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Important Questions Remain on the Effects of Anesthetics on Neurodevelopment in Infants

Initial data from a clinical trial of the effects of a short exposure to anesthesia on cognitive development in children under 6 months of age is encouraging, but important questions remain.

Preliminary information from the clinical trial, *General Anesthesia Compared to Spinal Anesthesia* (the GAS Study), found that children who had undergone either general anesthesia or regional anesthesia in a surgical procedure lasting less than 1 hour showed no difference in cognitive development at the 2-year timepoint. However, the primary endpoint of cognitive development -- performance on a test of intelligence at age 5 --may be more sensitive for detecting adverse changes. It is important not to draw definitive conclusions until this evaluation is complete, because animal data suggest that if a problem were to occur, changes might not be evident at age 2.

The GAS Study is an international, randomized controlled trial being conducted at 28 hospitals in 7 countries. Between February 2007 and January 2013, 722 children less than 6 months old needing hernia repair surgery were randomly assigned to receive awake-regional anesthesia or sevoflurane-based general anesthesia. Two-year outcome data were available for 532 children, with about half in each group. Cognitive development was measured at age 2 using a widely accepted standardized test, the composite cognitive score of the Bayley Scales of Infant and Toddler Development III. The children in the general anesthesia group were exposed to anesthesia for an average of 54 minutes. The primary outcome of the GAS Study will be performance on a test of intelligence at age 5, and may be able to detect changes not present at age 2.

Exposure of young animals to inhaled anesthetics and many sedative drugs commonly used in children has been shown to consistently produce injury to the developing brain with behavioral changes, depending on the dose of anesthetic and the duration of exposure. It is unknown whether these drugs have similar effects on the developing brain in humans. Preliminary outcomes from the GAS Study are consistent with most of the animal data and epidemiological studies, which suggest a single short duration exposure may not be harmful. Although this is encouraging, it is too soon to say with certainty that a single short duration exposure is safe.

The GAS study will provide important information about exposure to anesthetics lasting up to one hour. However, there are many questions that cannot be answered by the GAS study such as:

- Brain function is very complex and cannot be fully measured with a single cognitive test. How does exposure to anesthetics affect the development of other important functions such as memory, language, motor skills, and emotional development?
- Sevoflurane is only one of the drugs used in general anesthesia. Do other commonly used drugs produce similar results?
- Many procedures require a combination of two or more anesthetics. Do the effects change when drugs are combined?
- Different medical procedures may combine with anesthetics to produce other outcomes. Are the results the same for procedures other than hernia repair?

- Much brain development occurs throughout childhood. What are the effects of exposure to anesthetics in subsequent months or years?
- Animal and epidemiological data suggest that the risk of anesthetics to the developing brain increases with longer duration exposure or multiple exposures. Is this true for children?

Establishing cause and effect relationships in biology is a complex process that requires collecting and interpreting multiple pieces of evidence. Studies that produce definitive answers are rare. Randomized control trials like the GAS Study generate data that add important pieces to the puzzle and are helpful in bringing investigators closer to an answer. However, more research is needed before any definitive conclusions can be drawn.

It is not yet possible to know whether anesthetic drugs are safe for children in a single short-duration procedure. Similarly, it is not yet possible to know whether use of these drugs poses a risk, and if so, whether the risk is large enough to outweigh the benefit of needed surgery, tests, or other procedures. Until further research clarifies the significance of these findings, parents and caregivers should discuss the timing of planned procedures with their child's healthcare providers. Concerns regarding the unknown risk of anesthetic exposure to the child's brain development must be weighed against the potential harm associated with cancelling or delaying a needed procedure. Each child must be evaluated individually based on age, the type of procedure, level of urgency, and other health factors. Your child's healthcare providers are best able to give this advice.

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