Xenon as a neuroprotective treatment in neonatal encephalopathy

Therapeutic hypothermia has been adopted as a neuroprotective treatment for newborn infants with signs of moderate or severe hypoxic-ischaemic brain damage. This article discusses one of the new potential add-on treatments to cooling, the anaesthetic gas xenon. Its mechanism of action, the delivery method and the on-going randomised trials investigating the neuroprotective properties are reviewed.

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Keywords

neonatal encephalopathy; therapeutic hypothermia; xenon; neuroprotection; cooling

Key points

Smit E., Thoresen M. Xenon as a neuroprotective treatment in neonatal encephalopathy. *Infant* 2014; 10(1): 14-17.

1. Therapeutic hypothermia does not offer neuroprotection in all cases of neonatal encephalopathy.
2. Xenon combined with cooling has been shown to offer additional neuroprotection in animal models of neonatal encephalopathy.
3. Two randomised trials are currently investigating whether xenon combined with cooling offers additional neuroprotection compared to cooling alone.

Neonatal encephalopathy

Brain injury as a result of hypoxia and ischaemia in the perinatal period is a serious problem for term infants. It results in neonatal encephalopathy (NE) and can lead to death and disability in later life including epilepsy, deafness, blindness, developmental delay and cerebral palsy[1,2]. More subtle problems with behaviour, memory and cognition can also become apparent at school age[3,4]. Newborn infants with mild NE (Sarnat stage 1) appear hyperalert with an increase in tone and exaggerated reflexes. In moderate NE (Sarnat stage 2) infants appear lethargic and have reduced reflexes and tone, seizures are common. Severely affected infants (Sarnat stage 3) appear comatose with absent reflexes[5]. Following a hypoxic-ischaemic insult to the brain, neuronal cells become dysfunctional and start dying. Various pathways are activated leading to delayed apoptotic cell death and inflammation[6,7]. For any treatment to be effective, it will have to interact early to block these pathways. This is called the 'therapeutic window' and is generally accepted to be within the first six postnatal hours for therapeutic hypothermia.

Therapeutic hypothermia

Therapeutic hypothermia (TH) has emerged as a neuroprotective strategy in term infants affected by moderate or severe NE. The treatment involves a reduction of core body temperature to 33.5°C (whole-body cooling) or mild systemic hypothermia to 34.5°C with cooling of the head (selective head cooling.) In the UK both the British Association of Perinatal Medicine (BAPM) and the National Institute for Health and Care Excellence (NICE) have produced guidance on the use of TH[8,9]. A recently updated Cochrane review[2] included 11 trials with 1,505 subjects and confirmed a significant

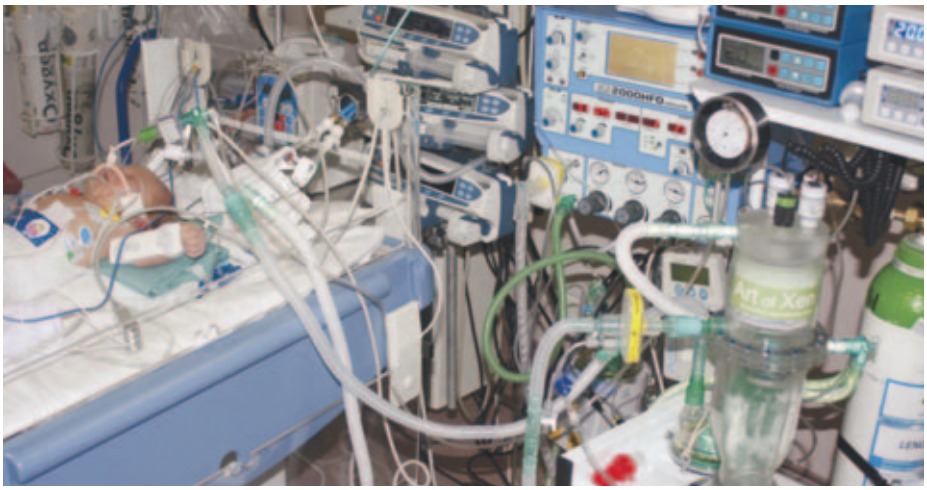

FIGURE 1 An infant receiving xenon via the closed-loop system.

reduction in the combined outcome of death or major disability in survivors for infants with moderate and also with severe encephalopathy. Sixty-one per cent of the infants treated in the normothermia arm of the trials died or were disabled at 18-24 months; this was reduced to 47% in the infants treated in the hypothermia arm. There was a typical risk reduction of -0.15 (95% confidence interval -0.2 to -0.1) and the number needed to treat for one additional beneficial outcome was seven (95% confidence interval 5-10).

