

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.

Girish P. Joshi, M.B., B.S., M.D., F.F.A.R.C.S.I., University of Texas Southwestern Medical Center, Dallas, Texas. girish.joshi@utsouthwestern.edu

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 ques-

tioned, 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

Paul S. Myles, M.B., B.S., M.P.H., M.D., F.A.N.Z.C.A.,* the ENIGMA Trial Investigators. *Alfred Hospital, Melbourne, Australia. p.myles@alfred.org.au

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