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Brain hypothermia therapy for status epilepticus in childhood

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Abstract. – OBJECTIVE: At the Dokkyo Medical University Hospital, we introduced a brain hypothermia therapy protocol for treating childhood status epilepticus and acute encephalitis/encephalopathy in 2004.

PATIENTS AND METHODS: This protocol focuses on infants with a minimum age of six months or 7.5 kg in weight. Applicable diseases include acute encephalitis/encephalopathy occurring from status epilepticus or seizures lasting for 30 minutes or longer, in cases such as near drowning, hypoxic-ischemic encephalopathy, post-resuscitation encephalopathy, cardio-respiratory arrest, severe head injury, or other diagnoses in which the pediatric neurologist recognizes the possibility of neurological complications. Brain hypothermia therapy is managed within the intensive care unit (ICU).

RESULTS: The target body temperature is a bladder or rectum temperature of 34.0 to 35.0 degrees. This body temperature is reduced to the target temperature within six hours of the seizures. Hypothermia is maintained for 48 hours and concomitant steroid pulse therapy may be used at appropriate times. Sodium thiopental is used to sedate and rewarming is carried out at 0.5 degrees per 12 hours. Osmotic diuretics, muscle relaxants and circulatory antagonists may be concomitantly used at appropriate times.

CONCLUSIONS: This paper reviews the brain hypothermia therapy protocol.

Key Words:
Hypothermia, Steroid pulse, Status epileptcus, Acute encephalopathy, Protocol.

Outline of Brain Hypothermia Therapy

Cool temperatures are an effective method for preserving cadavers. Conventionally, human beings have understood that "cooling things" offers a range of benefits. In medicine, cooling methods have been used in response to the onset of fever for over two thousand years. In ancient Greece, Hippocrates treated head injuries amongst the soldiers by cooling them with snow. Since the 1800s, researchers have been observing mammals in hibernation, and the resuscitating humans by covering them with snow has been attempted in Russia.

In modern-day medicine, a cancer treatment involving the cooling of cancer patients' body temperatures to 32 degrees to inhibit the proliferation of cancer cells was reported in 1940 in the USA[1]. Subsequently, cooling the whole body was used as a treatment for serious head injuries. During the 1950s, its benefits during open-heart surgery were reported[2]. During that same period, doctors began to notice the benefits of cooling in resuscitation. In 1962, Westin, in Sweden reported resuscitating babies born in a hypoxic state by placing them in cold water until they began to breathe [3]. In 1963, a man who nearly drowned in a river in Norway, and whose heart stopped, was resuscitated and subsequently fell into an accidental hypothermic state, from which he recovered without complications after six months in ICU[4]. Since this occurred, research for this particular therapy has gained momentum.

During the 1980s, researchers gathered evidence that the cerebral-neuroprotective action of cooling body temperature to 34 degrees in animal models was effective. In 1990, a mechanism was proposed to adjust the brain temperature under whole-body management, after which its clinical applications began in earnest. In 2002, an article was published explaining the clinical effectiveness of the brain hypothermia with regard to out-of-hospital cardiac arrest among adults[5,6], and in the same year, the American Heart Association (AHA) and the European Resuscitation Council (ERC) recommended brain hypothermia therapy for the treatment of cardio-respiratory arrest. In

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2010, the International Liaison Committee on Resuscitation (ILCOR) recommended the implementation of hypothermia therapy for newborns in neonatal hypoxic-ischemic encephalopathy cases[7].

Physiological Changes and Treatment Strategies in Status Epilepticus and Acute Encephalopathy

A wide range of acute encephalopathy conditions, including acute necrotizing encephalopathy (ANE)[8], acute encephalopathy with febrile convulsive status epilepticus (AEFCSE)[9], acute infantile encephalopathy predominantly affecting the frontal lobes (AIEF)[10], acute encephalopathy with biphasic seizures and late reduced diffusion (AESD)[11], clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS)[12], and acute encephalitis with refractory, repetitive, partial seizures (AERRPS)[13], which is an acute encephalopathy accompanied seizure excitotoxicity, have been proposed and detailed breakdowns considered. The main symptom across the acute encephalopathy spectrum is status epilepticus.

Physiological changes that accompany status epilepticus occur not only in the central nerves. In status epilepticus cases, increased blood flow is localized, leading to increased demand for oxygen consumption and glucose metabolism and resulting in the patient potentially developing brain edema or cerebral ischemia. This type of status epilepticus can occur against a background of excitotoxicity in nerve cells, mitochondrial dysfunction, and hypercytokinemia. Furthermore, secondary long seizures can trigger excessive release of glutamic acid, accumulation of free radicals or oxidant stress, mitochondrial beta-oxidation disorders, and caspase activation, evoking subsequent, delayed neurocyte apoptosis and glial generation.

