General Anesthesia Does Not Damage the Neonatal Pig Brain

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Introduction: Recent data has implicated several drugs routinely used in neonatal anesthesia to cause extensive brain damage. A six-hour exposure to midazolam, isoflurane, and nitrous oxide led to widespread neuronal apoptotis as well as long-lasting functional impairment in neonatal rats. These results have led to the recommendation that general inhalational anesthesia and sedation with midazolam should be avoided in infancy. (1) Before accepting this recommendation, the results should be confirmed in other neonatal species. Therefore this study examined the effects of anesthetics on neuronal survival in a neonatal pig model.

Methods: Ten 2 to 3-day old pigs were randomly assigned to anesthesia (n=5) or control (n=5). The anesthesia group received an intramuscular (IM) injection of midazolam 0.2 mg/kg, mask induction with 3% isoflurane, intravenous midazolam 0.4 mg/kg, followed by endotracheal intubation and a 6-hour anesthetic with controlled ventilation using 1 minimum alveolar concentration of isoflurane and 70% nitrous oxide in oxygen. Heart rate, oxygen saturation, rectal temperature, femoral arterial pressure and hourly blood gases were recorded. The control group received IM saline and was exposed to the operating room environment without further intervention. Postoperatively, animals were weighed and neurologically examined daily until sacrifice after 48h. Brains were removed and prepared for hematoxylin-eosin staining and examined by a neuropathologist blinded to group assignment. The percentage of dead neurons was determined in frontal, parietal, temporal, and occipital neocortex, as well as basal ganglia, thalamus, hippocampus, cerebellum, dentate nucleus, and brainstem.

Results: Functional impairment and widespread neuronal death were not observed in either anesthesia or control animals. Most brain regions contained no dead or injured cells, whereas some contained less than 1% of dead or injured cells, due to normal developmental neuronal apoptosis, without a difference between groups. (Table) Arterial pressure, oxygen saturation, blood gases, hematocrit, blood glucose, and rectal temperature in the anesthesia group remained within normal range for piglets.

Discussion: Neuronal cell death is not uncommon in the developing mammalian brain. However, a six-hour anesthesia with midazolam, isoflurane, and nitrous oxide in a neonatal pig model does not cause any additional neuronal death, in contrast to previous results in a neonatal rat model. (1) It is unclear if this discrepancy is related to animal species or other factors associated with the anesthesia in the neonatal rats, such as hypoxia-ischemia. To exclude species related phenomena, we will perform further testing in other animal models and results will be available during abstract presentation.

Table: Incidence of neuronal death after 6-hour anesthesia (n=5) or after no anesthesia (control, n=5)

	neocortex	bas. ganglia	thalamus	hippocamp.	cerebellum	brain stem
anesthesia	0%	20% (<1%)	0%	20% (<1%)	0%	0%
control	40% (<1%)	20% (<1%)	0%	0%	0%	0%

Percentage of animals with neuronal damage by brain region. Percentage of damaged cells for each region in parenthesis, where applicable.

Reference: 1. Jevtovic-Todorovic et al., J of Neuroscience 2003