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[Intervention Protocol]

Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly surgical patients

I. David Miller[1], Cliff L Shelton[2], Sharon R Lewis[3], Phil Alderson[4], Andrew F Smith[5]

[1]Academic Unit, North Cumbria University Hospitals, Carlisle, UK. [2]Lancaster Medical School, Lancaster University, Lancaster, UK. [3]Patient Safety Research Department, Royal Lancaster Infirmary, Lancaster, UK. [4]National Institute for Health and Care Excellence, Manchester, UK. [5]Department of Anaesthesia, Royal Lancaster Infirmary, Lancaster, UK

Contact address: I. David Miller, Academic Unit, North Cumbria University Hospitals, Cumberland Infirmary, Newtown Road, Carlisle, CA2 7HY, UK. 150jvf@gmail.com. David.miller@ncuh.nhs.uk.

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To compare maintenance of general anaesthesia for elderly surgical patients using total intravenous anaesthesia (TIVA) or inhalational anaesthesia on postoperative cognitive function, mortality, risk of hypotension, length of stay in the postanaesthetic care unit (PACU), and hospital stay.

BACKGROUND

Description of the condition

There are an estimated 187 million to 281 million surgical procedures worldwide each year (Weiser 2008). Alongside an aging population, the global use of anaesthetics in the elderly is increasing (Mandal 2009). Surgery and anaesthesia have a pronounced effect on elderly people, which can result in an increased risk of postoperative confusion and functional decline. Complications such as these have adverse effects on postoperative recovery and are associated with an increased length of hospital stay and an increased risk of mortality. It is hypothesized that the direct effect of anaesthesia on the brain, hypotension, and hypoxia may all have an influence on their development (Ballard 2012; Wang 2015).

Postoperative delirium is an acute condition, characterized by reduced awareness of the environment and a disturbance in attention (Deiner 2009). It typically occurs between 24 and 72 hours after surgery, following an initial lucid phase (Ballard 2012). It is thought to occur in around 10% of elderly patients (Rudolph 2011), although this can rise to 60% following certain types of surgery, such as hip fracture fixation (Ansaloni 2010; Bitsch 2004). Postoperative delirium is a defined condition according to the International Classification of Diseases (WHO 2016a), and there are a number of validated tools to assist in diagnosis and severity scoring, such as the confusion assessment method (CAM) (Inouye 1990).

Postoperative cognitive dysfunction is characterized by a chronic reduction in cognitive function, lasting weeks or months, compared with an individual's normal cognitive state (Newman 2007). It presents a diagnostic challenge as it has not been formally defined and diagnostic criteria are yet to be developed, but can include changes to circadian rhythm, psychomotor state, and memory deficit. The incidence of postoperative cognitive dysfunction varies depending on the surgery type and the definition of postoperative cognitive dysfunction used (Krenk 2011); it is associated with an inability to return to normal lifestyle postsurgery (Monk 2005; Steinmetz 2016,).

Description of the intervention

There are three phases involved in the provision of general anaesthesia: induction, maintenance, and emergence. Induction of anaesthesia is often undertaken using intravenous (IV) agents, typically propofol. This has the advantage of rapid onset, and therefore airway control can be quickly obtained. Inhalational induction of anaesthesia using a non-irritant volatile agent such as sevoflurane is an alternative which, though slower in onset, offers benefits in terms of the maintenance of spontaneous respiration and increased cardiovascular stability. In the majority of patients, anaesthesia is maintained by the inhalation of volatile agents (typically sevoflurane, desflurane, or isoflurane, historically also enflurane and halothane) (Eckenhoff 2004). The alternative technique for the maintenance of anaesthesia is the continuous administration of an IV infusion of an anaesthetic drug, typically propofol. This is known as total intravenous anaesthesia (TIVA). Neither maintenance technique provides analgesia, and this may be co-administered through a variety of techniques which may be used in combination. These include boluses or an infusion of opioid medication, the inhalation of nitrous oxide, or regional anaesthetic techniques. In this review, we will compare inhalational anaesthesia involving maintenance with sevoflurane, desflurane, isoflurane, or halothane (referred to as inhalational anaesthesia) with propofol-based TIVA (referred to as TIVA).

