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Hypothermia as a Treatment in Status Epilepticus: a narrative review

Stéphane LEGRIEL, MD (1) (2) (3) (4)

(1) Medico-Surgical Intensive Care Department, Centre Hospitalier de Versailles, 177 rue de Versailles, 78150 Le Chesnay cedex, France

(2) Paris Descartes University, Sorbonne Paris Cité–Medical School, Paris, France

(3) INSERM U970, Paris Cardiovascular Research Center, Paris, France

(4) IctalGroup, France

Corresponding author

Stephane LEGRIEL, MD

Intensive Care Department, Centre Hospitalier de Versailles - Site André Mignot, 177 rue de Versailles, 78150 Le Chesnay cedex, France

Tel: +33 139 638 839 Fax: +33 139 638 688

E-mail: stlegriel@gmail.com

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Abbreviations

SE: status epilepticus

TTM: targeted temperature management

Highlights

Therapeutic hypothermia is one of the available adjuvant treatments for refractory and super-refractory SE in adults who do not respond to conventional treatments.

Abstract

Status epilepticus (SE) is associated with high mortality and morbidity rates, notably in its refractory and super-refractory forms. This narrative review discusses recent data on the potential benefits of targeted temperature management. In studies of patients with cerebral injury due to various factors, therapeutic hypothermia had variable effects on survival and functional outcomes. Sources of this variability may include the underlying etiology, whether hypothermia was used for prophylaxis or treatment, the degree and duration of hypothermia, and the hypothermia application modalities. Data from animal studies strongly suggest benefits from therapeutic hypothermia in SE. In humans, beneficial effects have been described in anecdotal case-reports and small case-series, but the level of evidence is low. A randomized controlled trial found no evidence that moderate hypothermia (32-34°C) was neuroprotective in critically ill patients with convulsive SE. Nevertheless, some promising effects were noted, suggesting that therapeutic hypothermia might have a role as an adjuvant

to anticonvulsant drug therapy in patients with refractory or super-refractory SE. This article is part of a Special Issue entitled “Status Epilepticus”.

Keywords: Therapeutic hypothermia. Status epilepticus. Outcome. Intensive care unit. Targeted temperature management.

1. INTRODUCTION

Hyperthermia is one of the systemic complications associated with sustained motor activity in patients with status epilepticus (SE). Experimental studies found body temperatures of up to 40 °C after more than 90 minutes of ictal motor activity [1-3]. Hyperthermia is rare, however, in partial SE [4] and non-convulsive SE, in which there are no prominent motor symptoms [5, 6].

In the absence of treatment, seizure activity in pathophysiological models of SE can become self-sustaining, and life-threatening multiple organ failures may develop gradually [7]. In a rat model, prolonged SE was associated with potentially function- and life-threatening neuronal damage [8]. Among human patients with convulsive SE requiring intensive care or neurocritical care, about 20% die and about 50% experience residual functional impairments [9-13]. Corresponding proportions in patients with refractory or super-refractory SE are 40% and 60%-85% [11, 12, 14].

The objective of this narrative review is to discuss the potential anticonvulsant and neuroprotective effects of targeted temperature management (TTM), and more specifically of hypothermia, in patients with SE. After an overview of the use of TTM in neurocritical care, we describe the available experimental data and discuss their potential clinical implications for patients with SE.

2. USE OF TARGETED TEMPERATURE MANAGEMENT (TTM) IN NEUROCRITICAL CARE

The neuroprotective effects of TTM have been studied since the middle of the 20th century, particularly in health conditions associated with the occurrence of SE. The efficacy of TTM in protecting the brain was firmly established by two randomized controlled trials published in 2002 [15, 16]. Both trials used moderate hypothermia (32 °C to 34 °C) for 12-24 hours in patients with coma after out-of-hospital cardiac arrest with a shockable rhythm. This treatment significantly decreased mortality and increased the proportion of patients with a good neurological outcome. Based on these results, the indications of hypothermia were extended to all causes of cardiorespiratory arrest. Studies suggested that the optimal temperature target may be 32 °C to 36 °C [17]. This strategy is currently under re-evaluation [18]. A satisfactory level of evidence supports the use of moderate hypothermia in neonatal encephalopathy [19-21]. Studies of hypothermia in other neurological conditions such as ischemic and hemorrhagic stroke [22] have produced varying levels of evidence that leave some uncertainty about efficacy [23, 24]. In patients with traumatic brain injury, whether hypothermia is beneficial may depend on the presence of intracranial hypertension [25-30]. Finally, hypothermia was associated with increased mortality in comatose patients with bacterial meningitis [31].

