for the brain injury. Monitoring of the intracranial condition using an intracranial pressure (ICP) sensor is essential. In Cochrane Reviews, eight large-scale clinical studies of therapeutic hypothermia for adult head injury were investigated.34) In three of the studies, hypothermia was applied for 1–2 days and then rewarming was initiated without ICP monitoring following the protocol. No cerebroprotective effect of hypothermia was observed in any of those studies.34) In contrast, in the other five studies the temperature was controlled using ICP monitoring and rewarming was performed after ICP was controlled within the normal range; the cerebroprotective effect was observed in four of them.34) Murakami et al.8) continued hypothermia for 28 days until ICP was normalized on ICP monitoring in a patient in the most severe state [Glasgow Coma Scale (GCS) of 3] with dilation of the bilateral pupils on arrival, and achieved recovery of conversation and gait. Taken together, there appears to be no fixed optimum duration of hypothermia, and maintenance methods should be set corresponding to the pathology of individual patients under monitoring.

III. Rewarming

Marion et al.32) reported a clinical study involving patients incidentally hypothermic on admission in 1997. The outcome was poor in 66% of patients allocated to the normothermia (rapidly rewarmed) group.6) They considered that active rewarming of incidentally hypothermic patients was a reason.6) Subsequently, the rewarming method after hypothermia for the brain injury came to be regarded as important. Aggravation of TBI and cerebral microcirculation by rapid rewarming in experimental TBI models has been reported.20,35,36) Clinical reports one after another suggested that rewarming should be carefully performed in TBI patients incidentally hypothermic on admission, and rapid rewarming would aggravate the outcome.37,38) Regarding this mechanism, basic studies found an imbalance between cerebral blood flow and metabolism during rewarming and microcirculatory disorder in the brain due to cerebrovascular reaction.36,39) Hyperemia followed by acute cerebral swelling during rewarming in a clinical case has also been reported.1,40) We also noted cases of sudden elevation of the ICP during rewarming. When swelling occurs, we suspend rewarming, and reconfirm and correct all parameters.
Once ICP decreases, rewarming can be restarted (Fig. 1). Since cerebral circulation and metabolism are unstable during rewarming, ICP monitoring is important. Slow rewarming is an important element to improve the outcome. It is essential to simultaneously identify the condition of cerebral circulation and metabolism by monitoring.

IV. Temperature control corresponding to the diverse pathologies of TBI

In previous large-scale clinical studies of TBI, the subjects were roughly specified as patients with “severe TBI.” However, the pathology of head injuries is diverse and very complex. Head computed tomography (CT) findings include diverse conditions, such as acute subdural and epidural hematomas, brain contusion, traumatic subarachnoid hemorrhage, diffuse axonal injury, and mixed type. These diverse pathologies should be treated on an individual basis. Although Clifton et al.\(^2\) could not demonstrate the efficacy of hypothermia for TBI in NABIS:H II, on secondary analysis, they found a favorable outcome rate of 30% in the diffuse injury group, but 67% in the evacuated mass group (Table 2), showing a significantly higher rate.\(^2\) According to the Japan Neurotrauma Data Bank (project 2009), the pathology was distinguished based on the Traumatic Coma Data Bank (TCDB) classification on head CT, and the outcome associated with body temperature management was compared.\(^\text{41}\) No difference due to body temperature management was observed in the diffuse injury group, but the favorable outcome rate was significantly higher in the hypothermia than in the induced normothermia group in patients with evacuated mass lesion\(^\text{41}\) (Table 2). These findings show that the cerebroprotective effect of hypothermia varies among TBI pathologies, and that evacuated mass lesion is a good indication of hypothermia. A large-scale clinical study of cerebral hypothermia focusing on patients with evacuated mass lesion is expected.

