Nitrous oxide and perioperative cardiac morbidity (ENIGMA-II) Trial: Rationale and design

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Background Globally there are >200 million major surgical procedures undertaken annually, and about 20% of these involve patients who have coronary artery disease. Many receive nitrous oxide, which impairs methionine synthase, thus inhibiting folate synthesis and increasing postoperative homocysteine levels. Nitrous oxide anesthesia leads to postoperative endothelial dysfunction, and there is some evidence that it increases myocardial ischemia and, possibly, myocardial infarction. We have initiated the Nitrous oxide and perioperative cardiac morbidity (ENIGMA-II) Trial to test the hypothesis that in inpatients undergoing anesthesia for major noncardiac surgery, avoidance of nitrous oxide will reduce the incidence of death and major cardiovascular events.

Methods ENIGMA-II is a 7,000-patient, international randomized trial involving patients at risk of coronary artery disease undergoing noncardiac surgery. The patients, health care providers (except for the anesthesiologists), data collectors, and outcome adjudicators are blinded to whether patients receive nitrous oxide–containing or nitrous oxide–free anesthetic. The primary outcome is a composite of death and major nonfatal events (ie, myocardial infarction, cardiac arrest, pulmonary embolism, and stroke) at 30 days after surgery.

Results At present, ENIGMA-II has randomized >1,000 patients in 22 hospitals in 5 countries. To date, patients’ mean age is 70 years, 66% are men, 38% have a history of coronary artery disease, 19% have a history of cerebrovascular disease, and 84% have a history of hypertension. Most patients have undergone intra-abdominal 28%, vascular 32%, and orthopedic 16% surgery.

Conclusions The ENIGMA-II Trial will be the largest study yet conducted to ascertain the benefits and risks of removing nitrous oxide from the gas mixture in anesthesia. The results of this large international trial will guide the clinical care of the hundreds of millions of adults undergoing noncardiac surgery annually. (Am Heart J 2009;157:488–494.e1)
a major cardiovascular event (ie, cardiovascular death, nonfatal MI, or nonfatal cardiac arrest) within the first 30 days. A total of 2.7% of the patients died within the first 30 days, and 59% of the fatalities were adjudicated as a cardiovascular death. A perioperative MI has been estimated to add $15,000 to the costs of a hospital stay, whereas a death adds an incremental cost of >$20,000. The cost of perioperative cardiac events is estimated at $20 billion annually in the United States alone.

Nitrous oxide and anesthesia

Despite some concerns regarding the safety and usefulness of nitrous oxide,\textsuperscript{7} it is still commonly used in anesthetic practice around the world. Because of its limited potency, the usual practice is to administer nitrous oxide at concentrations as high as 70% in oxygen (inspired oxygen 30%) along with a potent inhalational anesthetic agent (eg, sevoflurane) or intravenous propofol to produce a depth of anesthesia sufficient for surgery. The prevailing view has been that nitrous oxide is a cheap, relatively "safe" drug that can reduce the exposure to other anesthetic drugs. We have previously summarized the perceived risks and benefits of nitrous oxide.\textsuperscript{7}

Nitrous oxide interferes with vitamin B\textsubscript{12} and folate metabolism.\textsuperscript{8,9} It oxidizes the cobalt atom and irreversibly inactivates the enzyme, methionine synthase. This impairs production of methionine (from homocysteine), used to form tetrahydrofolic acid and thymidine during DNA synthesis. These adverse effects are time exposure-dependent and are probably greater in systemically unwell patients.\textsuperscript{9} It is well established that prolonged exposure to nitrous oxide can lead to a clinical syndrome similar to pernicious anemia.\textsuperscript{7,10} Inhibition of methionine synthase by nitrous oxide can be rapid and long-lasting: Exposure beyond a few hours reduces methionine synthase activity by 50%,\textsuperscript{8} and 12 to 24 hours of exposure causes marked megaloblastic changes\textsuperscript{10} that can be ameliorated by administration of sufficient folate or vitamin B\textsubscript{12}.

