

# Perioperative outcome after nitrous oxide anaesthesia: an ENIGMA trial

MTV Chan \*, T Gin

## KEY MESSAGES

1. Nitrous oxide administration increased the rate of postoperative complications after major surgery, but was associated with lower rates of chronic postsurgical pain.
2. Anaesthesiologists should carefully consider the risk-benefit profile for each patient when opting to use nitrous oxide during anaesthesia.

Hong Kong Med J 2014;20(Suppl 3):S34-5

HHSRF project number: 02030051

MTV Chan \*, T Gin

Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Prince of Wales Hospital

\* Principal applicant and corresponding author: mtvchan@cuhk.edu.hk

Nitrous oxide is among the oldest anaesthetics that are still available. Since 1844, billions of patients have received it during surgery. It is a weak anaesthetic but provides substantial analgesia. Nonetheless, its disadvantages include postoperative nausea and vomiting, limiting the inspired oxygen concentration that can be used, and expansion of air spaces (such as pneumothorax). It also leads to other biochemical changes, including inhibition of methionine synthase and interference with folate metabolism. Despite advances in anaesthesia, there is no study with adequate power to inform anaesthetists on the benefits and safety of nitrous oxide.

The Evaluation of Nitrous oxide In the Gas Mixture of Anaesthesia (ENIGMA) Trial compared perioperative outcomes in patients who did or did not receive nitrous oxide anaesthesia.<sup>1</sup> In 2050 adult patients undergoing major non-cardiac surgery that lasted for >2 hours, nitrous oxide anaesthesia was associated with an increased 30-day risk of severe vomiting, wound infection, fever, pneumonia, and atelectasis (Table).<sup>1</sup> The higher rate of complications

markedly increased the financial burden associated with the use of nitrous oxide.<sup>2</sup>

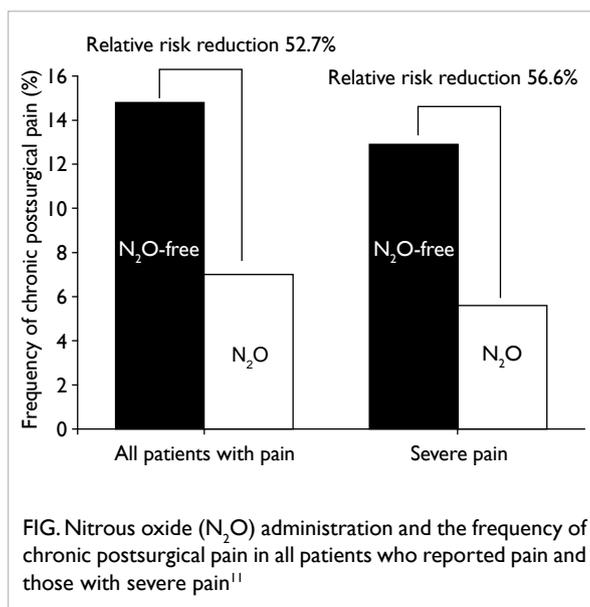
In a post-hoc analysis of the ENIGMA trial, even after adjusting for known risk factors, nitrous oxide was associated with a higher rate of severe postoperative nausea and vomiting (adjusted odds ratio [OR], 2.04; 95% confidence intervals [CI], 1.37-2.32;  $P < 0.0001$ ).<sup>3</sup> In a randomised controlled trial of patients having major colorectal resections, nitrous oxide exposure was associated with increased DNA damage in circulating leukocytes and postoperative wound infections.<sup>4</sup>

A follow-up study of the ENIGMA patients showed that nitrous oxide was associated with an increased long-term risk of myocardial infarction (adjusted OR, 1.59; 95% CI, 1.01-2.51;  $P = 0.04$ ).<sup>5</sup> This may be related to the inactivation of methionine synthase after nitrous oxide exposure, resulting in increased plasma homocysteine concentrations,<sup>6,7</sup> and subsequent endothelial dysfunction that can be inferred from a decrease in flow-mediated dilation of the brachial artery.<sup>8,9</sup> The exact relationship between nitrous oxide administration and perioperative cardiac morbidity and mortality may be revealed by the ENIGMA-II Trial, in which 7112 patients at risk of coronary artery disease have been randomised to receive 70% nitrous oxide or nitrous oxide-free anaesthesia with 30% oxygen in air. The primary outcome is a composite of death and major cardiovascular events within 30 days of surgery.<sup>10</sup>

The ENIGMA Trial also identified certain benefits of nitrous oxide anaesthesia. In a long-term follow-up study, 10.9% of the patients reported pain that persisted from the index surgery. Among them, 84.8% had severe pain warranting chronic pain medications, surgical or psychological interventions. Interestingly, nitrous oxide provided long-term analgesia (Fig).<sup>11</sup> In patients receiving nitrous oxide,

TABLE. Postoperative complications after nitrous oxide anaesthesia in 2010 adult patients undergoing major non-cardiac surgery<sup>1</sup>

Postoperative complication	Adjusted OR (95% CI)	P value
Severe nausea or vomiting	2.52 (1.95-3.24)	<0.001
Wound infection	1.40 (1.02-1.91)	0.036
Fever	1.36 (1.11-1.66)	0.003
Pneumonia	1.95 (1.03-3.68)	0.040
Atelectasis	1.83 (1.33-2.50)	<0.001
Myocardial infarction	1.74 (0.67-4.51)	0.260
Thromboembolism	0.63 (0.28-1.40)	0.250
Blood transfusion	1.05 (0.82-1.33)	0.710
Death within 30 days	3.06 (0.82-11.4)	0.096



this risk was reduced by >50% (adjusted OR, 0.48; 95% CI, 0.33-0.93; P=0.04). Although these findings need to be confirmed with further clinical studies, preventive analgesia with nitrous oxide has also been demonstrated in several animal pain models.

The ENIGMA Trial highlighted the risk of infection with nitrous oxide, but also demonstrated its potential role for preventive analgesia. When deciding whether to use nitrous oxide during anaesthesia, anaesthesiologists should consider the risk-benefit profile. In healthy patients undergoing clean surgery, nitrous oxide may be a simple means of preventing chronic postsurgical pain. In elderly patients undergoing surgery with contaminated wounds, avoiding nitrous oxide may improve postoperative outcomes.

## Acknowledgements

The ENIGMA Trial was supported in part by the Health and Health Services Research Fund, Food

and Health Bureau, Hong Kong SAR Government (#02030051) and a Direct Grant for Research, CUHK 2002.2.004 (Project code: 4450019). The results of this study were published in: 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.

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