What is the evidence associating the use of nitrous oxide during general anaesthesthia with mortality and serious cardiovascular complications? A systematic review and meta-analysis of randomized clinical trials.

Study Protocol

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Background

Nitrous oxide has been used as an anaesthetic drug, throughout the world, for many years. The prevalence of its use continues and many find it hard to imagine that a drug with such a long and extensive history could be causing harm. But habit alone does not make a safe practice and there is good reason to question the risk/benefit profile of nitrous oxide for general anaesthesia [1-3]. Of particular note, a number of studies have suggested an association between nitrous oxide and an increased risk of cardiovascular complications [4-6]. To investigate this association, the Enigma trial group has designed a large, multi-centre randomised controlled trial [7]. Enigma II, currently underway, is looking at high-risk patients and is powered to investigate a composite primary outcome of: mortality, non-fatal acute myocardial infarction, cardiac arrest, pulmonary embolism and stroke. In the context of nitrous oxide and perioperative medicine, Enigma II is asking an important question: in patients with increased risk, does nitrous oxide increase the risk of serious peri-operative cardiovascular events with a probable ischaemic origin?

When a new trial is planned, such as Enigma II, it is important to first summarize the existing evidence. This process allows readers to make the most informed decisions about how to conduct their practice. Recent evidence suggests that in research articles in the five high impact journals (Annals of Internal Medicine, BMJ, JAMA, The Lancet, and The New England Journal of Medicine), appropriate discussion of previous knowledge is still rare [8]. In response to these findings, The Lancet has asked that ‘a panel in the Discussion section should summarise the totality of evidence’ and that ‘authors should outline how they searched for previous evidence and assessed its quality’ [9]. Specifically, The Lancet has stated that ‘authors should either report their own, up-to-date systematic review or cite a recent systematic review of other trials, putting their trial into context’.

While a meta-analysis is not mandatory in a systematic review, it does represent the highest quality of evidence. Consequently, a thorough way to summarize existing evidence, and then add new information as it comes to light, is to do a meta-analysis and update it as each new trial is published. The Cochrane Collaboration, an international organization that prepares, maintains and promotes systematic reviews, advocates something similar, suggesting that systematic reviews should be updated every two years [10].

In our systematic review, we aim to summarise the totality of the evidence prior to Enigma II. Including a meta-analysis, we will summarise the existing evidence associating nitrous oxide use in general anaesthesia with mortality and cardiovascular outcomes. We then plan to update this meta-analysis when Enigma II and any other future trials are published. That is, we will continually update the information until we can be reasonably confident about the effects of nitrous oxide on these important outcomes.

Repeated updating of meta-analysis is an efficient and thorough way to summarise existing evidence. However, this process also presents statistical challenges. Continual updating involves repeated testing of the same statistical hypotheses over time and such multiplicity increases the risk of both type 1 and type 2 error [11-13]. Repeated updates in meta-analysis are analogous to interim analyses in a clinical trial. In clinical trials where interim analyses are performed, the concern about increased risk of false statistical inferences is well known and advanced sequential hypothesis testing techniques are used to control this increased risk [14;15]. In systematic reviews, similar sequential hypothesis testing techniques can also be applied.

Trial sequential analysis (TSA) is a methodology that applies sequential hypothesis testing to repeated updates in meta-analyses [16-19]. This methodology includes an assessment of the strength of the evidence and provides statistically adjusted boundaries for significance and futility. Empirical studies have shown that TSA may be effective in controlling the risks of false inferences in meta-analyses [16;18;19]. In summarizing the evidence associating nitrous oxide with mortality and cardiovascular complications, we will conduct TSA as part of our meta-analysis. We will use TSA as a framework on which to assess the existing evidence, and on which to add new information as it accumulates.

Objectives

To assess the current evidence associating nitrous oxide use during general anaesthesia with mortality and cardiovascular complications.