How the intervention might work

The mechanism of action of anaesthetic agents has not been fully elucidated. However, it is known that both IV and inhalational agents act at multiple receptor sites within the central nervous system to reduce neuronal activity (Koblin 2000). Both propofol and volatile agents are thought to act predominantly though the activation of the gamma-aminobutyric acid (GABA)-A receptor, with variable effects on other receptors. Of these, the nicotinic acetylcholine receptor may be of particular relevance to the subject of this review, as it has a role in cognition, and is inhibited by volatile agents at therapeutic levels, but by propofol only in high doses (Fodale 2010).

Inhalational anaesthesia has been associated with lower rates of postoperative cognitive dysfunction in the setting of cardiac surgery (Royse 2011; Schoen 2011), and inhalational induction has been shown to induce less hypotension than IV induction (Luntz 2004; Thwaites 1997). In inhalational anaesthesia, the end-tidal concentration of anaesthetic agent is measured and this can be compared to a known value at which 50% of patients move in response to a standard surgical stimulus, known as the mean alveolar concentration (MAC). In order to prevent awareness, it is suggested that the end-tidal volatile concentration should exceed 0.7 MAC. MAC is age-dependant, decreasing with advancing age, and should therefore be adjusted using nomograms or algorithms in order to reduce the risk of excessive dosing in the elderly population (Griffiths 2014).

There are a number of proposed benefits to the use of TIVA, including a more rapid recovery and a decreased incidence of postoperative nausea and vomiting (Weilbach 2004). However, propofol is associated with hypotension, thought to be mediated by the inhibition of sympathetic outflow, and this may be particularly pronounced in the elderly or those with cardiovascular disease (Robinson 1997). In TIVA, the anaesthetic agent is not measured, but the plasma and effect-site concentration is calculated using an algorithm built in to the infusion pump; the anaesthetic can then be administered to a target effect-site concentration, and this is known as a target-controlled infusion (TCI). The algorithm is dependant on the gender, age, height, and weight of the patient, but is less reliable in certain patient groups, including the elderly. As the concentration of anaesthetic agent is calculated rather than measured, it has been proposed that the depth of anaesthesia should be monitored using electroencephalogram (EEG)-based devices in patients undergoing TIVA in order to reduce the risk of accidental awareness (Checketts 2016).

The use of EEG-based depth of anaesthesia monitoring in the elderly population, in order to minimise the risk of the administration of excessive doses of sedative or anaesthetic agents, has been shown to reduce the incidence of postoperative cognitive complications and hypotension (Ballard 2012; Chan 2013; Sieber 2010). As a result of this, its use is advocated for general anaesthesia for the elderly, regardless of technique, in national and international guidelines (Griffiths 2014; NICE 2012).

Why it is important to do this review

Traditionally, surgical anaesthesia has been maintained with inhalational agents, however the introduction of TCI pumps has made IV maintenance a viable alternative technique which presents a number of possible advantages. In terms of postoperative cognitive outcomes the optimal technique remains unknown. This review aims to help identify the anaesthetic technique that is optimal for elderly surgical patients in terms of postoperative cognitive function, cardiovascular stability, mortality, and length

of stay in hospital in order to optimise the use of healthcare resources and reduce the overall healthcare costs.

OBJECTIVES

To compare maintenance of general anaesthesia for elderly surgical patients using total intravenous anaesthesia (TIVA) or inhalational anaesthesia on postoperative cognitive function, mortality, risk of hypotension, length of stay in the postanaesthetic care unit (PACU), and hospital stay.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all randomized controlled trials (RCTs) including quasi-randomized studies (for example, in which the method of assignment is by alternation, date of birth, or medical record number).

Types of participants

The United Nations defines the older population as 60 years of age and above (WHO 2016b). We will therefore include participants aged 60 years and above, undergoing surgery under general anaesthesia. We will exclude participants undergoing cardiac surgery due to the differences in the provision of general anaesthesia whilst on bypass, and the additional risk of postoperative cognitive complications associated with extracorporal support. If studies include participants who are aged under 60 years, we will include the study if it is possible to identify the ratio of participants who are aged over 60 years; if the ratio is above 75%, and this is distributed evenly between intervention groups, we will include these studies.

Types of interventions

We will include studies that compare maintenance of anaesthesia with propofol-based TIVA versus inhalational anaesthesia. Comparisons of inhalational maintenance anaesthesia will include both inhalational and IV induction of anaesthesia.

