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

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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 multicenter 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.

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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.[10] In 1938, Fay et al.[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.[12] Over the 1960s to 1970s, favorable outcomes of resuscitation after drowning in a frozen river and pond were reported,[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.[15] Around the same time, favorable outcomes of severe acute subdural hematoma patients with incidental hypothermia were also reported,[16] further attracting attention to therapeutic hypothermia for TBI. In 1991, the cerebroprotective effect of hypothermia in an experimental TBI model was reported,[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,[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,[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.[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,[21] calcium-dependent cascade,[22] cerebral metabolism,[23] reactive oxygen species and NO production,[24,25] apoptosis,[26] and the blood-brain barrier disturbance.[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
Glutamate acid release
Calcium-dependent cascade
Cerebral metabolism
Reactive oxygen species and NO production
Apoptosis
The blood-brain barrier disturbance
Complication
Infection
Electrolyte abnormality
Thrombocytopenia
Arrhythmia
Reduction of the cardiac output
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 micro circulation 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 reported1.[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.

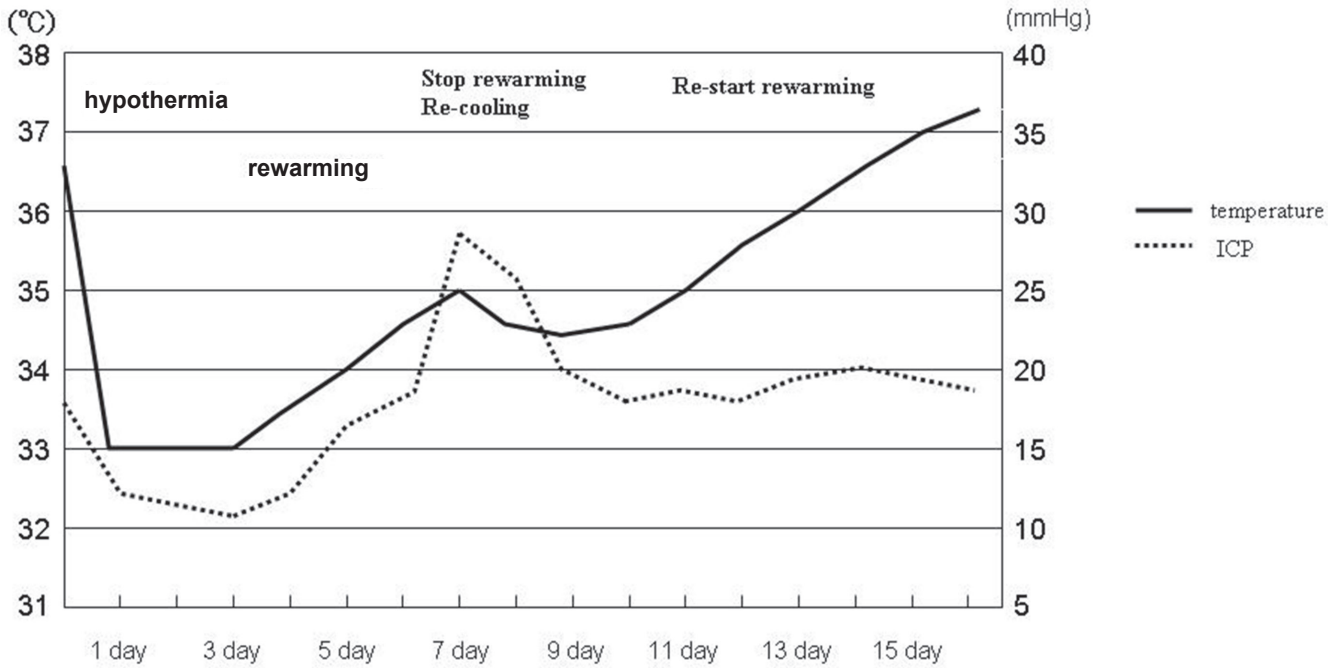

Fig. 1 Progress of body temperature and intracranial pressure (ICP) during hypothermia therapy. In rewarming phase, ICP was elevated suddenly, and rewarming was suspended. Once ICP decreased, rewarming could be restarted.

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.[29] 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.[29] 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.[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[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.[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.[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.[43]

Table 2 Clinical outcome according to pathophysiology in previous studies[29,41]

	Diffuse injury				Evacuated mass lesion			
	NABIS: H II[29]		The Japan Neurotrauma Data Bank[41]		NABIS: H II[29]		The Japan Neurotrauma Data Bank[41]	
	Favorable outcome	Mortality	Favorable outcome	Mortality	Favorable outcome	Mortality	Favorable outcome	Mortality
Induced normothermia	50.0%	9.0%	33.3%	33.3%	31.0%	39.0%	26.9%	23.1%
Hypothermia	30.0%	27.0%	14.3%	57.1%	67.0%*	13.0%	52.4%*	19.0%

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

Moreover, the complication and mortality rates were significantly lower than those in patients treated with hypothermia at 33°C.[43] 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.[44] 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%).[41] 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.[41] Kawakita et al.[45] 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.[45] 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.[41] 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.[41]

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.

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Conflicts of Interest Disclosure

All authors have no conflicts of interest. In addition, authors who are members of The Japan

Neurosurgical Society (JNS) state that all authors have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

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