Spinal Anesthesia in Infant Rats: Development of a Model, Preliminary Observations, and Assessment of Neurologic Outcomes

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INTRODUCTION: Spinal anesthesia is commonly performed in infants undergoing inguinal procedures as an alternative to general anesthesia. Recent concerns about potential neurodevelopmental toxicities of general anesthetics were initiated by laboratory observations involving infant rats [1]. In previous laboratory studies, prolonged general anesthetic exposure produced apoptotic neurodegeneration in the brains of infants, but not newborn rats, while very brief exposures did not [2]. Other infant rat models examined peripheral nerve blockade and age-related differences in local anesthetic systemic toxicity [3,4]. We hypothesized that spinal anesthesia in infant rats was technically feasible and that doses could be identified that were effective (producing lower extremity sensory and motor blockade), safe (absence of upper extremity block, respiratory distress, cyanosis, or mortality) and without any potential motor or neurodevelopmental effects.

METHODS: Laboratory protocols were approved by the Institutional Animal Care and Use Committee. Sprague-Dawley rats were anesthetized with 5% isoflurane in oxygen, kept for a week before being euthanized and perfused. Lumbar spinal cords sections from these animals were extracted for immunohistochemical analysis. Caspase 3 staining showed no increase in apoptosis in brain or spinal cord (G) in rats exposed 6 hours of isoflurane. Summary data on cleaved caspase-3 positive cells are shown for brain (B) and spinal cord (H). Data are presented as mean ± standard deviation, * p < 0.05 compared to each cohort. Scale bar 100 µm.

RESULTS: Following a learning curve, spinal anesthesia could be achieved with high success rates in all age groups studied. Saline control injections were benign, or produced no signs of sensory or motor impairment, in all treatment groups. Preliminary experiments with bupivacaine doses < 2 mg/kg showed signs of incomplete block. Dosing with 3.7 mg/kg or 7.5 mg/kg produced complete block of the lower extremities at 10 minutes in all animals, mid-thoracic levels of sensory block (Figure 1). None of the animals dosed with 3.7 mg/kg showed signs of block to cervical levels, cyanosis, or distress. However dosing with 7.5 mg/kg produced a slightly higher percentage of animals at all ages with cerebrovascular levels of severity (100% of all animals) in all groups. Dosing with 7.5 mg/kg or 7.5 mg/kg 1 hr exposure to isoflurane (Figure 2).

DISCUSSION: Regional anesthetic techniques are routinely utilized as alternatives to general anesthesia in appropriate surgical procedures in pediatric patients. However, the effect of spinal anesthesia on the developing central nervous system has not been previously investigated. Infant animal studies have the theoretical potential to detect age-specific toxicities and thereby prevent harm to human infants. This study demonstrates that spinal anesthesia with bupivacaine can be safely administered to neonatal rats resulting in a motor block and thermal anesthesia of the lower extremities. Spinal anesthesia appears technically feasible in infant rats, and a preliminary bupivacaine dose range of 3.75-7.5 mg/kg was identified that produced thoracic-blockade without cervical motor blockade or visible signs of respiratory difficulty. LG50s for peripheral extravascular dosing of bupivacaine in rats of different ages range from 30-90 µg/kg [4]. Thus, deaths occurring at doses above 7.5 mg/kg were likely due to respiratory and cardiovascular effects of high spinal anesthesia.

REFERENCES:

CONCLUSIONS: An infant animal model was developed to examine neurodevelopmental effects of spinal anesthesia. Under the conditions shown here, spinal anesthesia seems benign in terms of effects on brain and spinal cord neurotoxicity and long-term neurobehavioral consequences. An ongoing human randomized controlled trial of infant inguinal hernia repairs under general versus spinal anesthesia is expected to provide better information about neurodevelopmental consequences in humans.