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NHLBI Stops Enrollment in Study of Concentrated Saline for Patients with Traumatic Brain Injury

The National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health has stopped enrollment into a clinical trial testing the effects of highly concentrated (hypertonic) saline solutions on patients with severe traumatic brain injury (TBI) when given as soon as possible after the injury – that is, before the patient arrives at the hospital or emergency room. After reviewing data on more than 1,000 participants, the study's monitoring board and the NHLBI determined that the hypertonic saline solutions were no better than the standard treatment of normal saline and that it is unlikely that continuing to enroll new patients would change the outcome of the study. There were no concerns about safety. Previously enrolled participants who have not yet completed their six month follow-up visits will continue to be monitored according to the study design.

The TBI study is the largest randomized clinical trial ever conducted in this severely injured patient population. It is one of two clinical trials on the use of hypertonic saline for trauma being conducted by a network of clinical research sites in the United States and Canada called the Resuscitation Outcomes Consortium (ROC). In March, the NHLBI stopped a parallel study of hypertonic saline in trauma patients who went into shock due to severe bleeding because the highly concentrated saline solutions did not improve survival compared to standard saline solution.

Typically, in the crucial early minutes before blood transfusions can be safely administered in the hospital, trauma patients receive normal saline solution intravenously in the field to compensate for blood loss and to buy time. Compared to normal saline, concentrated saline solution was believed to compensate for blood loss more effectively, lessen excessive inflammatory responses, and prevent brain swelling.

"Improving treatment and survival of traumatic injury are critical public health problems," said Elizabeth G. Nabel, M.D., director of the NHLBI, the lead federal sponsor of the research effort. "While these study results did not show the expected benefit of one type of treatment, other findings by the resuscitation consortium researchers -- and the hundreds of emergency and fire services teams they are working with -- may lead to new life-saving intervention strategies."

In the ROC hypertonic saline trials, patients were randomly selected to receive intravenously a solution of about 8 ounces of normal saline, which has nearly the same concentration of salt as blood and is considered standard care; hypertonic saline, which has a higher salt concentration; or hypertonic saline with dextran, a carbohydrate which can prolong the effect of the hypertonic saline.

The TBI trial tests whether the hypertonic solutions improve brain function in severely injured patients as measured 6 months after injury, compared to usual care with normal saline. The study also compares the effects of the saline solutions on survival.

"Although hypertonic saline solutions showed promise for improving outcomes when used as quickly as possible after trauma, our findings do not support any significant benefit of hypertonic saline over standard saline in patients with either traumatic brain injury or shock from excessive bleeding," said David Hoyt, M.D., University of California, Irvine, a co-principal investigator of the ROC hypertonic saline studies and ROC vice chair for trauma. "Although these findings are disappointing, they nonetheless provide major contributions to our understanding of emergency medical care."

The NHLBI stopped enrollment in the TBI study based on a recommendation by the independent Data and Safety Monitoring Board (DSMB) that monitors ROC studies. The DSMB reviewed an interim analysis of data on 1,073 patients who had been followed for six months – about half of the total number of patients the researchers had planned to enroll. They found no differences in the benefits or risks of either of the two hypertonic saline solutions compared to normal saline. In addition, there was no evidence that either of the hypertonic saline solutions was harmful to these patients.

The DSMB is an independent group appointed by and reporting to the NHLBI. To ensure patient safety during the study, the DSMB reviews the accrued data approximately every six months, or more frequently if needed. The ROC DSMB includes experts in trauma, cardiac arrest, statistics, ethics, and the conduct of clinical trials.

Prior animal and smaller human studies suggested that using a highly concentrated saline solution might improve survival or reduce brain injury in these patients. This fluid is currently approved and used in 14 European countries and has a strong safety record based on previous clinical trials and reported use in Europe. Other evidence has also suggested that hypertonic saline may improve survival when given as early as possible after injury.

However, as announced on March 26, 2009, researchers in the ROC hypertonic saline for shock study found no difference in 28-day mortality between patients who received one of the hypertonic saline solutions and those who received normal saline. The NHLBI stopped the hypertonic saline for shock study upon recommendation of the DSMB based on analyses of the interim data that showed that deaths occurred earlier in patients who received hypertonic saline compared to those who received normal saline, but there was no significant difference in cumulative mortality between the hypertonic and normal saline groups at 28 days.

Data analyses of six-month follow-up of participants in the hypertonic saline for TBI study do not show such a trend toward earlier deaths among patients receiving hypertonic saline compared to those receiving normal saline. The investigators are completing analyses of the results from both hypertonic saline studies and will submit them for publication in a peer-reviewed scientific journal.

ROC is a clinical research network consisting of 10 clinical centers in the United States and Canada focusing on treating patients with life-threatening traumatic injury or cardiac arrest. The research is typically conducted in real-world settings, where patients collapse or are critically injured, before

they reach the hospital. Participating EMS providers give standard emergency care to all patients, with some patients randomly selected to receive the experimental treatment in addition to usual care.

"The Resuscitation Outcomes Consortium is the largest research network to study real-world, pre-hospital interventions for cardiopulmonary arrest and traumatic injury leading to arrest," noted George Sopko, M.D., program director in the NHLBI Division of Cardiovascular Science. "By conducting these studies through such a robust network, we can compare clinical interventions in meaningful ways and disseminate the results as quickly as possible, thus saving resources and providing information of immediate benefit to patients."

The clinical trials are conducted under strict FDA and Canadian guidelines that allow for patients in life-threatening situations to participate in research under an exception to informed consent, according to U.S. and Canadian laws.

In addition to clinical trials, ROC has established the world's largest data registry of prehospital cardiac arrest and life-threatening trauma, which will enable researchers to identify best practices to improve resuscitation success. To date, more than 60,000 cardiac arrest patients and 14,000 trauma patients have been enrolled.

The NHLBI is the lead sponsor of the ROC studies, and additional funding is provided by the NIH's National Institute of Neurological Disorders and Stroke, the Institute of Circulatory and Respiratory Health of the Canadian Institutes of Health Research, US Army Medical Research & Materiel Command, American Heart Association, Defence Research and Development Canada, and the Heart and Stroke Foundation of Canada.

To interview an NHLBI spokesperson, contact the NHLBI Communications Office at 301-496-4236 or at nhlbi news@nhlbi.nih.gov. To interview Dr. Hoyt, contact John Murray/Tom Vasich at 714-456-7759.

More information:

- Resuscitation Outcomes Consortium, https://roc.uwctc.org/tiki/tiki-index.php.
- The NHLBI Halts Study of Concentrated Saline for Patients with Shock due to Lack of Survival Benefit, http://public.nhlbi.nih.gov/newsroom/home/GetPressRelease.aspx?id=2632
- Traumatic Brain Injury, http://www.ninds.nih.gov/disorders/tbi/detail_tbi.htm

Part of the National Institutes of Health, the National Heart, Lung, and Blood Institute (NHLBI) plans, conducts, and supports research related to the causes, prevention, diagnosis, and treatment of heart, blood vessel, lung, and blood diseases; and sleep disorders. The Institute also administers national health education campaigns on women and heart disease, healthy weight for children, and other topics. NHLBI press releases and other materials are available online at: www.nhlbi.nih.gov.

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