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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 craniosynostosis 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 craniosynostosis 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 craniosynostosis 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-

atively and 72% during the first 24 h after surgery. Furthermore, none of the children in the TXA group required blood transfusion in the first 24 h postoperatively, whereas 50% who did not receive TXA required transfusion. TXA administration significantly diminished (by two-thirds) the exposure of patients to transfused blood compared to placebo (medians: 1 unit *vs.* 3 units, $P < 0.001$).

We do not concur with the conclusions *Meyer et al.* drew by comparing two study doses of different trial designs. Our study used TXA alone, and Dadure *et al.* used a combination of TXA and pretreatment with erythropoietin.[7,6]

Meyer *et al.* have misread our study; we did not include "faciosynostosis," nor did our patient population require "various types of procedures." Our patient collective had major reconstruction surgeries that involved fronto-orbital advancement and cranial vault reconstruction with an average of 70 ± 18% of the entire skull bone undergoing reconstructive surgery. The procedures were performed by the same pediatric neurosurgeon and one of two plastic surgeons.

Meyer *et al.*'s statement that "including, in a small sample of patients, numerous subgroups requiring various surgical managements could significantly attenuate the power of a study" is not relevant to our study. We are not sure to which "subgroups" or which "various surgical managements" they are referring. Our randomized controlled trial simply consisted of craniosynostosis patients requiring major craniofacial reconstructive surgery.

We agree with Meyer *et al.* that the type of surgical procedure is an important predictor of blood loss. However, it is not the only major determinant, as it is well known that certain high-risk groups, such as those with recognized craniofacial syndromes, pansynostosis, operating time greater than 5 h, and age of 18 months or younger at the time of the procedure, have significantly greater blood loss during craniosynostosis repair.[8] Furthermore, our study and other studies support the fact that there is an inverse relationship between the child's age and the amount of blood loss and transfusion requirements during craniosynostosis reconstructive surgery.[6,8–10] Blood loss during craniosynostosis surgery may seem to be disproportionately greater in infants (less than 10 kg) than older children because the head represents a larger percentage of total body surface area.[11] These high-risk groups in particular may benefit from TXA.

We agree with Meyer *et al.* that a large-scale study is needed to verify the findings of studies with small sample sizes. This will require multicenter collaboration. However, we disagree that the patients who would benefit most are those with "simple suture involvement," because all craniosynostosis patients would surely benefit from "efficient adjunctive techniques to reduce intraoperative blood loss."

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# Puzzling ENIGMA: Cost-Benefit Analysis of Nitrous Oxide

*To the Editor:*

I read with interest the article by Graham *et al.*[1] In this study the authors performed a retrospective cost-analysis of data from the ENIGMA trial, in which patients randomly received nitrous oxide nitrous oxide-based anesthesia (70% $N_2O$ and 30% $O_2$) or nitrous oxide-free anesthesia (80% $O_2$ and 20% $N_2$). The authors concluded, "Despite nitrous oxide reducing the consumption of more expensive potent inhalational agent, there were marked additional costs associated with its use in adult patients undergoing major surgery because of an increased rate of complications. There is no cogent argument to continue using nitrous oxide on the basis that it is an inexpensive drug."

It is interesting that in this cost-analysis the authors neglected to include one of the benefits of nitrous oxide: anal-