Treatments to reduce anesthesia-induced injury in children show promise in animal studies

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Recent clinical studies have shown that general anesthesia can be harmful to infants, presenting a dilemma for both doctors and parents. But new research at Wake Forest Baptist Medical Center may point the way to treatment options that protect very young children against the adverse effects of anesthesia.

As detailed in a study published in the March 23 online edition of the journal *Neuroscience*, Wake Forest Baptist scientists explored a number of strategies designed to prevent anesthesia-induced damage to the brain in infants.

Using an animal model, the researchers tested the effectiveness of a fragment of a neuroprotective protein called ADNP, as well as vitamin D3, a low-level dose of anesthetic and aspirin. They found that three of the four strategies tested protected the brain from injury induced by 20 mg ketamine, a commonly used general anesthetic.

"What didn't work was aspirin, which was a surprise because aspirin is known to protect the brain from injury," said Christopher P. Turner, Ph.D., assistant professor of neurobiology and anatomy at Wake Forest Baptist and lead author of the study. "In fact, in our study aspirin actually increased the severity of injury from the anesthesia, possibly because it prevents the generation of substances that may be neuroprotective."

Turner and his team studied rats at ages equivalent to children from birth to age 4.

In separate tests, the rodents were injected with: NAP, a peptide fragment of activity-dependent neuroprotective protein (ADNP), 15 minutes before ketamine was administered; two 20-mg doses of vitamin D3, at 24 hours and at 15 minutes before 20 mg ketamine; a non-toxic (5 mg) doses of ketamine 24 hours before a toxic dose of 20 mg ketamine was administered; and a 30-mg dose of aspirin 15 minutes before exposure to ketamine.

The Turner lab found that NAP, vitamin D3 and prior exposure to low (non-toxic) ketamine could all prevent injury from exposure to a toxic (20 mg) level of ketamine. However, aspirin appeared to enhance ketamine-induced injury.

"We designed our studies to give doctors several possible treatment options because not all of these strategies may work in clinical applications," Turner said. "However, because vitamin D3 is already in clinical use, our findings show that it is quite promising with few risks. Further, NAP is currently in clinical trials to diminish the severity of other types of brain injury, so we feel this discovery represents a breakthrough for anesthesia-induced neurotoxicity. However, there may be a critical window of efficacy for NAP, which we need to explore further.

"Of all the approaches that our team studied, using a low dose of ketamine may be both the simplest and most cost-effective, as it suggests children can be pre-treated with the same anesthesia that will be used when they undergo general surgery," Turner added. "In essence, a low-level dose of ketamine primes the child's brain so that the second, higher dose is not as lethal, much like an inoculation."