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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References

1. Holcomb JB: Tranexamic acid in elective craniosynostosis surgery: It works, but how? Anesthesiology 2011; 114:737–8
2. Czerwinski M, Hopper RA, Gruss J, Fearon JA: Major morbidity and mortality rates in craniofacial surgery: An analysis of 8101 major procedures. Plast Reconstr Surg 2010; 126:181–6
3. Dahmani S, Orliaguet GA, Meyer PG, Blanot S, Renier D, Carli PA: Perioperative blood salvage during surgical correction of craniosynostosis in infants. Br J Anaesth 2000; 85:550–5
4. Meyer P, Renier D, Arnaud E, Jarreau MM, Charron B, Buy E, Buisson C, Barrier G: Blood loss during repair of craniosynostosis. Br J Anaesth 1993; 71:854–7
5. Monk TG, Goodnough LT, Brecher ME, Colberg JW, Andriole GL, Catalona WJ: A prospective randomized comparison of three blood conservation strategies for radical prostatectomy. Anesthesiology 1999; 91:24–33
6. Goobie SM, Meier PM, Pereira LM, McGowan FX, Prescilla RP, Scharp LA, Rogers GF, Proctor MR, Meara JG, Soriano SG, Zurakowski D, Sethna NF: Efficacy of tranexamic acid in pediatric craniosynostosis surgery: A double-blind, placebo-controlled trial. Anesthesiology 2011; 114:862–71
7. Dadure C, Sauter M, Bringuier S, Bigorre M, Raux O, Rochette A, Canaud N, Capdevila X: Intraoperative tranexamic acid reduces blood transfusion in children undergoing craniosynostosis surgery: A randomized double-blind study. Anesthesiology 2011; 114:856–61
8. White N, Marcus R, Dover S, Solanki G, Nishikawa H, Millar C, Carver ED: Predictors of blood loss in fronto-orbital advancement and remodeling. J Craniofac Surg 2009; 20:378–81
9. Stricker PA, Shaw TL, Desouza DG, Hernandez SV, Bartlett SP, Friedman DF, Sesok-Pizzini DA, Jobes DR: Blood loss, replacement, and associated morbidity in infants and children undergoing craniofacial surgery. Paediatr Anaesth 2010; 20:150–9
10. Faberowski LW, Black S, Mickle JP: Blood loss and transfusion practice in the perioperative management of craniosynostosis repair. J Neurosurg Anesthesiol 1999; 11:167–72
11. Livingston EH, Lee S: Percentage of burned body surface area determination in obese and nonobese patients. J Surg Res 2000; 91:106–10

(Accepted for publication November 9, 2011.)

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-

gesia. In fact, in another study, again from a retrospective analysis of the ENIGMA trial data,[2] the same authors reported that intraoperative administration of nitrous oxide reduced the risk of chronic postsurgical pain by more than half. The authors also found that chronic postsurgical pain was common after major noncardiac surgery. The authors state, "The presence of chronic postsurgical pain cannot be considered as a trivial event. Our data indicate that it affects all dimensions of general health status, including social function, physical activities, emotion, and mental health. Chronic postsurgical pain also has a major impact on patients' daily living, including loss of productivity, an increase in medical expenses, and costs of repeated hospital admissions."

It is highly likely that a cost-benefit analysis that includes the benefits of nitrous oxide (*i.e.*, reduced chronic postsurgical pain) may tilt the balance toward nitrous oxide. I think the authors may have rushed to conclude that nitrous oxide has no role in modern anesthetic practice. Unfortunately, such selective reporting may inappropriately dissuade anesthesia practitioners from using nitrous oxide and deprive our patients from some potential long-term benefits from its use.

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References

1. Graham AM, Myles PS, Leslie K, Chan MT, Paech MJ, Peyton P, El Dawlatly AA: A cost-benefit analysis of the ENIGMA trial. Anesthesiology 2011; 115:265–72
2. Chan MT, Wan AC, Gin T, Leslie K, Myles PS: Chronic postsurgical pain after nitrous oxide anesthesia. Pain 2011; 152: 2514–20

(Accepted for publication November 21, 2011.)

In Reply:

We appreciate the interest Joshi has taken in our *post hoc* studies of the ENIGMA trial.[1] As we stated in our article, we measured costs from the perspective of an implementing hospital. We did not consider postdischarge costs. The results of the persistent pain study, conducted at one of the institutions involved in the multicenter ENIGMA trial, was not anticipated and had not yet undergone peer review at the time of publication of the cost-benefit study. It should thus be considered as hypothesis-generating rather than as compelling evidence of a protective effect of nitrous oxide. When considered alongside the results of the ENIGMA trial it is possible that nitrous oxide may have adverse effects in the short-term (infection, cardiac events), but if the patient survives these, then nitrous oxide may be beneficial (for pain).

We must emphasize that at no point have we stated that nitrous oxide has no role in modern anesthetic practice. We have previously concluded that the routine use of nitrous oxide in patients undergoing major surgery should be questioned, and that there is no cogent argument to continue using nitrous oxide on the basis that it is an inexpensive drug. We have emphasized that further studies are needed, and are now measuring long-term pain data in such a trial of 7,000 patients that is currently underway.[2]

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References

1. Graham AM, Myles PS, Leslie K, Chan MT, Paech MJ, Peyton P, El Dawlatly AA: A cost-benefit analysis of the ENIGMA trial. Anesthesiology 2011; 115:265–72
2. Myles PS, Leslie K, Peyton P, Paech M, Forbes A, Chan MT, Sessler D, Devereaux PJ, Silbert BS, Jamrozik K, Beattie S, Badner N, Tomlinson J, Wallace S, ANZCA Trials Group. Nitrous oxide and perioperative cardiac morbidity (ENIGMA-II) trial: Rationale and design. Am Heart J 2009; 157:488.e1–94.e1

(Accepted for publication November 21, 2011.)

Intranasal Application of Xenon: A Shortcut to the Brain or Just a Longer Way to It through the Lungs?

To the Editor:

Intranasal application of low-dose xenon has recently been reported to have beneficial effects on perioperative analgesia in patients undergoing abdominal hysterectomy.[1] This is a novel route of xenon application that could help to circumvent the problem of its high cost and allow wider use of this gaseous anesthetic. However, we have several concerns regarding the pharmacokinetics and route of action of intranasally applied xenon suggested by the authors.

As shown by blood gas analysis undertaken by the authors in two healthy volunteers, a steady-state concentration of approximately 500 nl/ml xenon was reached in the blood of the internal jugular vein (IJV) within 10 min after commencement of intranasal delivery of xenon at 1 l/h. Simultaneously, as stated by the authors, samples of peripheral venous blood were ≤20 nl/ml xenon. The authors consider the concentration of xenon in the IJV to be a reflection of xenon content in cranial blood and target brain tissue.

Here, as well as in their previous work,[2] the authors advocate a direct delivery route of xenon from the nose to brain that is supposedly accountable for the beneficial effects of xenon on pain. Although it is not clearly explained in their article, the authors previously suggested that xenon could reach brain tissue by diffusion from the venous sinuses of the cranial cavity.[2]

A portion of nasal venous blood is indeed diverted to intracranial veins *via* direct communication between the ophthalmic veins, pterygoid plexus, and cavernous sinus, but the other portion of blood is drained extracranially by facial