

This access also implied a blind needle advancing behind clavicular bone.

There are no statistically reliable data on the real rate of displacement of catheters in the supraclavicular brachial plexus. The 40% rate mentioned (Hauritz *et al.*<sup>5</sup>) exclusively referred to sciatic nerve approach, but our report speaks of ultrasound-guided access to the brachial plexus. On the other hand, Heil *et al.*<sup>6</sup> reported a study in 10 healthy volunteers in whom access was different from the one we propose (supraclavicular tip, supraclavicular access), rendering it difficult to make comparisons. In addition, a large part of the literature analyzes displacement rates based on degrees of pain in high VAS, according to the authors, and only during the first 24 h: when indicated, a catheter for continuous block is usually necessary for a longer time. In any case, the lowest published rate of displacement is not less than 10%. In our center, after more than 8 yr of experience and a large sample of cases with the described technique (infraclavicular entry point, supraclavicular tip), the rate of displacement during the first 3 days is close to 8%.

We do not propose this new technique with the intention of changing regional anesthesia practice, but we believe that the accumulated experience and the good results obtained make it at least advisable to share this knowledge with our colleagues.

### Competing Interests

The authors declare no competing interests.

**Carles García-Vitoria, M.D., Ana María López Navarro, M.D., Ph.D.** Hospital Intermutual de Levante, Valencia, Spain. carlesgvitoria@gmail.com

### References

1. García-Vitoria C, Vizuete J, López Navarro AM, Bosch M: Costoclavicular space: A reliable gate for continuous regional anesthesia catheter insertion. *ANESTHESIOLOGY* 2017; 127:712
2. Jeng CL, Rosenblatt MA: Considerations when performing ultrasound-guided supraclavicular perineural catheter placement. *J Ultrasound Med* 2011; 30:423–4
3. Perlas A, Lobo G, Lo N, Brull R, Chan VW, Karkhanis R: Ultrasound-guided supraclavicular block: Outcome of 510 consecutive cases. *Reg Anesth Pain Med* 2009; 34:171–6
4. Charbonneau J, Fréchette Y, Sansoucy Y, Echave P: The ultrasound-guided retroclavicular block: A prospective feasibility study. *Reg Anesth Pain Med* 2015; 40:605–9
5. Hauritz RW, Pedersen EM, Linde FS, Kibak K, Børghlum J, Bjoern S, Bendtsen TF: Displacement of popliteal sciatic nerve catheters after major foot and ankle surgery: A randomized controlled double-blinded magnetic resonance imaging study. *Br J Anaesth* 2016; 117:220–7
6. Heil JW, Ilfeld BM, Loland VJ, Mariano ER: Preliminary experience with a novel ultrasound-guided supraclavicular perineural catheter insertion technique for perioperative analgesia of the upper extremity. *J Ultrasound Med* 2010; 29:1481–5

(Accepted for publication March 8, 2018.)

## Nitrous Oxide and Decreased White Matter Integrity and Volume during Childhood

*To the Editor:*

The article by Block *et al.*<sup>1</sup> reports that 94% of teenagers with broadly distributed, decreased white matter integrity and volume on magnetic resonance imaging of their brains inhaled nitrous oxide for over an hour during surgery and anesthesia in their first year of life. A manuscript cited by Block *et al.* reports that 88% of children between the ages of 5 and 18 yr with lower gray matter density in the occipital cortex and cerebellum inhaled nitrous oxide during surgery and anesthesia before their fourth birthday.<sup>2</sup> Nitrous oxide is the only inhalational anesthetic that causes demyelination, cerebral atrophy, and loss of developmental milestones in a susceptible child after use in clinical concentrations and durations.<sup>3</sup> One hour of nitrous oxide administration is sufficient to inactivate methionine synthase by oxidation of cobalt in its vitamin B<sub>12</sub> cofactor.<sup>4</sup> Up to 20% of infants and children in North America express one or more alleles that impair the activity of enzymes in single carbon pathways in which methionine synthase is the pivotal participant.<sup>4</sup> Up to 25% of infants and children before the age of 10 yr are deficient in vitamin B<sub>12</sub> with levels less than 148 pmol/l.<sup>5</sup> Accordingly, up to 5% of infants have *both* an inborn and an acquired deficiency of vitamin B<sub>12</sub> at the time they are anesthetized with nitrous oxide. The incidence of both inborn and acquired deficiencies of vitamin B<sub>12</sub> are far greater in children living in Latin America, Africa, and Asia.<sup>6</sup> In children with all but extreme phenotypes, vitamin B<sub>12</sub> deficiency may be asymptomatic and undiagnosed before surgery. Not surprisingly, use of nitrous oxide for anesthetic maintenance has declined markedly in the United States and Europe in recent years.<sup>7</sup>

In view of their findings and the facts above, do Block *et al.* presently recommend use of nitrous oxide for anesthetic maintenance in infants having procedures lasting an hour or longer? If not, what is the relevance of the author's findings to contemporary pediatric anesthesia practice in which anesthetic maintenance with nitrous oxide is diminished? Is it not timely to reassure parents that at least one inhaled anesthetic associated with white and gray matter damage in susceptible children is no longer in widespread use?

