Infants undergoing therapeutic hypothermia for hypoxic ischemic encephalopathy are at risk for rebound seizures during and after the rewarming phase. We report a term male infant who was cooled for hypoxic ischemic encephalopathy. He developed electrographic seizures for the first time during the warming phase, which continued in the hours after rewarming. The seizures stopped within 30 minutes of recooling to 33.5°C without anticonvulsant medication. He was uneventfully cooled for an additional 24 hours and then rewarmed with no recurrence of seizures. Hypothermia appeared to have an antiepileptic effect in this case and may be worthy of additional investigation as an adjunct to antiepileptic drug therapy in newborns. *Pediatrics* 2012;130:1–5
Therapeutic hypothermia has emerged as the first safe and effective treatment of moderate to severe hypoxic-ischemic encephalopathy and has become a standard of care in the United Kingdom. Previous case reports have described rebound seizures during rewarming from therapeutic hypothermia, and infants who were cooled had fewer seizures than similarly affected normothermic infants. We report a case of hypoxic-ischemic encephalopathy with seizures noted for the first time during and after rewarming who was re-cooled with immediate cessation of seizure activity without any need for additional anticonvulsant drugs.

CASE REPORT

A male infant was born at 39+1 weeks’ gestation after an uneventful pregnancy with a birth weight of 3630 g. After a prolonged second stage of labor, there was a fetal bradycardia lasting ~10 to 15 minutes before an emergency forceps delivery. On initial assessment, the infant was pale and floppy, with no spontaneous respiratory effort and no heart sounds heard on auscultation. He received intermittent positive pressure ventilation and cardiac compressions until 2 minutes of life when a heart rate of >60 beats per minute was detected. His Apgar scores were 1 at 1 minute and 3 at 5 minutes; cord arterial pH was 6.80 and base excess of -21.6. The infant was transferred, ventilated, to the neonatal unit at 11 minutes of age. In view of his poor condition, the radiant warmer had been turned off at 5 minutes of life to allow passive cooling. On admission to the NICU, he was noted to be lethargic and hypotonic and was thought clinically to have a seizure with abnormal arm extension. He was given a loading dose of phenobarbitone (20 mg/Kg) and commenced on active cooling by using a servo control CritiCool system (MTRE, Charter Kontron, Milton Keynes, UK).

EEG monitoring was commenced by using a NicOne digital video EEG system (Carefusion, Madison, WI). Electrodes were applied to the scalp by using soft paste to achieve impedances of below 5 kOhms, at F3, F4, C3, C4, P3, P4, O1, O2, and Cz to record EEG activity from the frontal, central, parietal, and occipital areas. The background EEG over the first 12 hours was severely suppressed with little or no identifiable activity. By 14 hours of age, short 1- to 5-second bursts of activity had returned with interburst intervals of 10 to 30 seconds and an amplitude-integrated EEG (aEEG) amplitude of 1 to 25 μV. By 24 hours of age, longer bursts of activity were seen lasting up to 30 seconds with interburst intervals of 5 to 10 seconds. Activity continued to improve slowly, but short periods of discontinuity persisted up to 72 hours of age with an aEEG amplitude of 3 to 25 μV (Figs 1 and 2A). No electrographic seizures had been seen. Cranial ultrasound was normal days 1 to 3 with a resistance index in anterior cerebral artery of 0.72 at 36 hours. On completion of therapeutic hypothermia, he was rewarmed at a rate of 0.25°C per hour. Approximately 9 hours into rewarming (rectal temperature of 36°C), short

![Figure 1](image.png)

**FIGURE 1**

Forty-eight-hour aEEG recording (top) and band power during the cooled, rewarming, normothermia, and recooling periods. Note the increase in EEG power during rewarming phase, which then decreases again during recooling. The seizures seen on EEG (not visible at this scale on the cross-channel aEEG) are marked at the bottom of the figure. Labels a, b, and c show when the EEG recordings shown in Fig 2 were taken.
FIGURE 2
electrographic seizures were evident on the EEG, initially over the left side but also occurring less frequently over the right (Figs 1 and 2B). These persisted for \( \sim 14 \) hours. Once these had been recognized on review of the EEG, a decision was made to recool the infant for another 24 hours. Seizures stopped within 30 minutes of recooling without additional anticonvulsant drugs (Figs 1 and 2C). There were no additional seizures either during the additional 24 hours of therapeutic hypothermia or after the second rewarming.

**DISCUSSION**

Neonatal seizures associated with hypoxic ischemic encephalopathy classically emerge in the phase of secondary energy failure some 12 to 24 hours after initial insult and then resolve at \( \sim 72 \) hours.\(^6\) Therapeutic hypothermia has been shown to prevent secondary energy failure in animal models of hypoxic ischemic encephalopathy.\(^1\) A recent study of infants undergoing therapeutic hypothermia showed that clinical and subclinical seizures were a risk factor for moderate-severe brain injury on MRI. These seizures were more likely to be of later onset, multifocal, and refractory to treatment compared with seizures seen in infants with minimal or no brain injury.\(^7\) The treatment of subclinical in addition to clinical seizures in infants with hypoxic ischemic encephalopathy appears to be associated with improved outcomes;\(^8\) however, the infants in this study were not treated with therapeutic hypothermia.

Rebound seizures during the rewarming phase after therapeutic hypothermia have been described in human infants and newborn animal models of hypoxic ischemic brain injury.\(^3,9\) In the current report, this occurred despite extremely slow rewarming. Recoiling of the infant to \( 33.5^\circ C \) resulted in complete cessation of seizures within 30 minutes, and these did not recur on rewarming after an additional 24 hours of therapeutic hypothermia. Although it is possible that the cessation of seizure activity was unrelated to recoiling, the rapid and complete effect observed makes this unlikely. Evidence from animal models and infants suggest that brain temperature may modulate epileptiform activity. In addition to promotion of neuronal survival, hypothermia has been shown to reduce the release and accumulation of excitatory neurotransmitters during hypoxia\(^10\) and ischemia.\(^11,12\) Hypothermia has also been shown to increase the threshold for seizures and status epilepticus\(^13,15\); conversely, it can reduce the threshold for seizures.\(^14\) In a separate study we have previously noted that infants treated with therapeutic hypothermia had a reduced seizure burden compared with historic normothermic controls despite there being no difference in the severity of hypoxic-ischemic encephalopathy between the groups.\(^4\) A combination of increased neuronal excitability and excitotoxin release may contribute to the development of rebound seizures seen on rewarming after therapeutic hypothermia.\(^6\) Alternatively, therapeutic hypothermia may delay the secondary energy failure that occurs in neonatal hypoxic ischemic brain injury; seizures on rewarming then occur in combination with a late form of secondary energy failure. It is unclear from this single case whether therapeutic hypothermia is acting as an anticonvulsant or whether it is interrupting a delayed secondary energy failure. However, because the infant was recooled almost 14 hours after the onset of seizures, it is less likely that the observed effect was caused by interruption of delayed secondary energy failure.

The successful use of therapeutic hypothermia as an anticonvulsant in adult and pediatric patients with refractory status epilepticus has previously been described.\(^16–18\) Taken together, these data suggest that investigation of the role of therapeutic hypothermia as a neonatal anticonvulsant therapy in hypoxia ischemia and in other neonatal seizure disorders is worthy of additional research.

**REFERENCES**


Recooling for Rebound Seizures After Rewarming in Neonatal Encephalopathy
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