V. Changes in body temperature management in Japan

Following the lack of findings for the cerebroprotective effect of hypothermia for TBI in the randomized controlled trial performed by Clifton et al.\(^6\) in 2001, it became difficult for institutions in Japan to actively apply hypothermia for TBI. Thus, reverting to basic experiments of induced normothermia, Sakurai et al.\(^\text{42}\) prepared a rat model of mild head injury using fluid-percussion to compare normothermic and hyperthermic managements. They observed significantly larger contusion brain volume in rats with hyperthermic management.\(^\text{42}\) In clinical cases, it has been reported that ICP could be sufficiently managed in mild hypothermia at 35°C, without decreasing the body temperature to 33°C.\(^\text{43}\)
Moreover, the complication and mortality rates were significantly lower than those in patients treated with hypothermia at 33°C. When 21 severe head injury patients were divided into those with strict control at 36°C using a body temperature lowering device (induced normothermia group) and those with conventional body temperature management in which antipyretics were administered when fever developed, the induced normothermia group showed significantly reduced and stable ICP. The results of these initial reports encouraged the application of induced normothermia for TBI patients in Japan. Currently, hypothermia therapy requiring strict whole-body management of TBI patients is avoided, while induced normothermia applicable under relatively simple whole-body management is now preferred. The importance of brain temperature management as a part of treatment for the acute phase of TBI is now undisputed.

According to the Japan Neurotrauma Data Bank (project 2009), 225 patients were treated without active brain temperature management, accounting for the largest rate (56.1%), while induced normothermia was performed in 129 (32.2%), and hypothermia in 47 (11.7%). The mean age of these patient groups were 61.5 ± 24.0, 53.6 ± 22.6, and 46.9 ± 24.6 years old, showing that the brain temperature was managed mainly in young patients. Kawakita et al. reported a favorable outcome on discharge in the active brain temperature management group (induced normothermia and hypothermia) of 28.0%, which was significantly better compared to the group that did not receive active brain temperature management (18.3%). However, these outcomes based on brain temperature management or pathologies of TBI were strongly influenced by the age of the patient. Multivariate logistic analysis showed only age as the independent factor related to favorable outcome. Based on these results, we re-analyzed these patients, with the exclusion of patients with cardiopulmonary arrest before or on arrival (CPAOA) to simplify pathologies of patients, and the product of age and GCS on admission (age*GCS) was added as explanatory variables of multivariate analysis to eliminate a superfluous interaction between the two variables. The results of the multivariate analysis showed that age, GCS, age*GCS, pupil abnormality, and hypothermia were independent factors related to favorable outcome in all patients. When the multivariate analysis was evaluated relative to the pathologies of TBI described in the previous chapter, the independent factors related to favorable outcome were only GCS and age*GCS in patients with diffuse injury and GCS, age*GCS, and hypothermia in patients with evacuated mass lesion.

**Table 2** Clinical outcome according to pathophysiology in previous studies

| Pathology                  | Favorable outcome | Mortality | Favorable outcome | Mortality |
|----------------------------|-------------------|-----------|-------------------|-----------|
| **Diffuse injury**         |                   |           |                   |           |
| NABIS: H II                 | 50.0%             | 9.0%      | 33.3%             | 33.3%     |
| The Japan Neurotrauma Data Bank | 31.0% | 39.0% | 26.9% | 23.1% |
| **Evacuated mass lesion**  |                   |           |                   |           |
| NABIS: H II                 | 30.0%             | 27.0%     | 14.3%             | 57.1%     |
| The Japan Neurotrauma Data Bank | 67.0%* | 13.0% | 52.4%* | 19.0% |

*: p < 0.05, NABIS: H: the National Acute Brain Injury Study: Hypothermia.

**Conclusion**

The current state and methods of brain temperature management for TBI were reviewed. Many basic and clinical studies on therapeutic hypothermia for TBI have been reported and have clarified that early introduction and long-term maintenance of hypothermia and slow rewarming are required. The cerebroprotective effect of hypothermia varies among the pathologies of TBI, and the effect for evacuated mass lesions is expected. Introduction of induced normothermia has recently progressed, replacing hypothermia, because complexity of whole-body management and the risk of systemic complication can be reduced and its cerebroprotective effect may be greater than that of hypothermia depending on the pathology. Further application of induced normothermia in the future is expected.

