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What parents should know about the use of general anesthesia in toddlers

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Following a recent FDA warning about anesthesia for children younger than 3, Adriana Barton explores why Canadian hospital officials say parents have little to fear

Children's hospitals across Canada are advising parents not to delay necessary surgeries out of fears raised by a U.S. Food and Drug Administration warning that repeated or lengthy exposure to general anesthesia may harm brain development in children under 3.

The FDA warning, issued in December, has drawn criticism from doctors who say it is based on inconclusive data and may cause undue alarm among parents of children who must undergo general anesthesia.

"Right now, there is really no strong evidence that we should delay surgeries because of the anesthetic risk," said Dr. Jason Maynes, director of research in anesthesia and pain medicine at the Hospital for Sick Children in Toronto, Canada's largest pediatric hospital.

Findings from two major Canadian studies, both published in 2016, show no increased risk of learning or behavioural problems in infants and toddlers exposed to general anesthesia.

The FDA warning emphasized that a single, short exposure (for surgeries such as the insertion of ear tubes or the treatment of dental decay) "is unlikely to have negative effects on behaviour or learning." But in studies of young or pregnant animals, the use of general anesthetics and sedatives for more than three hours "caused widespread loss of nerve cells in the brain" and long-term cognitive deficits, the warning said.

In the United States, the safety announcement will result in a warning label on 11 common general anesthetics and sedatives.

Health Canada is conducting its own review of general anesthesia and sedation in children under the age of 3 and pregnant women in their third trimester. In a statement to The Globe and Mail, the department underlined the "uncertainty" of the science in this area. "There have been no clinically confirmed cases of anesthetic-induced behaviour or learning difficulties in children reported in Canada," it said.

Here's what parents need to know about general anesthesia and why its effects on a child's developing brain remain unclear.

Kids and anesthesia

Doctors refer to general anesthesia as "sleep" to avoid upsetting patients. But general anesthesia alters brainwave activity and is best described as a "reversible, drug-induced coma," according to a 2010 paper in the New England Journal of Medicine (NEJM).

Each year across Canada, an estimated 46,000 children under the age of 5 have day surgery under general anesthesia (the figure excludes the numbers in Quebec, which are unavailable).

In Canadian preschoolers, the most common procedures requiring general anesthesia are dental surgeries for tooth decay, followed by surgeries to insert ear tubes and tonsil removal. These surgeries typically last an hour or less.

Surgeries that last more than an hour are uncommon for young children. They include heart, bowel or brain surgeries and complex orthopedic procedures. In some cases, surgeries in the lower half of the body can be done using a spinal anesthetic instead of general anesthesia. But otherwise there are no alternatives for children younger than 3.

The evidence

The long-term effects of anesthetics are difficult to study because it would be unethical to deny surgery to a group of children and then compare their development to that of children who had undergone surgery under general anesthesia. Much of the available research consists of animal studies and observational studies in children, which may find associations between drug exposure and neurological problems but cannot confirm cause and effect.

Studies in rodents and small monkeys show that, under experimental conditions, general anesthesia kills brain cells and causes long-lasting cognitive deficits.

But results in animal studies do not necessarily apply to humans, said Maynes of SickKids. Lab animals have different physiologies and may be at different developmental stages than an infant or toddler. Animal studies often use six-day-old mice, he said, but "nobody knows what that corresponds to in a human."

Moreover, caged animals lack the kind of mental and physical stimulation a child would have. In a 2012 study, researchers from the University of California, San Francisco, found that providing rats with an "enriched environment" – ramps, running wheels, tunnels and toys – seemed to reverse the neurological effects of anesthesia.

Measuring cognitive effects in children is more difficult because of the complex variables involved. Healthy children do not normally need lengthy or repeated surgeries under general anesthesia, noted an opinion paper published last month in the NEJM. For example, the brains of children born with congenital heart disease may be damaged by inflammation or oxygen deprivation before the children undergo surgery.