Clinical trials comparing hypothermia and normothermia initiated treatment within six hours and experimental evidence suggests reduced effectiveness by delayed cooling. Early cooling within three hours after birth has been shown to improve motor outcome in asphyxiated newborns[10]. The exact mechanism of action for TH is not entirely understood and probably involves several processes, including a reduction of the brain's metabolic rate, anti-inflammatory and anti-apoptotic effects and a reduction in neuronal excitotoxicity[11]. The UK TOBY register collected information on all infants undergoing TH[12]. Between December 2006 and July 2011, 74 centres registered cooled infants. Since the introduction of the NICE guidance on TH a median of 68 infants were cooled each month in the UK.

Add-on treatments to cooling

Since TH does not offer complete neuroprotection, several add-on treatments to cooling are being investigated. Combination treatments for infants with NE are attractive in view of the potential increase in neuroprotective effect by targeting multiple underlying disease processes and include erythropoietin, magnesium sulphate, melatonin, topiramate and xenon. For a brief overview of these add-on treatments, refer to Levene[13]. The remainder of this article will focus on the use of xenon in combination with cooling.

What is xenon?

Xenon is an odourless, dense noble gas with anaesthetic properties. It is present in the atmosphere in very small quantities. It is used in light bulbs and headlights for cars, where it gives off a purple-blue light. Xenon can also be added to double-glazing, where it increases the insulating effect of the double-glazing in view of its density and lower thermal conductivity compared to air. As an anaesthetic gas, xenon is not being used in routine practice in view of its high cost of around £30 per litre. Xenon has minimal side-effects in adult studies[14] and its effects are easily reversible. It has also been shown to have cardioprotective effects in an animal model of newborn hypoxia-ischaemia[15].

Xenon's neuroprotective properties have been demonstrated in cell culture[16], a rodent model of hypoxia-ischaemia[17-21] and a neonatal pig model of global hypoxia-ischaemia[22,23]. Xenon acts as an N-methyl-D-aspartate (NMDA) receptor antagonist by binding to the glycine site of the receptor[24]. This prevents post-synaptic binding of glutamate, which is an excitatory neurotransmitter. Xenon may also have anti-apoptotic effects[17].

Xenon delivery

In view of the high cost of xenon, it would not be cost-effective to run xenon through a normal ventilator circuit. Dr John Dingley designed a purpose-built, closed-loop delivery system that continuously recirculates exhaled xenon[25] and the Neonatal Neuroscience team in Bristol have now given xenon to 30 neonates using this closed-loop system (**FIGURE 1**). A real advantage of the system is the ability to change oxygen concentrations without having to interrupt xenon adminstration, which is known to be a problem in other closed-loop systems. To avoid any xenon leaks, the infant requires intubation with a cuffed endotracheal tube. As it is important that xenon is delivered to the infant early and because around half of the infants with NE in the southwest region are out-born, the xenon delivery system has been fitted in the ambulance for use during transport. Xenon use during transport was successfully launched in April 2013 and has enabled the Bristol Neonatal Neuroscience team to offer xenon therapy as part of the CoolXenon2 study earlier and to more infants (**FIGURE 2**). Furthermore, an automated xenon delivery system is being worked on, to make the treatment even more practical to administer[26].

A criteria Infants ≥36 weeks gestation with at least one of the following:	Apgar score ≤5 at 10 minutes Continued need for resuscitation, including tracheal or mask ventilation, at 10 minutes Acidosis defined as either umbilical cord pH or any arterial, venous or capillary pH within 60 minutes of birth <7.00 Base deficit ≥16mmol/L in umbilical or any blood sample within 60 minutes of birth
B criteria Moderate or severe encephalopathy as evidenced by any of the following:	Altered state of consciousness and at least one or more of the following: ■ hypotonia ■ abnormal reflexes ■ absent or weak suck ■ clinical seizures
C criteria At least 30 minutes duration of amplitude integrated EEG that shows:	Normal background with some electrical seizure activity (>5 min) Moderately abnormal activity (upper margin of trace >10μV, lower margin <5μV) Suppressed activity (upper margin <10μV and lower margin <5μV) Definite seizure activity

TABLE 1 Cooling entry criteria. Key: EEG = electroencephalography.

- Intubated, ventilated, sedated, being cooled
- Cooled within three hours
- Postnatal age <5 hours
- FiO_2 <0.4
- Positive end expiratory pressure on ventilator <6cmH_2O
- Arterial pCO_2 <7kPa
- Seizures under control
- Weight >2nd centile for gestational age
- Mean arterial blood pressure >40mmHg
- No evidence of infection
- Absence of major congenital abnormalities
- Situation not futile

TABLE 2 CoolXenon2 study: additional eligibility criteria.