### Competing Interests

The author declares no competing interests.

**Kirk Hogan, M.D., J.D.,** University of Wisconsin, Madison, Wisconsin. khogan@wisc.edu

### References

1. Block RI, Magnotta VA, Bayman EO, Choi JY, Thomas JJ, Kimble KK: Are anesthesia and surgery during infancy associated with decreased white matter integrity and volume during childhood? *ANESTHESIOLOGY* 2017; 127:788–99

2. Backeljauw B, Holland SK, Altaye M, Loepke AW: Cognition and brain structure following early childhood surgery with anesthesia. *Pediatrics* 2015; 136:e1–12
3. Selzer RR, Rosenblatt DS, Laxova R, Hogan K: Adverse effect of nitrous oxide in a child with 5,10-methylenetetrahydrofolate reductase deficiency. *N Engl J Med* 2003; 349:45–50
4. Sanders RD, Weimann J, Maze M: Biologic effects of nitrous oxide: A mechanistic and toxicologic review. *ANESTHESIOLOGY* 2008; 109:707–22
5. Monsen AL, Refsum H, Markestad T, Ueland PM: Cobalamin status and its biochemical markers methylmalonic acid and homocysteine in different age groups from 4 days to 19 years. *Clin Chem* 2003; 49:2067–75
6. Green R, Allen LH, Bjorke-Monsen AL, Brito A, Gueant JL, Miller JW, Molloy AM, Stabler S, Toh BH, Ueland PM, Yajnik C: Vitamin B12 deficiency. *Nat Rev Dis Primers* 2017; 3:1–19
7. Sessler DI: Nitrous oxide is an effective and safe anesthetic. *Turk J Anaesthesiol Reanim* 2017; 45:1–2

(Accepted for publication March 9, 2018.)

#### *In Reply:*

We thank Dr. Hogan for his interest in our article<sup>1</sup> and for offering his interpretation of our findings. He is correct that 94% of our subjects exposed to general anesthesia received nitrous oxide. However, the duration of nitrous oxide exposure was variable and often brief. During the time that our cohort of subjects underwent their surgical procedures as infants, it was a common and prevailing practice at our study site to use nitrous oxide during induction only and discontinue it during maintenance. All subjects who received nitrous oxide also received one or more other anesthetics during their surgery. Therefore, our study findings cannot be attributed to the effect of nitrous oxide alone. Although we accept Hogan's statement that nitrous oxide may inactivate methionine synthase, the only evidence that he cites that nitrous oxide causes demyelination, cerebral atrophy, and loss of developmental milestones is his own case report of a single child with 5,10-methylenetetrahydrofolate reductase deficiency.<sup>2</sup>

The relevance of our study to contemporary pediatric anesthesia practice is that anesthetics have been shown to have

neurotoxic effects in neonatal animals and pertinent human evidence is limited. Therefore, we sought to probe the long-term effects of anesthetic agents in a structural neuroimaging study. We emphasized that, although our findings may be related to anesthesia and surgery during infancy, other explanations are possible. Our study sought to examine brain structure years after anesthetic exposure. Although this approach provides important information, one limitation is that anesthetic practices change over the years, so that, for maximal value, this approach needs to be combined with other approaches, including shorter-term follow-up as well as longitudinal studies. Our findings provide no basis to recommend for or against use of nitrous oxide when providing anesthesia for infants undergoing surgery, nor to reassure parents about contemporary anesthesia safety based on changes in anesthetics used in clinical practice. At present, we believe that individual pediatric anesthesiologists should decide whether to use nitrous oxide based on current evidence and their own clinical judgment of risks and benefits. Finally, we think that Hogan's belief that nitrous oxide use is associated with neurotoxicity in young children merits further evaluation.

#### Competing Interests

The authors declare no competing interests.

**Robert I. Block, Ph.D., Vincent A. Magnotta, Ph.D., Emine O. Bayman, Ph.D., James Y. Choi, M.D., Joss J. Thomas, M.D., Karolie K. Kimble, R.N., B.A.** Roy J. and Lucille A. Carver College of Medicine, University of Iowa, Iowa City, Iowa (R.I.B.). robert-block@uiowa.edu

#### References

1. Block RI, Magnotta VA, Bayman EO, Choi JY, Thomas JJ, Kimble KK: Are anesthesia and surgery during infancy associated with decreased white matter integrity and volume during childhood? *ANESTHESIOLOGY* 2017; 127:788–99
2. Selzer RR, Rosenblatt DS, Laxova R, Hogan K: Adverse effect of nitrous oxide in a child with 5,10-methylenetetrahydrofolate reductase deficiency. *N Engl J Med* 2003; 349:45–50

(Accepted for publication March 9, 2018.)