This systematic review is examining adverse effects of nitrous oxide. We aim to carry out a narrow-focused evaluation and to use a systematic approach to gather and interpret all level one evidence that pertains to mortality and cardiovascular complications after exposure to nitrous oxide. We do not aim to conduct a widely-scoped review examining the adverse effects of nitrous oxide in general [20].

Methods

Criteria for including studies

Types of studies

We will include all randomised clinical trials, irrespective of language or publication status. We will exclude quasi-randomized trials.

Participants

We will include trials with patients receiving general anaesthesia, for any surgery, age equal to or greater than 18 years.

We will define a general anaesthetic as any procedure where inhalational agents and/or systemic agents are given as part of general anaesthesia for the purposes of undertaking a medical procedure. We will not include studies where nitrous oxide was given for the purpose of sedation. We define sedation as administration of sedating agents at a level usually not requiring airway intervention (such as a laryngeal mask or an endotracheal tube)

We will exclude studies conducted on non-humans.

Intervention and control groups

We will include trials where patients receiving nitrous oxide are compared with patients receiving no nitrous oxide. The group receiving nitrous oxide will represents the intervention group and the group not receiving nitrous oxide will represent the control group.

We will include trials where it was clear that the control group received no nitrous oxide throughout the duration of the perioperative period. For example, we will exclude studies in which the period of controlled intervention was only during induction.

We will exclude trials where participants were randomised to different anaesthetic techniques (apart from the administration of nitrous oxide). For general anaesthesia, nitrous anaesthesia is given in combination with other anaesthetic agents. Consequently, randomisation of patients to receive either nitrous oxide or no nitrous oxide may include randomisation to different overall anaesthetic techniques. For example, a volatile anaesthetic given with oxygen and nitrous oxide might be compared with an intravenous anaesthetic given with oxygen and air. If the randomisation includes differences apart from the administration of nitrous, these differences represent potential confounders.

We will include studies independent of the length of operation.

Outcomes

1. Mortality

All causes.

We will include all trials where mortality data is available for the same follow-up period in both the exposure and control groups.

We will include trials when we judge that mortality – for a defined period – has been measured and is clear. Where such clarity is not present in the text of the paper, we will attempt to contact the authors of the trial for confirmation.

We will do two comparisons for the mortality outcome:

a. Mortality within 30 days postoperatively

Including the longest follow-up from trials starting from the end of the anaesthetic and ending within 30 days postoperatively, aiming to measure the effect of nitrous oxide on this outcome in this immediate postoperative period.

We will include only trials with patients at high risk for cardiovascular complications. See below for which patients will be classified as high risk.

b. Mortality including all follow-up periods

Including the longest follow-up from trials starting from the end of the anaesthetic and ending at any time postoperatively.

We will include all eligible trials for this comparison, independent of risk.

2. Stroke

We will include only trials with patients at high risk for cardiovascular complications. See below for which patients will be classified as high risk.

3. Myocardial Infarction (MI)

We will include only trials with patients at high risk for cardiovascular complications. See below for which patients will be classified as high risk.

4. Pulmonary embolis (PE)

We will include only trials with patients at high risk for cardiovascular complications. See below for which patients will be classified as high risk.

5. Cardiac arrest

We will include only trials with patients at high risk for cardiovascular complications. See below for which patients will be classified as high risk.

For stroke, MI, PE and cardiac arrest, we will include data from any trials where the proportion of these outcomes was measured in both the exposure and control groups.

We will accept all clear and reasonable definitions of these outcomes in individual trials, as long as they are used consistently in both groups.

Definition of high risk patients

We will define a participant as being at high risk if they fulfil any of the following criteria:

a. Are undergoing surgery defined as moderate or high risk surgery in the ACC/AHA guidelines for perioperative cardiovascular evaluations for non-cardiac surgery[21] or are undergoing cardiac surgery.
b. Have clinical predictors (mild, moderate or severe) of increased perioperative cardiovascular risk as defined in the ACC/AHA guidelines for perioperative cardiovascular evaluations for non-cardiac surgery[21].