Several points can be extracted from these data. The clinical presentation of patients in whom TTM may deserve consideration is admission to the intensive care unit (ICU) or neurocritical care unit with major neurological failure requiring mechanical ventilation. TTM has been used both as a preventive strategy and as a treatment in patients with existing brain damage [29, 30]. The target temperature and hypothermia duration varied across studies and according to the underlying condition [17, 24, 30, 31]. Finally, the methods used to induce

and maintain hypothermia have evolved over time, and servo-regulated devices to ensure lowering of the central body temperature are now required [32].

3. THERAPEUTIC HYPOTHERMIA IN STATUS EPILEPTICUS (SE)

3.1. ANTICONVULSANTS AND NEUROPROTECTIVE PROPERTIES: EXPERIMENTAL DATA

Animal studies of the effects of therapeutic hypothermia in SE used a wide variety of parameters. For instance, the hypothermia was mild (32-35°C), moderate (28-32°C), or **deep** (<28°C). Hypothermia was used either as a prophylactic strategy or applied during the ictal phase. Both the neuroprotective and the anticonvulsant properties of hypothermia have been assessed. In some studies, the ability of hypothermia to control the epileptic activity when used alone or in combination with anticonvulsants to treat SE or refractory SE was investigated. The animals studied were either juveniles or adults. Most animal studies investigated inaugural SE as opposed to SE on a background of chronic epilepsy.

3.1.1. *Anticonvulsant and neuroprotective effects in different animal models*

3.1.1.1. *Adult animal models managed with various degrees of hypothermia*

The first work, published in 1983, was carried out in cats with generalized convulsive SE induced by cryoprobe gel application at -25 °C for 30 seconds on the mesencephalic reticular formation [33]. After 3 weeks of recovery, the cryoprobe at -5 °C was applied during epileptic activity. This second application had no deleterious effects on the previously injured

areas. When it occurred at the inferior thalamic peduncles, the frequency of the epileptic abnormalities diminished.

In male adult rats, self-sustaining SE induced by electrical stimulation via intracerebral electrodes was accompanied with a fever of 39.2 ± 0.6 °C (range, 38-40.5 °C) [34]. The rats were divided into three groups, managed without hypothermia or with hypothermia at 30 °C or 20 °C followed after 120 minutes by gradual rewarming, respectively. Cooling to 20 °C completely suppressed the seizures, which did not usually recur after rewarming to 37.3 ± 0.4 °C. Cooling at 30 °C was only partially effective and was followed by seizure recurrence after rewarming.

In a rat model of kainic acid-induced SE, the effect of milder hypothermia (28 °C) was studied [35]. Hypothermia halved the proportion of animals with persistent seizure activity compared to the untreated rats (core temperature, 36.7 ± 0.4 °C), which consequently had a significantly longer seizure duration. In the hypothermia group, the seizures recurred upon rewarming. When SE was induced after body temperature elevation to 42 °C, all the animals died within 2 hours. The pathological examination of brains from animals that died or were sacrificed showed no hippocampal lesions in the 28 °C group, contrasting with localized neuronal loss in the carinactivase-1 (CA1) and CA3 hippocampal regions in the normothermia and hyperthermia groups. In another rat model of kainic acid-induced SE, the time to epileptic activity onset was significantly longer when the intra-tonsillar kainic acid injection was performed in rats whose body temperature was decreased to 30 °C versus rats at 37 °C [36]. Local cerebral glucose utilization assessed by ¹⁴C-deoxyglucose autoradiography was diminished in the ipsilateral amygdala, entire hippocampus, and cerebral cortex of the hypothermic rats compared to the normothermic controls. In rats given metaphit to induce audiogenic seizures, hypothermia at 30 °C suppressed the epileptic activity, which recurred upon warming to 37 °C [37].

