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Original Article

Therapeutic hypothermia for pediatric refractory status epilepticus May Ameliorate post-status epilepticus epilepsy

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ARTICLE INFO

Article history:
Received 5 November 2019
Accepted 17 April 2020
Available online 21 April 2020

Keywords:
Therapeutic hypothermia
Pediatric refractory status epilepticus
Pharmacoresistant refractory status epilepticus
Post-status epilepticus epilepsy
Febrile infection-related epilepsy syndrome
Temperature management system

ABSTRACT

Background: To compare the clinical characteristics and outcomes of pediatric patients with refractory status epilepticus (RSE) and super-refractory status epilepticus (SRSE) who received therapeutic hypothermia (TH) plus anticonvulsants or anticonvulsants alone.
Methods: Two-medical referral centers, retrospective cohort study. Pediatric Intensive Care Unit (PICU) at Taoyuan Chang Gung Children's hospital and Kaohsiung Chang Gung Memorial Hospital. We reviewed the medical records of 23 patients with RSE/SRSE who were admitted to PICU from January 2014 to December 2017. Of these, 11 patients received TH (TH group) and 12 patients did not (control group).
Results: The selective endpoints were RSE/SRSE duration, length of PICU stay, and Glasgow Outcome Scale (GOS) score. We applied TH using the Artic Sun® temperature management system (target temperature, 34–35 °C; duration, 48–72 h). Of the 11 patients who received TH, 7 had febrile infection-related epilepsy syndrome (FIRSE), one had Dravet syndrome, and three had traumatic brain injury. The TH group had significantly shortern seizure durations than did the control group (hrs; median (IQR) 24(40) vs. 96(90), $p < 0.05$). Two patients in the TH group died of pulmonary embolism and extreme brain edema. The length of PICU stay was similar between the groups (days; median (IQR) 30(42) v.s 30.5(30.25)). The TH group had significantly better long-term outcomes than did the control group (GOS score, median (IQR) 4(2) v.s 3 (0.75), $p = 0.01$*). The TH group had a significantly lower incidence of later chronic refractory epilepsy than did the control group (TH v.s non-TH, 5/11 (45%) v.s. 12/12(100%), $p < 0.01$).

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Peer review under responsibility of Chang Gung University.
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https://doi.org/10.1016/j.bj.2020.04.004

Conclusions: TH effectively reduced the seizure burden in patients with RSE/SRSE. Our findings support that for patients with RSE/SRSE, TH shortens the seizure duration, ultimately reducing the occurrence of post-status epilepticus epilepsy and improving patients' long-term survival.

At a glance of commentary

Scientific background on the subject

Therapeutic hypothermia (TH) is applied for various medical conditions, however, studies employing TH for status epilepticus are limited in pediatric population. This study aimed to compare the clinical outcomes of pediatric patients with refractory status epilepticus (RSE) and super-refractory status epilepticus (SRSE) who received TH plus anticonvulsants or anticonvulsants alone.

What this study adds to the field

Our results support that TH effectively shortens the seizure duration in pediatric patients with RSE/SRSE. And, shortened seizure durations in the acute symptomatic phase of SE can reduce the occurrence of post-status epilepticus epilepsy as well as improve long-term functional outcome.

Status epilepticus (SE) is defined as convulsions persisting for >5 min [1–3]. The gold standard treatment for SE is antiepileptic drugs (AEDs). However, up to 44% of SE cases cannot be controlled by first-line agents, with many such cases exhibiting refractory status epilepticus (RSE) [4]. Refractory status epilepticus is defined as clinical or electroencephalographic seizures lasting >60 min despite treated with at least one first-line AED (e.g., benzodiazepine) and one second-line AEDs (e.g., phenytoin, phenobarbital, or valproate) [2,5,6]. Super-refractory status epilepticus (SRSE) is defined as SE that has persisted or recurred for ≥24 h after the onset of general anesthesia treatment [7]. Both RSE and SRSE are considered neurologic emergencies, because the patient can develop complications including hypoglycemia, brain injury, rhabdomyolysis, related kidney injury, prolonged intensive care unit (ICU), hospital stays, and even death [4,8]. The current treatment option for RSE/SRSE is to use continuous anestheticagents, such as propofol, midazolam, barbiturate, or ketamine, until a burst-suppression pattern is observed during electroencephalography [2,3,5,9,10]. Unfortunately, these medications only achieve this effect in 64–78% of patients [10]. Thus, alternative therapeutic approaches with better efficacies are needed for patients with RSE/SRSE.