The paper implied that the FDA warning was premature because it came ahead of new evidence expected this year from two well-designed clinical trials. Among them is a Mayo Clinic study measuring neurological outcomes in children who have not had general anesthesia, those with a single anesthetic exposure and those with multiple exposures.

"We are concerned that the FDA warning will cause delays for necessary surgical and diagnostic procedures that require anesthesia, resulting in adverse outcomes for patients," the NEJM authors wrote.

New Canadian data

Maynes questioned whether the FDA considered new evidence from the two major Canadian studies. The largest, published in August, 2016, and co-authored by Maynes, involved 84,276 children in Ontario, of which 28,366 had undergone general anesthesia before entering kindergarten.

To flag potential neurological effects, researchers used results from the Early Development Instrument (EDI), a short questionnaire completed by kindergarten teachers across Canada. The study found that children who had undergone general anesthesia before the age of 2 – the most vulnerable period for brain development – showed no developmental delays compared with those with no exposure to the drugs. Children exposed to general anesthetics after the age of 2 had a slightly increased risk of delays. But the magnitude of the risk was small, Maynes said, and "not of practical significance."

A separate 2016 study of 18,056 Manitoba children also found no link between anesthesia and developmental delays in children before the age of 2, based on results from EDI assessments. In children who had undergone general anesthesia between the ages of 2 and 4, however, single and multiple anesthetic exposures were associated with decreases in EDI scores. But these delays may have had non-drug causes. The authors cited previous research showing that socially disadvantaged children are more likely to require surgical interventions and also more likely to have lower EDI scores independent of surgery.

Dr. Michael Rieder, chair of the drug therapy committee of the Canadian Paediatric Society, noted that while the FDA reviewed a range of studies on general anesthesia among children, "some of those may not be applicable to Canada." He added: "Our Canadian data, to date, is reassuring."

The FDA's stand

Asked whether the FDA warning considered data from the two recent Canadian studies, an FDA spokesperson outlined the limitations of observational studies. Compared with tightly controlled clinical trials, observational studies have a higher potential for bias in selecting participants and less ability to evaluate non-drug factors in study results. Moreover, observational studies have tended to include different durations of anesthesia exposure, different drugs and different age groups, making it difficult to draw conclusions. The recent Canadian studies are "subject to many of these limitations," the FDA spokesperson wrote in a statement to The Globe.

The FDA warning was based "substantially" on the weight of evidence accumulated from animal studies, the statement said. While children do not generally undergo surgeries unless they are essential to their health, the FDA said, in some cases "it may be possible to delay some procedures."

Hospitals weigh in

At BC Children's Hospital in Vancouver, Dr. Norbert Froese, head of pediatric anesthesia, noted that the FDA warning has increased awareness of potential risks among the general public. But, he said in a statement, "[it] does not add additional information to the understanding of this issue."

BC Children's approach "is to work together with the family to discuss the risks of anesthesia as much as they are known, along with the benefits of the proposed procedure or diagnostic test, to determine the best way forward for each child," Froese wrote.

Alberta Children's Hospital in Calgary has no specific policy regarding the use of anesthesia, said a spokesperson with Alberta Health Services. However, the region's pediatric anesthesia departments are aligned with consensus statements from the Canadian Pediatric Anesthesia Society and SmartTots, an FDA-endorsed research project aimed at mitigating the risks of anesthesia use for children. Both urge health-care professionals and parents to discuss the risks, benefits and timing of any treatment.

In Toronto, SickKids has created a policy statement to address concerns about general anesthesia, Maynes said. In conversations with parents, surgical teams explain that all surgery involving young children is undertaken after extensive discussion about the medical need for the procedure. "We would never put a child under anesthetics for a procedure that they don't absolutely need."

Doctors explain the risks of general anesthesia – which include respiratory depression, short-term amnesia, nausea and vomiting – as well as the risks of delaying surgery. "Likely, the impact of delaying surgery is far more significant than any effect of the anesthetic on neurodevelopment," Maynes said.

The policy has been in place for almost two years, he added. "We haven't changed anything as a result of the FDA warning."