Most relevant to those with coronary artery disease is that nitrous oxide results in increased plasma homocysteine and myocardial ischemia after surgery.\textsuperscript{11-13} In addition, nitrous oxide can increase pulmonary artery pressure and is contraindicated in pulmonary hypertension.\textsuperscript{7} Nitrous oxide activates the sympathetic nervous system and can sensitize the myocardium to the arrhythmogenic effects of epinephrine.\textsuperscript{14} Lastly, the inclusion of nitrous oxide in the anesthetic gas mixture increases the likelihood of intraoperative or postoperative hypoxia.\textsuperscript{7}

Nitrous oxide was the first anesthetic discovered and remains a mainstay of anesthesia throughout the world; it has probably been given to more than a billion patients since 1844. It thus has a long history, and its side effect and safety profile are thus thought to be well understood. Its notable feature is that it allows a dose reduction of other anesthetic drugs that are usually more expensive and presumably more toxic. These perceived benefits support critical evaluation of its safety in a large clinical trial.\textsuperscript{15}

Nitrous oxide, homocysteine, and cardiovascular events

Nitrous oxide–induced inactivation of methionine synthase increases plasma homocysteine after surgery.\textsuperscript{11-15} Importantly, a recent study showed that plasma levels of homocysteine remain elevated for at least a week after surgery with nitrous oxide anesthesia.\textsuperscript{16} Long-term elevation of plasma homocysteine concentration is an independent risk factor for cardiovascular disease,\textsuperscript{17} and an acute increase in plasma homocysteine causes endothelial dysfunction\textsuperscript{18,19} and hypercoagulability.\textsuperscript{17} Consequently, hyperhomocysteinemia is associated with increased risk of venous thromboembolism and stroke.\textsuperscript{20}

Plasma homocysteine concentration is acutely raised after oral methionine and is reliably associated with endothelial dysfunction as measured by flow-mediated vasodilation.\textsuperscript{18,19} Nitrous oxide–induced elevation of homocysteine concentration may mirror that produced by oral methionine, with a recent study demonstrating nitrous oxide–based anesthesia significantly impaired endothelial function as measured by flow-mediated dilation in patients undergoing noncardiac surgery.\textsuperscript{13} Thus, nitrous oxide may also be a risk factor for perioperative myocardial ischemia.

Badner et al\textsuperscript{11} randomly allocated 90 patients to anesthesia with or without nitrous oxide. The nitrous oxide group had significantly increased homocysteine levels and a higher incidence of myocardial ischemia (46% vs 25%, *P < .05*), more ischemic events (82 vs 53, *P < .02*), and had more ischemic events lasting 30 minutes (23 vs 14, *P < .05*). This is a particularly relevant finding because it is known that the incidence of myocardial ischemia is highest in the hours after surgery and that it is strongly associated with postoperative MI.\textsuperscript{2}

Our recent studies

We recently completed a moderate-sized multicenter clinical trial of 2,050 patients undergoing noncardiac surgery—the ENIGMA (Evaluation of Nitrous Oxide In the Gas Mixture for Anesthesia) Trial.\textsuperscript{15} Patients were assigned to a nitrous oxide, or nitrous oxide–free, anesthetic. We found that the avoidance of nitrous oxide decreased the risk of wound infection (odds ratio [OR] 0.7, *P = .034*), severe vomiting (OR 0.4, *P < .001*), and pneumonia (OR 0.5, *P = .031*). In addition, patients given nitrous oxide had a greater length of stay in the intensive care unit (ICU) (*P = .02*), suggesting an increased
incidence of more serious complications. These findings were contrary to an earlier study that did not show these differences. However, in the ENIGMA Trial, we did not equalize the inspired oxygen concentrations in both groups, and so, it is possible that some of the benefits of avoiding nitrous oxide could be attributed to supplemental oxygen. The proposed trial (ENIGMA-II) will address this issue.

The ENIGMA Trial was not designed for and had insufficient power to detect a difference in the less common, but serious complications of MI or death. We nevertheless identified a possible increased risk of confirmed MI in patients receiving nitrous oxide, 1.3% versus 0.7% (adjusted \( P = .19 \)). Interestingly, if patients with new electrocardiogram (ECG) changes or cardiac enzyme elevation, but not both (ie, unconfirmed MIs), are included, there was a marked increase in the nitrous oxide group, 30 versus 10 cases (\( P = .002 \)); this requires further study. There were 10 postoperative deaths (1.0%) in the nitrous oxide group and 4 (0.4%) in the control group (\( P = .26 \)).

