

Hypercapnic acidosis following hypoxia-ischaemia as neuroprotectant: is the time right for a clinical trial in the human newborn?

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Background: A severe hypoxic-ischaemic (HI) insult to the developing brain can lead to death or permanent neurological impairment and since detection methods of intrapartum asphyxia have a low positive predictive value, prevention is often difficult. Current clinical care of the baby with HI is based on restoring the physiological environment to 'normal' with new evidence that mild hypothermia is a neuroprotectant with a modest effect size. Studies in both rat and *in vitro*, suggest that mild hypercapnic acidosis is neuroprotective. Despite the fact that hypercapnic acidosis has been shown in meta-analysis to have a beneficial role in newborn care to minimise lung injury, neurodevelopmental outcomes have not been reported.

Aim: In a newborn piglet model of asphyxia¹ we aimed to (i) determine whether hypercapnic acidosis reduces HI neuropathology and (ii) establish a timeline of events in the cell death cascade to better understand the 'window' in which hypercapnia might best be applied.

Methods: 72, 1-day old piglets in 4 groups (HI, HI+hypercapnia, control, control+hypercapnia) were anaesthetised and ventilated to maintain PaO₂ 60-100 and PaCO₂ 35-45 mmHg. SaO₂, T, ECG, and EEG were monitored continuously. Hypoxia was induced by decreasing FiO₂ to 4% and maintaining EEG amplitude <5 µV for 30 min. Hypercapnia was induced immediately post-insult for 1h to maintain end tidal CO₂ 60-70 mmHg. Plasma samples were collected prior to hypoxia, immediately following hypoxia and at the point of euthanasia. Piglets in each group were euthanased at 1, 8, 24 and 72h post-insult, the brain coronally sectioned and samples of frontal and occipital cortex placed in 0.32M sucrose and frozen at -80°C and the remaining sections fixed in paraformaldehyde. Haematoxylin and eosin (H&E) staining, MAP2 and Caspase-3 immunocytochemistry were performed. Plasma and brain samples were analysed for MDA concentration.

Results: H&E neuronal injury score¹ showed a trend to more severe injury in the HI+hypercapnia group compared with the HI group (p = 0.067) at 72 h. MAP2 showed significantly more injury in the HI+hypercapnia group compared with the HI group at 72 h (p < 0.05). There were no significant differences in Caspase 3 or MDA at any time point between the 2 study groups.

Discussion: We found moderate hypercapnic acidosis applied for a short period after an HI insult, was not neuroprotective in the newborn piglet. Nonetheless, given its efficacy in other studies and widespread use in the human without apparent deleterious effects, we discuss whether now is the time to systematically study, in conjunction with hypothermia, its potential neuroprotectant role in the human newborn.

1. Foster KA, *et al.* (2001) *Brain Research* 919:122-131.