One such approach that has been used as a complementary treatment in RSE is therapeutic hypothermia (TH) [2,5,8,11]. The use of TH dates back to early as 400BC when Hippocrates used snow and ice to reduce hemorrhage [5]. Moreover, Britton published a medical report on the use of TH in 1930. Since then, TH has been utilized in variable conditions to protect neurons and improve outcomes. A variety of studies have been published demonstrating the effects of TH in open-heart surgery [12–14], cardiac arrest [15,16], neonatal hypoxic ischemic encephalopathy [17–19], and traumatic brain injury [20]. However, studies employing TH for seizure control are still limited, and the results are diverse, especially in pediatric groups [2,21]. Therefore, the aim of the present study was to compare the short-term and long-term outcomes between patients with RSE who did and did not receive TH.

Material and methods

Patient population

We reviewed the medical records of all patients with RSE/SRSE who were admitted to the Pediatric Intensive Care Unit (PICU) of the Department of Pediatrics at two medical referral centers, Taoyuan Chang Gung Children's hospital and Kaohsiung Chang Gung Memorial Hospital, between January 2014 and December 2017. Taoyuan Chang Gung Children's hospital and Kaohsiung Chang Gung Memorial Hospital are two of the largest tertiary referral centers in northern and southern Taiwan, and each contains 20 beds for children with critical medical conditions. The study was approved by the institutional review board of the Chang Gung Memorial Hospital.

The enrolled patients were aged between 1 week and 17 years. All patients with clinical or electroencephalographic seizures lasting >60 min despite being treated with at least one first-line or second-line AED (e.g., benzodiazepine) and one second-line AED were diagnosed with RSE. Patients encountered status epileptics that has persisted or recurred for ≥24 h after the onset of being treatedwith general anesthesia were diagnosed as SRSE [2,5,6]. The patients with RSE/SRSE were divided into the TH group (received anticonvulsants and TH to control seizures) or the control group (received only anticonvulsants to control seizures). Patients who had contraindications for TH (e.g., coagulopathy) or economic concerns were categorized into the control group.

We collected the demographic and clinical data of the patients in both groups, including age, sex, length of PICU stay, RSE/SRSE duration, AEDs regimens, 1- year outcome, as measured with the Glasgow Outcome Scale (GOS) and Post-Status Epilepticus Epilepsy 1 year later. The GOS scores were classified as grade 1, dead; grade 2, vegetative state; grade 3,

severely disabled; grade 4, moderately disabled; grade 5, good (no remained neurological sequelae).

Therapeutic hypothermia

We introduced TH as an adjunctive treatment for RSE/SRSE by using the Artic Sun® temperature management system with Artic Gel™ pads (Medivance, Inc. of Louisville, Colorado,U.S.A.). The pads feature a thin hydrogel coating that ensures they maintain contact with the patient's skin throughout the treatment.

The TH protocol is shown in Fig. 1. Hemodynamic monitoring with arterial pressure measurement and Patient Monitor (IntelliVue MP 60, Philips Monitor) were set up before TH. Midazolam continuous infusion and Rocuronium continuous infusion for sedation and anti-shivering were also administered before TH. In our TH cooling protocol for SE, the target temperature was set at 34–35 °C and the cooling period was 48–72 h. For rewarming, the temperature was increased by 0.05° per hour. The rewarming period was 1–2 days or until the body temperature reached 36 °C. Following this, normothermia (36 °C) was maintained for 1–2 days. We recorded all of the complications that occurred during TH, including electrolyte imbalances, arrhythmia, infection, and coagulopathy, among others (Fig. 2).

Statistical analysis

The age, sex, RSE/SRSE duration, length of PICU stay, AED regimen, and GOS score of patients with RSE/SRSE from the two clinical groups were compared using the Mann–Whitney U test was utilized for the age comparisons, RSE/SRSE duration and length of PICU stay. In addition, the chi-square test or Fisher's exact test was applied for categorical variables analysis. Statistical testing was performed using the SPSS software (version 18; _SPSS Inc., Chicago, Ill., USA). Differences were considered significant at a p-value ≤ 0.05.

