PEDIATRICS

Anesthesia in Kids: Research and Practice

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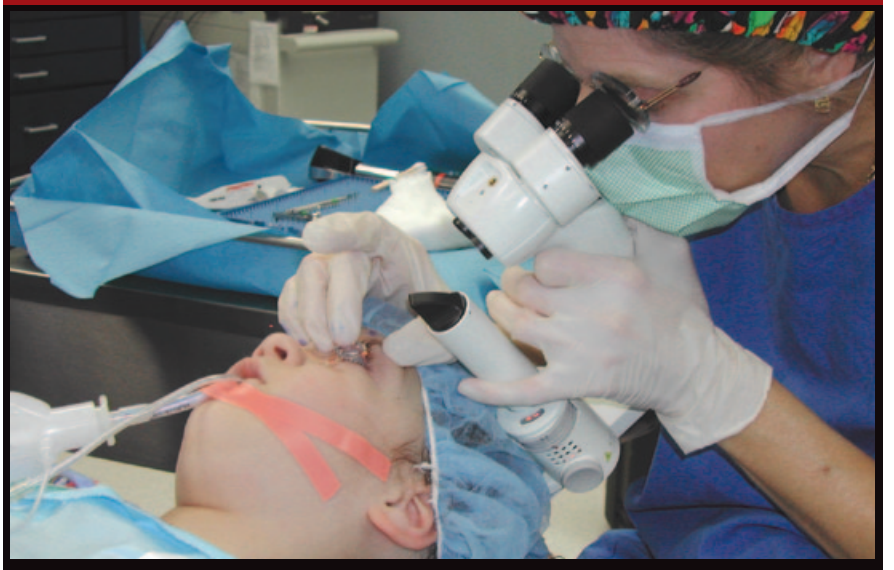
INTERVIEWING GEORGE S. ELLIS JR., MD, RANDALL P. FLICK, MD, MPH, AND CONSTANCE S. HOUCK, MD

In recent years, anesthesiology journals have been replete with articles about anesthetic neurotoxicity in young children, broadcasting an urgent need for research into the potential risks. Most of the work has been done in young animals and shows a correlation between exposure to anesthetic agents during periods of rapid brain growth and brain cell death or learning problems. Yet a crucial question remains: Is general anesthesia harming children's brain development?

"This issue first became a real concern in 2003," said Constance S. Houck, MD, associate professor of anaesthesia at Harvard Medical School and chairperson of the American Academy of Pediatrics section on anesthesiology and pain medicine. That is when research in *Journal of Neuroscience* showed not only widespread neurodegeneration in the developing rat brain after six hours of exposure to anesthesia but also persistent learning and memory deficits into adolescence and adulthood.[1] "We didn't think this was happening in children because we weren't seeing any deficits. With appropriate anesthesia, kids go to sleep and appear to wake up just fine." But even though the animal research now gives us reason for concern, forgoing anesthesia isn't an option, Dr. Houck said. She added, however, that if further research does link exposure to anesthesia to long-term neurologic problems, decisions to perform surgery will become extremely challenging because most young children who receive anesthesia need the surgery.

Exam Under Anesthesia



The pediatric ophthalmologist performs gonioscopy using a handheld slit lamp and a Koeppe gonioscopy lens during examination under anesthesia.

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Some Research Raises Concerns

An association with learning disability in human subjects. Since 2009, a series of epidemiologic studies has linked exposure to anesthesia at a young age to the development of learning disabilities. The first study, reported by Mayo Clinic researchers who examined the records of more than 5,000 children, found an association between a child's having received two or more exposures to anesthesia before age 4 and the development of learning deficits by age 18.[2] In another U.S. study, researchers conducted a retrospective cohort analysis of children who had received anesthesia during hernia repair before the age of 3 and found that the children exposed to anesthesia were more than twice as likely to be subsequently diagnosed with a developmental or behavioral disorder than were controls.[3]

No association found in other studies. Elsewhere in the literature, two European studies did not find an association between anesthesia exposure and neurologic problems.[4,5] Randall P. Flick, MD, MPH, chairman of pediatric anesthesiology and associate professor of anesthesiology at the Mayo Clinic in Rochester, Minn., explained the apparent discrepancies among the

studies. "The studies published so far show a fairly consistent pattern. Those that looked at single exposures to anesthesia or could not determine the number of exposures do *not* find an association. Studies that do differentiate between single and multiple exposures *do* tend to find an association."

Confounding factor: overall health. Most human studies have examined whether children with or without learning disabilities had been exposed to anesthesia at a young age. The inherent weakness of these studies is that they typically infer a child's exposure to anesthesia during surgery but provide no information on the type of anesthetic or duration of exposure. Dr. Flick noted that the studies also do not indicate whether the learning deficits were coincidental, in that children who need repeated and/or lengthy surgeries are typically less healthy than children who have not undergone these operations. As a result, a child's overall health status—not the anesthetic exposure—may be a significant contributor to the learning deficit.