Accordingly, treatment of status epilepticus involves stopping the occurrence of multiple seizures, implementing cerebroprotective therapy, and preventing brain hypertension, as well as maintaining blood pressure and dynamic circulation, respiratory management to prevent hypoxemia and hypercapnia, fluid infusion to correct acidosis and electrolytes and manage blood sugar. As such, the whole-body management must be thoroughly implemented subsequently to the occurrence of status epilepticus. Furthermore, brain hypothermia therapy, is expected to be effective against delayed neurocyte disorders after status epilepticus.

Observations Related to the Protective Effect of Brain Cell Protection During Brain Hypothermia

Cooling the brain is known to have a range of protective benefits with regard to neurocytes. Low body temperature reduces brain activity, but at the same time controls brain metabolism and is beneficial to reducing the consumption of oxygen, fructose, adenosine triphosphate. When applied in conditions causing cellular edema such as status epilepticus and acute encephalopathy, it can not only prevent reperfusion injury, but also improve the homeostasis of Ca^{2+} in the brain, thereby, reducing damage to brain neurocytes. Furthermore, a low temperature state is effective in maintaining glutamic acid concentration and hypostasis between neurocytes. In addition, in a state of cerebral ischemia it has been reported that it may prevent an increase in free radicals, in addition to preventing irreversible delayed neurocyte-damaging apoptosis[5-7]. As such, brain hypothermia therapy shows promise in minimizing the mechanisms that evoke delayed neurocyte damage subsequent to status epilepticus.

Implementation of Brain Hypothermia Therapy

At the hospital, we developed a protocol for a brain hypothermia therapy for the treating childhood status epilepticus and acute encephalitis/encephalopathy in 2004. The process by which we implement low body temperature therapy is as follows. A doctor accompanying the helicopter transferring the infant with seizures, administers first-line anti-seizure medication (Dormicum, either via nasal cavity or intravenously). When the helicopter delivers the doctor and patient to the emergency unit examining room, the second-line drug (Fosphenytoin or intravenous Phenobarbital) is administered. Complex cases, in which the patient resists these treatments and multiple seizures occur, are then referred for brain hypothermia therapy.

This protocol (Table I) is applied to cases of acute encephalitis/encephalopathy occurring as a result of status epilepticus or seizures lasting for

Table I. Proposed protocol for brain hypothermia therapy (Dokkyo Medical University Hospital ICU: April 2014).

Anti-seizure medication treatment for status epilepticus

A) Midazolam (0.5 mg/kg) administered via the nasal cavity or cheek mucosa
B) Midazolam (0.15 mg/kg) intravenously (i.v.) administered (up to two doses possible)
C) Between ages 0 and 2: intravenous phenobarbital, between 15 and 20 mg/kg (10 minsi.v.), 2 years or older: Fosphenytoin 22.5 mg/kg (10 minsi.v.)
D) Sodium thiopental between 3 and 5 mg/kg (slow i.v.)

Brain hypothermia therapy

This protocol applies to infants weighing 7.5 kg or over, aged 6 months or older.

Introductory period

1. Status epilepticus/acute encephalopathy admission: ICU (request for admission), contact brainwave dept/radiology (brain and chest CT)
2. Check vital signs, establish a peripheral line
3. Establish central venous line: establish double/triple lumen catheter + arterial line
4. Fluid infusion between 80 and 100 ml/kg/day: under whole-body management, fluid control must not be reduced more than necessary in order to maintain blood pressure and cerebral circulation. Blood pressure is evaluated using an arterial pressure monitor. Maintenance fluids comprise an acetic acid preparation maintenance fluid and a lactic acid preparation. Vitamins are administered. When theophylline is administered, vitamin B6 is measured (light-shielding blood collection tube: administer vitamin B6 for theophylline-related seizures. Take care not to induce cardiac arrest by sudden administration of B6).
5. Management of blood count, electrolytes, blood sugars, albumin, clotting value. Ferritin, IL-2R, β2MG, procalcitonin, immune globulin, etc. submitted.
6. Mannitol 3-5 ml/kg × 4-6 times/day (administered over an hour).
7. Harvest spinal fluid (after first administration of mannitol). General spinal fluid + various cytokines (IL-6, IL-1β, TNF-α), Tau protein, submitted. Freeze and store the remaining fluid at -80 degrees.
8. If possible time/wise implement MRI (DWI/ADC-map).
9. Intratracheal intubation (if difficult, use muscle relaxant or inhalation anesthetic)
10. Artificial ventilation: PCO_2 at 35 to 40 mmHg (do not over-ventilate). PEEP kept slightly low taking brain hypertension into consideration. Raise head 10 degrees. If brain hypertension occurs: request placement of cerebral pressure monitor by neurosurgeon.
11. Steroid pulse therapy: methylprednisolone 30 mg/kg over two hours for three days, during which heparin or fragmin therapy is continued. APTT 1.5 or above.
12. Administer famotidine 0.5 mg/kg twice, or alternatively, omeprazole.
13. Brain hypothermia therapy use a whole-body blanket-cooling method, to induce target body temperature (direct intestine/bladder temperature 34.0 to 35.0 degrees) within six hours of onset. If necessary, cool the head or wash the stomach with normal saline solution while taking care not to cause electrolyte abnormalities, or use chilled fluid infusion.
14. Anti-seizure medication:sodium thiopental, 5-10 mg/kg/hr (if this cannot be used, consider midazolam, 0.3 to 0.9 mg/kg/hr).
15. Sedation depth should be confirmed by portable electroencephalograph/paperless electroencephalograph (Makin2) as reaching suppression burst within six hours of beginning therapy.