Results

Case descriptions of patients in the TH group

During the study period, 11 patients with RSE/SRSE received TH with the Artic Sun® temperature management system, and these patients were categorized into the TH group. The demographic and clinical characteristics of these patients are listed in Table 1. 7 patients (A, B, G, H, I, J, K) had an underlying etiology of newly diagnosed FIRES, suffered from relatively long SE durations (48 and 96 h, respectively), and exhibited poor responses to multipleAEDs. The SE of these patients was finally controlled (achieved a burst-suppression pattern) with continuous thiamydial infusions and propofol infusions plus TH. These patients also had relatively long PICU stays. Unfortunately, Patient B suddenly passed away due to pulmonary embolism while recovering from FIRES. However, the complication was related to prolonged immobility in the PICU, not to TH.Patient C (an 8-year-old boy) had an underlying disease of Dravet syndrome, which was genetically proven to be related to an *SCN1A* mutation. He developed refractory SE due to an influenza infection. Poor responsiveness to AEDs was observed due to persistent high fever. We applied TH along with continuous midazolam infusions. Soon after, burst suppression was achieved. The patient recovered well after rewarming, without cognition or motor function deteriorations.

Patient D (8-month-old boy) had a traumatic brain injury owing to a car accident. He underwent subdural hematoma decompression immediately after arrival. However, his SE continued, despite the administration of multiple AEDs. The application of TH successfully controlled his SE, and the patient recovered with post-status epilepticus epilepsy.

Patients E (6-month-old boy) and F (2-month-old boy) presented with head trauma owing to abuse. The SE in these patients continued despite decompressive craniectomy and the administration of multiple AEDs. We applied TH along with continuous midazolam infusions to both patients, and the convulsions remitted within 24 h. However, although the SE was well controlled, patient E died of extreme brain edema.

Control group

Another 12 patients presented with RSE/SRSE during the study period did not receive TH due to contraindications or financial restrictions. Therefore, we included these patients in the control group. Most patients in the control group had FIRES as the etiology (7/12, 58.3%).

Comparisons between the TH and control groups

Details regarding the comparisons of clinical information between the TH and control groups are shown in Table 2. As shown in Table 2, no significant differences in age or AED regimen used were identified between the groups, indicating that the baseline conditions of the two groups were similar.

RSE/SRSE duration

The seizure durations ranged from 3 to 96 h in the TH group and from 6 to 192 h in the control group. The seizure duration was significantly shorter in the TH group than it was in the control group (hrs; median (IQR) 24(40) vs. 96(90), $p < 0.05$).

Length of PICU stay

The PICU stay in the TH group ranged from 8 to 83 days, while that in the control group ranged from 4 to 58 days. No difference in the length of PICU stay was identified between the TH and control groups (days; median (IQR) 30(42) v.s 30.5(30.25)).

GOS score

3 of the 11 patients (27.2%) in the TH group had an excellent GOS score of 5, while another 2 patients (18.2%) died of extreme brain edema or deep vein thrombosis with pulmonary embolization. The remaining 5 patients in the TH group (45.4%) had a GOS score of 4, which indicated that they had recovered, with moderate functional disabilities. 2 of the 12 patients (16.6%) in the control group had a GOS score of 5. 1 had a score of 4 (33.3%), 9 of the 12 patients had a GOS score of 3 (75%). Comparisons of the GOS scores between the groups revealed that patients with RSE/SRSE who did not receive TH exhibited significantly worse outcomes (GOS scores) compared to patients who received TH ($p < 0.05$).

