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Does anaesthesia with nitrous oxide affect mortality or cardiovascular morbidity? A systematic review with meta-analysis and trial sequential analysis

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Editor's key-points

- The authors reviewed publications exploring cardiovascular outcomes after nitrous oxide anaesthesia.
- The evidence-base was insufficient to draw robust conclusions regarding the effect of nitrous oxide anaesthesia on cardiovascular outcomes.

Background. The role of nitrous oxide in modern anaesthetic practice is contentious. One concern is that exposure to nitrous oxide may increase the risk of cardiovascular complications. ENIGMA II is a large randomized clinical trial currently underway which is investigating nitrous oxide and cardiovascular complications. Before the completion of this trial, we performed a systematic review and meta-analysis, using Cochrane methodology, on the outcomes that make up the composite primary outcome.

Methods. We used conventional meta-analysis and trial sequential analysis (TSA). We reviewed 8282 abstracts and selected 138 that fulfilled our criteria for study type, population, and intervention. We attempted to contact the authors of all the selected publications to check for unpublished outcome data.

Results. Thirteen trials had outcome data eligible for our outcomes. We assessed three of these trials as having a low risk of bias. Using conventional meta-analysis, the relative risk of short-term mortality in the nitrous oxide group was 1.38 [95% confidence interval (CI) 0.22–8.71] and the relative risk of long-term mortality in the nitrous oxide group was 0.94 (95% CI 0.80–1.10). In both cases, TSA demonstrated that the data were far too sparse to make any conclusions. There were insufficient data to perform meta-analysis for stroke, myocardial infarct, pulmonary embolus, or cardiac arrest.

Conclusion. This systematic review demonstrated that we currently do not have robust evidence for how nitrous oxide used as part of general anaesthesia affects mortality and cardiovascular complications.

Keywords: meta-analysis; nitrous oxide; review, systematic

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Nitrous oxide has been used as a general anaesthetic for more than 160 years. Collective anecdotal experience with this drug must be larger than with any other drug used in anaesthesia. Despite this experience, opinions about the role of nitrous oxide in modern-day practice continue to diverge.[1 2] One concern is that exposure to nitrous oxide may increase the risk of cardiovascular complications. Nitrous oxide oxidizes the cobalt atom in vitamin B12, inactivating methionine synthase, causing a decrease in folate metabolism and an increase in homocysteine.[3] Homocysteinaemia after exposure to nitrous oxide has been well demonstrated in vivo[4–6] and long-term homocysteinaemia is known to be associated with an increased risk of ischaemic heart disease.[7] It remains unclear, however, whether this information about this surrogate outcome translates into real clinical risk. To investigate the possible causal association between mortality, cardiac morbidity, and nitrous oxide, the ENIGMA (Evaluation of Nitrous oxide In the Gas Mixture for Anaesthesia) trial group has designed a large, multi-centre randomized clinical trial: ENIGMA II is enrolling at-risk patients and is powered to investigate a composite primary outcome of mortality, non-fatal acute myocardial infarction, cardiac arrest, pulmonary embolism, and stroke.[8]

While this trial is underway, several observational studies have been published looking at similar outcomes. Using data from the Intraoperative Hypothermia in Aneurysm Surgery

Trial,[9] a secondary analysis was performed, finding an association between nitrous oxide exposure and delayed ischaemic neurological deficits.[10] Sanders and colleagues[11] also performed a secondary subgroup analysis on 1615 participants from the General Anaesthesia compared with Local Anaesthesia for Carotid Surgery Trial, finding no evidence that nitrous oxide increases the risk of perioperative vascular adverse events.[12] Turan and colleagues[13] published a retrospective cohort study of 49,016 patients and found that patients who had received nitrous oxide had *decreased* odds for 30-day mortality. Leslie and colleagues[14] performed a *post hoc* analysis on 5133 of the patients from the Perioperative Ischemic Evaluation trial, and found no association between nitrous oxide and cardiovascular adverse events. These studies herald a focusing interest on the association between nitrous oxide and cardiovascular adverse events and they certainly contribute to the debate. Being *post hoc* observational studies, however, potential confounders, especially those confounding by indication, increase the risk of bias and prevent any conclusions from being definitive.

