Anesthesia and Neurotoxicity Study Design, Execution, and Reporting in the Nonhuman Primate: a Deep Dive

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Reference(s):
1. Association Between a Single General Anesthesia Exposure Before Age 36 Months and Neurocognitive Outcomes in Later Childhood. 2016;315:2312-2320. 2. Neurodevelopmental outcome at 5 years of age after general anesthesia or awake-regional anesthesia in infancy (GAS): an international, multicenter, randomized, controlled equivalence trial. 2019;393:664-677. 3. FDA Drug Safety Communication. 2016; https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-review-results-new-warnings-about-using-general-anesthetics-and. Accessed January, 12, 2021. 4. Physiological disturbance may contribute to neurodegeneration induced by isoflurane or sevoflurane in 14 day old rats. 2014;9:e84622. 5. Relevance of experimental paradigms of anesthesia induced neurotoxicity in the mouse. 2019;14:e0213543. 6. Hypoxia, hypercarbia, and mortality reporting in studies of anesthesia-related neonatal neurodevelopmental delay in rodent models: A systematic review. 2020;37:70-84.

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Introduction:
Concern for role of anesthesia in developmental delay in children primarily originated from neonatal rodent and non-human primate (NHP) studies, yet prospective clinical trials, including Pediatric Anesthesia Neuro Development Assessment (PANDA) and General Anesthesia versus Spinal Anesthesia (GAS), have largely not supported this concern (1-2). Largely relying on these neonatal animal studies, the FDA issued the 2016 "Drug Safety Communication" warning on general anesthetics as potentially neurotoxic agents to young children (3). Lately, the legitimacy of the rodent data has been called into concern by recent studies on confounding factors of hypoxia and hypercarbia during experiments (4-6). However, the validity NHP data has not been reviewed in a

systematic fashion. Herein, we present an objective and quantitative assessment of published NHP study rigor in experimental design, conduct, and reporting of outcomes.

Methods:
We conducted a systematic MEDLINE search from 2005 to November 2019 focusing on animals between postnatal age 0 to 40 days who underwent anesthetic exposure (Figure 1). Article screening and data extraction were conducted by 2 independent reviewers, with all conflicts reviewed and resolved by the principal investigator. A total of eighteen manuscripts were included (Table 1). We extracted anesthetic, route, dose, frequency and duration of exposures, age at exposure, ventilation, mortality, sample size, vitals, blood gases, anesthesia monitoring, behavioral and neuroapoptosis outcomes. We also assessed adherence to the ASA (American Society of Anesthesiologist) monitoring and ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines. Data were summarized as median (25th-75th percentile) and mean (SD).

Results:
Important deficits in study design, execution, and reporting were identified in neonatal NHP studies. Critical issues identified in study design included (Table 2): lack of blinding in data acquisition (56%) and analysis (100%), supratherapeutic (4-12 fold) maintenance dosing in 28% of studies, lack of sample size justification (89%) resulting in a mean (SD) sample size of 6 (3) animals per group. Critical items identified in the conduct and reporting of studies included (Table 3): documentation of anesthesia provider (0%), electrocardiogram monitoring (40%), arterial monitoring (5%), spontaneous ventilation employed (40%), failed intubations resulting in commingling ventilated and unventilated animals in data analysis, inaccurate reporting of failed intubation, and only 50% reporting on survival. Inconsistencies were also noted in drug related induction of neuroapoptosis and region of occurrence. Further, 66-100% of behavior outcomes were not significantly different from controls (Figure 2).

Conclusion:
Important deficits in study design, execution, and reporting were identified in neonatal NHP studies. These results raise concern for the validity and reliability of these studies and may explain in part the divergence from results obtained in human neonates.

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Affirmations

The study was approved by the appropriate IRB or other local review board.