Finally, in adult rats with fluothyl-induced SE, hyperthermia between 39.5 °C and 42 °C promoted seizure occurrence and exacerbated lesion severity in the neocortical and hippocampal neurons [38]. These effects were decreased by hypothermia at 32.5 °C. The abnormalities varied with seizure duration, location of neuronal damage, and depth of hypothermia. Thus, neuronal lesion density increased when seizure duration increased from 20 to 25 to 45 minutes. Neuronal damage was exacerbated by higher body temperatures (39.5 °C to 41 °C) and was mitigated by lower body temperatures (37.5 °C and 32.5 °C). More specifically, the density of damaged neocortical neurons was lower at 32.5 °C or 37.5 °C than at 39.5 °C. Conversely, neuronal loss in the hippocampal CA1 regions and dentate gyrus was not significantly different across these three temperature groups. Finally, the decrease in damaged neuron density associated with hypothermia at 32.5 °C versus 37.5 °C or 39.5 °C was greatest in the locus niger and pallidum [38].

3.1.1.2. *Immature animal models*

In juvenile rats with SE induced by intraperitoneal pilocarpine injection, hypothermia at 33±1 °C for 120 minutes increased seizure onset latency and decreased seizure duration, compared to normothermia. The crude mortality rate was not significantly different between the two groups, but neuronal damage in the CA1, CA2, and CA3 hippocampal regions was significantly less marked in the hypothermia group [39].

3.1.1.3. *Models of hypothermia used as adjuvant anticonvulsant therapy*

The anticonvulsant effect of hypothermia is potentiated by benzodiazepine therapy [40]. In one study, rats with SE induced by electrical stimulation of the brain were randomly allocated to diazepam alone, hypothermia between 29 °C and 33° C for at least 3 hours, both,

or neither. Diazepam alone had no effect on the SE, whereas hypothermia alone or with diazepam decreased the epileptic discharges. When both treatments were combined, the effect was more marked than with hypothermia alone and persisted after rewarming. These results support the efficacy of hypothermia as an adjuvant to anticonvulsant therapy [40].

3.1.1.4. Model of refractory status epilepticus (SE)

In adult Wistar rats in which SE induced by lithium and pilocarpine injection was refractory to midazolam, the effects of deep hypothermia (20 °C) were assessed comparatively to normothermia [41]. Seizure duration in the normothermia group was 4.1±1.1 hours. In contrast, deep hypothermia suppressed the seizures within 12 minutes and restored the initial brain activity within 23.8±3.9 minutes. Epileptic activity recurrence was diminished in the hypothermia group after re-warming. The normothermic rats had extensive necrotic neuronal damage in the CA1 and CA3 hippocampal regions, frontoparietal cortex, piriform cortex, entorhinal cortex, caudoputamen, thalamus, and dentate gyrus hila. With hypothermia, in contrast, only 3 of 9 rats displayed evidence of neuronal injury. Blood-brain barrier breakdown was widespread in the normothermic group but absent in the hypothermic group [41]. Similar results were found when rats were managed with hypothermia at 31±0.6 °C [42].

3.1.1.5. Chronic epilepsy model

In a study of 15 rats with induced chronic epilepsy, SE was triggered by a kainic acid injection. Half the animals had their body temperature lowered to 30±0.6 °C for 1 hour every 8 hours for 48 hours, and the other half were left in normothermia at 37±0.6 °C. Compared to the control group, the hypothermia group had a lower rate of recurrent epileptic activity and less postictal working memory loss [43].

3.1.2. Mechanisms of the anticonvulsant and neuroprotective effects of hypothermia

Hypotheses about the mechanisms underlying the anticonvulsant and neuroprotective effects of hypothermia in SE can be developed based on available data about cerebral injury due to various causes and about the pathophysiology of epilepsy and of the related neurotoxicity. In addition, specific mechanisms of action of hypothermia in SE can be investigated (Figure 1).

3.1.2.1. Mechanisms of anticonvulsant and neuroprotective effects of hypothermia in cerebral injury due to various causes

The neuroprotection afforded by therapeutic hypothermia is related to effects on the pathophysiological mechanisms of neurotoxicity that are active regardless of the cause of cerebral injury. Thus, hypothermia decreases the release of pro-excitatory amino acids (glutamate), blocks and/or slows intracellular Ca^{++} flows, mitigates mitochondrial dysfunction, prevents DNA damage, decreases free radical production and lipid peroxidation, inhibits inflammatory responses and cytokine release, and decreases the capillary hyperpermeability induced by ischemia. Hypothermia combats increases in blood-brain barrier and vascular permeability, thereby decreasing edema formation and the risk of intracranial hypertension. Finally, although this is not recognized as its major mechanism of action, hypothermia decreases brain metabolism, by 6% to 10% for each decline of 1 degree below 37 ° C [44].