This protocol applies for patients with status epilepticus or suspection of acute encephalitis / encephalopathy

1. Admission to PICU with intensive critical care
2. Assure the patient has the following supportive equipment before hypothermia therapy:
    a. Endotracheal intubation (RSI, Rapid Sequence Intubation) with artificial ventilation to keep PCO2 at 35 to 40 mmHg (do not over-ventilate).
    b. If possible, set up arterial catheter to monitor arterial pressure
    c. If possible, set up CVP catheter to assess fluid volume. Goal CVP 6-10 mmHg
3. Asses the patient's clinical status before initiating hypothermia therapy
    a. Obtain continuous core temperature via esophageal probe
    b. Assess baseline 12 Lead EKG
    c. Check ABG, CBC/DC, PT/APTT, Fibrinogen, D-Dimer, BUN/Cr, Na/K/Ca/Cl/P/Mg, AST, Bil (T/D), albumin, CRP, lactate, amylase, lipase, cardiac enzyme, CPK isoenzyme
4. Sedate patient with midazolam continuous infusion [2-20mcg/kg/min] and anti-shivering drug as Rocuronium [6-12mcg/kg/min].
5. Intracranial pressure is controlled by the followings:
    a. Fluid infusion between 80 and 100 ml/kg/day. Fluid control must not be reduced more than necessary in order to maintain blood pressure and cerebral circulation.
    b. Maintain head of bed at 30 degrees.
    c. Submitted hypertonic 3% NaCl
6. Steroid pulse therapy: methylprednisolone 30 mg/kg over three hours for three days
7. Administer esomeprazole or other PPI drugs to prevent stress ulcer.
8. Cooling phase:
    a. Brain hypothermia therapy uses Arctic Sun cooling system, to induce target body temperature (direct esophageal temperature 34.0 to 35.0 degrees) within three hours of onset.
    b. Anti-seizure medication: midazolam, 2 to 20 mcg/kg/min or Thiamylal Sodium, 2-5 mg/kg/hr.
    c. Sedation depth should be confirmed by portable electroencephalograph (Nicolet) as reaching suppression burst within six hours of beginning therapy.
9. Cooling period:
    a. Target temperature to be maintained for 48 hours (or maximum 72 hours).
    b. Patients achieving a positive sedation depth should reduce the anti-seizure medication dose prior to rewarming
    c. [Caution] If spikes remain with suppression bursts, consider complete suppression
    d. Manage electrolyte abnormalities and blood glucose.
    e. Administer antibiotics appropriate.
10. Rewarming period
    a. Rewarming is implemented at a pace of 0.05 degrees per hour.
    b. When the body temperature backs up to 36.0 degrees, we will keep body temperature at 36.0 degrees for 24 hours to prevent rebounding IICP.

Fig. 1 Our protocol of therapeutic hypothermia therapy for patients with status epileptics or suspection of acute encephalitis/ encephalopathy.

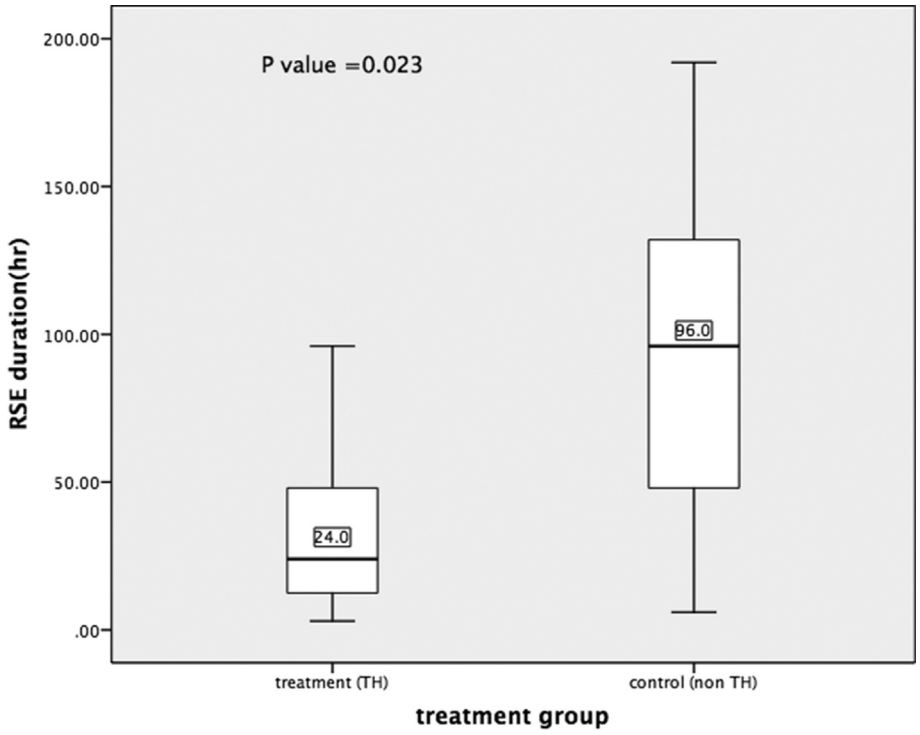

Fig. 2 Boxplot for comparing the two groups of the RSE duration. We found the TH group had significantly shorter RSE duration than control group.

