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## Timing still key to treating hypoxic ischaemic brain injury



Perinatal hypoxic ischaemic encephalopathy is a devastating disorder that affects roughly two per 1000 term infants despite modern obstetric care. The important breakthrough in clinical and experimental studies was that, in many cases, brain oxidative metabolism transiently recovers to normal for some hours even after severe hypoxia-ischaemia before then failing again.<sup>1,2</sup> This observation suggested the hypothesis that exposure to low oxygen levels triggers active cell-death pathways that could be inhibited. The results of preclinical studies then showed that mild cerebral hypothermia started within around 6 h of birth, before the onset of delayed energy failure, and continued until resolution of secondary events such as seizures, substantially reduced injury and improved behavioural recovery.<sup>3</sup> The results of randomised clinical trials in full-term infants with moderate-to-severe hypoxic ischaemic encephalopathy supported the finding that mild induced hypothermia consistently improved survival and disability, including cerebral palsy and neurocognitive outcomes.<sup>4</sup>

The challenge is now to improve outcomes for the 45% of infants who die or survive with disability despite mild therapeutic hypothermia. In work in animals, one of the most promising add-on agents was the noble gas xenon.<sup>5</sup> In *The Lancet Neurology*, Denis Azzopardi and colleagues report the results of their multicentre, randomised controlled trial,<sup>6</sup> which showed that the addition of 30% xenon ventilation for 24 h to mild hypothermia did not further improve outcomes in term infants with hypoxic ischaemic encephalopathy compared with mild hypothermia alone.

The study was well done: the investigators had collected strong previous safety data and obtained rigorous consent, and randomisation included minimisation for disease severity. Their use of MRI and magnetic resonance spectroscopy to measure outcome is an important innovation, which allowed this proof-of-concept study to be completed with roughly a tenth of the sample size that would have been needed for a pragmatic clinical trial to have 90% power to show a 10% improvement. This approach will substantially speed up initial testing of potential treatments in future trials, although large pragmatic studies will remain essential to confirm the clinical benefits of treatments.

Why did the findings of neuroprotection with xenon in animals not translate to human beings? The probable reason is not failure of the trial, but rather the trial's setting. Xenon is expensive, and necessitates a specialised recirculating ventilator. Thus, treatment could not be started by non-specialist centres or during transport in the largely outborn population. This practical limitation meant that initiation of treatment was delayed until a median of 10 h (IQR 8.2–11.2, range 4.0–12.6)—well outside the probable therapeutic period.

Therapeutic hypothermia needs to be begun within roughly 6 h of birth to achieve neuroprotection, and earlier initiation—typically 3 h or less after birth<sup>3</sup>—is better for outcomes. Xenon is thought to act through anti-excitatory mechanisms, which occur early in the cascade leading to delayed cell death. Consistent with this hypothesis, Chakkarapani and colleagues<sup>7</sup> showed an additive effect in piglets when xenon treatment and mild hypothermia were begun immediately after hypoxia-ischaemia. Faulkner and colleagues<sup>8</sup> showed a subadditive effect with combined treatment started 2 h after hypoxia-ischaemia, such that xenon-augmented hypothermia reduced cell death and cerebral abnormalities (as detected with magnetic resonance spectroscopy) compared with normothermia, but not compared with mild hypothermia alone. The effect of delay in treatment with xenon in small animals is variable. A study showed an additive benefit only with immediate but not delayed treatment,<sup>9</sup> whereas in other studies benefit was noted when treatment was delayed by as much as 4–6 h after hypoxia-ischaemia.<sup>5</sup> Thus, preclinical evidence strongly suggests that xenon needs to be started soon after resuscitation to allow neuroprotection, and definitely within 6 h. Although Azzopardi and colleagues reported no apparent effects related to timing of treatment with xenon, only seven (15%) of 46 infants started xenon before 6 h of age.<sup>6</sup>

The important message from this trial is that early treatment initiation might be as central to studies of add-on therapy as it was for the successful clinical translation of therapeutic hypothermia. The use of rapid, short-term but highly precise outcomes in this study is an important innovation that could allow many therapies to be tested in the time that it would

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take to complete a single pragmatic trial. More than 300 years passed from when therapeutic hypothermia was first proposed until it was established in clinical practice. Further waiting before testing the many other promising add-on therapies is not necessary.<sup>5</sup> We propose that the motto of the neonatal community both for when to treat brain injury and for when to undertake further clinical trials should be do not delay.

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