**Acknowledgments**

This work was supported by JSPS KAKENHI Grant Number 25462219.

**Conflicts of Interest Disclosure**

All authors have no conflicts of interest. In addition, authors who are members of The Japan Neurotrauma Data Bank (project 2009) were not involved in the re-analysis of patients with evacuated mass lesions.
Neurosurgical Society (JNS) state that all authors have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

References

1) Bouma GJ, Muizelaar JP, Choi SC, Newlon PG, Young HF: Cerebral circulation and metabolism after severe traumatic brain injury: the elusive role of ischemia. *J Neurosurg* 75: 685–693, 1991

2) Maxwell WL, Irvine A, Adams JH, Graham DI, Gennarelli TA: Response of cerebral microvasculature to brain injury. *J Pathol* 155: 327–335, 1988

3) Clifton GL, Allen S, Barrodale P, Plenger P, Berry J, Koch S, Fletcher J, Hayes RL, Choi SC: A phase II study of moderate hypothermia in severe brain injury. *J Neurotrauma* 16: 263–271; discussion 273, 1993

4) Marion DW, Obrist WD, Carlier PM, Penrod LE, Darby JM: The use of moderate therapeutic hypothermia for patients with severe head injuries: a preliminary report. *J Neurosurg* 79: 354–362, 1993

5) Shiozaki T, Sugimoto H, Taneda M, Yoshida H, Iwai A, Yoshioka T, Sugimoto T: Effect of mild hypothermia on uncontrollable intracranial hypertension after severe head injury. *J Neurosurg* 79: 363–368, 1993

6) Clifton GL, Miller ER, Choi SC, Levin HS, McCauley S, Smith KR, Muizelaar JP, Wagner FC, Marion DW, Luerssen TG, Chesnut RM, Schwartz M: Lack of effect of induction of hypothermia after acute brain injury. *N Engl J Med* 344: 556–563, 2001

7) Jiang JY, Xu W, Li WP, Gao GY, Bao YH, Liang YM, Luo QZ: Effect of long-term mild hypothermia or short-term mild hypothermia on outcome of patients with severe traumatic brain injury. *J Cereb Blood Flow Metab* 26: 771–776, 2006

8) Murakami M, Tsukahara T, Ishikura H, Hatano T, Nakakuki T, Ogiwara E, Aoyama T: Successful use of prolonged mild hypothermia in a patient with severe head injury and diffuse brain swelling. Case report. *Neurol Med Chir (Tokyo)* 47: 116–120, 2007

9) Qiu W, Zhang Y, Sheng H, Zhang J, Wang W, Liu W, Chen K, Zhou J, Xu Z: Effects of therapeutic mild hypothermia on patients with severe traumatic brain injury after craniotomy. *J Crit Care* 22: 229–235, 2007

10) Furnas DW: Topical refrigeration and frost anesthesia. *Anesthesiology* 26: 344–347, 1965

11) FAY T: Early experiences with local and generalized refrigeration of the human brain. *J Neurosurg* 16: 239–259; discussion 259–260, 1959

12) Rosomoff HL: Hypothermia and cerebral vascular lesions. I. Experimental interruption of the middle cerebral artery during hypothermia. *J Neurosurg* 13: 332–343, 1956.