However, the most recent Mayo study stands out because it controlled for health status yet still found an association.[6] The strength of this study also arises from the researchers' full access to the medical and school records of each child. "We looked at children under age 2 in a matched-cohort design that controlled for characteristics that we know affect the likelihood of developing learning disabilities, such as gestational age, gender and maternal education, as well as health status," Dr. Flick said. "We found that multiple exposures to anesthesia prior to age 2 are associated with a near doubling of the incidence of learning disability. Together, the Mayo studies suggest a dose response: The more cumulative general anesthetic exposure a child has, the more likely he or she is to have a learning disability recognized later in life."

Injectable agents also implicated. Dr. Flick noted that human studies to date are based on inhalation anesthetics and that this may create the misconception that the injectable agents more commonly used in pediatric ophthalmology today have not been implicated. But that is not the case, he said. "Virtually all the anesthetic and sedative agents we use (including benzodiazepines, propofol/barbiturates, nitrous oxide, all volatile agents, ketamine and etomidate) come from two classes of drugs, and the animal data clearly implicate both classes."

Dangers are unproven. Dr. Flick urged caution when interpreting the human studies, which represent retrospective research based on large epidemiologic databases. "We have to put together a lot more information from numerous studies using different methodologies to answer the causality question. We're not there yet."

And research continues. In fact, at time of press, the *AJO* published a prospective, observational study of 21 children, aged 5 to 10, who underwent strabismus surgery and were under general anesthesia for a mean of 51.3 minutes. The authors tested complex cortical function before and four weeks after surgery and found no significant difference that could be attributed to exposure to the anesthesia.[7] (See Journal Highlights, page 24.)

At this point, said Dr. Flick, "There is no direct evidence that anesthetics are unsafe for children." In fact, the FDA convened an advisory panel in March 2011 that concluded that the evidence was insufficient to warrant advising a change in practice.[8]

The Surgeon's Considerations

In light of the unresolved questions surrounding the use of general anesthesia in young children, the surgeon may want to consider alternatives. Delaying a procedure until a child is older is one; switching to a regional or local anesthetic is another. Of course using regional or local anesthetics is not practical for many procedures, and most surgeries performed on young children should not be delayed.

Sooner is usually better. To get the best result, most procedures need to be performed as soon as the problem is diagnosed, said George S. Ellis Jr., MD, director of ophthalmology at Children's Hospital New Orleans and clinical associate professor of ophthalmology and pediatrics at Tulane and LSU Medical Schools. A child with infantile esotropia needs to have the eyes straightened before age 2 to have the best chance of fusion and before age 1 to have the best chance of stereoacuity. "Visually significant infantile cataracts need to be removed as soon as they are diagnosed to achieve the best result. Congenital cataracts—a real emergency—should be operated on and optically corrected before 3 to 4 months of age. Likewise, for infantile glaucoma," he added.

Consider delaying some surgeries. "But a few procedures, such as those for ocular dermoids, lacrimal obstruction and non–vision-threatening ptosis, sometimes can be delayed until after age 2." Dr. Ellis added that putting off these surgeries until a child is 2 or 3 may be an inconvenience for the child and family, but it is unlikely to pose a risk of damage to the eye. From the physician's standpoint, delaying procedures like these until the child is older presents minimal if any consequence. "We would need to follow the children more closely to be sure that there is no change for the worse, but it can be done," he said.

Dr. Ellis noted that the vast major-

How to Support Research Efforts

When asked how ophthalmologists can contribute to research, Dr. Houck suggested partnering with anesthesiologist colleagues on research projects and donating to SmartTots—Strategies for Mitigating Anesthesia-Related Neuro-Toxicity in Tots—a public-private partnership between the FDA and the International Anesthesia Research Society. The group coordinates and funds research intended to make surgery, anesthesia and sedation safer for infants and young children (www.smarttots.org).

ity of surgeries can be performed in less than one hour—and some in as little as 30 minutes by an experienced pediatric ophthalmologist. "Occasionally, the most complex cases can take two or three hours," he said, "but it's unusual for pediatric ophthalmology cases to last that long." Dr. Ellis said that, to date, "We know for sure that the visual benefits of early eye surgery exist," but, he went on to say, there is no clear-cut evidence indicating that the shorter anesthesia exposures more typical of surgery in pediatric ophthalmology cause brain damage in humans.

More Definitive Answers Are Expected

Several important studies of anesthesia in early childhood are under way, including a prospective study involving centers in Europe, the United States and Australia. This study is expected to generate results in three to five years, Dr. Flick said. "In the meantime, I think parents can be reassured that brief single exposures to anesthesia have not been associated with a problem—or at least we can't detect an association using the tests that we have been using."

1 Jevtovic-Todorovic V et al. *J Neurosci.* 2003;23(3):876-882.
2 Wilder RT et al. *Anesthesiology.* 2009; 110(4):796-804.
3 DiMaggio C et al. *J Neurosurg Anesthesiol.* 2009;21(4):286-291.
4 Bartels M et al. *Twin Res Hum Genet.* 2009;12(3):246-253.
5 Hansen TG et al. *Anesthesiology.* 2011; 114(5):1076-1085.
6 Flick RP et al. *Pediatrics.* 2011;128(5): e1053-e1061.
7 Yang HK et al. *Am J Ophthalmol.* 2012; 153(4):In press.
8 FDA Minutes, Meeting of the Anesthetic and Life Support Drugs Advisory Committee, March 10, 2011. Available at www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM251283.pdf

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