Incidence of progression to post-status epilepticus epilepsy

As illustrated in Table 2, 5 of the 11 patients (45.4%) in the TH group developed chronic refractory epilepsy later in life. All patients (100%) in the control group developed chronic refractory epilepsy, causing severe functional disabilities. Comparisons of the incidences between the groups revealed that fewer patients in the TH group vs. the control group progressed to post-status epilepticus epilepsy after 1- year follow-up period. ($p < 0.005$).

Discussion

Applying TH within 6 h after birth is considered a standard treatment for moderate to severe neonatal hypoxic ischemic encephalopathy [21,22]. Further, TH reportedly improves the survival rate and neurologic outcome of neonatal hypoxic ischemic encephalopathy survivors [17,18]. Although the precise mechanisms remain unclear, TH is thought to reduce epileptic discharges in patients with neonatal hypoxic ischemic encephalopathy [23]. Interestingly, TH also reportedly decreases brain activity in cardiac arrest patients post-resuscitation [24,25] and decreases intracranial pressure while preserving adequate cerebral perfusion in patients with traumatic brain injury [26]. In animal studies, TH exhibits attenuating effects on apoptosis [27] and mitigates the altered extrahippocampal neurotransmitters in animals with pilocarpine-induced SE [28]. Given these findings, TH is being considered an alternative, non-invasive physical treatment option for cardiac arrest, traumatic brain injury, and SE [29].

In a trial on adult patients with SE who were under mechanical ventilation in the ICU, adding TH to standard SE care did not result in better neurologic outcomes, but a

Table 1 Clinical information of patients underwent therapeutic hypothermia.

	Age at onset/Sex	Etiology for SE	TH Target temp (°C)	TH Duration (hrs)	Complications of TH
Patient A	13yo/M	FIRES	35	72	Electrolyte imbalance, Bradycardia
Patient B	13yo/M	FIRES	34.5	72	Bradycardia, Infection
Patient C	8yo/M	Dravet syndrome	35	48	Electrolyte imbalance, Infection
Patient D	8 mo/M	TBI post minor neurosurgery	34	72	Electrolyte imbalance
Patient E	6 mo/M	TBI post minor neurosurgery	34	72	Electrolye imbalance, Coagulopathy
Patient F	2 mo/M	TBI post minor neurosurgery	35	48	Electrolye imbalance, Coagulopathy
Patient G	8yo/M	FIRES	34	120	Electrolye imbalance
Patient H	4yo/M	FIRES	35	72	Electrolye imbalance
Patient I	6yo/F	FIRES	35	48	Electrolye imbalance
Patient J	6yo/F	FIRES	35	48	Electrolye imbalance
Patient K	10yo/M	FIRES	33	120	Electrolye imbalance, Tachycardia

Table 2 Outcome measurement between treatment-and control-group.

	Treatment Group (n = 11)	Control group (n = 12)	*p* value
Age (yrs; median (IQR))	6.5(9.8)	9(6.25)	0.30
Sex (M/F)	9/2	7/5	0.092
RSE duration (hrs; median (IQR))	24(40)	96(90)	**0.023***
ICU stay (days; median (IQR))	30(42)	30.5(30.25)	0.666
AEDs kinds (median (IQR))	5(3)	3(1.5)	0.086
GOS score (median (IQR))	4(2)	3(0.75)	**0.01***
Chronic Epilepsy (numbers, (%))	5(45)	12(100)	**0.005****

Statistically significant *p* values are bolded. *$p < 0.05$; **$p < 0.01$.

possible anticonvulsive effect was observed [30,31]. However, research on the beneficial effects of TH for pediatric patients with SE is limited. Control of pharmaco-resistant RSE after TH application was reported in several case series [2,31–33]. In pediatric patients with SE, age, seizure etiology, and duration of SE all affect outcome [34]. Moreover, the timely administration of first-line benzodiazepines leads to a lower death rate and risk of AED-infusion dependency [35]. Nevertheless, efficient treatment options for controlling pharmaco-resistant RSE are lacking in current clinical practice.

