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IMPROVED NEUROPROTECTION WITH MELATONIN-AUGMENTED HYPOTHERMIA VS HYPOTHERMIA ALONE IN A PERINATAL ASPHYXIA MODEL: A RANDOMIZED STUDY

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Background: Melatonin (N-acetyl-5-methoxytryptamine) is a naturally occurring hormone, anti-oxidant and cellular pro-survival factor, used safely in children with sleep disorders. Melatonin is beneficial following brain injury in adult animals. It is unknown if melatonin augments hypothermic neuroprotection in the developing brain.

Aims: To assess the neuroprotective efficacy of melatonin combined with cooling to 33.5°C in a piglet model of perinatal asphyxia.

Methods: Seventeen anaesthetised male piglets, < 24h old, underwent transient hypoxia-ischaemia (HI), then were cooled to 33.5°C 2-26h after HI and randomised to i) hypothermia alone(n=8); or ii) hypothermia+melatonin (5mg/kg infused over 6h starting 10 min after HI and repeated at 24h, n=9). Cortical white matter (WM) and ventromedial forebrain (vmFB) proton (1H) and forebrain (FB) were obtained at baseline, and 24 and 48h following HI.

Results: Compared to hypothermia alone, melatonin and hypothermia significantly decreased the areas under the post HI time-series curves for vmFB lactate (Lac)/N-acetylaspartate(NAA) and Lac/creatine(Cr) ($p< 0.05$); as well as reducing the drop in WM NAA/Cr ($p< 0.05$) (Fig1). Heart rate, mean arterial blood pressure and inotrope use did not differ between groups.

Conclusions: Validated MRS biomarkers suggested cooling plus melatonin augmented hypothermic neuroprotection in both vmFB and WM. Melatonin is a promising candidate for clinical trials of neuroprotection in the future.

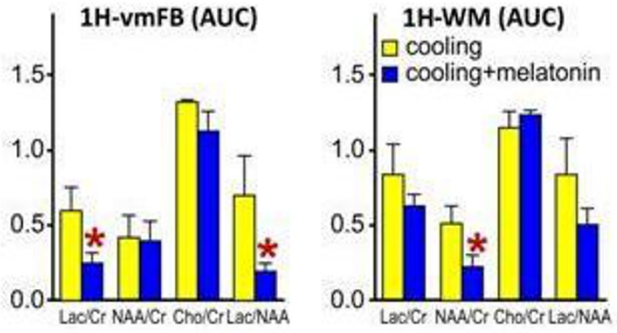

Fig 1: VmFB and WM 1 H metabolite-ratio areas under the curves (AUC) 48 h post HI. Yellow: cooling only; blue cooling plus melatonin. Cho - choline. (*p<0.05 two sided t-test)

[figure 1]

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