The association between nitrous oxide and cardiovascular complications remains unclear, and the results from ENIGMA II are keenly awaited. We thus performed a systematic review and meta-analysis of the five outcomes used as the composite primary outcome in ENIGMA II. We plan to update this meta-analysis when the results from ENIGMA II, and any other future trials, are available. Repeated updates in meta-analysis are analogous to those in interim analyses in a clinical trial. In clinical trials where interim analyses are performed, the concern about increased risk of type 1 error because of repetitive testing and sparse data is well known and sequential hypothesis testing designs and procedures are used to control this increased risk.[15 16] In systematic reviews with meta-analysis, similar sequential hypothesis testing procedures, such as Trial Sequential Analysis (TSA), can also be applied.[17–21] Given our plan to update our meta-analysis in the future, we performed TSA as part of our current analysis.

Methods

Protocol and registration

The protocol for the review was published on the website of the Copenhagen Trial Unit (www.ctu.dk) in January 2011. The protocol was registered with the PROSPERO database in December 2011 (registration no CRD42011001831). There were two small deviations from this protocol. First, there were errors in the search strategies published in the protocol. These errors were corrected before the searches were run. The corrected searches are provided in Appendix 1. Secondly, we clarified the definition of patients at increased risk of cardiovascular complications slightly, by stating that we considered patients undergoing day surgery as being at low risk of cardiovascular complications.

Systematic literature search

We conducted a sensitive systematic literature search of Medline, EMBASE, the Cochrane controlled trial register, CINAHL, and ISI Web of Science, updated until May 2012. There were no date or language restrictions. We also checked the references of included studies. Two authors (G.I. and A.O.) independently screened all of the abstracts produced by the search to identify eligible studies.

Study selection, data extraction, and quality assessment

We included all randomized clinical trials, irrespective of language or publication status. We included trials with human adult patients receiving general anaesthesia, for any surgery. We defined a general anaesthetic as any procedure where inhalation agents, systemic agents, or both are given as part of general anaesthesia for the purposes of undertaking a medical procedure. We did not include studies where nitrous oxide was given for the purposes of sedation.

We included trials where patients receiving nitrous oxide were compared with patients receiving no nitrous oxide. We included trials only when it was clear that the control group received no nitrous oxide throughout the perioperative period. We excluded trials where participants were randomized to different anaesthetic techniques (apart from the administration of nitrous oxide).

We included studies that were able to provide data on any of the following outcomes:

(1) Mortality (all cause)—including all trials where mortality data were available for the same follow-up period in both the exposure and control groups. We included two comparisons for the mortality outcome:
- Mortality—short term, follow-up ranging from discharge from the perioperative care unit (PACU) until 30 days after operation (or discharge from hospital). The end point needed to be consistent in the two intervention groups.
- Mortality—long term, including the longest follow-up starting from 30 days after operation.

(2) Stroke.
(3) Myocardial infarction (MI).
(4) Pulmonary embolus (PE).
(5) Cardiac arrest.

For short-term mortality, stroke, MI, PE, and cardiac arrest, we included data from any trials where the patients were at increased risk of cardiovascular complications. See Appendix 2 for our definition of this increased risk. We accepted all clear and reasonable definitions of these outcomes in individual trials, as long as they were used consistently in both groups and reported explicitly.

We selected possible inclusions on the basis of the trial type, participants and interventions described in the abstract and retrieved full copies of these publications. For trials that fulfilled these parameters, but did not report relevant outcomes, we wrote to the authors to ask whether any unpublished data were available. When no email address was available on the publication, we searched for previous contact email addresses for authors and we contacted departments, co-authors of other publications, or both, in order to find contact details. In