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31 July 2014

Dr Pamela Cairns, Chair
South West Research Ethics Committee – Central Bristol
Level 3, Block B
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Dear Dr Cairns

Ethics Committee Ref: 09/H0106/64 : MHRA ref: CH/2009/3187
FINAL Report on: Feasibility study of adding xenon to cooling therapy in babies at high risk of brain injury following poor condition at birth
Short title of trial: The CoolXenon Study Trial Identifier: ISRCTN75602528

I refer to our interim reports sent in July 2011 and November 2012. This is the Final Report - to be submitted within 12 months of the conclusion of the study (which was July 2013).

Cooling therapy after perinatal asphyxia became standard of care in the UK from May 2010: however, in our hospital all eligible infants have been cooled since the randomised trial TOBY stopped recruiting on 31 November 2006.

Based on our experimental safety and efficacy data (2003-2010) we were allowed to give the inert gas xenon to infants with moderate or severe perinatal asphyxia in a feasibility study of increasing the percentage of gas and duration of xenon delivery. Fifty percent xenon for 18 hours had given the best effect in our piglet studies, hence dose and time increased to this level by the time 14 patients had been recruited.

This feasibility study started recruitment on 28 March 2010 and the last patient was recruited on 5 April 2011. Three of 14 infants (21%) died in hospital in the neonatal period due the severity of the asphyxial insult. Twenty percent mortality was predicted based on historical data in our own region. The inclusion criteria was necessarily pragmatic regarding the time taken to start delivering xenon. This was due to the practicalities of transferring outborn babies (those born elsewhere in the region) back to St Michael's Hospital - as well as allowing time for the anaesthetist, Dr Dingley, to arrive from Swansea. In this first study, the special delivery system made for xenon was ***always*** run by Dr Dingley; this responsibility has since been taken over by our trained staff.

As is standard practice, the cooling treatment should start within 6 hours after birth and for the Xenon Feasibility study, delivery of xenon within 18 hours.

There were no technical problems with the delivery system. One child did not receive the full treatment because of increasing need for oxygen. This was due to immature lungs which responded to surfactant treatment (the baby was delivered at 36 weeks with mum not in labour). The other 13 patients received the allocated duration of xenon.

All surviving children were followed up until 2 years. By 18-22 months they underwent a Bayley examination (Bayley III) and by 24 months a clinical examination as per cooling follow-up programme. By 24 months we did not observe any adverse effects that could be attributed to the xenon treatment, including being ventilated with a cuffed endotracheal tube.

Detailed data and follow-up has been published in the Journal 'Pediatrics' (Dingley J et al. Xenon Ventilation during Therapeutic Hypothermia in Neonatal Encephalopathy - a feasibility study. Pediatrics E-pub 28.4.2014. DOI: 10.1542/peds.2013-0787) and a copy of this paper is enclosed.

This study was not an outcome study and the data do not answer the question of whether adding xenon improves outcome. It asks the question whether it is feasible to give xenon to babies undergoing cooling therapy - and it is. Regarding safety data, we observed that the blood pressure was stable and that the usual clinical and metabolic parameters monitored in these patients were no different from those babies that received 'cooling only'. We observed that breathing xenon (which is an anaesthetic - and 50% xenon is a sedative dose) depressed the EEG background voltage. This is likely to be a positive effect and a part of the protection. Xenon stops or reduces seizure activity.

The trial received good and positive publicity, including being featured in the BBC Horizon programme, 'Back from the Dead' broadcast in 2010.

We are of course unable to know of any unforeseen long-term adverse effects. We therefore intend to have long term follow-up of all infants who have received xenon, funding permitted.

We thank the Research Ethics Committee for permission to undertake the feasibility study – as a result of which, the first baby in the world received xenon gas combined with cooling therapy. We also thank the staff at St Michael's hospital for their support and parents for consenting to take part in the study as well as attending for follow-up appointments.

On behalf of the investigators, Drs Dingley, Tooley and Chakkarapani.

Yours sincerely

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