Several studies have shown that patients with short SE durations have better outcomes [36–39] owing to fewer SE-related complications, such as tachycardia, hypoglycemia, hypotension, or rhabdomyolysis, although a few studies yielded inconclusive results [40]. Patients with acute symptomatic SE have a three-fold greater risk of developing chronic epilepsy compared to patients with acute symptomatic seizures [1]. Although the etiology for RSE/SRSE is the pivotal predictor for RSE/SRSE outcome [30], the downstream mechanisms of SE, including neuronal death, reactive oxygen stress production, blood–brain barrier breakdown, and adenosine triphosphate depletion, contribute to the long-term consequences of SE, such as chronic epilepsy and cognitive problems [2]. In our study, since the TH group had significantly shorter seizure durations than did controls, this may also have led to the improved long-term functional outcomes and reduced incidence of chronic epilepsy in the patients who received TH. Our data highlight the beneficial effects of TH on patients with RSE/SRSE, and are consistent with the data supporting the positive effects of TH on patients with cardiac arrest.

Here, the most frequently observed complication was electrolyte abnormalities. During TH, serum electrolyte disturbances occur because of the increased renal excretion of electrolytes and the resulting intracellular shift [41]. The most common situation was hypokalemia, the clinical effects of which include cardiac arrhythmias, muscle weakness, rhabdomyolysis, renal failure, and elevated blood sugar levels (due to the suppression of insulin secretion) [41]. Given the potential complications of electrolyte disturbances, preventing electrolyte imbalances caused by hypothermia should be the clinician's main goal [42].

Several limitations of this study should be noted. First, we had a relatively small sample size due to the high cost of receiving TH with the Artic Sun® temperature management system in Taiwan. Second, as this was a retrospective study, data collection was limited by the available documentation. Third, we only utilized the GOS score, not a detailed neurologic outcome evaluation tool, to determine outcome. Finally, the etiologies of RSE/SRSE were diverse. Hence, we could not directly compare the outcomes among the groups. These variables may be important contributors to outcome, and thus additional studies with larger sample sizes that address these issues are needed to confirm our findings.

Conclusions

Collectively, our findings support that TH effectively shortens the seizure duration in pediatric patients with RSE/SRSE. Although there were some manageable complications during TH, it was otherwise safe for use in pediatric patients with RSE/SRSE. Our study provides evidence that shortened seizure durations in the acute symptomatic phase of SE can reduce the occurrence of post-status epilepticus epilepsy and improve patients' long-term functional outcomes.

Declaration

Part of the content of this article was presented at the 2nd congress of Pediatric Neurocritical care consortium, 8 June, 2019, Taipei, Taiwan.

Conflicts of interest

All authors declare no conflicts of interest.

Acknowledgements

This study was supported by grants from the Research Support Scheme of Chang Gung Memorial Hospital (CMRPG8G0951). We appreciated the Biostatistics Center, Kaohsiung Chang Gung Memorial Hospital for statistics work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bj.2020.04.004.

REFERENCES

[1] Brophy GM, Bell R, Claassen J, Alldredge B, Bleck TP, Glauser T, et al. Guidelines for the evaluation and management of status epilepticus. Neurocritical Care 2012;17:3–23.

[2] Guilliams K, Rosen M, Buttram S, Zempel J, Pineda J, Miller B, et al. Hypothermia for pediatric refractory status epilepticus. Epilepsia 2013;54:1586–94.

[3] Bayrlee A, Ganeshalingam N, Kurczewski L, Brophy GM. Treatment of super-refractory status epilepticus. Curr Neurol Neurosci Rep 2015;15:66.

[4] Hocker SE, Britton JW, Mandrekar JN, Wijdicks EF, Rabinstein AA. Predictors of outcome in refractory status epilepticus. JAMA Neurol 2013;70:72–7.

