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# ENIGMA-II, and can an old dog be taught new tricks?

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## Introduction

Nitrous oxide ($N_2O$) interferes with vitamin $B_{12}$ and folate metabolism. This impairs the production of methionine (from homocysteine), used to form tetrahydrofolate and thymidine during DNA synthesis. $N_2O$ increases postoperative homocysteine levels. Chronic hyperhomocysteinaemia is associated with cardiovascular disease, and we have demonstrated that $N_2O$ leads to postoperative endothelial dysfunction.[1]

In our previous trial, ENIGMA, 2 050 patients were studied, and some serious adverse effects identified,[2] but these were secondary end-points, and it has been argued that the differences in inspired oxygen concentration could explain some or all of the findings. In addition, most patients were not at risk of coronary artery disease, so we could not reliably assess serious cardiac complications.

We conducted an international, randomised, assessor-blinded trial in patients with known or suspected coronary artery disease undergoing major non-cardiac surgery.[3] Patients were randomly assigned to receive a general anaesthetic, with or without $N_2O$. The primary outcome measure was a composite of death and cardiovascular complications (non-fatal myocardial infarction, a stroke, pulmonary embolism or cardiac arrest) within 30 days of surgery. Secondary end-points included surgical site infection, severe nausea and vomiting, and hospital length of stay.

Of 10 102 eligible patients, 7 112 consenting patients were enrolled. Three thousand five hundred and forty-three were assigned to the $N_2O$ group and 3 569 to the non-$N_2O$ group. The primary outcome occurred in 283 (8.1%) patients in the $N_2O$ group and in 296 (8.4%) patients in the non-$N_2O$ group (relative risk 0.96, 95% confidence interval: 0.82-1.13; p-value 0.64). Surgical site infection occurred in 9.2% and 8.9% of patients (p-value 0.85), and severe nausea and vomiting in 15% and 11% of patients (p-value < 0.001) in the non-$N_2O$ and $N_2O$ groups, respectively. The median hospital length of stay was 6.1 days (interquartile range 3.3-10 days) in both groups (p-value 0.69). The outcomes are shown in Table I.

$N_2O$ did not increase the risk of death and cardiovascular complications or surgical site infection in patients undergoing major non-cardiac surgery. It is possible that $N_2O$ may reduce the risk of persistent pain after surgery.[4]

## References

1. Myles PS, Chan MTV, Kaye DM, et al. Effect of nitrous oxide anesthesia on plasma homocysteine and endothelial function. Anesthesiology. 2008;109(4):657-663.
2. Myles PS, Leslie K, Chan MTV, et al. Avoidance of nitrous oxide for patients undergoing major surgery: a randomized controlled trial. Anesthesiology. 2007;107(2):221-231.
3. Myles PS, Leslie K, Chan MTV, 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(9952):1446-1454.
4. Chan MTV, Wan ACM, Gin T, et al. Chronic postsurgical pain after nitrous oxide anesthesia. Pain. 2011;152(11):2514-2520.

**Table I:** ENIGMA-II outcomes

| Outcomes | $N_2O$, n (%) (n = 3 543) | Non-$N_2O$, n (%) (n = 3 569) | RR, n (%) (95% CI) | p-value |
|---|---|---|---|---|
| One-degree end-point: death, MI, a stroke, cardiac arrest or PE | 283 (8.1) | 296 (8.4) | 0.96 (0.82-1.13) | 0.64 |
| Death | 42 (1.2) | 57 (1.6) | 0.74 (0.50-1.11) | 0.14 |
| MI | 215 (6.2) | 219 (6.2) | 0.99 (0.82-1.19) | 0.91 |
| A stroke | 26 (0.7) | 19 (0.6) | 1.38 (0.76-2.49) | 0.29 |
| Cardiac arrest | 15 (0.4) | 19 (0.5) | 0.80 (0.40-1.56) | 0.51 |
| PE | 18 (0.5) | 22 (0.6) | 0.82 (0.4-1.53) | 0.54 |

CI: confidence interval, MI: myocardial infarction, $N_20$: nitrous oxide PE: pulmonary embolism, RR: relative risk