Editorial

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Therapeutic hypothermia for newborns who suffer hypoxic–ischemic birth injury

Can whole-body cooling reduce the rate of cerebral palsy and thus help OBs limit their professional liability?

CASE Risky decision to let labor continue

The baby was born blue and limp, after a long labor complicated by maternal fever and a prolonged fetal heart rate deceleration.

Earlier, just before the mother was raced to the OR for emergency cesarean delivery, the fetal heart rate had increased sufficiently for the OB to decide to permit labor to continue—the goal being rapid vaginal delivery.

In hindsight, that decision appears to have been potentially fateful for this newborn: Apgar scores were 1 at 5 minutes and 3 at 10 minutes. Umbilical artery pH was 6.98; base deficit, –13 mmol/L. The pediatricians made a preliminary diagnosis of hypoxic-ischemic injury and recommended whole-body cooling of the newborn to limit neural damage.

The frightened parents prayed the treatment would work. Later, recalling news reports that they had read about spinal cord-injured football players and survivors of cardiac arrest who received therapeutic cooling with apparent success, they grew more optimistic about the potential benefit of this treatment for their baby.

How does the partial pressure of arterial oxygen ($Pa0_2$) in a newborn compare with that of an adult breathing ambient air near the summit of Mount Everest?

Take the **Instant Quiz** on page 13

In animal models of hypoxic-ischemic neural injury, reducing core body temperature minimizes long-term neural consequences of the injury. Experiments have demonstrated that the optimal course is to induce hypothermia immediately after the neural injury, but initiating hypothermia even as long as 6 hours after injury has a protective effect.

Reducing core temperature appears to limit neural injury by decreasing oxygen requirements and suppressing the accumulation of harmful cytotoxic amino acids, cytokines, and free radicals. In contrast to the beneficial effect of hypothermia, *raising* body temperature by only 1°C or 2°C in experimental animals that have undergone an isolated hypoxic-ischemic event makes neural damage *worse*.

Clinical trials in newborns

The beneficial effect of whole-body cooling for newborns who have hypoxic-ischemic encephalopathy has been reported in several randomized clinical trials.

In a multicenter trial, supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, 208 newborns in severe acidosis at birth were randomized to whole-body cooling or usual care.[1] Whole-body cooling, initiated within 6 hours of birth, was achieved by:

- placing subjects on a cooling blanket precooled to 5°C
- inserting an esophageal temperature probe
- adjusting the temperature of the cooling blanket to achieve an esophageal temperature of 33.5°C for 72 hours
- slow rewarming.

Abdominal-wall skin temperature was also monitored in these newborns.

Subjects in the usual care group were nursed in an incubator, with the radiant heat element adjusted to maintain skin temperature of 36.5°C to 37°C.

Investigators determined that the composite end-point of **risk of death or disability at 20 months of life was significantly reduced by whole-body cooling** (relative risk, 0.72; 95% confidence interval [CI], 0.54–0.95; $P = .01$).

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Death occurred in 24% of subjects in the hypothermia group and in 37% of subjects in the usual care group (risk ratio, 0.68; 95% CI, 0.44–1.05; P = .08). The rate of cerebral palsy was 19% in the hypothermia group and 30% in the usual care group (risk ratio, 0.68; 95% CI, 0.38–1.22; P = .20).

The rate of blindness was 7% in the hypothermia group and 14% in usual care group. The rate of hearing impairment was 4% and 6% percent (P - not significant).[1]

In a second clinical trial, the Total Body Hypothermia for Neonatal Encephalopathy (TOBY) trial of whole-body cooling, 325 newborns with hypoxic-ischemic encephalopathy were randomized to whole-body cooling or usual care.[2] Whole-body cooling was achieved by nursing the infant in an incubator on a cooling blanket set at 25°C to 30°C, with the goal of maintaining a rectal temperature in the newborn of 33°C to 34°C. In this group, the heat element in the incubator was turned off.

