

Clinical pathology selected abstracts

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A clinical trial evaluating tranexamic acid in children with traumatic injury

December 2022—Tranexamic acid is an antifibrinolytic drug that improves survival in adults with traumatic hemorrhage. To the authors' knowledge, it has not been evaluated in a trial of injured children. Because trauma is the leading cause of death and disability in children in the United States and long-term outcomes are related to the degree of hemorrhage, stopping hemorrhaging quickly may reduce the number of interventions, complications, and disabilities and improve recovery times in children. Tranexamic acid (TXA) blocks plasmin-mediated fibrin clot breakdown and attenuates bleeding in the surgical setting. Although the efficacy and safety of the drug have not been proven in children, TXA is routinely administered to severely injured children in the United Kingdom and Europe. The authors performed a pilot trial to assess the ability to identify children with severe hemorrhagic injuries and enroll them in a trial evaluating two doses of TXA and a placebo. The pilot trial was designed to determine the feasibility of a large-scale phase-three efficacy trial of the drug. Thirty-one children ranging from newborn to 18 years of age (mean age, 10.7 years) were entered into a double-blind randomized trial in which they received a TXA 15-mg/kg bolus dose followed by a 2-mg/kg per hour infusion over eight hours, or a TXA 30-mg/kg bolus dose followed by a 4-mg/kg per hour infusion over eight hours, or a normal saline placebo bolus and infusion. The trial was performed at four U.S. pediatric level-one trauma centers between June 2018 and March 2020. When parents were unable to provide consent, children were enrolled under the federal exception from informed consent (EPIC) procedures. The target annual enrollment rate was 1.25 patients per site per month. Feasibility outcomes included the rate of enrollment, adherence to intervention arms, and ability to measure the primary clinical outcome. Clinical outcomes included global functioning, working memory, total amount of blood products transfused, intracranial hemorrhage progression, and adverse events. The mean time from injury to randomization was 2.4 hours. Sixteen patients had isolated brain injuries and 15 had isolated torso injuries. The enrollment rate was 1.34 patients per site. All eligible enrolled patients received a study intervention and had the primary outcome measured. The authors found no statistically significant differences in clinical outcomes based on the type of intervention. They concluded that, based on enrollment rate, protocol adherence, and measurement of the primary outcome, a larger scale randomized trial evaluating the safety and efficacy of TXA in severely injured children is feasible. The authors noted that use of EPIC consent procedures would be critical to the trial's success since more than 70 percent of patients were enrolled using such procedures.

Nishijima DK, VanBuren JM, Linakis SW, et al. Traumatic injury clinical trial evaluating tranexamic acid in children (TIC-TOC): A pilot randomized trial. *Acad Emerg Med*. 2022;29:862-873.

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Link between HDL cholesterol and cardiovascular outcomes in high-risk populations

High-density lipoprotein cholesterol levels have been inversely associated with an increased risk of cardiovascular disease. Investigators have begun to question the effectiveness of therapies designed to increase HDL cholesterol levels, such as cholesteryl ester transfer protein inhibition, in reducing the disease. Some recent epidemiological studies involving populations that are free of cardiovascular disease have linked exceedingly high levels of HDL cholesterol with higher mortality risk. The authors conducted a study to investigate the association between HDL cholesterol levels and outcomes in patients with coronary artery disease (CAD). They hypothesized that very high HDL cholesterol levels would be associated with greater mortality risk in people with CAD and that some people may be genetically predisposed to such risk. The primary outcome for the study was all-cause death, and the secondary outcome was cardiovascular disease death. The authors assessed HDL cholesterol levels greater than

80 mg/dL relative to mortality in patients with CAD. They also investigated the relationship between HDL cholesterol genotypes and higher HDL cholesterol levels. The prospective multicenter cohort study, which began in 2006 in the United Kingdom and 2003 in Atlanta, was ongoing at the time the authors published their findings. The authors conducted their data analyses from May 10, 2020 to April 28, 2021. The study enrolled 14,478 participants from the UK Biobank (median follow-up, 8.9 years) and 5,467 participants from the Emory Cardiovascular Biobank (median follow-up, 6.7 years). The investigators observed a U-shaped association, with higher risk linked to low and very high HDL cholesterol levels compared with mid-range values. Exceedingly high HDL cholesterol levels, when compared with HDL cholesterol levels of 40 to 60 mg/dL, were associated with increased risk of all-cause and cardiovascular disease death. Even after adjusting for the HDL cholesterol genetic risk score, the associations were present. It is important to note that the associations were independent from the common polymorphisms linked to higher HDL cholesterol levels. The authors concluded that HDL cholesterol levels greater than 80 mg/dL are associated with higher risk of all-cause and cardiovascular disease death in people with CAD. They noted that these findings impact risk prediction and future therapies. Researchers need to further investigate the link between exceedingly high HDL cholesterol levels and all-cause outcomes.

Liu C, Dhindsa D, Almuwaqqat Z, et al. Association between high-density lipoprotein cholesterol levels and adverse cardiovascular outcomes in high-risk populations. *JAMA Cardiol.* 2022;7(7):672-680.

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