ENIGMA participants were an unselected group of surgical patients, but the findings suggest that nitrous oxide may be particularly detrimental in those at risk of cardiac events.

In summary, there is an established association between nitrous oxide and hyperhomocysteinemia, and flow-mediated vasodilation, after surgery. There is also evidence from a small clinical trial and post hoc results from the ENIGMA Trial to suggest that avoidance of nitrous oxide may lead to a reduction in postoperative cardiac events and mortality.

**Trial objectives**

The overall study goal of the ENIGMA-II Trial is to assess whether removal of nitrous oxide from the anesthetic gas mixture reduces the incidence of major perioperative cardiac events in patients with, or at risk of, coronary artery disease who are undergoing major noncardiac surgery. Specifically, we will test the hypothesis that in inpatients undergoing anesthesia for major noncardiac surgery, avoidance of nitrous oxide will reduce the incidence of death and major cardiovascular events. The study is funded by the Australian National Health and Medical Research Council (ID 436677).

**Trial design**

The ENIGMA-II study is a multicenter, international, randomized, parallel-group, controlled trial, with patients randomly allocated to either nitrous oxide-containing (70% nitrous oxide in oxygen [inspired oxygen fraction 0.3]) or nitrous oxide-free (70% nitrogen in oxygen [inspired oxygen fraction 0.3]) anesthetic.

**Study methods**

**Patient population**

ENIGMA-II will evaluate patients undergoing noncardiac surgery who are at risk of a perioperative major cardiac event (Table I). We will enroll 7,000 patients in 30 to 40 participating sites in Australasia, Asia, North America, and Europe. Centers will obtain institutional review board approval before enrolling patients, and all patients must provide informed consent to participate in ENIGMA-II.

**Assessment for eligibility**

After first obtaining agreement from anesthesiologists at each site, all elective noncardiac surgery patients are screened for eligibility. The patients who are eligible but not recruited into the trial are recorded in a study log that includes the reasons for the lack of participation.

**Allocation and randomization**

After the patient's consent has been obtained, center personnel will telephone a central 24-hour interactive voice recognition system that prompts the researcher or study coordinator to identify their study site, and randomly allocates patients to a treatment group (1:1) from a computer-generated list. Randomization is stratified by site. The sample size is sufficiently large to ensure comparable baseline characteristics, including surgical risk factors, surgical technique, anesthetic technique, and other aspects of perioperative care. ENIGMA-II is an intention-to-treat trial. Any participant who is enrolled and randomized to treatment group is followed for the duration of the trial.

**Definitions of end points**

**Primary end point**

The primary end point is a composite of death and major nonfatal cardiovascular events (MI, cardiac arrest, pulmonary embolism, and stroke) at 30 days after surgery.

**Secondary end points**

Secondary end points include the following: (i) MI, (ii) cardiac arrest, (iii) pulmonary embolism, (iv) stroke, (v) wound infection, (vi) severe nausea and vomiting, all up to 30 days after surgery; plus (vii) duration of stay in the ICU and hospital. For specific definitions, please see Table II.

Data pertaining to study end points are sent to a separate end point adjudication committee (see below).

**Death**: All deaths within 30 days of surgery from any cause.

**Myocardial infarction**: requires any one of the following criterion:

1. A typical rise of troponin or a typical fall of an elevated troponin with at least one value above the
Nitrous oxide is unavailable for use. Specific circumstances where nitrous oxide is contraindicated include:

1. History of coronary artery disease as indicated by a history of any one of the following:
   a) Angina
   b) MI
   iii. Segmental wall motion abnormality on echocardiography or a fixed defect on radionuclide imaging
   iv. A positive exercise stress test for cardiac ischemia
   v. A positive radionuclide exercise, echocardiographic exercise, or pharmacological cardiovascular stress test for cardiac ischemia
   vi. Coronary revascularization (CABG or PTCA)
   vii. Angiographic evidence of atherosclerotic stenosis ≥50% of the diameter of any coronary artery
   viii. ECG with pathological Q waves in 2 contiguous leads