Types of outcome measures

We aim to establish if one type of maintenance of anaesthesia reduces postoperative delirium and postoperative cognitive dysfunction in participants as these are associated with both an increased length of hospital stay and risk of mortality. Our secondary outcomes establish if one method reduces the incidence of hypotension (a proposed cause of postoperative delirium and postoperative cognitive dysfunction), mortality, length of stay in the PACU, and overall hospital admission time, as these have significant cost implications to healthcare settings.

Primary outcomes

1. Postoperative delirium; as measured by a validated tool or diagnostic criteria, e.g. Diagnostic and Statistical Manual of Mental Disorders (DSM-5 2013), confusion assessment method (CAM) (Inouye 1990), International Classification of Diseases-10 (WHO 2016a).
2. Postoperative cognitive dysfunction; as defined and measured by the study authors.

Secondary outcomes

1. Mortality at 30 days.
2. Intraoperative hypotension as defined by the study authors (for example, mean arterial pressure (MAP) < 65 mmHg, drop in MAP > 20% from baseline value).
3. Length of stay in the PACU.
4. Length of hospital stay.

Search methods for identification of studies

Electronic searches

We will search for eligible trials in the following databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (via Ovid) (from 1946 to the present), PsycINFO (from 1967 to present), and Embase (via Ovid) (From 1974 to the present). The Cochrane highly sensitive filter for RCTs will be applied in MEDLINE and Embase. Our search strategy for MEDLINE is in Appendix 1. We will adapt this strategy for searching other databases. We will not use any restriction on language of publication.

We will also search the trial registers: ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform for ongoing trials (who.int/ictrp/network/en).

Searching other resources

We will undertake backward citation tracking of any potentially relevant reviews identified during the database searches. We will carry out forward citation tracking of any studies identified for inclusion. We will also carry out grey literature searching through Opengrey (available at opengrey.eu).

Data collection and analysis

Two review authors will independently assess trial quality and extract data (DM and CS), consulting with a third review author for disagreements (SRL). We will use standard Cochrane methodological procedures, including assessment of risk of bias for all studies.

Selection of studies

We will use reference management software to collate the results of the searches and to remove duplicates (Endnote 2011). We will use Covidence software to screen the results of the search from the titles and abstracts and identify any potentially relevant studies from this information alone (Covidence 2016). We will source the full texts of all those potentially relevant studies and consider whether they meet the inclusion criteria. We will include abstracts at this stage. However, we will only include these in the review if they contain sufficient information and relevant results that include denominator figures for each intervention/comparison group. We will record the number of papers retrieved at each stage and report this using a PRISMA flow chart (Moher 2009). We will report brief details of closely-related, but excluded papers in the review.

Data extraction and management

We will use Covidence software to extract data from individual studies (Covidence 2016). A basic template of the data extraction forms are available at www.covidence.org. We will adapt the template to include the following information.

- Methods: type of study design, setting, dates of study, funding sources.
- Participants: number randomized to each group, baseline characteristics (age, urgency of surgery, American Society of Anesthesiologists (ASA) grade and type of surgery).
- Intervention: details of anaesthetic techniques (induction technique, type of volatile agents used, use of depth of anaesthesia monitoring, dose of anaesthetic agents given (i.e. mean alveolar concentration (MAC)/target-controlled infusion (TCI)/manual infusion), use and dose of concomitant drugs (i.e. analgesics, anticholinergics, antiemetics, hypnotics, vasoactive drugs), use of regional anaesthesia in addition to general anaesthesia).
- Outcomes: data for all reported review outcomes to include study author definitions, measurement tools, and time points.

We will consider the applicability of information from individual studies and generalizability of the data to our intended study population (i.e. the potential for indirectness in our review). If there are associated publications from the same study, we will create a composite data set from all the eligible publications.

Assessment of risk of bias in included studies

We will assess study quality, study limitations, and the extent of potential bias using the Cochrane 'Risk of bias' tool (Higgins 2011). We will consider the following domains.

1. Sequence generation (selection bias).
2. Allocation concealment (selection bias).
3. Blinding of participants, personnel, and outcomes assessors (performance and detection bias).
4. Incomplete outcome data (attrition bias).
5. Selective outcome reporting (reporting bias).
6. Other - use of concomitant drugs.