13) Kvittingen TD, Naess A: Recovery from drowning in fresh water. *Br Med J* 1: 1315–1317, 1963

14) Siebke H, Rod T, Breivik H, Link B: Survival after 40 minutes; submersion without cerebral sequae. *Lancet* 1: 1275–1277, 1975

15) Busto R, Dietrich WD, Globus MY, Valdés I, Scheinberg P, Ginsberg MD: Small differences in intraschismic brain temperature critically determine the extent of ischemic neuronal injury. *J Cereb Blood Flow Metab* 7: 729–738, 1987

16) Strachan RD, Whittle IR, Miller JD: Hypothermia and severe head injury. *Brain Inj* 3: 51–55, 1989

17) Clifton GL, Jiang JY, Lyeth BG, Jenkins LW, Hamm RJ, Hayes RL: Marked protection by moderate hypothermia after experimental traumatic brain injury. *J Cereb Blood Flow Metab* 11: 114–121, 1991

18) Clark KS, Kochanek PM, Marion DW, Schidinger JK, White M, Palmer AM, deKosky ST: Mild posttraumatic hypothermia reduces mortality after severe controlled cortical impact in rats. *J Cereb Blood Flow Metab* 16: 253–261, 1996

19) Globus MY, Alonso O, Dietrich WD, Busto R, Ginsberg MD: Glutamate release and free radical production following brain injury: effects of posttraumatic hypothermia. *J Neurochem* 65: 1704–1711, 1995

20) Suehiro E, Povlishock JT: Exacerbation of traumatically induced axonal injury by rapid posthypothermic rewarming and attenuation of axonal change by cyclosporin A. *J Neurosurg* 94: 493–498, 2001

21) Busto R, Globus MY, Dietrich WD, Martinez E, Valdés I, Ginsberg MD: Effect of mild hypothermia on ischemia-induced release of neurotransmitters and free fatty acids in rat brain. *Stroke* 20: 904–910, 1989

22) Mitani A, Kadoya F, Kataoka K: Temperature dependence of hypoxia-induced calcium accumulation in gerbil hippocampal slices. *Brain Res* 562: 159–163, 1991

23) Yager JY, Asselin J: Effect of mild hypothermia on cerebral energy metabolism during the evolution of hypoxic-ischemic brain damage in the immature rat. *Stroke* 27: 919–925; discussion 926, 1996

24) Kader A, Frazzini VI, Baker CJ, Solomon RA, Trifiletti RR: Effect of mild hypothermia on nitric oxide synthesis during focal cerebral ischemia. *Neurosurgery* 35: 272–277; discussion 277, 1994

25) Kil HY, Zhang J, Piantadosi CA: Brain temperature alters hydroxyl radical production during cerebral ischemia/reperfusion in rats. *J Cereb Blood Flow Metab* 16: 100–106, 1996

26) Xu RX, Nakamura T, Nagao S, Miyamoto O, Jin L, Toyoshima T, Itano T: Specific inhibition of apoptosis after cold-induced brain injury by moderate postinjury hypothermia. *Neurosurgery* 43: 107–114; discussion 114–115, 1998

27) Smith SL, Hall ED: Mild pre- and posttraumatic hypothermia attenuates blood-brain barrier damage following controlled cortical impact injury in the rat. *J Neurotrauma* 13: 1–9, 1996

28) Clifton GL, Miller ER, Choi SC, Levin HS, McCauley S, Smith KR, Muizelaar JP, Marion DW, Luerssen TG: Neurol Med Chir (Tokyo) 54, November, 2014
Hypothermia for Traumatic Brain Injury

Hypothermia on admission in patients with severe brain injury. J Neurotrauma 19: 293–301, 2002

29) Clifton GL, Valadka A, Zygun D, Coffey CS, Drever P, Fourwinds S, Janis LS, Wilde E, Taylor P, Harshman K, Conley A, Puccio A, Levin HS, McCauley SR, Bucholz RD, Smith KR, Schmidt JH, Scott JN, Yonas H, Okonkwo DO: Very early hypothermia induction in patients with severe brain injury (the National Acute Brain Injury Study: Hypothermia II): a randomised trial. Lancet Neurol 10: 131–139, 2011

30) Dietrich WD, Alonso O, Busto R, Globus MY, Ginsberg MD: Post-traumatic brain hypothermia reduces histopathological damage following concussive brain injury in the rat. Acta Neuropathol 87: 250–258, 1994