3.1.2.2. Mechanisms of the anticonvulsant and neuroprotective effects of hypothermia in status epilepticus (SE)

SE induced by an intraperitoneal pilocarpine injection is characterized by presynaptic hyperactivity with an increase in the release of pro-excitatory neurotransmitters (glutamate, glutamine), which is proportionally greater than the increase in inhibitory gamma-aminobutyric acid (GABA) neurotransmitters. Glutamine release increases the production of nitric oxide (NO), causing oxidative stress with lipid peroxidation and, potentially, increased neurotoxicity. Although NO exerts neuroprotective effects via nitrosylation of NR1 and NR2 N-methyl-D-aspartate (NMDA) receptors, its unbalanced production leads to an interaction with the reactive oxygen anion superoxide, inducing neuronal toxicity. The antioxidant enzyme superoxide dismutase inhibits this interaction, thereby providing protection against reactive oxygen species, in combination with the antioxidants glutathione (GSH) and GSH peroxidase.

Hypothermia before SE induction has been reported to decrease the production of pro-excitatory neurotransmitters, thereby potentially affording neuroprotection. However, results from murine models are somewhat conflicting regarding these effects of hypothermia, with one source of variability being the measurement site (hippocampus vs. cortex) [45, 46].

3.1.2.3. Calcium entry blockade

In Sprague-Dawley rats treated with diazepam to suppress pilocarpine-induced SE, hypothermia at 30-33 °C for 4 hours was not only associated with less neuronal damage in the hippocampal gyrus and CA1 regions (negligible versus 60% in normothermic animals), but also with a decrease in mortality (7% vs. 21%, respectively). In this study, calcium entry blockade was demonstrated in the hypothermia group [47].

3.1.2.4. Regulation of cell-surface aminomethylphosphonic acid (AMPA) receptor expression

In one study, juvenile Wistar rats were given pilocarpine to induce SE then diazepam alone or with hypothermia at 33 ° C. The combined treatment was associated with better control of epileptic activity and less necrosis and apoptosis in the CA1 and CA3 hippocampal regions. Another effect of adding hypothermia to diazepam versus diazepam alone was regulation of the membrane expression of glutamate AMPA receptors, with downregulation of GluR1 subunits and upregulation of GluR2 subunits [48].

3.1.2.5. Regulation of cell-surface NMDA receptor expression

In juvenile Wistar rats with pilocarpine-induced generalized convulsive SE, neuronal damage and necrosis in the hippocampal CA1 and CA3 regions were more marked with diazepam alone than with both diazepam and hypothermia [49]. In addition, adding hypothermia was associated with decreased hippocampal expression of NMDAR1 and its mRNA and with increased expression of the antiapoptotic c-Jun protein and its mRNA.

3.1.2.6. Regulation of nitric oxide (NO) production

In a study of female rabbits with SE induced by a kainic acid injection during hypothermia at 33 °C or normothermia (37 °C), the hypothermic group exhibited significantly less damage to the hippocampal CA3 region and less cerebral NO overproduction [50].

3.1.2.7. Decreased brain edema in ictal areas

In rats with chronic epilepsy, hypothermia at 30±0.6 °C started after SE induction was associated with significantly less post-ictal cerebral edema in the frontal lobes and hippocampus, less recurrence of epileptic activity, and less post-ictal cognitive impairment, compared to controls managed at 37±0.6 °C, [43].

3.2. CLINICAL APPLICATIONS OF TARGETED TEMPERATURE MANAGEMENT (TTM) IN STATUS EPILEPTICUS (SE)

The exacerbating effect of hyperthermia on seizure activity has also been demonstrated in humans [51]. Therapeutic hypothermia has been studied as an adjunctive therapy for refractory epilepsy [52] and during neurosurgery [53]. Therapeutic hypothermia has been used successfully in patients with refractory or super-refractory SE epilepticus and has been evaluated as a neuroprotective strategy.