It will not be feasible to blind personnel to the study intervention, and we acknowledge that this introduces an unavoidable risk of performance bias in any eligible study. However, it is feasible for outcome assessors to be blinded for all outcomes, except hypotension, and possibly length of stay in the PACU. In addition to the standard risk of bias domains, we will also collect data on the use of concomitant drugs such as opiate analgesics, anticholinergics, antiemetics, and benzodiazapines, which are known or suspected to increase the risk or delirium (Clegg 2011).

For each domain, two review authors (CS and DM) will judge whether study authors have made sufficient attempts to minimize bias in their study design. We will make judgements using three measures - high, low, or unclear risk of bias. We will record this in 'Risk of bias' tables and present a summary 'Risk of bias' figure.

Measures of treatment effect

We will collect dichotomous data for 30-day mortality. We anticipate that postoperative delirium and postoperative cognitive dysfunction will be measured using a scale, either validated (for example, CAM) or determined by the study authors. We will establish an appropriate cut-off on such scale (delirium versus no delirium), so that the data can be recorded as dichotomous. We will record data for hypotension as dichotomous using cut-offs defined by the study authors. We will collect length of recovery in the PACU and length of hospital stay as continuous data.

Unit of analysis issues

It is possible that studies may compare TIVA against different anaesthetic induction and maintenance strategies in multi-arm study designs. For example, TIVA could be compared against an IV induction with inhalational maintenance, and also against an inhalational induction with inhalational maintenance within the same study. For our primary analysis, we will combine the two

comparison groups for comparison with TIVA. In subgroup analysis, however, we will analyse these comparison groups separately against TIVA, and will use the 'halving' method for the TIVA group to ensure that no double-counting occurs (Higgins 2011).

Dealing with missing data

We will contact authors to request any missing outcome data. If we are unable to obtain this data, we will impute the missing values with replacement values based on 'worst-case' and 'best-case' scenarios alongside clinical judgement as appropriate. In the case of missing statistics, for example, standard deviations, we will impute missing values with replacement values based only on those of other included studies that use the same scale. In the absence of equivalent study data we will impute a change-from-baseline standard deviation using a correlation coefficient as described by (Higgins 2011, chapter 16.1.3.2.).

Assessment of heterogeneity

We will assess whether there is evidence of inconsistency within our results through consideration of heterogeneity. We will assess clinical heterogeneity by comparing similarities between the participants, the interventions, and outcomes in our included studies. We will assess statistical heterogeneity by calculation of the Chi^2 (with an associated P value) or I^2 statistic (with an associated percentage). We will judge any heterogeneity above 60% as a reason not to pool the data, unless we consider the heterogeneity to be not clinically important.

As well as looking at the statistical results, we will consider the point estimates and the overlap of confidence intervals (CIs). If the CIs overlap, then the results are more consistent. However, it is also possible for combined studies to show a large consistent effect, but with significant heterogeneity. We will therefore interpret heterogeneity with caution (Guyatt 2011a).

Assessment of reporting biases

We will attempt to source published protocols for each of our included studies using clinical trial registers. We will compare published protocols with published study results to assess the risk of selective reporting bias. If there are sufficient studies, i.e. more than 10 (Higgins 2011), we will generate a funnel plot to assess the risk of publication bias in the review; an asymmetric funnel plot may indicate potential publication of only positive results (Egger 1997).

Data synthesis

We will complete a meta-analysis for outcomes for which we have comparable effect measures from more than one study, and where measures of heterogeneity indicate that pooling of results is appropriate. We will use the statistical calculator in Review Manager 5 (RevMan 2014).

For dichotomous outcomes, for example, mortality rate, we will calculate the odds ratio using the summary data presented in each trial. We will use the Mantel-Haenszel effects model, unless events are extremely rare (1 per 1000), in which case we will use Peto (Higgins 2011). For continuous outcomes, for example, length of hospital stay, we will use mean difference. Our final choice of fixed-effect or random-effects statistical model will be influenced by the level of identified heterogeneity and the number of studies. We will calculate CIs at 95% and will use a P value of 0.05 or below to judge if a result is statistically significant. We will consider whether there is imprecision in the results of analysis by assessing the CI around an effects measure; a wide CI would suggest a higher level of imprecision in our results. A small number of studies may also reduce the precision (Guyatt 2011b).

