Medical Xpress

Do excess fluids cause brain injuries in children with diabetic ketoacidosis?

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For decades, clinicians have worried that giving too much intravenous fluid to children with diabetic ketoacidosis (DKA) may contribute to brain swelling and injury, and even death. Now, after a national study that examined more than a thousand patients with DKA, UC Davis researchers and their colleagues from around the country have shown that fluid infusion does not cause brain injury in children with DKA.

The study is published in the June 14, 2018 issue of the *New England Journal of Medicine* (*NEJM*).

"For three decades, we have been giving children too little fluids because we've been taught that fluids cause brain injuries in children with DKA," said Nathan Kuppermann, distinguished professor and chair of emergency medicine and first author on the paper. "It's not about the fluid, it's about something else. It's time we started looking beyond fluids and addressing the other factors that are important."

When insulin is in short supply, cells cannot take in sugar for energy. As a result, the body begins breaking down fat and muscle, releasing fatty acids and generating ketones—the process that causes DKA. The condition is a serious complication of diabetes and can be fatal if not promptly addressed.

In the 1980s, clinicians noticed that children who had suffered brain swelling during DKA had received what appeared to be more fluids than children who had not had this life-threatening complication. They

hypothesized that the infused intravenous fluids were generating brain swelling and became more cautious when administering these fluids.

Kuppermann and his wife and research partner Nicole Glaser began working on the problem nearly 20 years ago. They noted that early research did not control for the severity of the children's conditions when assessing the impact of fluid therapy during cases of brain injury/swelling.

"The severity of dehydration in the child is strongly linked to the risk of brain injury," said Glaser, professor of pediatrics and senior author on the paper. "Of course, kids who are more dehydrated, receive more fluids. You can erroneously make the conclusion that fluids are causing the brain swelling, when it's just a reflection of the fact that children who are sickest and have the greatest dehydration are the ones at greatest risk."

In a paper published in *NEJM* in 2001, Glaser, Kuppermann and colleagues showed it was unlikely that fluids were causing brain injury. However, because it wasn't a randomized prospective study—long considered the gold standard for clinical research—the findings did little to change fluid management choices among clinicians.

The research study described in the current paper takes a more robust approach. Conducted at 13 centers over six years as part of the nationwide Pediatric Emergency Care Applied Research Network (PECARN), the team assessed how fluid administration and other factors influenced neurological outcomes in 1,389 childhood DKA cases. The study was divided into four arms, separating patients by rate of infusion and salinity of fluids.

Statistically, there were no significant differences between any of the groups. While kids who received fluids more rapidly had a lower

frequency of brain injuries, these results were not statistically significant. In a subset of cases—the children who were most severely ill (i.e. most acidotic) - rapid fluids did offer statistical improvements in some brain function measures.

Kuppermann and Glaser feel the findings will now enable clinicians to more comfortably use their best professional judgment in fluid management for pediatric patients with DKA.

"We don't consider this a license to give fluids inappropriately," said Kuppermann, who also is a professor of pediatrics. "But it does allow clinicians to give children the fluids they need clinically rather than inappropriately withholding fluids. If they're dehydrated, give them fluids without fear."

Though they are pleased to have delineated the lack of relationship between fluids and neurological damage from DKA, Kuppermann and Glaser want to better understand the true causes. They hope to build on previous research that showed abnormal blood flow to the brain, combined with inflammatory proteins, may be a primary culprit in neurological damage.

"Now we want to stop thinking about fluids, and we're really going after what we think is the pathologic mechanism that's causing brain injury," said Glaser. "These studies might point us towards treating patients with anti-inflammatory medications to protect the brain."

Provided by UC Davis