31) Palmer AM, Marion DW, Botscheller ML, Redd EE: Therapeutic hypothermia is cytoprotective without attenuating the traumatic brain injury-induced elevations in interstitial concentrations of aspartate and glutamate. J Neurotrauma 10: 363–372, 1993

32) Marion DW, Penrod LE, Kelsey SF, Obrist WD, Kochanek PM, Palmer AM, Wisniewski SR, DeKosky ST: Treatment of traumatic brain injury with moderate hypothermia. N Engl J Med 336: 540–546, 1997

33) Jiang J, Yu M, Zhu C: Effect of long-term mild hypothermia therapy in patients with severe traumatic brain injury: 1-year follow-up review of 87 cases. J Neurosurg 93: 546–549, 2000

34) Sydenham E, Roberts I, Alderson P: Hypothermia for traumatic head injury. Cochrane Database Syst Rev CD001048, 2009

35) Povlishock JT, Wei EP: Posthypothermic rewarming considerations following traumatic brain injury. J Neurotrauma 26: 333–340, 2009

36) Suehiro E, Ueda Y, Wei EP, Kontos HA, Povlishock JT: Posttraumatic hypothermia followed by slow rewarming protects the cerebral microcirculation. J Neurotrauma 20: 381–390, 2003

37) Kinoshita K, Utagawa A, Ebihara T, Furukawa M, Sakurai A, Noda A, Moriya T, Tanjoh K: Rewarming following accidental hypothermia in patients with acute subdural hematoma: case report. Acta Neurochir Suppl 96: 44–47, 2006

38) Thompson HJ, Kirkness CJ, Mitchell PH: Hypothermia and rapid rewarming is associated with worse outcome following traumatic brain injury. J Trauma Nurs 17: 173–177, 2010

39) Nakamura T, Miyamoto O, Yamagami S, Hayashida Y, Itano T, Nagao S: Influence of rewarming conditions after hypothermia in gerbils with transient forebrain ischemia. J Neurosurg 91: 114–120, 1999

40) Iida K, Kurisu K, Arita K, Ohtani M: Hyperemia prior to acute brain swelling during rewarming of patients who have been treated with moderate hypothermia for severe head injuries. J Neurosurg 98: 793–799, 2003

41) Suehiro E, Koizumi H, Kunitsugu I, Fujisawa H, Suzuki M: Survey of brain temperature management in patients with traumatic brain injury in the Japan neurotrauma data bank. J Neurotrauma 31: 315–320, 2014

42) Sakurai A, Atkins CM, Alonso OF, Bramlett HM, Dietrich WD: Mild hyperthermia worsens the neuropathological damage associated with mild traumatic brain injury in rats. J Neurotrauma 29: 313–321, 2012

43) Tokutomi T, Miyagi T, Takeuchi Y, Karukaya T, Katsuki H, Shigemori M: Effect of 35 degrees C hypothermia on intracranial pressure and clinical outcome in patients with severe traumatic brain injury. J Trauma 66: 166–173, 2009

44) Puccio AM, Fischer MR, Jankowitz BT, Yonas H, Darby JM, Okonkwo DO: Induced normothermia attenuates intracranial hypertension and reduces fever burden after severe traumatic brain injury. Neurocrit Care 11: 82–87, 2009

45) Kawakita K, Hatakeyama T, Abe Y, Nakamura T, Kawai N, Kuroda Y, Tamia T: Current situation of temperature management for severe traumatic brain injury: analysis of Japan Neurotrauma Data Bank Project 2009. Neurotraumatology 36: 45–51, 2013 (Japanese)

Address reprint requests to: Eiichi Suehiro, MD, PhD, Department of Neurosurgery, Yamaguchi University School of Medicine, Minami-Kogushi, Ube, Yamaguchi 755-8505, Japan.

E-mail: suehiro-nsu@umin.ac.jp