



Impact of ENIGMA trials on nitrous oxide: a survey of Canadian anesthesiologists and residents

Davinder Jain, MD · Heung Kan Ma, MD · Norman Buckley, MD, FRCPC

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To the Editor,

Nitrous oxide (N₂O) has been part of anesthetic practice for almost 200 years. However, administration of the gas has declined dramatically over the last decade, perhaps because of an incidental finding of the N₂O in the gas mixture for anesthesia (ENIGMA) trial.¹ The ENIGMA trial results suggested a possible association between N₂O use and cardiac morbidity following non-cardiac surgery (adjusted odds ratio, 1.59; 95% confidence interval [CI], 1.01 to 2.51). The ENIGMA trial was not designed or adequately powered to detect a difference in cardiac events and was criticized for having different inspired oxygen levels in the N₂O and control groups. These concerns were specifically addressed in a follow-up trial (ENIGMA-II) that found no significant difference in cardiac events (relative risk, 0.96; 95% CI 0.83 to 1.12).² The roles of these two studies in affecting practice and reasons for abandoning N₂O were raised at one of our regular “Journal Club” discussions.

The purpose of this survey was to identify the current views on N₂O among practicing anesthesiologists and trainees. Because there appeared to have been a decline in the use of N₂O following ENIGMA, we specifically questioned the roles the ENIGMA and ENIGMA-II trials played in shaping practice. This study was approved by the Hamilton Integrated Research Ethics Board on 7 November 2016.

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D. Jain, MD (✉) · H. K. Ma, MD · N. Buckley, MD, FRCPC
Department of Anesthesia, McMaster University, Hamilton, ON,
Canada
e-mail: davinder.jain@medportal.ca

We developed an 11-item English-language questionnaire to collect demographics of respondents and perceptions of N₂O as an anesthetic gas through various time periods between ENIGMA and ENIGMA-II (see the Electronic Supplementary Material for the instrument and full results). This survey was distributed through the Canadian Anesthesiologists' Society mailing list of anesthesiologists and trainees across the country.

We received 383 responses to our survey with 365 of 1785 (20%) anesthesiologists and 16 of 634 (3%) residents. Of those responding, 330 of 383 (86%) completed their anesthesia training in Canada and 366 of 382 (95%) practiced anesthesia a minimum of two to three times per week (Table 1).

Although prone to recall bias, ENIGMA appeared to have decreased the frequency of clinical N₂O use. There was no resurgence of N₂O use following publication of ENIGMA-II although it was a large, international trial. A total of 310 of 380 (82%) felt that the results of ENIGMA-II led to no change in their N₂O usage. When asked, those who decreased or stopped using N₂O following ENIGMA reported diverse reasons with postoperative nausea and vomiting (PONV) ranked the highest with 169 responses. This was despite the fact that the risk was almost completely mitigated by PONV prophylaxis in ENIGMA-II.³ Other responses included N₂O being environmentally unfriendly (with an atmospheric lifetime of 114 years),⁴ being inferior to newer agents, and individuals being unconvinced of current evidence of safety. It is difficult to determine the extent that ENIGMA alone affected N₂O use but our survey suggests that the results of ENIGMA-II did not strongly modify clinical practice.

While 318 of 380 (84%) surveyed felt there was still a role for N₂O in anesthesia, it appears to be used infrequently. Only 121 of 381 (32%) respondents

Table 1 Current perceptions of N₂O

Survey question	Respondents (n = 383)	
	n	%
Frequency of N ₂ O use after ENIGMA-II		
Every day	63	16.5
2-3 times per week	58	15.2
Few times a month	62	16.3
Once a month	21	5.5
Few times a year	104	27.3
Never	73	19.2
N/A	0	0
Effect of ENIGMA-II on frequency of N ₂ O use		
Increase	32	8.4
Decrease	31	8.2
No change	310	81.6
N/A	7	1.8
Reasons if decreased or stopped use of N ₂ O since ENIGMA (choose all that apply)		
PONV risk	169	
Environmentally unfriendly	124	
Lack of institutional support	11	
Lack of experience	10	
Inferior to newer agents	87	
Not convinced of current evidence of safety	26	
Other	61	
Is there a current role for N ₂ O in anesthesia?		
Yes	318	83.7
No	62	16.3

ENIGMA = evaluation of nitrous oxide in the gas mixture for anesthesia; N₂O = nitrous oxide; PONV = postoperative nausea and vomiting

reported using N₂O two to three times per week or more often. Qualitatively, many referred to its usefulness in obstetric and pediatric populations, which were not specifically addressed in our survey. We believe that though N₂O usage has declined, it retains characteristics beneficial to patients and should remain in clinical practice. Our survey suggests that the previous association of N₂O and cardiovascular complications is unlikely to have been the only factor driving the clinical decision to decrease its usage.

Conflict of interest None declared.

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References

1. Myles PS, Leslie K, Chan MT, et al. Avoidance of nitrous oxide for patients undergoing major surgery: a randomized controlled trial. *Anesthesiology* 2007; 107: 221-31.
2. Myles PS, Leslie K, Chan MT, et al. The safety of addition of nitrous oxide to general anaesthesia in at-risk patients having major non-cardiac surgery (ENIGMA-II): a randomised, single-blind trial. *Lancet* 2014; 384: 1446-54.
3. Myles PS, Chan MT, Kasza J, et al. Severe nausea and vomiting in the evaluation of nitrous oxide in the gas mixture for anesthesia II trial. *Anesthesiology* 2016; 124: 1032-40.
4. Sulbaek Andersen MP, Nielsen OJ, Wallington TJ, Karpichev B, Sander SP. Assessing the impact on global climate from general anesthetic gases. *Anesth Analg* 2012; 114: 1081-5.