Newborns assigned to the usual care group were nursed in an incubator with the heat element turned on and set to maintain a rectal temperature of 37°C.

The rate of death was similar in the two groups, and the rate of severe neurodevelopmental disability in each of the groups was not significantly different. Among surviving infants, however, whole-body cooling was associated with a higher rate of intact neurologic function and a diminished risk of cerebral palsy (compared to what was seen in the usual-care group). Among surviving newborns, cerebral palsy occurred in 28% of those treated with whole-body cooling and in 41% of those receiving usual care (relative risk 0.67; 95% CI, 0.47–0.96; P = .03).

No major adverse effects were observed with whole-body cooling,

Therapeutic hypothermia for cardiac arrest and coma in adults

A devastating complication of cardiac arrest is coma and long-term neurologic dysfunction. Randomized trials have reported that therapeutic hypothermia is beneficial for comatose survivors of cardiac arrest.

In one study, 275 comatose survivors of cardiac arrest were randomized to therapeutic hypothermia (core temperature, 32°C to 34°C) or usual care. At 6 months, mortality was 41% in the hypothermia group and 55% in the usual care group (risk ratio 0.74; 95% CI, 0.58–0.95). At 6 months, the rate of favorable neurologic recovery among survivors was 93% in those who had been treated with hypothermia and 87% in those given usual care.[1]

One protocol for inducing moderate hypothermia that has been studied in adults is to infuse, intravenously, approximately 2 L of cold (4°C) lactated Ringer's solution and to cover the body with refrigerated cooling pads. The typical target is a core temperature of 32°C to 34°C, maintained for 24 hours.

Reference

1. The Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med. 2002;346(8):549–556.

when compared against usual care. **A 2007 meta-analysis of four trials** of therapeutic hypothermia in newborns reported a significant reduction in the composite endpoint of death or in moderate or severe neurodevelopmental disability (relative risk 0.76; 95% CI, 0.65–0.88). The number that needed to be treated to prevent one endpoint event was 6 (95% CI, 4–14).[3]

Note that some pediatricians remain cautious about using therapeutic hypothermia, because long-term data on the safety and efficacy of the practice have not been reported.

Impact on your practice

For decades, newborns in neonatal intensive care units received their care in warm incubators designed to maintain a body temperature of approximately 37°C. Could the standard practice of warming newborns have contributed to neurologic problems in those who suffered hypoxic-ischemic injury?

Whole-body cooling appears to reduce the rate of cerebral palsy in newborns after hypoxic-ischemic injury. For OBs, this treatment could significantly reduce their exposure to litigation that is based on a theory of hypoxic-ischemic birth injury—by reducing the number of surviving infants who have cerebral palsy.

Does your nursery have a protocol for rapidly instituting therapeutic cooling?

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References

1. Shankaran S, Laptook AR, Ehrenkranz RA, et al, for National Institute of Child Health and Human Development Neonatal Research Network. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. N Engl J Med. 2005;353(15):1574–1584.
2. Azzopardi DV, Strohm B, Edwards AD, et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. N Engl J Med. 2009;361(14):1349–1358.
3. Shah PS, Ohlsson A, Perlman M. Hypothermia to treat neonatal hypoxic ischemic encephalopathy: systematic review. Arch Pediatr Adolesc Med. 2007;161(10):951–958.

Instant Quiz

Atop the "Balcony" near the summit of Mount Everest (27,559 ft above sea level), humans breathing ambient air have been reported to have a partial pressure of arterial oxygen ($Pa0_2$) of approximately 25 mm Hg (range, 19–30 mm Hg). At this altitude and $Pa0_2$, problems such as pulmonary edema and cerebral dysfunction are common, and might be caused by hypoxia.

Compare this finding to the mean $Pa0_2$ in the umbilical artery of normal term fetuses, which is approximately:

- ❑ 5 mm Hg
- ❑ 15 mm Hg
- ❑ 25 mm Hg
- ❑ 35 mm Hg
- ❑ 50 mm Hg

See page 68 for the answer.