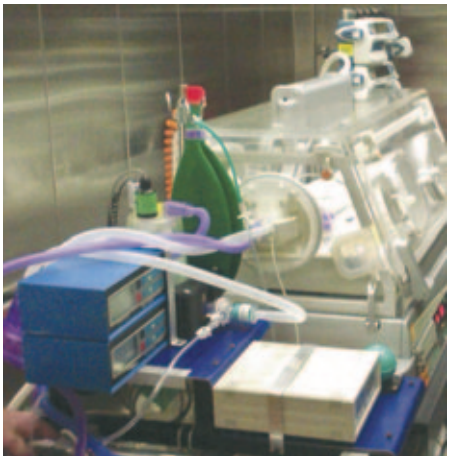

FIGURE 2 The xenon delivery system mounted onto a transport trolley.

CoolXenon1 study

The CoolXenon1 feasibility study (current controlled trials identifier ISRCTN 75602528) was conducted in St Michael's Hospital, Bristol between March 2010 and April 2011. This was the first time a newborn infant received xenon. In total 14 newborn infants with moderate or severe NE were enrolled and received varying durations (3-18 hours) and concentrations (25-50%) of xenon. The aim of this study was to investigate the feasibility of administering xenon with the newly designed delivery system.

CoolXenon2 study

This study is a randomised trial that is currently recruiting patients (clinical trials identifier NCT01545271). Eligible infants should be ≥36 weeks of gestation and fulfil the standard cooling entry criteria (**TABLE 1**). The additional study entry criteria are summarised in **TABLE 2**. TH needs to be commenced by three hours and xenon delivery started by five hours. Following informed consent, infants are randomised to 'cooling alone' or 'cooling + xenon' with equal numbers in each arm. All infants enrolled undergo treatment at St Michael's Hospital and receive 50% xenon for 18 hours if randomised to the xenon arm. The aim is to recruit 84 patients.

St Michael's Hospital is one of the two regional cooling centres in the Southwest Neonatal Network. For out-born infants a research fellow joins the Newborn Emergency and Stabilisation Transport (NEST) team to assist in the retrieval process, to obtain informed consent from the parents and start xenon delivery as soon as possible within the five-hour time window. Xenon delivery, together with active cooling using a servo-controlled device, is then continued throughout the transport and continued without a break on the neonatal unit in Bristol.

Blinded outcome measures include a structured neurological examination on day 7 of life and prior to discharge, magnetic resonance imaging (MRI) with spectroscopy (MRS) performed between days 7-10 and neurodevelopmental examination at 18-20 months (Bayley-III).

	CoolXenon2	TOBY Xe
Cooling initiated	<3 hours	<6 hours
Randomisation	<5 hours	<12 hours
FiO_2 maximum	0.4	0.6
Xenon concentration	50%	30%
Xenon duration	18 hours	24 hours

TABLE 3 Comparison between the CoolXenon2 and TOBY Xe studies.

TOBY Xe study

Imperial College London and the National Perinatal Epidemiology Unit (NPEU) are running this study with recruitment in four centres (clinical trials identifier NCT00934700). Entry criteria are very similar to those in the CoolXenon2 study, with three major exceptions: cooling needs to be started within six hours; xenon delivery needs to commence by 12 hours; maximum FiO_2 is 0.6 (**TABLE 3**). The study protocol differs slightly compared to the CoolXenon2 study: the TOBY Xe study gives 30% xenon for 24 hours, while the CoolXenon2 study gives 50% for 18 hours. A different xenon delivery device is being used[27,28]. Planned recruitment is 130 patients and outcome measures include a structured neurological examination in the first week and prior to discharge, and MRI and MRS between days 5-14.

Conclusions

TH offers neuroprotection in newborn infants with neonatal encephalopathy. The number needed to treat to prevent one infant dying or surviving with a major disability stands at seven. Two randomised trials are currently recruiting infants to investigate the neuroprotective effects of xenon in combination with cooling. It will be very exciting to see the outcome of both trials, which use a different dose and duration of xenon. Even though the current two trials are not powered to compare whether one is superior to the other, it may be possible to answer the question: 'Does xenon provide additional neuroprotection if used in combination with therapeutic hypothermia?' Furthermore the results of both trials will provide valuable information on the dose and duration of xenon to be used. The results of smaller trials do however not always provide a straightforward answer. This was the case in some of the cooling trials, where no significant effect from TH was seen. It was only by combining several smaller studies in a meta-analysis that a convincing effect was seen. Following completion of the current two xenon trials, larger trials may therefore be required to answer this question.

Acknowledgement

The authors would like to thank all parents and infants who took part in the CoolXenon1 study and those who took part and are still taking part in the CoolXenon2 study. They would also like to thank all staff on the NICU at St Michael's Hospital, the NEST team in Bristol and all referring neonatal units in the Southwest Neonatal Network for their support in recruiting patients.

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