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Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery (Review)

Miller D, Lewis SR, Pritchard MW, Schofield-Robinson OJ, Shelton CL, Alderson P, Smith AF

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[Intervention Review]

Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery

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ABSTRACT

Background

The use of anaesthetics in the elderly surgical population (more than 60 years of age) is increasing. Postoperative delirium, an acute condition characterized by reduced awareness of the environment and a disturbance in attention, typically occurs between 24 and 72 hours after surgery and can affect up to 60% of elderly surgical patients. Postoperative cognitive dysfunction (POCD) is a new-onset of cognitive impairment which may persist for weeks or months after surgery.

Traditionally, surgical anaesthesia has been maintained with inhalational agents. End-tidal concentrations require adjustment to balance the risks of accidental awareness and excessive dosing in elderly people. As an alternative, propofol-based total intravenous anaesthesia (TIVA) offers a more rapid recovery and reduces postoperative nausea and vomiting. Using TIVA with a target controlled infusion (TCI) allows plasma and effect-site concentrations to be calculated using an algorithm based on age, gender, weight and height of the patient.

TIVA is a viable alternative to inhalational maintenance agents for surgical anaesthesia in elderly people. However, in terms of postoperative cognitive outcomes, the optimal technique is unknown.

Objectives

To compare maintenance of general anaesthesia for elderly people undergoing non-cardiac surgery using propofol-based TIVA or inhalational anaesthesia on postoperative cognitive function, mortality, risk of hypotension, length of stay in the postanaesthesia care unit (PACU), and hospital stay.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 11), MEDLINE (1946 to November 2017), Embase (1974 to November 2017), PsycINFO (1887 to November 2017). We searched clinical trials registers for ongoing studies, and conducted backward and forward citation searching of relevant articles.

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Selection criteria

We included randomized controlled trials (RCTs) with participants over 60 years of age scheduled for non-cardiac surgery under general anaesthesia. We planned to also include quasi-randomized trials. We compared maintenance of anaesthesia with propofol-based TIVA versus inhalational maintenance of anaesthesia.

Data collection and analysis

Two review authors independently assessed studies for inclusion, extracted data, assessed risk of bias, and synthesized findings.

Main results

We included 28 RCTs with 4507 randomized participants undergoing different types of surgery (predominantly cardiovascular, laparoscopic, abdominal, orthopaedic and ophthalmic procedures). We found no quasi-randomized trials. Four studies are awaiting classification because we had insufficient information to assess eligibility.

All studies compared maintenance with propofol-based TIVA versus inhalational maintenance of anaesthesia. Six studies were multi-arm and included additional TIVA groups, additional inhalational maintenance or both. Inhalational maintenance agents included sevoflurane (19 studies), isoflurane (eight studies), and desflurane (three studies), and was not specified in one study (reported as an abstract). Some studies also reported use of epidural analgesia/anaesthesia, fentanyl and remifentanil.

We found insufficient reporting of randomization methods in many studies and all studies were at high risk of performance bias because it was not feasible to blind anaesthetists to study groups. Thirteen studies described blinding of outcome assessors. Three studies had a high of risk of attrition bias, and we noted differences in the use of analgesics between groups in six studies, and differences in baseline characteristics in five studies. Few studies reported clinical trials registration, which prevented assessment of risk of selective reporting bias.

We found no evidence of a difference in incidences of postoperative delirium according to type of anaesthetic maintenance agents (odds ratio (OR) 0.59, 95% confidence interval (CI) 0.15 to 2.26; 321 participants; five studies; very low-certainty evidence); we noted during sensitivity analysis that using different time points in one study may influence direction of this result. Thirteen studies (3215 participants) reported POCD, and of these, six studies reported data that could not be pooled; we noted no difference in scores of POCD in four of these and in one study, data were at a time point incomparable to other studies. We excluded one large study from meta-analysis because study investigators had used non-standard anaesthetic management and this study was not methodologically comparable to other studies. We combined data for seven studies and found low-certainty evidence that TIVA may reduce POCD (OR 0.52, 95% CI 0.31 to 0.87; 869 participants).

