Tranexamic Acid in Elective Craniosynostosis Surgery

It Works, but How?

In this issue of Anesthesiology, Dadure et al. and Goobie et al. separately present two prospective, randomized, and blinded studies using tranexamic acid (TXA) in elective craniosynostosis surgery patients. The goal was to study intravascular adjuncts to surgical hemostasis. These are important articles. Although there are some differences in design, dosing, and duration between the studies, they are remarkably similar. The strengths of these articles are their international perspective; prospective, randomized, and blinded design; and lack of influence from industry. Weaknesses include the single-center design, small numbers, and a lack of standard resuscitation protocols. The strengths are cause for celebration, whereas the weaknesses make one pause and consider the generalizability of these impressive positive results. However, any intervention evaluated in a prospective, randomized, blinded fashion that decreases blood loss (17 and 45%) or erythrocyte transfusion (57–66%) deserves serious attention.

As we well know, every additional unit of blood products transfused carries an additional and cumulative risk, and decreased blood loss results in decreased transfusion of blood products. The former is hard to measure accurately, but the latter is not and is the most important outcome from the vast majority of bleeding studies. Conversely, operative blood loss not requiring transfusion is largely of little clinical significance. The clinically important endpoint (transfusion reduction) must be considered a reasonable endpoint in trials leading toward new indications for hemostatic drugs and devices.

Several issues require comment. Without mortality, intensive care unit, or hospital day differences, the economic implications of the studies are limited to the very real cost savings of blood products and the infrequent but huge costs of infectious and/or immune complications. Interestingly, in the Dadure et al. study the single operating surgeon did not subjectively notice any difference between the two groups. This important observation suggests that coagulopathic (fibrinolytic) bleeding was not different or at least noticeable between the two groups after treatment with the study drug. Because the decrease in blood loss–transfusion was profound, why wasn’t a clinical difference noticed? Both studies report relatively large urine outputs (8–11 ml/kg), suggesting excessive crystalloid (50 ml/kg), albumin (23 ml/kg), and hydroxyethyl starch (10 ml/kg) resuscitation. This in and of itself might drive blood loss from an iatrogenic fibrinolytic state, thus setting the stage for an antifibrinolytic agent to decrease blood loss. Perhaps we should just give less crystalloid and artificial colloids. There were significant differences in volume (from 7.2 to 56 ml/kg) of total erythrocyte transfusions between centers, pointing to the huge variability in resuscitation practices between centers. This may be attributed to the varying age and weight of the patients, surgeon variability, and non-erythrocyte transfusion practices, including but not limited to use of human albumin, plasma, platelets, cryoprecipitate, artificial colloid, large-volume crystalloid, and various erythrocyte transfusion triggers. All these issues point to the need for evidence-based versus tradition-guided resuscitation protocols.

Many Questions Remain

1. What is the optimal dose of TXA? Is the bolus or continuous method superior? Should TXA be continued postoperatively? For how long? The answers remain to be elucidated in future studies.

2. What is the effect of nonstandardized transfusion protocols in these types of studies? If the endpoint of these studies is transfused units, then all aspects of infusion and transfusion must be standardized.

3. Why did some patients have large effects and others minimal to none?

4. It is unfortunate that more sophisticated measurements of fibrinolysis were not measured. Future studies should examine these values. Why did the thromboelastogram values not change between groups if the mechanism of action is really as an antifibrinolytic agent? Bolliger et al. suggested that thromboelastometry may not be sensitive enough to measure clinically important fibrinolysis.

The last question leads me to wonder whether we really know how TXA works. The randomized CRASH-2 study in 20,000 trauma patients showed a difference in survival without a decrease in erythrocyte units transfused. The Goobie et al. study shows a decrease in transfused erythrocytes of 40%, but reveals no evidence of fibrinolysis on the thromboelastograms. Finally, in these three randomized trials, there were no apparent safety issues, whereas other studies have noted increased seizure rates.

Nevertheless, hemostasis studies such as the two published in this volume of Anesthesiology are extremely important, and the authors are to be congratulated. Level I data

driving transfusion practices have been lacking for the past 100 yr. It seems that finally attention (by industry, Department of Defense, National Institutes of Health, regulators, and clinicians) is being paid to this most critical area of research, and rational, evidence-based practices are beginning to emerge. Based on these results, TXA likely will become used more and more often in both elective and emergency bleeding situations.

John B. Holcomb, M.D., F.A.C.S., Division of Acute Care Surgery, Center for Translational Injury Research, University of Texas Health Science Center, Houston, Texas, john.holcomb@uth.tmc.edu

References


