

Calgary, Alberta—Premature infants and neonates exposed to anesthesia do not suffer clinically meaningful drawbacks as assessed by subsequent cognitive outcomes.

The research from the University of Calgary concluded that although exposed infants and neonates had propensity-matched full-scale IQ (FSIQ) scores that were almost 3 points lower than those of their unexposed counterparts at 3 years of age, these results were neither statistically nor clinically significant.

“Worldwide, many millions of neonates, infants and children receive sedatives, analgesics and anesthetics each year,” said Joanna J. Moser, MD, PhD, a resident at the University of Calgary, in Alberta. “The majority of drugs used in these contexts have therapeutic effects via the NMDA [*N*-methyl-*D*-aspartate] receptor and GABA [gamma-aminobutyric acid] receptor. These receptors are thought to play an integral role in early brain development, where interference may lead to abnormalities in neuronal survival and function.

“Recently published large clinical trials, such as the GAS [*Lancet* 2019;393(10172):664-677] and PANDA [*J Neurosurg Anesthesiol* 2019;31(1):103-107] studies, suggest that early exposure to anesthetics does not harm the developing brain,” Dr. Moser said. “However, no published study has actually focused on the neurocognitive impact of anesthetic exposure to the preterm infant population, whose brains have yet to fully mature and form complex neural connections. This is potentially the most vulnerable population.”

[image](#)

IQ Is Primary Outcome

To explore this possible association, Dr. Moser and her colleagues analyzed data from 493 very premature infants, who were born at 29 weeks or less of gestation between Jan. 1, 2006, and Dec. 31, 2012, and received anesthetics, sedatives and/or opioids during their first 44 weeks of life. Children were excluded from the analysis for various reasons, including complex congenital anomalies, metabolic/chromosomal abnormalities, severe intrauterine growth restriction, premature white matter injury and intraventricular hemorrhage (IVH).

The researchers quantified medication exposure by dose and duration. “Patients who received a single dose for [a] brief procedure, such as intubation of the trachea, were classified as unexposed because we did not want to skew our data,” Dr. Moser said.

The trial’s primary outcome was FSIQ, as measured by the Wechsler Preschool and Primary Scale of Intelligence, at 36 months of age.

Primary outcome data were obtained for 304 infants (182 exposed, 122 unexposed). Medications included volatile anesthetics, IV anesthetics, barbiturates, benzodiazepines and opioids.

“Interestingly, we found that infants and neonates in the exposed group had a lower gestational age, lower birth weight, greater SNAP-II score [a composite of six adverse physiologic measures], and more comorbid conditions and associated treatments than the unexposed infants in our cohort,” Dr. Moser said. “These results were statistically significant.”

Reporting at the 2019 annual meeting of the Canadian Anesthesiologists’ Society (abstract 637631), Dr. Moser revealed that after adjusting for other variables, no significant difference was found in mean FSIQ scores between infant groups. Patients exposed to anesthetics had a mean FSIQ of 94.0 ± 14 , compared with 96.7 ± 16 for unexposed infants ($P=0.21$).

[image](#)

“Although medication exposure was associated with an FSIQ deficit of 4 points,” Dr. Moser explained, “this intergroup difference is considered to be very small. After propensity score matching to adjust for confounding patient factors, the difference was attenuated to only 2.7 IQ points, which I think is quite remarkable.”

No significant interactions were found between anesthetic exposure and FSIQ; exposure and birth weight; exposure and academic performance; or exposure and SNAP-II score.

“Now, you may ask if a statistical drop of 4 IQ points prior to propensity score matching is clinically relevant,” Dr. Moser said. “The GAS study used a noninferiority margin of 5 IQ points — which is one-third of the standard deviation of 15 points — to define a clinically significant decrease. So, despite there being a statistically significant drop of 4 IQ points prior to propensity score matching, it is not clinically significant.”

Although the study does not establish definitive neurocognitive safety of the evaluated medications, it provides evidence that anesthetic and sedative medications commonly administered to very premature infants were not associated with adverse cognitive outcomes at 3 years of age.

“As such, our present study does not support minimizing opioids in the setting of sedation, where pain relief is indicated, nor delaying required surgery for infants because of pharmacologic concerns,” Dr. Moser said.

Sample Size Limited, However

Gregory M. Hare, MD, PhD, called the study “very informative.” Dr. Hare, a professor of anesthesia at the University of Toronto, said, “Yet, even though these are very important and very hard-to-get data, your sample sizes are still low. What would you say to people who question the validity of your results based on your limited sample size?”

“Our sample was a convenience sample, so we had a neonatology group that would follow up with these children at ages 3 and 5,” Dr. Moser said. “As you can imagine, at the five-year data [point] there’s more [children] lost to follow-up. That’s why we chose the three-year outcome.

“We were originally very excited to review 732 charts,” she said. “But then we had to eliminate the IVH babies, which was about 300 patients or so. Interestingly, we did a side analysis to figure out what those IVH babies looked like in terms of FSIQ, and we found that as children progressed from IVH grades 1 to 4, there was a corresponding drop in IQ. So, one limitation of this study is there are a lot of preterm infants who have IVH, and that definitely affects the developing brain and the IQ scores.”

Increasing the study population would likely require a multicenter study, according to Dr. Moser. “In order to get a number that compares with the GAS and PANDA studies, we would need at least [800] or 900 patients in each group, and we just didn’t have the numbers to get there.”

“I’m not a pediatric anesthesiologist, but as a parent I would be concerned with repeated exposure to anesthetics,” commented Harsha Shanthanna, MD, an associate professor of anesthesiology at McMaster University, in Hamilton, Ontario. “Does this study answer that [question], or did you exclude babies with repeated exposures?”

“Yes, we did look at that,” Dr. Moser replied. “We calculated exactly the dose and duration of all medications, and we found that repeated exposures did not have any

influence on neurocognitive outcomes.”

—*Michael Vlessides*

The research was honored as one of the best resident abstracts presented at the meeting. Drs. Moser, Hare and Shanthanna reported no relevant financial disclosures.