Initial assessment of targeted temperature management with normothermia by surface cooling device effectiveness in neurological intensive care unit

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Summary

Objective: To evaluate effects of targeted temperature management by surface cooling device in patients suffering from acute brain injury with refractory fever. *Subject and method:* Patients of traumatic brain injury, intracerebral hemorrhage with refractory fever in the first 24 hours and without exclusion criteria. *Result:* They were successfully treated with surface cooling device with normothermia. *Conclusion:* Targeted temperature management by surface cooling device is effective to control refractory fever in patients suffering from hemorrhagic stroke, severe traumatic brain injury with refractory fever.

Keywords: Targeted temperature management, hemorrhage stroke, severe traumatic brain injury, refractory fever.

I. BACKGROUND

Fever is common in critically ill patients with neurological conditions. In those with acute stroke or traumatic brain injury, fever can contribute to secondary brain injury, and is associated with poorer functional outcomes and higher morbidity and mortality[2]. Targeted temperature management (TTM) is often used in neurocritical care to minimize secondary neurologic injury and improve outcomes. TTM encompasses therapeutic hypothermia, controlled normothermia, and treatment of fever. TTM has been explored in acute ischemic stroke, traumatic brain injury (TBI), and intracranial hemorrhage (ICH) patients. Critical care clinicians using TTM must select appropriate cooling techniques, provide a reasonable rate of cooling, manage shivering, and ensure adequate patient monitoring among other challenges[6, 9]. In Vietnam, TTM in neurological intensive care units was conducted but the number of patient was still limited. Therefore, we perform this study to evaluate the effectiveness of TTM in TBI and ICH stroke patients suffered from refractory fever.

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II. SUBJECT AND METHOD

2.1. Subject

We show 05 patients underwent TTM by surface cooling devices after acute brain injury with refractory fever.

Inclusion criteria included: Any form of traumatic brain injury, intracerebral hemorrhage stroke and temperature 39°C for two or more consecutive hours after the oral administration of 1000mg of acetaminophen.

Exclusion criteria included: Age < 18 years of age. Refusal of consent. Pregnancy. A preexisting skin condition that precluded the use of adhesive cooling pads. Withholding or withdrawing of intensive care. Refractory hypotension requiring multiple pressors.

Eligible patients were identified by two doctors at the NICU. If a patient's temperature fell below

39.0°C after enrollment, but before the start of cooling, the study intervention was postponed until the next observed temperature 39.0°C. All patients were treated with broad-spectrum antibiotics, either empirically or on the basis of culture results during ICU stays. The requirement for written informed consent was waived because the study was felt to pose no significant risk to its participants; verbal consent to participate was obtained from each subject or his or her surrogate after receiving a description of the trial procedures, risks, and benefits.

2.2. Method

Subjects meeting the enrollment criteria were assigned a subject identification number treated with the Arctic Sun Temperature Management System (Figure 1). The control module for this device adjusts the temperature of the water circulating through the cooling pads (range 10-44°C) to maintain core body temperature at a target level, which was set at 37 ± 0.5°C. Patients continued to receive 500mg of acetaminophen orally every 4 hours if their temperature exceeded 38.5°C.

Data Collection: Baseline demographic, clinical, and laboratory data pertaining to each subject were obtained and recorded through medical record review. Vital signs and the presence or absence of shivering or any other treatmentrelated complications were recorded hourly by the nursing staff. Glasgow Coma Scale (GCS) scores were recorded by doctor every 2 hours, as per protocol in our ICU.

Figure 1. A patient with normothermia by surface cooling device

III. RESULT

Many patients developed sustained fever (T > 39°C on two consecutive measurements 1 hour apart), but only 5 patients were enrolled. The most common reasons for failure to enroll were fever reduction in response to acetaminophen. All subjects had a primary diagnosis of traumatic brain injury and intracranial hemorrhage (Table 1).