We found no evidence of a difference in mortality at 30 days (OR 1.21, 95% CI 0.33 to 4.45; 271 participants; three studies; very low-certainty evidence). Twelve studies reported intraoperative hypotension. We did not perform meta-analysis for 11 studies for this outcome. We noted visual inconsistencies in these data, which may be explained by possible variation in clinical management and medication used to manage hypotension in each study (downgraded to low-certainty evidence); one study reported data in a format that could not be combined and we noted little or no difference between groups in intraoperative hypotension for this study. Eight studies reported length of stay in the PACU, and we did not perform meta-analysis for seven studies. We noted visual inconsistencies in these data, which may be explained by possible differences in definition of time points for this outcome (downgraded to very low-certainty evidence); data were unclearly reported in one study. We found no evidence of a difference in length of hospital stay according to type of anaesthetic maintenance agent (mean difference (MD) 0 days, 95% CI -1.32 to 1.32; 175 participants; four studies; very low-certainty evidence).

We used the GRADE approach to downgrade the certainty of the evidence for each outcome. Reasons for downgrading included: study limitations, because some included studies insufficiently reported randomization methods, had high attrition bias, or high risk of selective reporting bias; imprecision, because we found few studies; inconsistency, because we noted heterogeneity across studies.

Authors' conclusions

We are uncertain whether maintenance with propofol-based TIVA or with inhalational agents affect incidences of postoperative delirium, mortality, or length of hospital stay because certainty of the evidence was very low. We found low-certainty evidence that maintenance with propofol-based TIVA may reduce POCD. We were unable to perform meta-analysis for intraoperative hypotension or length of stay in the PACU because of heterogeneity between studies. We identified 11 ongoing studies from clinical trials register searches; inclusion of these studies in future review updates may provide more certainty for the review outcomes.

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PLAIN LANGUAGE SUMMARY

Injected versus inhaled medicines to maintain general anaesthesia during non-cardiac surgery for cognitive outcomes in elderly people

Background

Anaesthesia during surgery in elderly people (more than 60 years of age) is increasing.

Traditionally, general anaesthesia is maintained with an inhaled drug (a vapour which the patient breathes in) which needs to be adjusted to ensure that the patient remains unconscious during surgery without receiving too much anaesthetic. An alternative method is to use propofol which is injected into a vein throughout the anaesthetic procedure; this is called total intravenous anaesthesia (TIVA).

Elderly people are more likely to experience confusion or problems with thinking following surgery, which can occur up to several days postoperatively. These cognitive problems can last for weeks or months, and can affect the patients' ability to plan, focus, remember, or undertake activities of daily living. We looked at two types of postoperative confusion: delirium (a problem with awareness and attention which is often temporary) and cognitive dysfunction (a persistent problem with brain function).

TIVA with propofol may be a good alternative to inhaled drugs, and it is known that patients who have TIVA experience less nausea and vomiting, and wake up more quickly after anaesthesia. However, it is unknown which is the better anaesthetic technique in terms of postoperative cognitive outcomes.

Review question

To compare maintenance of general anaesthesia for elderly people undergoing non-cardiac surgery using TIVA or inhalational anaesthesia on postoperative cognitive function, number of deaths, risk of low blood pressure during the operation, length of stay in the postanaesthesia care unit (PACU), and hospital stay.

Study characteristics

The evidence is current to November 2017. We included 28 randomized studies with 4507 participants in the review. We are awaiting sufficient information for the classification of four studies.

All studies included elderly people undergoing non-cardiac surgery and compared use of propofol-based TIVA versus inhalational agents during maintenance of general anaesthesia.

Key results

We found little or no difference in postoperative delirium according to the type of anaesthetic maintenance agents from five studies (321 participants). We found that fewer people experienced postoperative cognitive dysfunction when TIVA with propofol was used in seven studies (869 participants). We excluded one study from analysis of this outcome because study authors had used methods to anaesthetize people which were not standard.

We found little or no difference in the number of deaths from three studies (271 participants). We did not combine data for low blood pressure during the operation or length of stay in the PACU because we noted differences in studies, which may be explained by differences in patient management (for low blood pressure), and differences in how length of stay in the PACU is defined in each study . We found little or no difference in length of hospital stay from four studies (175 participants).