Subgroup analyses

We plan to conduct one subgroup analysis for each outcome.

Constant inspired fraction of oxygen (FiO_2)

We will include trials were the intervention group and the control group received the same inspired concentration of oxygen (within 20% FiO_2 absolute difference).

When nitrous oxide is used, it limits the maximal concentration of FiO_2 that can be used. Conversely, when nitrous oxide is omitted, it is possible to give any concentration of FiO_2. Consequently, randomisation of patients to receive either nitrous oxide or no nitrous oxide may include randomisation to different FiO_2s. While currently contentious, it is possible that FiO_2 may have an affect on post-operative outcomes, including mortality and cardiovascular complications. Consequently, in our review, FiO_2 is a variable associated with both our intervention and potentially with our outcomes, and as such, it is a potential confounder. We will therefore conduct a subgroup analysis, investigating whether FiO_2 alters any conclusions we are able to make.

Sensitivity analyses

In order to examine the effect of risk of bias of the included trials, we will conduct two sensitivity analyses for each comparison:

1. Including only trials with a low risk of bias.
2. Including only trials with a high risk of bias.

Search technique

We will search the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library (The Cochrane Library*, Issue 5, 2010), MEDLINE (via Ovid,1966 to May 2010, see); EMBASE (via Ovid, 1980 to May 2010); CINAHL (via EBSCOhost, 1982 to May 2010) and ISI Web of Science (1945 to May 2010).

See Appendix 1 for the search strategies we will use for each database.

We will also search the following websites for ongoing or unpublished trials: http://www.controlled-trials.com/, http://clinicaltrials.gov/, and http://www.centerwatch.com/.

We will review the reference lists of all included trials and we will contact the included main authors and other experts in the field and enquire about any ongoing or unpublished studies.

Data collection and analysis

Selection of included studies

Two authors (GI and AO) will independently screen all of the abstracts produced by the above search. We will retrieve a full copy of all the possible inclusions and review them for eligibility. We will document the reasons for exclusions.

Assessment of risk of bias of included studies

Two authors (GI and AO) will review all included trials with regard to their quality. We will rate the risk of bias for each included study, using the guide provided in The Cochrane Handbook of Systematic Reviews of Interventions[22]. We will assess each trial for sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. When all of the five first assessment categories are assessed as adequate, as defined in the Cochrane handbook, we will rate the trial as having a low risk of bias. When one or more categories are assessed as inadequate, we will assess the trial as having a high risk of bias.

Data extraction

Two authors (GI and AO) will independently extract data from the included studies. When there is missing data, we will contact the authors of each trial an attempt to retrieve that data.

Statistical Analysis

Measures of effect
We will communicate effect measures as relative risks.

Zero event data

Because our review is examining adverse effects that may be rare, we expect to find zero event trials. These trials represent important information and should be included in the analysis. We will therefore use an empirical continuity correction for these trials, adding a small, arbitrary event rate into both groups[23], thereby allowing their inclusion.

Missing data

If we are unable to retrieve missing data, we will use a 'complete case analysis' approach, which excludes from the analysis all participants with the outcome missing. We will conduct analyses of best and worst case scenarios (with respect to the intervention) to assess possible uncertainty due to missing or lost to follow up data.

Assessment of heterogeneity

The degree of heterogeneity will be quantified using diversity (D^2)[24] and using inconsistency factor (I^2)[22]. If $I^2 = 0$, we will only report the results from the fixed-effect model. In the case of $I^2 > 0$ we will report the results from both the fixed-effect model and the random-effects models.

Assessment of publication bias

If we have more than 10 studies in a meta-analysis, we will assess publication bias/small study effects using Egger's test[25] and Begg's test[26].