2. AT increased risk of cardiac events, defined as any of the following:
   a) Development of new pathological Q waves on an ECG if troponin levels were not obtained or were obtained at times that could have missed the clinical event
   b) Development of pathologic Q waves present in ≥2 contiguous leads
   c) History of coronary artery disease (CAD) as indicated by a history of any one of the following:
      i. Angina
      ii. MI
      iii. Segmental wall motion abnormality on echocardiography or a fixed defect on radionuclide imaging
      iv. A positive exercise stress test for cardiac ischemia
      v. A positive radionuclide exercise, echocardiographic exercise, or pharmacological cardiovascular stress test for cardiac ischemia
      vi. Coronary revascularization (CABG or PTCA)
      vii. Angiographic evidence of atherosclerotic stenosis ≥50% of the diameter of any coronary artery
      viii. ECG with pathological Q waves in 2 contiguous leads

3. Development of new or presumed new cardiac wall motion abnormality on echocardiography or new or presumed new fixed defect on radionuclide imaging

4. Development of new pathological Q waves in any 2 contiguous leads that are ≥30 milliseconds

5. Development of ST segment elevation ≥1 mm in at least 2 contiguous leads

6. Development of ST segment depression ≥1 mm, or symmetric inversion of T waves ≥1 mm in at least 2 contiguous leads

7. Development of new pathological Q waves on an ECG

8. Previous surgical revascularization (CABG or PTCA)

9. History of a transient ischemic attack (TIA) (ie, a transient focal neurological deficit that lasted ≤24 h and thought to be vascular in origin)

10. History of a stroke (ie, cerebrovascular disease)

11. History of a myocardial infarction (MI)

12. History of angina

13. History of congestive heart failure

14. History of a transient ischemic attack (TIA)

15. History or diagnosis of chronic obstructive pulmonary disease (COPD)

16. History of diabetes

17. History of high cholesterol

18. History of previous stroke or TIA

19. History of peripheral vascular disease

20. History of previous MI

21. History of previous CABG or angioplasty

22. History of previous MI

ASA physical status

- I: 66
- II: 33
- III: 62
- IV: 3.9

Impaired exercise ability

28

Preexisting major medical conditions

1. Hypertension
2. Coronary artery disease
3. Previous MI
4. Previous CABG or angioplasty
5. Myocardial ischemia on perfusion scan
6. Heart failure
7. Peripheral vascular disease
8. Previous stroke or TIA
9. High cholesterol
10. Diabetes
11. Asthma/COPD
12. Infection/Fever
13. Other

Medications

1. Aspirin within the past 5 d
2. NSAID within the past 2 d
3. Clotidogrel
4. Ticlopidine
5. Heparin
6. Ticlopidine
7. Warfarin last 7 d
8. Heparin
9. Nitrate
10. Statin
11. ACE inhibitor
12. Amiodarone
13. β-Blocker
14. Diuretic
15. Calcium channel blocker
16. Digoxin
17. Insulin
18. Oral hypoglycemic
19. Antibiotic

ASA, American Society of Anesthesiologists; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; NSAID, nonsteroidal anti-inflammatory drug; COX, cyclooxygenase; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

* Estimated <3 metabolic equivalents.
Cardiac arrest: Defined as a successful resuscitation from either documented or presumed ventricular fibrillation or sustained ventricular tachycardia or asystole.

Pulmonary embolism: high probability on VQ scan or documented on pulmonary angiogram or spiral computed tomography or at autopsy.

Stroke: cerebral infarction or intracerebral hemorrhage on computed tomography or magnetic resonance imaging scan, or new neurological signs (paralysis, weakness, or speech difficulties) lasting >24 hours or leading to earlier death.

Severe nausea and vomiting: at least 2 episodes of severe nausea or vomiting >6 hours apart, or if requiring >2 doses of antiemetic medication.

Wound infection: associated with purulent discharge and/or a positive microbial culture.

ICU stay: including initial ICU admission and additional time after any readmission.

Hospital stay: from the start (date, time) of surgery until actual hospital discharge.

End point adjudication committee

The committee consists of an internal medicine physician with board-equivalent anesthesiology training and 2 cardiac anesthesiologists. Their role is to verify each of the study end points and to resolve any uncertainty as to any of the above outcomes.

Surgical and anesthetic techniques

Preoperative demographic characteristics and details of each patient's medical and surgical history are recorded. They will also undergo a 12-lead ECG, chest x-ray, pathology testing, and other routine investigations.