Subgroup analysis and investigation of heterogeneity

We will undertake a subgroup analysis when there are sufficient studies which report the relevant characteristic (Higgins 2011). The United Nations' definition of old age is over 60 years, however many surgical patients in early old age (under 80 years of age) are fit with few comorbidities, whilst patients aged 80 years and over are at an increased risk of adverse outcomes (NCEPOD 2010). Other sources of potential heterogeneity include the urgency of surgery, with non-elective surgery being associated with an increased risk of postoperative cognitive problems (Raats 2015), and the use of depth of anaesthesia monitoring, which is associated with a reduction in intra- and postoperative complications (Ballard 2012; Chan 2013). We will also use subgroup analysis to explore differences in results for the inhalational maintenance group, in which induction may be undertaken using either inhalational or IV agents. We will only conduct a subgroup analysis based on information presented in the written paper. In summary, subgroups will be:

1. elderly (60 to 79 years of age) versus late elderly (80 years of age or older);
2. elective versus non-elective surgery;
3. inhalational induction versus IV induction (as a subgroup of inhalational maintenance only);
4. TCI versus non-TCI maintenance of anaesthesia (as a subgroup of TIVA only); and
5. use of depth of anaesthesia monitoring.

Sensitivity analysis

We will explore the potential effects of decisions made as part of the review process as follows.

1. We will exclude all studies that we have judged to be at high or unclear risk of selection bias.

2. We will assess decisions made for missing data, conducting meta-analysis using alternate data (for example, 'worst-case' or 'best-case' scenario data).

3. We will conduct a meta-analysis using the alternate meta-analytic effects model (fixed-effect or random-effects).

We will compare effect estimates from the above results with effect estimates from the main analysis. We will report differences that alter interpretation of the effect.

Summary of findings

The GRADE Working Group approach incorporates assessment of indirectness, study limitations, inconsistency, publication bias, and imprecision (Atkins 2004). We will make these assessments at each stage of our analysis detailed above (Data collection and analysis; Assessment of risk of bias in included studies; Assessment of heterogeneity; Assessment of reporting biases; Data synthesis). This approach gives an overall measure of how confident we can be that our estimate of effect is correct (Guyatt 2008).

We will use the principles of the GRADE system to give an overall assessment of the evidence relating to each of the following outcomes: postoperative delirium, postoperative cognitive dysfunction, mortality within 30 days, intraoperative hypotension, length of stay in the PACU, and overall hospital length of stay.

Two review authors (DM and CS) will independently use the GRADEpro software to create a 'Summary of findings' table for each comparison (GRADEpro GDT 2014). We will reach consensus and resolve disagreements using a third review author (SRL), if required.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

1. Anesthesia, Intravenous/ or Anesthesia, Inhalation/ or (an?esthe* adj2 (iv or intravenous or inhalation* or volatile)).mp. or (TIVA or propofol or halothane or enflurane or isoflurane or desflurane).mp.
2. (Geriatric* or Elder* or old-age* or pensioner*).ti,ab.
3. ((Aging or aged or senior or old*) adj2 (wom#n or m#n or lady or ladies or adult* or citizen* or population*1 or people or person)).ti,ab.
4. exp Aged/ or exp geriatrics/
5. 2 or 3 or 4
6. 1 and 5
7. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (animals not (humans and animals)).sh.
8. 6 and 7

CONTRIBUTIONS OF AUTHORS

David Miller (DM), Cliff Shelton (CS), Sharon R Lewis (SRL), Phil Alderson (PA), Andrew F Smith (AS)

Conceiving the review: SRL, PA, AS

Co-ordinating the review: SRL

Undertaking manual searches: DM, CS, SRL

Screening search results: DM, CS

Organizing retrieval of papers: SRL

Screening retrieved papers against inclusion criteria: DM, CS

Appraising quality of papers: DM, CS

Extracting data from papers: DM, CS

Writing to authors of papers for additional information: DM, CS

Obtaining and screening data on unpublished studies: DM, CS

Data management for the review: DM, CS, SRL

Entering data into Review Manager (RevMan 2014): DM

RevMan statistical data: DM, CS, SRL

Other statistical analysis not using RevMan: DM, CS, SRL

Interpretation of data: DM, CS

Statistical inferences: DM, CS

Writing the review: DM

Securing funding for the review: AS, DM, CS

Guarantor for the review (one author): AS

Person responsible for reading and checking review before submission: SRL

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