[5] Bennett AE, Hoesch RE, DeWitt LD, Afra P, Ansari SA. Therapeutic hypothermia for status epilepticus: a report, historical perspective, and review. Clin Neurol Neurosurg 2014;126:103–9.

[6] Wilkes R, Tasker RC. Pediatric intensive care treatment of uncontrolled status epilepticus. Crit Care Clin 2013;29:239–57.

[7] Aroor S, Shravan K, Mundkur SC, Jayakrishnan C, Rao SS. Super-refractory status epilepticus: a therapeutic challenge in paediatrics. J Clin Diagn Res 2017;11:SR01–4.

[8] Kowski AB, Kanaan H, Schmitt FC, Holtkamp M. Deep hypothermia terminates status epilepticus-an experimental study. Brain Res 2012;1446:119–26.

[9] Shrestha GS, Joshi P, Chhetri S, Karn R, Acharya SP. Intravenous ketamine for treatment of super-refractory convulsive status epilepticus with septic shock: a report of two cases. Indian J Crit Care Med 2015;19:283–5.

[10] Ferlisi M, Shorvon S. The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy. Brain 2012;135:2314–28.

[11] Buttram SD, Au AK, Koch J, Lidsky K, McBain K, O'Brien N, et al. Feasibility study evaluating therapeutic hypothermia for refractory status epilepticus in children. Ther Hypothermia Temp Manag 2015;5:198–202.

[12] Cooley DA. Open heart surgery by two technics: hypothermia and extracorporeal circulation. Nebr State Med J 1957;42:77–81.

[13] Coelho HM, Dye WS, Grove WJ, Julian OC, Sadove MS. Hypothermia in open heart surgery. AMA Arch Surg 1956;73:493–502.

[14] Lewis FJ. Hypothermia for open heart surgery. Am J Cardiol 1958;2:287–91.

[15] American Heart A. 2005 American Heart Association (AHA) guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiovascular care (ECC) of pediatric and neonatal patients: pediatric basic life support. Pediatrics 2006;117:e989–1004.

[16] Wira C, Martin G, Stoner J, Margolis K, Donnino M. Application of normothermic cardiac arrest algorithms to hypothermic cardiac arrest in a canine model. Resuscitation 2006;69:509–16.

[17] Tagin MA, Woolcott CG, Vincer MJ, Whyte RK, Stinson DA. Hypothermia for neonatal hypoxic ischemic encephalopathy: an updated systematic review and meta-analysis. Arch Pediatr Adolesc Med 2012;166:558–66.

[18] Azzopardi DV, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E, et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. N Engl J Med 2009;361:1349–58.

[19] Satas S, Hoem NO, Melby K, Porter H, Lindgren CG, Whitelaw A, et al. Influence of mild hypothermia after hypoxia-ischemia on the pharmacokinetics of gentamicin in newborn pigs. Biol Neonate 2000;77:50–7.

[20] Crossley S, Reid J, McLatchie R, Hayton J, Clark C, MacDougall M, et al. A systematic review of therapeutic hypothermia for adult patients following traumatic brain injury. Crit Care 2014;18:R75.

[21] Lin JJ, Lin KL, Hsia SH, Wang HS, Group CS. Therapeutic hypothermia for febrile infection-related epilepsy syndrome in two patients. Pediatr Neurol 2012;47:448–50.

[22] Lin JJ, Hsia SH, Chiang MC, Lin KL. Clinical application of target temperature management in children with acute encephalopathy - A practical review. Biomed J 2020;43:211–7.

[23] Guidotti I, Lugli L, Guerra MP, Ori L, Gallo C, Cavalleri F, et al. Hypothermia reduces seizure burden and improves neurological outcome in severe hypoxic-ischemic encephalopathy: an observational study. Dev Med Child Neurol 2016;58:1235–41.

[24] Bisschops LL, Hoedemaekers CW, Simons KS, van der Hoeven JG. Preserved metabolic coupling and cerebrovascular reactivity during mild hypothermia after cardiac arrest. Crit Care Med 2010;38:1542–7.

