

## HYPOTHERMIA

### Use

Early controlled hypothermia can reduce the long term disability caused by serious intrapartum asphyxia in the term and near term baby, but it does not reduce the number who are so seriously affected that they die.

### Pathophysiology

One of the first major advances in neonatal care came with the recognition that allowing a small baby to become cold greatly decreases the chance of survival – a lesson driven home by the late Bill Silverman's early ground-breaking randomised controlled trials. Now, after another 50 years, we finally have equally good evidence that deliberate cooling can *improve* the chance of disability-free survival in the term baby who has suffered serious intrapartum asphyxia. Hypothermia was long used, before the development of heart-lung by-pass technology, to double the time the heart could be stopped to make complex surgery possible without damaging the brain. However the recognition that much of the damage caused by asphyxia only occurs during the recovery phase, eventually sparked a search for ways to mitigate this *secondary* damage.

No drug has yet been shown to be of benefit, but we do now know that some combination of respiratory support with sedation or paralysis, anticonvulsant treatment and a controlled lowering of body temperature to 33–34°C for 3 days can reduce the secondary damage done by acute neonatal anoxic or asphyxial cerebral injury, and that an attempt should be made to stop body deep body temperature from rising above 37.5°C even if active cooling is not attempted. Animal evidence suggests that cooling should be started within 3 hours if possible, but clinical trials have shown clear benefit as long as cooling is started within 6 hours of birth. However cooling does little to help neonates with really severe injury, and does *not* improve outcome in older children suffering brain trauma or a stroke. The first trial tried to selectively cool the head, but whole body cooling is now known to be safe and more effective. Continuous aEEG (amplitude integrated EEG) analysis using a cerebral function monitor is one established way to identify babies justifying such intervention. A 2-channel bedside monitor may offer improved discrimination, but monitoring does not pick up all seizure activity. Term babies with a flat trace, a continuous low voltage or a burst suppression pattern that persists for more than 24–36 hours who survive are nearly always left with severe spastic quadriplegia.

One early 8 mg/kg IV dose of theophylline (q.v.) seems to reduce some of the adverse renal consequences of perinatal asphyxia. The use of magnesium sulphate (q.v.) has shown promise, and a range of anti-oxidant drugs are currently being studied in animal models. Babies who display clinically obvious seizure activity have a much worse long term outcome than those who do not seem to fit, over and above of what can be predicted from damage visible on an MRI scan at 4–6 days. There may not be a causal link here but, because there is good animal evidence that seizure activity can itself be damaging, the search is now on for better ways to prevent or control seizure activity. Giving phenobarbital (q.v.) before seizures occurred seemed to show benefit in one small trial but not another, while a study using thiopental (q.v.) also delivered little benefit. Hypocapnia and hyperoxia both seem to be harmful, and any respiratory support needs to be managed with this in mind.

### Indications

Babies of  $\geq 36$  weeks gestation who remain hypotonic or stuporose, or who fit after birth, **and** who had a pH of  $< 7.0$  or a base deficit of  $\geq 16$  mmol/l within an hour of delivery **or** where sustained resuscitation was needed.

### Management

Cooling must start within 6 hours of birth at most. Lowering deep body temperature to 33.5°C within 2 hours, holding it there to within  $\pm 0.5^\circ\text{C}$  for 72 hours and then letting it rise gently over 12 hours does not cause a fall in cardiac output. Cooling is best achieved with a servo-controlled blanket but can be started with a covered ice pack or fan. Later phases of care are best managed in a unit with access to neuroimaging and EEG facilities.

### Case notification

More will be learnt if all UK use is reported to the TOBY register ([www.npeu.ox.ac.uk/tobyregister/contact](http://www.npeu.ox.ac.uk/tobyregister/contact)).

### Hypothermia can affect drug clearance

Many drugs mainly metabolised in the liver, such as the barbiturates and opiates, are cleared more slowly during hypothermia. This is also likely to be true of carbamezipine, phenytoin and the benzodiazepines, but we know much less about whether cooling also alters the effectiveness of many of these drugs. The clearance of renally excreted antibiotics will only be affected if hypothermia is severe enough to reduce cardiac output.

### References

- See also the Cochrane review ©
- Klinger G, Beyene J, Shah P, *et al.* Do hyperoxaemia and hypocapnia add to the risk of brain injury after intrapartum asphyxia? *Arch Dis Child* 2005;**90**:F49–52.
- Shellhaas RA, Soaita AI, Clancy RR. Sensitivity of amplitude-integrated electroencephalography for neonatal seizure detection. *Pediatrics* 2007;**120**:770–7.
- Polderman KH. Induced hypothermia and fever control for prevention and treatment of neurological injuries. *Lancet* 2008;**371**:1955–69. [SR]
- Barks JD. Current controversies in hypothermic neuroprotection. *Semin Fetal Neonatal Med* 2008;**13**:30–4.
- Thorensen M. Supportive care during neuroprotective hypothermia in the term newborn: adverse effects and their prevention. *Clin Perinatol* 2008;**35**:749–63. (See also the article by Barks on pp 765–75.)
- Glass HC, Glidden D, Jeremy RJ, *et al.* Clinical neonatal seizures are independently associated with outcome in infants at risk of hypoxic-ischaemic brain injury. *J Pediatr* 2009;**155**:318–23. (See also 305–6.)
- Azzopardi DV, Strohm B, Edwards AD, *et al.* Moderate hypothermia to treat perinatal asphyxial encephalopathy. *N Engl J Med* 2009;**361**:1349–58. [RCT]