On the day of surgery, patients are allocated to 1 of the 2 treatment groups. All other perioperative clinical care is according to standard practice at each site, as this is an effectiveness trial designed to represent "real-world" practice. This includes choice of anesthetic drugs, analgesic regimens and/or regional analgesia techniques, antiemetics, and initiation or continuation of perioperative cardiac medications including anticoagulant and antiplatelet therapy. These vary and are allowable in the trial. All such relevant perioperative data are recorded on the study case report form.

Blood is collected postoperatively at 6 to 12, 24, 48, and 72 hours for cardiac enzyme (troponin and/or creatine kinase-MB) levels, and a 12-lead ECG is performed on days 1 and 3 after surgery to detect MI. Additional tests are ordered if clinically indicated (eg, chest pain, dyspnea, circulatory instability). In addition, patients are contacted by telephone at 30 days and their medical record reviewed to ascertain if they have experienced any adverse outcomes.

Study medications and duration

After induction of anesthesia, patients allocated to the nitrous oxide group will have their anesthesia maintained with 70% nitrous oxide (inspired) in 30% oxygen and 1 of 4 other hypnotic agents (isoflurane, sevoflurane, desflurane, or propofol) at the discretion of the anesthesiologist. Patients allocated to the nitrous oxide-free group will receive 30% oxygen in an oxygen/medical air mixture and have their anesthesia maintained with one of the above hypnotic agents (also according to anesthesiologist preference). In both cases, depth of anesthesia can be adjusted according to clinical judgment and/or data from depth of anesthesia monitoring devices (if available). All other perioperative clinical care will be according to standard practice. All relevant factors will be recorded on a trial case report form.

Study procedures, blinding, and follow-up

Anesthesiologists will have knowledge of group after randomization (for safe use of nitrous oxide), but administration and group identity will be concealed from the surgeon. Anesthesiologists participating in the conduct of the study will receive education explaining the importance of, reasoning for, and methods to ensure blinding from surgeons and others. The anesthetic machine flow meters will be concealed from the surgical staff, using drapes or cardboard screen. To ensure blinding of all the other staff, the anesthesiologist will place the original anesthesia record after surgery in a sealed opaque envelope; the envelope is to be stored in the patient's hospital record and should not be opened until after the 30-day follow-up unless there is a clinical imperative. Patients, surgeons, and research staff collecting data and interviewing patients postoperatively will be blind to treatment allocation.

Collection of data

Data are collected by local research staff and entered onto a paper case report form. All data are subsequently entered onto a database on the study Web site (www.enigma2.org.au). This is managed by Monash University's Center for Clinical Research Excellence in Therapeutics (Melbourne, Australia), where all data and processes are reviewed each day at the data management center (see below). Data fields are checked, and in conjunction with the local site research staff, missing data or inconsistencies are corrected, before being automatically downloaded on to a confirmed database. At the end of the trial, site-specific data will be sent to each site investigator on a CD-ROM for long-term storage.
Statistical considerations

Sample size and power
The recently revised international guidelines for the diagnosis of MI should result in an increase in cardiac events because of increased sensitivity (ie, identifying small infarcts). The sample size is based on a clinically important (≥25%) reduction in cardiac events or death, from 8% to 6%. These estimates are based on our previous research and large observational studies. A type I error of 0.05 and a type II error of 0.1 require 7,000 patients to be included in this study. We tested these assumptions with our ENIGMA Trial database. When the above trial entry criteria were used, we identified 656 comparable patients (313 nitrous oxide group, 343 control). Nitrous oxide was associated with a higher incidence of reported MI (OR 2.4, 95% confidence interval [CI] 1.1-5.3, exact \( P = .029 \)) and a trend to increased mortality (OR 7.3, 95% CI 0.80-50, exact \( P = .07 \)).

Statistical methods
All patients who are randomly allocated to study drug administration will be considered as comprising the intention-to-treat population for all primary, secondary, and safety analyses. Baseline characteristics of the 2 treatment groups will be tabulated using appropriate summary statistics.

Stratification will be by center, but not other factors as these are likely to be balanced in this large trial. Intention-to-treat analyses will be undertaken. The cumulative incidence of the combined end point will be analyzed using Fisher exact test, with covariate adjustment performed by logistic regression. Results will be expressed with risk ratios and exact 95% CIs. Other secondary end points will be compared with Cox proportional hazards and Wilcoxon rank sum tests.

