

[N-75] Combination of mild hypothermia and sevoflurane affords long-term protection in a modified neonatal mouse model of cerebral hypoxia-ischemia

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Background: Infant brain injury from hypoxia-ischemia (HI) can lead to life-long impairment (1), but protective strategies are lacking. Short-term, but not long-term protection has been demonstrated in the Rice-Vannucci neonatal brain ischemia model (RVM) by volatile anesthetic administration prior to HI (2), while exposure during HI has not been tested. The current study evaluated a combination of sevoflurane and mild hypothermia as a protective approach during HI by introducing intubation and mechanical ventilation to the RVM.

Methods: The right common carotid artery was ligated in 10 day-old mice during brief sevoflurane anesthesia, followed by a 2-hr recovery with the dam. Littermates were then randomized to following conditions for 60 min: HI spontaneously breathing 10% oxygen (the classical RVM); HI-Protect) mild hypothermia and orotracheal intubation and mechanical ventilation with 3.5% sevoflurane in 10% oxygen; or Room Air) spontaneously breathing room air. Cerebral oxygenation was monitored in the area at risk and the contralateral hemisphere during HI or HI-Protect using visible-light spectroscopy (Spectros Corp.). Mean arterial pressure, heart rate, and arterial blood gases were measured. Right/left brain hemispheric weight ratios and brain damage scores were determined 1 week following HI. Learning and behavior were assessed in young adulthood (9 weeks) using spontaneous locomotion, Morris water maze (MWM), and apomorphine injection.

Results: During HI, ipsilateral and contralateral brain oxygenation, arterial pressures, blood gases, and glucose levels were similar in both ischemic groups, while heart rate was lower in the HI-Protect group. Brain hemispheric weight ratios and injury scores in several brain regions were significantly worse following HI, compared with HI-Protect. MWM hidden platform and reversal platform escape latencies, measures of spatial memory function, were superior following HI-Protect, compared with HI ($P < 0.0001$). HI-Protect animals demonstrated significantly less circling behavior after an apomorphine challenge ($P < 0.0001$), a measure of striatal integrity.

Conclusions: In order to test the neuroprotective effects of volatile anesthetics during neonatal brain ischemia, we developed a modification of the RVM. By utilizing mechanical ventilation and endotracheal intubation, sevoflurane administration during HI was survivable. The combination of sevoflurane administration and mild hypothermia during HI conferred not only short-term structural, but also long-term functional protection. These findings warrant further studies in order to improve neurological outcome in critically ill infants.

References:

1. van Handel M, Swaab H, deVries LS, et al. *Eur J Pediatr* 2007; 166: 645-54.
 2. McAuliffe JJ, Loepke AW, Miles L, et al. *Anesthesiology* 2009;111:533-46.
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