Cooling period

16. Target temperature to be maintained for 48 hours (or maximum 72 hours). Confirm BIS monitor value at suppression burst (aim for 40 or below) and adjust the sodium thiopentaldose administered based on the BIS value as appropriate. Cases achieving a positive sedation depth should have their sodium thiopental dose reduced prior to rewarming at a BIS value between 60 and 70, and at body temperature 35.0 degrees.
    [Caution] If spikes remain with suppression bursts, consider complete suppression (pupils will constrict to mydriasis, and response to light is lost: BIS value of 20 or lower).
17. UseINVOS™ at an appropriate time to check oxygen saturation at the left and right front scalp, to evaluate brain circulation.
18. Blood pressure maintenance: appropriate dose of dopamine hydrochloride (5 μg/kg/min = 0.3 mg/kg/h = 0.015 ml/kg/h), manage electrolyte abnormalities and blood glucose. Heart rate will fall to bradycardia with falling body temperature.
19. Administer antibacterials as appropriate. In applicable conditions, cerebroprotectiveedaravone, sivelestat Na as a neutrophil elastase inhibitor, and aciclovir.

Rewarming period

20. Rewarming is implemented at a pace of 0.5 degrees per 12 hours. Care should be taken to avoid pneumonia in line with increased sputum secretions. Aim to remove the patient from artificial respiration on the 5th to 7th day. For cases in which laryngitis is likely, intravenous dexamethasone or epinephrine should be administered prior to removal of the tube.
21. For cases in which critical complications are envisaged, TRH therapy should be initiated at an early stage.
22. Including rehabilitation, aim to discharge the patient one month after onset.
23. Prior to discharge, evaluate brain waves, implement neuroradiological images/nuclear medicine tests and assess development. Where necessary, anti-seizure mediation should be periodically administered for preventative purposes.

30 minutes or more. These cases include near-drowning, hypoxic-ischemic encephalopathy, post-resuscitation encephalopathy, cardio-respiratory arrest, severe head injury, or other diagnoses in which the pediatric neurologist recognizes a possibility of neurological complications.

Introductory Period

Brain hypothermia therapy is implemented in the Intensive Care Unit (ICU), where a target body temperature equivalent to bladder temperature between 34.0 and 35.0 degrees is induced using a catheter with a temperature sensor attached, within six hours of the occurrence of status epilepticus. If this body temperature is difficult to achieve, chilled fluid transfusion or chilled water injected via a gastric tube may be used. The use of muscle relaxants is effective in controlling the shivering. Strict care is required, however, to monitor the brain waves, as there is a possibility that non-convulsive status may be missed. Sedation is administered using 5 to 10 mg/kg sodium thiopental per hour, under whole-body management, and within six hours of the occurrence. The depth of sedation should be induced at which suppression and burst can be achieved, while monitoring the brain waves. If an electroencephalograph is not available in the ICU, the Makin2 (manufactured by GMS) paperless portable electroencephalograph, or the bispectral index (BIS) monitor (manufactured by COVIDIEN, Dublin, Ireland) may be used. Brain wave suppression and burst is achieved at a BIS value of 40 or lower[14]. If there are multiple spikes mixed in with burst waveforms, the sedation depth is lowered further to complete suppression (flat brain waves), at a BIS value of 20 or lower. In such cases, the left and right pupils will constrict to mydriasis at 4 mm or above, and response to light is lost. For cases in which cerebral blood vessel damage or cerebral edema causes brain oxygen metabolism issues, the non-invasive mixed oxygen saturation monitoring device INVOS™ (manufactured by COVIDIEN) used in brain or cardiac surgery may be used on the scalp to monitor localized brain perfusion irregularities, ischemia and oxygen trends. Cases in which stable sedation cannot be achieved using sodium thiopental require the cooperation of an anesthetist, who will administer a mixture of oxygen and isoflurane or sevoflurane at between 1 and 2 MAC (1.15-2.3%), inducing suppression and burst within a few minutes.