Two interim analyses are planned for the ENIGMA-II Trial. These will be performed after enrolment of 3,000 and 5,000 patients, that is, at 43% and 71% of the target recruitment number of 7,000. The study statistician (A. F.) will perform the interim analyses, and the results will be discussed by the Data Safety and Monitoring Committee (DSMC), according to an agreed charter. The interim analysis will be adjusted according to an O’Brien and Fleming Type I error spending function, using a combined \( P \) value <.05.

Planned substudies
ENIGMA-II will support a cohort study of the incidence, clinical importance, risk factors, and economic costs of cardiac events and mortality in patients undergoing anesthesia for major surgery. This will provide a unique opportunity to collect extensive and accurate data on 7,000 surgical patients with known or suspected coronary artery disease. This will allow reliable estimation of the true incidence of cardiac events and death in this population and will provide important information for future patients and their families, as well as for government and other health care agencies. The relative clinical importance can be determined (impact on daily living, social activities, requirement for rehospitalization, long-term disability). In addition, the most important risk factors for serious postoperative complications can be identified. Thus, the database will be examined using a variety of exploratory regression techniques to address each of these issues.

We also plan to conduct an exploratory analysis for cointerventions believed to reduce perioperative cardiac events. There are several interventions believed to reduce perioperative cardiac events in surgical patients with known or suspected coronary artery disease, but all have been based on small trials or meta-analysis of small trials. We plan to use propensity scores and logistic regression analysis to investigate the following factors: perioperative \( \beta \)-blockade, perioperative statin therapy, intraoperative hypothermia, spinal or epidural local analgesic block, and perioperative calcium antagonists, with corresponding null hypotheses that none of these factors are associated with the incidence of postoperative cardiac events in surgical patients with elevated cardiovascular risk.

Data safety and monitoring committee
The DSMC consists of a clinical epidemiologist (Chair), anesthesiologist independent statistician, and a clinical pharmacologist. The DSMC will discuss the interim results and vote for continuation or stopping the trial. This will be communicated to the Steering Committee.
according to a stopping rule of $P < .001$ for the primary study end point and consideration of other evidence relevant to the recommendation of the DSMC. The conduct of the DSMC is to be guided by the paper by DeMets et al.50

Current status of the trial

ENIGMA-II is currently recruiting patients in 23 centers within 5 countries and has randomized 1,258 patients as of November 2008. Tables II and III report on characteristics of the first 929 patients enrolled in the trial. These data demonstrate a cohort of patients at increased risk of cardiovascular events after surgery.

Conclusion

Exposure to nitrous oxide impairs methionine synthase, folate and DNA production, and increases homocysteine levels. These adverse effects are likely to be enhanced in at-risk patients; we will thus focus our trial on patients with coronary artery disease and those with risk factors for coronary artery disease. When considering the widespread use of nitrous oxide around the world, small differences in outcome would have major implications for surgical practice.

Disclosures

None of the authors has declared any conflict of interest.

References

Appendix A. ENIGMA-II trial organization and Committees

Sponsor: Alfred Hospital, Melbourne, Australia
Funding sources: Australian National Health and Medical Research Council (NHMRC) project grant ID 436677

Steering Committee: Paul Myles (Chair and Principal Investigator), Kate Leslie, Phil Peyton, Mike Peach, Brendan Silbert, Philip J Devereaux, Dan Sessler, Andrew Forbes, Scott Beattie; Research Manager, Sophia Wallace

Chief and Associate Investigators: Paul Myles, Kate Leslie, Phil Peyton, Mike Peach, Brendan Silbert, Philip J. Devereaux, Dan Sessler, Andrew Forbes

End Point Adjudication Committee: James W. Tomlinson, David R. McIlroy, Neal Badner
Clinical Pharmacologist: Henry Krum
Statistician: Andrew Forbes
Data and Safety Monitoring Committee: Konrad Jamrozik (Chair), John Rigg, Henry Krum; Independent Statistician, Philip Ryan
Data Management and Quality Control: Sophia Wallace, Adam Meehan
Website Design and Maintenance: Adam Meehan