3.2.1. Therapeutic hypothermia for the adjuvant treatment of refractory or super-refractory status epilepticus (SE)

Many reports describe the use of therapeutic hypothermia for refractory or super-refractory SE [54-69]. Patient ages ranged from a few months to 75 years, with an equal distribution between children and adults [55, 69] and a predominance of males (63%). Comorbidities responsible for impaired self-sufficiency before the SE episode were reported in nearly 19% of patients [56, 58, 60, 65]. SE was inaugural in 77% of cases. The causes of SE were conditions usually associated with pharmaco-resistant seizures such as autoimmune encephalitis [55, 58, 60, 61, 63, 66] and viral encephalitis [59, 61], although some patients had metabolic causes [54, 55] or no identifiable etiology [55, 64].

Hypothermia was generally applied in patients with highly refractory clinical and/or electroencephalographic epileptic activity that remained uncontrolled despite several days of pharmacological treatment. Continuous EEG monitoring was performed in 93% of cases. The most common presentation was non-convulsive SE with coma but no prominent motor signs [70]. Therapeutic hypothermia was started 1 to 60 days after SE onset [58-61, 64, 65], the

target temperature ranged from 30 to 35°C [55, 56, 60, 61, 67], and hypothermia duration varied from 20 to 240 hours [55, 66]. Hypothermia was reported to be effective in controlling the epileptic activity in 82% of cases, but rewarming was followed by recurrence in 49% cases [55, 56, 58, 60, 61, 63, 64, 69].

3.2.2. Therapeutic hypothermia as an adjuvant neuroprotective treatment in convulsive status epilepticus (SE)

A single randomized controlled trial investigated the potential neuroprotective effects of therapeutic hypothermia in adults with convulsive SE requiring mechanical ventilation [71]. All patients received anticonvulsant therapy in compliance with current guidelines. Patients were randomized to treatment with or without added hypothermia between 32 and 34 °C for 24 hours. Rewarming was passive and gradual at a rate of 0.25 to 0.5 °C per hour. All components of the management strategy were standardized, including continuous EEG monitoring with centralized EEG interpretation. The only difference between the two groups was the use of therapeutic hypothermia [71]. Functional outcomes were assessed 90 days after SE onset using the Glasgow Outcome Scale (GOS) score. The proportion of patients whose GOS was 5 on day 90 was not significantly different between the hypothermia and control groups (49% and 43%, respectively; $P=0.43$) [72].

In this study, evaluation of the potential anticonvulsant effects of therapeutic hypothermia was a secondary objective. Nonsignificant trends toward less refractory SE on the first day of management and toward less progression to super-refractory SE were noted. Therapeutic hypothermia was significantly associated with less progression to SE in patients with coma but no prominent motor signs (11% versus 22% in controls, $P=0.009$) [72].

Given the promising animal data, hypotheses formulated speculating on the reasons for the failure of this randomized controlled trial to demonstrate an effect of hypothermia are as follow. First, the choice of a Glasgow Outcome Scale score of 5 at day-90 as primary judgment criterion may have been too optimistic. For instance, a harder primary criterion such as hospital mortality, or conversely a more subtle functional evaluation based on the reduction of cognitive sequelae, may have been chosen. Second, time to targeted temperature was quite long and expected neuroprotective benefits of hypothermia could thus have been minimized. Finally, animal's data explored a deeper degree of hypothermia that could not be reached without complications in humans.

4. CONCLUSION

Strong experimental evidence supports anticonvulsant and neuroprotective effects of hypothermia in SE. In humans, hypothermia as an adjuvant to anticonvulsant therapy for refractory or super-refractory SE has been reported to be effective in a few cases, but the level of evidence remains inadequate. No proof exists that hypothermia is neuroprotective in a population of patients with convulsive SE. Therapeutic hypothermia is currently recommended as one of the available adjuvant treatments for refractory and super-refractory SE in adults who do not respond to conventional treatments [73-76].

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FIGURE LEGENDS

Figure 1. Mechanisms potentially underlying the anticonvulsant and neuroprotective effects of hypothermia in status epilepticus

The green crosses indicate mechanisms of action of hypothermia in cerebral injury due to various causes and the red crosses mechanisms specific to status epilepticus.