Table 1. Baseline characteristics of the study patients

	Case 1	Case 2	Case 3	Case 4	Case 5
Demographics					
Age (years)	30	32	76	67	64
Gender	Male	Male	Male	Female	Male
BMI (kg/m^2)	22.0	22.5	19.5	21.5	23.9
History of hypertension	No	No	Yes	No	Yes

	Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**
History of diabetes	No	No	No	Yes	Yes
Brain CT scan	SAH, Cerebral Contusion	Subdural hematoma, Cerebral Contusion	Pontine hematoma	ICH with ventricular extension	Supratentorial intraparenchymal haemorrhage
Ventilated	Yes	Yes	Yes	Yes	Yes
Diagnostic category	TBI	TBI	ICH	ICH	ICH
Baseline clinical features prior to enrollment					
Maximal temperature in esophagus in prior 24 hours (°C)	40.4	40.1	40.2	41.2	40.2
Heart rate (beats per minute)	145	155	129	149	135
Mean arterial pressure (mmHg)	135	125	140	141	120
Respiration rate (breaths per minute)	35	41	33	32	36
Glasgow Coma Scale score	7	5	6	6	6
Pupillary diameter	2	2	2	2	2
Pupillary reactivity	Reacting	Reacting	Reacting	Reacting	Reacting
Leukocyte count	5.51	9.51	6.53	8.55	9.65
Procalcitonin (ng/ml)	0.15	0.12	0.09	0.25	0.07
Chest X-rays	Normal	Normal	Normal	Normal	Normal
Blood cultures	Negative	Negative	Negative	Negative	Negative
APACHE II	26	30	32	33	31
Approximated in hospital mortality rates (%)	35	73	73	73	73

All subjects, the cause of fever was unexplained despite a complete diagnostic evaluation such as Leukocyte count, procalcitonin, chest X-rays and blood cultures suggestive of central fever. All patients suffered from maximal temperature in prior 24 hrs > 40.0°C. Approximated in hospital mortality rates based on The Acute Physiology and Chronic Health Evaluation II (APACHE II) of these patients was very high from 35 to 73 percent.

Table 2. Primary and secondary outcome measures

	Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**
Efficacy outcome measures					
Time febrile (T ≥ 39.0°C), hours	5	3	4	3	6
Time to normothermia, minus	125	168	138	174	126
Secondary outcome measures					
Times of shivering during trial	8	12	0	2	0

	Case 1	Case 2	Case 3	Case 4	Case 5
BSAS score	3	3	0	2	0
Pharmacologic antishivering therapy	Yes	Yes	No	No	No
GCS score at completion of trial	13	6	6	6	6
GCS score improved from baseline	6	1	0	0	0
Time of using TTM with normothermia (days)	11	15	15	22	9
Duration of mechanical ventilation (days)	15	22	23	27	15
Length of ICU stay (days)	22	33	39	42	31

In the intention-to-treat analysis of the primary efficacy outcome measure (Table 2), treatment with surface cooling device resulted in controlled temperature in normothermia and time to targeted temperature < 3 hours. Three of five patients developed BSAS level 2 or 3 shivering despite protocol-directed measures to counteract this and times of shivering during trial was from 2 to 12. Of the three patients who shivered, in one it subsided without intervention and two patients required pharmacologic antishivering therapy. Patients were treated for shivering using a standardized institutional protocol[3]. This anti-shivering protocol includes standing acetaminophen (for T > 38.3°C), magnesium infusion and skin counter-warming, with subsequent stepwise interventions of fentanyl and propofol. Time of using TTM with normothermia from 9 to 22 days.