Data synthesis

The multiplicity caused by repeated updates (sequential multiplicity) increases the risk of type 1 and type 2 error. In order to reduce that risk to our desired 0.05 and 0.10 respectively, we will perform the meta-analysis using trial sequential analysis (TSA)[16;18;19]. We will calculate an information size to detect or reject an ***a priori*** 20% and 10% relative risk reduction for each of the five outcomes, using a type I error of 0.05, a type II error of 0.10. We will also calculate an information size estimated by the relative risk reduction from the included trials with a low risk of bias. D^2 will be used for heterogeneity adjustment of the required information size[24]. Control event proportions will be estimated from included studies. We will review external observational evidence to confirm the reliability of these estimates and if there is doubt, we will include analyses with a range of possible control event proportions. We will construct a cumulative Z-curve for each outcome. For each comparison, we will construct monitoring boundaries for significant (superiority and inferiority) and for futility (non-inferiority and non-superiority).

Internal Multiplicity

Our study is looking at five outcomes. We have not designated any of these outcomes as primary; we are interested in assessing the evidence for each of these questions equally. One outcome – mortality – will be considered with two comparisons. For each comparison, we have planned a subgroup analyses and two sensitivity analyses. Therefore, if we find enough data to do all the analyses we have planned, we will conduct 12 comparisons for mortality and 6 for each of the other outcomes . The presence of multiplicity within a systematic review (internal multiplicity) increases the risk of type 1 error. If we find statistically significant results, we will consider the possibility that this result is a chance finding. This consideration will include a discussion of: the size of the effect, the size of the statistical significance, the consistency between results and the biological plausibility of what find. We plan to conduct a second study to investigate quantitatively the effect of internal multiplicity on the effect measures calculated in this meta-analysis.

Contribution of authors

Georgina Imberger - GI
Kristian Thorlund - KT
Annabel Orr – AO
Jørn Wetterslev – JW
Paul Myles – PM
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Conceiving the review; GI, KT, AO, JW, PM, AM
Co-ordinating the review: GI
Undertaking the search: GI
Screening the abstracts from the search: GI, AO
Retrieving the full papers for review: GI
Reviewing full papers for inclusions: GI, AO
Contacting authors of review to confirm outcome measurement: GI
Appraising quality of included papers: GI, AO
Abstracting data from included papers: GI, AO
Data management for the review: GI, KT, JW
Statistical analysis: GI, KT, JW
Interpretation of data: GI, KT, JW, PM, AM
Writing the review: GI (principal), KT, AO, JW, PM, AM

Appendix 1 – Search strategies

ISI Web of Science

# 5	#4 AND #3
# 4	TS=(random* or placebo* or prospective* or multicenter*) or (TS=(clinical or controlled) SAME TS=(trial*)) or TS=((single or double or triple or treble) SAME (mask* or blind*))
# 3	#2 AND #1
# 2	TS=(surg* or anaesth* or anesth*)
# 1	TS=(nitrous oxid* or NO2)

CINAHL (EBSCO host)

S5	S3 and S4
S4	TI (surg* or anaesth* or anesth*) or AB (surg* or anaesth* or anesth*)
S3	S1 or S2
S2	TI (nitrous oxid* or NO2) or AB (nitrous oxid* or NO2)
S1	(MM "Nitrous Oxide")

CENTRAL

#1	MeSH descriptor Nitrous Oxide explode all trees

#2 (nitrous oxid* or NO2):ti,ab
#3 (#1 OR #2)
#4 (surg* or anaesth* or anesth*):ti,ab
#5 (#3 AND #4)

MEDLINE (Ovid SP)

1 exp Nitrous Oxide/
2 (nitrous oxid* or NO2).ti,ab.
3 1 or 2 (20607)
4 (surg* or ana?sth*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
5 3 and 4
6 ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.
7 5 and 6

EMBASE (Ovid SP)

1 exp nitrous oxide/
2 (nitrous oxid* or NO2).ti,ab.
3 1 or 2
4 (surg* or ana?esth*).mp.
5 3 and 4
6 (placebo.sh. or controlled study.ab. or random*.ti,ab. or trial*.ti,ab.) not (animals not (humans and animals)).sh.
7 5 and 6

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