Cooling Period

Cooling is done using a whole-body cooling blanket (manufactured by MAC8). The standard required cooling period is 48 hours, which is extended to 72 hours if required. Depending on the symptoms, the head may also be cooled. Conditions diagnosed against a background of hypercytokinemia are administered with steroid pulse therapy, using 30 mg/kg methylprednisolone for three days. In addition to managing sufficient fluid transfusion to maintain brain circulation, an osmotic diuretic and a circulator antagonist may be used as appropriate. In cases where significant brain hypertension is noted, a neurosurgeon is consulted and an intracranial pressure monitor may be used.

Rewarming Period

Rewarming is done at a pace of 0.5 degrees per 12 hours. Brain hypothermia therapy is implemented in partnership between a dedicated ICU physician and a pediatrician (Figure 1).

Points to Note With Regard to Brain Hypothermia Therapy

A range of adverse effects can occur as a result of the changes in vital signs accompanying a reduction in body temperature. For this reason, the management of anesthesia, respiration, circulation, intracranial pressure, body temperature, must be monitored and the patient placed on artificial respiration. It is, therefore, imperative that the case be managed by ICU. Potential complications include hypotension, arrhythmia, electrolyte abnormality, hyperglycemia, edema of the larynx, pulmonary atelectasis, cutaneous ulceration, pressure ulcers, and reduced white blood cell count, clotting fibrinolytic disorders, reduced immunity and increased susceptibility to infection, among others.

Conclusions

Sufficient evidence exists to demonstrate the protective effects of brain hypothermia on brain neurocytes. The clinical benefits of brain hypothermia therapy have still not been established for status epilepticus and acute encephalopathy. Recently, reports have begun to appear[15-17] suggesting the effectiveness of brain hypothermia therapy for childhood seizure disorders. Hopeful-

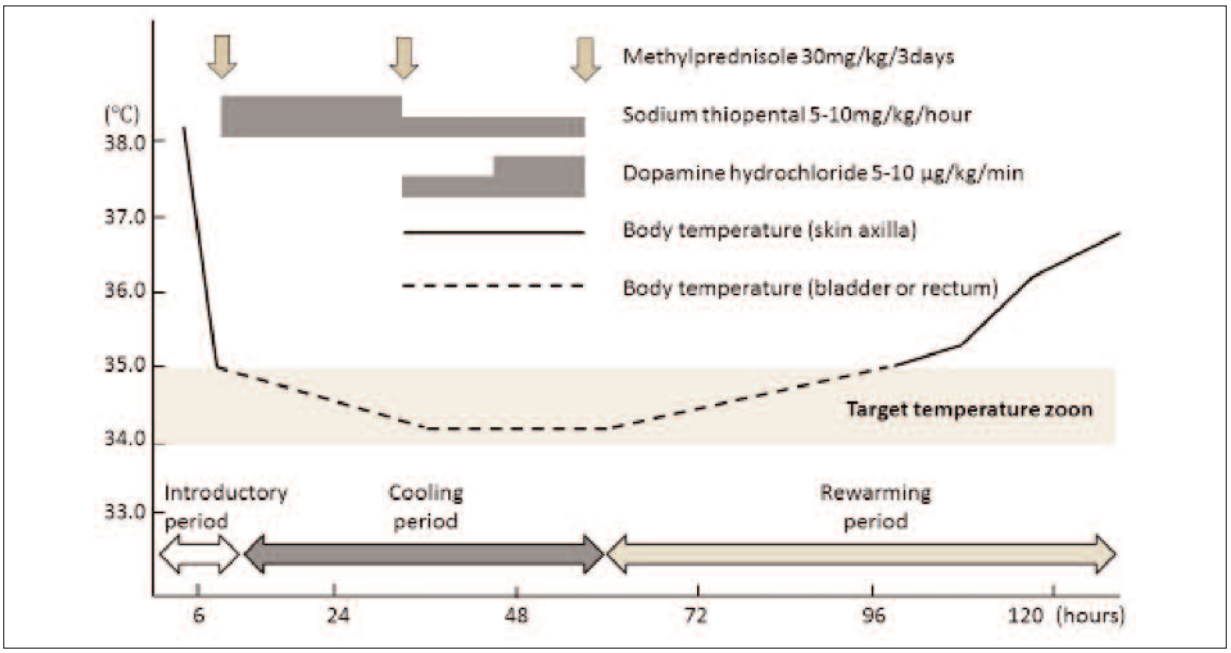

Figure I. Clinical course of brain hypothermia therapy (cooling period: 48 hours).

ly, clinical applications for brain hypothermia therapy will be established in the near future, thereby eliminating neurological complications related to infant status epilepticus.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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