

Reducing Blood Losses and Transfusion Requirements in Craniosynostosis Surgery: An Endless Quest?

To the Editor:

We read with great interest the recent papers and the joint editorial reporting intraoperative tranexamic acid use in craniosynostosis surgical repair,^{1,2,3} and we do agree with Holcomb's point of view: "It works, but how?" and in whom? In our pediatric craniofacial surgical center we, as many others involved in craniosynostosis surgical management, are still facing two problems that could be finally considered incompatible: uncompressible large blood losses proportional to suture involvement and surgical techniques, that remain difficult to precisely evaluate,⁴ and limited total blood volume in low-weight children. Reducing blood losses and transfusion requirements has been a major issue in the past 20 yr with active research on development of minimally invasive surgical techniques,⁵ autologous transfusion methods,⁶ and adjunctive medical treatments. Eliminating the need for intraoperative homologous blood transfusion could be considered as the final goal of these attempts, but remains, in daily practice, an inaccessible dream in malformations with multiple sutures, requiring complex surgical procedures. It could be only considered as a reasonable objective in children with scaphocephaly, requiring simple linear craniotomies.

To be relevant, clinical studies have some prerequisites. The first one is the need for a valuable evaluation of perioperative blood losses, based upon calculation of estimated erythrocyte volume lost, that was used by Goobie *et al.*, after others,^{1,4,6} but not by Dadure *et al.* The second one is a need for strict hemodilution guidelines with commonly defined transfusion thresholds, eliminating the biases related to overhydration with inadequate fluid loading⁷ and underestimation of minimally required hemoglobin level. These issues are illustrated in the two papers that both concluded that tranexamic acid could reduce the need for blood transfusion. In Goobie *et al.*'s study, hematocrit threshold for blood transfusion was 30% (estimated hemoglobin 9 to 10 g/dl), all children were finally transfused, and calculated blood losses were significantly reduced with tranexamic acid. In Dadure *et al.*'s study, hemoglobin threshold was 7g/dl, 63% of the children did not have transfusions, and even though blood losses, which were not really estimated, did not differ between the two groups, the questioning conclusion was that tranexamic acid did decrease the need for transfusion. It could be concluded by readers either that tranexamic acid 50 mg/kg could reduce blood transfusion requirement by the

means of reduced preoperative blood losses, or that tranexamic acid 15 mg/kg reduces blood transfusion requirement but not blood losses by the means of an unknown mechanism in children with acute normovolemic hemodilution. Despite well-designed, double-blinded, randomized studies, the authors should be aware that important issues for determining the efficiency of a medical treatment are the homogeneity of the study population, the size of the sample, and the reproducibility of the protocol in clinical practice. Both these studies included around 40 patients, with various surgical conditions ranging from severe syndromic faciosynostosis to simple scaphocephaly, and requiring various types of procedures. It has been previously clearly demonstrated that the type of malformation and the type of resulting surgical procedure is the main determinant of preoperative blood losses.⁴ Including, in a small sample of patients, numerous subgroups requiring various surgical managements could significantly attenuate the statistical power of a study. It could be therefore more efficient to further determine the benefit of tranexamic acid in a large, homogenous series of patients with simple suture involvement, the population who may most benefit from efficient adjunctive techniques to reduce intraoperative blood losses in craniosynostosis surgical repair. Finally, as underlined by Holcomb, an important question remains unanswered: If tranexamic acid could be efficient to reduce intraoperative blood losses and transfusion requirements in infants, how does it work?

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The author of the original editorial, Dr. Holcomb, did not feel a reply to this letter was necessary.—James C. Eisenach, M.D., Editor-in-Chief

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In Reply:

We thank Vergnaud *et al.* for their interest in our publication.¹ We partly agree with them concerning the difference of blood loss in function of type of craniofacial malformation. Effectively, cranial malformation with multiple suture involvement requiring complex surgery has a lot of risk of substantial bleeding and transfusion requirements.² Nevertheless, surgery for multiple suture malformation is less common and, in our study, both groups were comparable concerning the type of malformations. The number of patients included in our study is low, but it relates statistically to the answer of our primary hypothesis. Sample-size calculation was evaluated by our institutional biostatistics department from the previous study of Helfaer *et al.*³ We agree again that our results concerning blood loss are slightly different from Goobie's, but we used a lower tranexamic acid initial bolus. This probably explains the nonsignificant difference between our two groups. Goobie *et al.*⁴ used calculation of estimated erythrocyte volume lost to evaluate the intraoperative blood losses. Nevertheless, with strict hemodilution guidelines and the regular hematocrit measurements used in our study,¹ the evaluation of blood losses measured from surgical aspiration and weighing surgical sponges is a surrogate of erythrocyte volume losses. Moreover, concerning the transfusion threshold, in the study of Goobie *et al.*,⁴ the hematocrit threshold for packed erythrocytes transfusion was 25% and not 30% (estimated hemoglobin 7 to 8 g/dl), close to the threshold that we used in our study (hemoglobin: 7 g/dl).

We again thank Vergnaud *et al.* for their interest in our publication and we encourage them to realize other studies with large homogenous series of children in this field to determine the real benefit of tranexamic acid: to limit transfusion requirements in major pediatric craniofacial surgery.

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In Reply:

We appreciate the interest of Meyer *et al.* in our article and thank them for their thoughtful comments. We would like to respond to each comment individually.

We agree with Meyer and the editorial viewpoint by Holcomb that tranexamic acid (TXA) "works, but how? ... and in whom?"¹ The goal of our study was to investigate the efficacy of TXA in craniostomosis surgery in a defined group of children at our institution. Therefore, we determined that "it works" in our patient population of children aged 6 months to 6 yr having craniostomosis reconstruction surgery. We agree that the exact mechanism of action is not fully understood and requires further research.

We agree with Meyer *et al.* in their statement that "to be relevant, clinical studies" need to have "a valuable evaluation of perioperative blood losses" (as they point out, we used calculated blood loss instead of the estimated blood loss, which is inaccurate) and "need for strict hemodilution guidelines." Indeed, we performed strict hemodilution in our study and administered conservative volumes of crystalloids/colloids to maintain safe and stable mean arterial blood pressure of 45 mmHg or greater without using medication for pressure support. As pointed out by Meyer *et al.*, there tends to be rapid and substantial blood loss during craniostomosis surgery that can lead to persistent hypotension, permanent neurologic impairment, cardiac arrest, and death.² Our standard intraoperative approach for treating rapid blood loss is similar to that reported in the literature and by Meyer's own institution: "Isovolemic compensation of blood loss was strictly observed with fluid replacement based upon hemodynamic variables (to maintain mean arterial blood pressure in range of 45-55 mmHg) using colloid and blood transfusion."^{3,4}

We disagree with Meyer *et al.* for characterizing our study as including "acute normovolemic hemodilution," which is defined as "an autologous blood collection technique involving removal of blood from a patient on the day of surgery shortly before surgical blood loss."⁵ Our study did not include this technique.

In our study, the hematocrit threshold for blood transfusion was not 30%, as Meyer *et al.* suggest. It was 25% (hemoglobin of approximately 8g/dl), as stated on page 863 in the Materials and Methods section.⁶

It is true that all our patients required transfusion intraoperatively; however, we concluded that TXA significantly reduced the volume of packed erythrocytes transfused by a mean value of 32%. In addition, TXA significantly reduced the calculated blood loss by a mean value of 38% intraoper-