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Studies Explore Effects of Anesthesia on Children

by Karen Blum

Children exposed to general anesthetics before their first birthday are 4.5 times more likely to develop learning disabilities by age 12 than children not exposed to anesthesia, according to a study by researchers in Singapore.

That finding comes from a trio of recent studies looking at the effects of anesthesia on the brains of children and related issues of pediatric surgery. Researchers presented two of the studies at the 2012 International Assembly for Pediatric Anesthesia (IAPA) meeting in Washington, D.C. The third study appeared in a recent issue of *Anesthesiology*.

For the Singapore work (abstract GA2-44), investigators at the KK Women's and Children's Hospital searched the institution's database for children born in 1998-1999 with no preexisting medical conditions, who were exposed to general anesthesia (GA) with sevoflurane during minor surgical procedures such as herniotomies, circumcision, cystoscopies and pyloromyotomies before their first birthday. They compared the performance of 100 of these children on the Primary School Leaving Examination (PSLE), a national examination children take in school at age 12, with that of 106 children not exposed to anesthesia. They also interviewed parents about their children's medical history, school and home environment.

"We have kids who are born otherwise healthy who come in for minor procedures, and we like to think they would wind up all right," Choon Bong, MBChB, FRCA, lead author of the study and consultant anesthetist at the hospital, told *Anesthesiology News*. But after accounting for variables including race, sex, maternal and paternal education, domestic living arrangements and afterschool activities, the only significant predictor of formally diagnosed learning disability was previous exposure to GA.

Fifteen percent of children with early exposure to GA had a learning disability formally diagnosed by a medical or educational professional compared with 3.77% of controls ($P<0.001$). Of parents whose children were exposed to GA, 27% perceived their children to have learning difficulties such as dyslexia, difficulty with math and problem-solving skills, or language problems compared with 4.7% of parents in the control group ($P<0.001$).

Dr. Bong said the study does not prove a causative link between exposure to GA and subsequent developmental difficulties. But it "has alerted us that if an infant doesn't really need urgent surgery, it may be prudent to consider waiting." She said she and her colleagues plan to conduct a larger, prospective study.

First Cut Often Not the Last

Also at the IAPA meeting, researchers at the University of Vermont College of Medicine (UVM), in Burlington, reported that a large proportion of children who undergo surgery return for more procedures during childhood (abstract GA2-41).

The researchers studied medical records from 1,024 children in the Vermont Infant Spinal Registry, a clinical database of every infant undergoing spinal anesthesia at UVM between 1998 and 2003. They then examined full UVM medical records for these patients, noting the initial surgery type, anesthetic technique and duration.

Complete medical records were available for 711 patients, of whom 215 (30.2%) had received more than one anesthetic before the age of 5 years. Infants who originally came to UVM for inguinal hernia repair had a 28.8% incidence of subsequent surgeries.

"Since cognitive delay after exposure to anesthesia and surgery is most strongly associated with multiple exposures, anesthesiologists caring for young children should take note of the nontrivial likelihood that infants may return for

another surgery at an early age," said Robert Williams, MD, associate professor of anesthesia and pediatrics UVM, who helped conduct the study.

To minimize children's exposure to general anesthesia, Dr. Williams said, anesthesiologists should consider alternatives when practical, including regional anesthesia and the use of adjuvants like IV acetaminophen, ketorolac and α-2 medications such as clonidine.

The Trouble With Lactate

In a third study, researchers at Stony Brook University School of Medicine, in Long Island, N.Y., have found that sevoflurane affects children's brains differently from propofol. Sevoflurane produced significantly more lactate, which increases during brain activation and in children may be associated with higher risk for anxiety and delirium upon emerging from anesthesia.

For the study, published in the November issue of *Anesthesiology* (117:1062-1071), researchers studied 59 children ages 2 to 7 years scheduled for magnetic resonance imaging under GA. The children were randomized to receive either sevoflurane or propofol. All children received inhalational mask induction with sevoflurane for one to two minutes. Children randomized to receive propofol then were immediately converted to an IV propofol infusion. The duration of anesthesia in each group was about one hour.

The researchers mapped the metabolic patterns of the children's brains during the last 10 minutes of their procedures using proton magnetic resonance spectroscopy. The scans revealed that the parietal cortex of children who received sevoflurane had about twice the amount of lactate and 20% more glucose than did the brains of children receiving propofol.

During emergence from anesthesia, recovery room nurses assessed each child for emergence delirium using the Pediatric Anesthesia Emergence Delirium Scale (PAED). The average total PAED score for those receiving sevoflurane was significantly higher than for those receiving propofol (average 7.0 vs. 3.9; P=0.037) indicating more agitation and delirium associated with emergence from sevoflurane. Recovery time was shorter for those receiving propofol versus sevoflurane (average 42 vs. 53 minutes; P=0.02). The researchers noted a positive relationship between the magnitude of the PAED score and lactate, suggesting that elevated lactate might predict emergence delirium.

Helene Benveniste, MD, PhD, senior author of the paper and vice chair for research at Stony Brook's Department of Anesthesiology, said her group is trying to tease apart the relationship between lactate and delirium.

"Lactate increases when the brain is activated, so the higher level of lactate in the brain of a child administered sevoflurane is likely the result of more neuronal firing during the unconscious state," Dr. Benveniste said. "It's like having a motor running but the car is not going anywhere. It could also mean that lactate is not being cleared from the brain, and the buildup may increase the chance of children becoming anxious or delirious."

The results are too preliminary to suggest changes in practice, said Dr. Benveniste, who plans to continue studying metabolic changes in other areas of the brain and from different anesthetics.