Neuroprotective effect of hypothermia combined with inhaled xenon following perinatal asphyxia

Lead Research Organisation: Imperial College London

Department Name: Dept of Medicine

Go back

Overview Organisations People Publications Outcomes

Abstract

The proposal is to study the effects on the brain of treatment with the combination of mild hypothermia (cooling) and the gas xenon following perinatal asphyxia. Perinatal asphyxia is defined as a lack of oxygen occurring usually during labour and delivery and affects approximately 3/1000 births in the UK. Infants with perinatal asphyxia have an increased risk of death or severe handicap in survivors and less severely affected children have lower intelligence scores. Perinatal asphyxia leads to major litigation claims for NHS Trusts.

Trials of mild hypothermia show that it is possible to reduce brain injury following perinatal asphyxia. However, despite treatment with hypothermia, approximately 50% of these infants have a poor outcome; therefore, further brain protective treatments need to be sought.

In studies in animals we found that the combination of inhaled xenon together with mild hypothermia reduced the damaging biological processes that follow asphyxia. We found that the benefit was greater than the sum of effect of the individual treatments (that is the combination had synergistic benefits).

We will use non invasive magnetic resonance brain scans to assess whether the combination of mild hypothermia and inhaled xenon reduces abnormality in brain biochemistry and protects brain tissue following perinatal asphyxia.

With the consent of the parents, term infants suffering perinatal asphyxia will be treated at random with mild hypothermia or mild hypothermia with xenon. Hypothermia will be started within 6 hours of birth and continued for 72 hours. Infants allocated to mild hypothermia plus xenon will also receive 30% xenon (and oxygen according to the baby?s needs) for 24 hours through a purpose designed delivery system. A standard neurological examination will be done daily during the 1st week after birth and at discharge from hospital. Blood will be collected on day 1 and day 4 for storage (for future genetic studies) and for measurement of markers of brain injury. Magnetic resonance brain scans will be performed once between 4-10 days of age. The data will be analysed by investigators who will be unaware of the treatment the baby received, to avoid bias. We plan to study 130 infants over 30 months.

If the results show that the combination of mild hypothermia and xenon has brain protective effects we intend to do a larger clinical trial to find out if this treatment reduces the risk of death or disability following perinatal asphyxia.

Technical Summary

Perinatal asphyxia leading to hypoxic-ischaemic encephalopathy occurs in approximately 3/1000 births, is associated with a high risk of death or severe handicap, often leads to major litigation claims and is a major burden for the individual, the family and for society. Trials of mild hypothermia have recently proved that in principle neuroprotective therapy after delivery is possible but the therapeutic benefit of hypothermia is modest.

This proposal builds from our studies which found that inhaled xenon is neuroprotective after hypoxia-ischaemia in immature animals and has a synergistic benefit when combined with hypothermia. We now propose an experimental study to determine if xenon administered in combination with hypothermia has neuroprotective effects following perinatal asphyxia in human infants.

In a randomised controlled trial of 130 infants enrolled over 30 months, we propose to compare the combination of xenon and hypothermia with hypothermia alone, and to measure the effect using two biomarkers: (i) proton magnetic resonance spectroscopy (MRS) to measure the cerebral lactate to N acetylaspartate ratio; and (ii) quantitative magnetic resonance imaging of the posterior limb of the internal capsule. The biomarkers are: mechanistically relevant; clinically prognostic of severe neurological impairment; affected by therapy; and MRS is a bridging biomarker which detects the effect of neuroprotective therapy in animal studies.

Hypothermia will be started within 6 hours of birth and maintained using an approved cooling system which uses a fluid filled mattress with the temperature of the fluid adjusted to maintain the rectal temperature at 33.5 +/- 0.5 C. Xenon treatment will be initiated as close as possible to the induction of hypothermia and no later than 12 hours after birth. Xenon will be administered for 24 hours through a closed-system ventilator, which is designed for delivery of Xenon. Target concentration for end-tidal xenon will be 30%.

Together with neurological neonatal assessment the biomarker data will help determine whether phase 3 clinical trials should be undertaken. If the data give confidence of a therapeutic effect, phase 3 trials could be started within 4 years.

Funded Value:

£1,088,609

Funded Period:

Oct 09 - Dec 14

Funder:

MRC

Project Status:

Closed

Project Category:

Research Grant

Project Reference:

G0701714

Principal Investigator:

Denis V Azzopardi

Health Category:

Reproductive Health and Childbirth (100%)

Research Activity:

6.1 Pharmaceuticals (100%)