Table 3. Adverse events

Complications	Case 1	Case 2	Case 3	Case 4	Case 5
Respiratory tract infection	No	Yes	No	Yes	Yes
Urinary tract infection	No	Yes	Yes	No	Yes
Sepsis	No	No	No	Yes	No
Skin lesions	No	No	No	No	No
Thrombosis	No	No	No	No	No
Arrhythmias	No	No	No	Yes	Yes
Hypotension	No	No	No	Yes	Yes
Rebound fever	No	No	No	No	No

There was no observed skin injury or irritation upon removal of the device for any patients. Two of five patients developed respiratory tract infection, Urinary tract infection despite all patients were treated with broad-spectrum antibiotics, either empirically or on the basis of culture results during ICU stays. However, no patient developed sepsis during ICU stays. Two of five patients developed arrhythmias, hypotension. No patient experienced a rebound fever within 4 hours of ending the therapy.

Table 4. Outcomes

Outcomes	GOS at hospital discharge	GOS at 1 month	mRS at 3 months	mRS at 6 months
Case 1	4	5	1	1
Case 2	2	2	5	5
Case 3	2	2	5	5
Case 4	2	2	5	5
Case 5	2	2	5	5

All patients was discharged and after one month. One of five patients had Glasgow Outcome Score (GOS) was 5 at 1 month. After 3 months and 6 months, four of five patients had modified Rankin Scale (mRS) was 1.

IV. DISCUSSION

After neurologic injury, the brain is vulnerable to secondary damage from ischemia, edema, impaired metabolism, and other factors which can extend the zone of injury. Fever is often a contributor to secondary injury and is associated with greater morbidity and mortality. As such, TTM is often used in neurocritical care to minimize secondary neurologic injury and improve outcomes. It has also been explored in ischemic stroke, TBI and ICH stroke patients. Refractoriness was defined as a lack of decline in core temperature during the hour following the administration of a single dose of 500 mg acetaminophen enterally. When neurogenic fever is detected, TTM should be initiated rapidly if antipyretic agents fail to control the temperature within 1 hour, and should then be maintained for as long as there is potential for secondary brain damage. The recommended target temperature for TTM is 36.5-37.5°C. The use of advanced TTM methods that enable continuous, or near continuous, temperature measurement and precise temperature control is recommended. The treatment device uses an ice water circulating system embedded in hydrogel-coated, energy transfer pads. Its thermoregulatory feedback control uses cold water and was set at 36.5°C for this study. There were no significant differences in the survival to hospital discharge and the good neurological outcomes between surface cooling devices and intravascular cooling devices[4]. In this study, fever control using the Arctic Sun Temperature Management System was initiated. During the induction and maintenance of normothermia, patients were monitored for the presence of shivering[1, 6]. In our study, all patients had a high fever within 19-30 hours from the onset of the disease and the infectious cause was excluded by blood tests, chest X-rays and blood culture test. Acetaminophen is a drug commonly used in resuscitation to reduce fever and relieve pain[1, 2]. Acetaminophen dosage in our study was calculated based on weight of 10-15mg/kg/time and the total dose was not more than 4000mg/24 hours. The target temperature for patients with acute brain injury is 37.0 ± 0.5°C[1]. Achieving normothermia is feasible in patients with ischemic or hemorrhagic stroke, subarachnoid hemorrhage and traumatic brain injury. Pharmacological strategies are frequently ineffective and physical (i.e. cooling devices) therapies are often required[2].

In patients with severe brain injury treated with induced normothermia, shivering correlated with the intensity of cooling. Monitoring of therapeutic cooling with computerized thermoregulatory systems may help prevent shivering and optimize the management of induced normothermia[7]. A significant proportion of patients undergoing temperature modulation can be effectively treated for shivering without over-sedation and paralysis[3,5]. In our study, the number of patients was very limited, research needs to be conducted with a larger number to evaluate the effectiveness and complications when conducting targeted body temperature control.

V. CONCLUSION

Targeted temperature management with normathermia is initially effective in controlling body temperature in acute brain injury patients suffered from refractory fever. Research needs to be perform with a larger number of patients to evaluate the effectiveness of TTM with a surface cooling device in patients with stroke and severe TBI with refractory fever.

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