[25] Lin JJ, Lin CY, Hsia SH, Wang HS, Chiang MC, Lin KL. 72-h therapeutic hypothermia improves neurological outcomes in paediatric asphyxial out-of-hospital cardiac arrest-An exploratory investigation. Resuscitation 2018;133:180–6.

[26] Tokutomi T, Morimoto K, Miyagi T, Yamaguchi S, Ishikawa K, Shigemori M. Optimal temperature for the management of severe traumatic brain injury: effect of hypothermia on intracranial pressure, systemic and intracranial hemodynamics, and metabolism. Neurosurgery 2007;61(1 Suppl):256–65. discussion 65-6.

[27] Ichinose M, Kamei Y, Iriyama T, Imada S, Seyama T, Toshimitsu M, et al. Hypothermia attenuates apoptosis and protects contact between myelin basic protein-expressing oligodendroglial-lineage cells and neurons against hypoxia-ischemia. J Neurosci Res 2014;92:1270–85.

[28] Mohammed HS. Hypothermia mitigates neurochemical alterations in rat's cerebral cortex during status epilepticus induced by pilocarpine. Gen Physiol Biophys 2015;34:425–32.

[29] Kuroda Y. Neurocritical care update. J Intensive Care 2016;4:36.

[30] Legriel S, Lemiale V, Schenck M, Chelly J, Laurent V, Daviaud F, et al. Hypothermia for neuroprotection in convulsive status epilepticus. N Engl J Med 2016;375:2457–67.

[31] Legriel S, Resche-Rigon M, Cariou A. In response to "hypothermia for neuroprotection in convulsive status epilepticus". J Emerg Med 2017;53:140–1.

[32] Orlowski JP, Erenberg G, Lueders H, Cruse RP. Hypothermia and barbiturate coma for refractory status epilepticus. Crit Care Med 1984;12:367–72.

[33] Shein SL, Reynolds TQ, Gedela S, Kochanek PM, Bell MJ. Therapeutic hypothermia for refractory status epilepticus in a child with malignant migrating partial seizures of infancy and SCN1A mutation: a case report. Ther Hypothermia Temp Manag 2012;2:144–9.

[34] Sanchez Fernandez I, Abend NS, Agadi S, An S, Arya R, Brenton JN, et al. Time from convulsive status epilepticus onset to anticonvulsant administration in children. Neurology 2015;84:2304–11.

[35] Gainza-Lein M, Sanchez Fernandez I, Jackson M, Abend NS, Arya R, Brenton JN, et al. Association of time to treatment with short-term outcomes for pediatric patients with refractory convulsive status epilepticus. JAMA Neurol 2018 Apr 1;75:410–8.

[36] Legriel S, Azoulay E, Resche-Rigon M, Lemiale V, Mourvillier B, Kouatchet A, et al. Functional outcome after

convulsive status epilepticus. Crit Care Med 2010;38:2295–303.
[37] Halawa EF, Draz I, Ahmed D, Shaheen HA. Predictors of outcome of convulsive status epilepticus among an Egyptian pediatric tertiary hospital. J Child Neurol 2015;30:1736–42.
[38] Reig Saenz R, Sanchez Miralles A, Herrera Murillo M, Gonzalez Lorenzo M, Martinez Salcedo E, Almanza Lopez S. [Markers of poor prognosis in convulsive status epilepticus]. An Pediatr 2005;63:307–13.
[39] Ostrowsky K, Arzimanoglou A. Outcome and prognosis of status epilepticus in children. Semin Pediatr Neurol 2010;17:195–200.
[40] Hommady RH, Alrifai MT, Mubayrik OK, Alayed RS, Alsemari MA, Arumayyan A, et al. Retrospective review of pediatric status epilepticus in 116 Saudi patients: predictors of outcome. Ann Saudi Med 2017;37:455–60.
[41] Soleimanpour H, Rahmani F, Golzari SE, Safari S. Main complications of mild induced hypothermia after cardiac arrest: a review article. J Cardiovasc Thorac Res 2014;6:1–8.
[42] Nolan JP, Morley PT, Vanden Hoek TL, Hickey RW, Kloeck WG, Billi J, et al. Therapeutic hypothermia after cardiac arrest: an advisory statement by the advanced life support task force of the International Liaison Committee on Resuscitation. Circulation 2003;108:118–21.