Quality of the evidence

Many studies did not report randomization methods adequately and all studies were at high risk of bias from anaesthetists, who needed to be aware of which anaesthetic agent they used. Outcome assessors in some studies were aware of which study group participants were in. We noted a large loss of participants in three studies, and some studies had differences between groups in the types of drugs used for pain, the types of monitors used to assess how deeply-unconscious the patients were, and participant characteristics at the start of the studies; these factors may have influenced the results. Few studies had reported clinical trials registration. We found few studies for two outcomes (mortality and length of hospital stay), which made the results less precise. We judged evidence for postoperative delirium, number of deaths, length of stay in the PACU, and length of hospital stay to be very low certainty, and evidence for postoperative cognitive dysfunction, and low blood pressure during the operation to be low certainty.

TIVA with propofol may reduce postoperative cognitive dysfunction. We are uncertain whether the choice of anaesthetic agents (TIVA with propofol, or inhalational agents) affects postoperative delirium, mortality and length of hospital stay. We found 11 ongoing studies

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in database and clinical trials register searches. Inclusion of these studies in future review updates will provide more certainty for the review outcomes.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Intravenous maintenance of anaesthesia compared with inhalational maintenance of anaesthesia in elderly people undergoing non-cardiac surgery

Participants: elderly people, aged 60 years and above, undergoing non-cardiac surgery under general anaesthesia
Settings: hospitals in: Belgium, Canada, China, Egypt, France, Germany, Greece, Ireland, Japan, Norway, South Korea, Spain, Sweden, Turkey, UK, USA
Intervention: intravenous maintenance of anaesthesia with: propofol
Comparison: inhalational maintenance of anaesthesia with: sevoflurane, isoflurane, or desflurane

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Inhalational maintenance	Risk with TIVA				
Postoperative delirium (One study used DRS, three studies used CAM and in one study diagnostic tool was not reported) Time points were up to 4 days postoperatively	Study population		OR 0.59 (0.15 to 2.26)	321 (5 studies)	**very low** [a]	
	61 per 1,000	37 per 1,000 (10 to 129)				
Postoperative cognitive dysfunction (9 studies used MMSE, and 2 of these studies used additional diagnostic tools; 1 study used Trail Making Test and additional diagnostic tools; 3 studies did not report diagnostic tools) Time points were up to 30 days postoperatively	Study population		OR 0.52 (0.31 to 0.87)	869 (7 studies)	**low** [b]	Overall, 13 studies (3215 participants) reported data for this outcome. We performed meta-analysis on 7 studies We excluded 1 large study from this analysis which used non-standard anaesthetic management 5 studies reported data in formats that could

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						not be combined. Of these 5: we noted no apparent differences in mean MMSE scores in 3 studies; 1 study reported similar scores in each group; 1 study included data at 2 years and was not comparable with our other data
	285 per 1,000	172 per 1,000 (110 to 257)				
Mortality At 30 days	Study population		OR 1.21, (95% CI 0.33 to 4.45)	271 (3 studies)	**very low**[c]	Overall, 4 studies reported mortality. We did not include 1 study in analysis because number of deaths (3 in total) were not reported by group
	29 per 1,000	35 per 1,000 (10 to 119)				
Intraoperative hypotension (defined by study authors as change in MAP from baseline)	-	See comment	-	1145 (12 studies)	**low**[d]	Overall, 12 studies (1145 participants) reported intraoperative hypotension. 1 study reported data in a format that could not be combined with other study data (we noted little or no apparent difference in hypotension in this study) We did not pool data in 11 studies; we noted inconsistencies in visual inspection of the data which could be explained by variation

						in clinical management and medication used to manage hypotension in
Length of stay in PACU (measured in minutes)	-	see comment	-	567 (8 studies)	**very low**[e]	We did not pool data in seven studies: we noted inconsistencies in visual inspection of the data and we expected that studies used different definitions of time points to assess length of time in the PACU Data were unclearly reported in one study
Length of hospital stay (measured in days)	-	MD 0 days higher (1.32 days lower to 1. 32 days higher)	-	175 (4 studies)	**very low**[f]	Overall, 6 studies (375 participants) reported data for this outcome. Of 4 combined studies, mean scores in the inhalational maintenance group ranged from 1. 3 days to 15 days. 2 studies reported data that could not be combined with other studies (we noted little or no difference in median length of stay between groups)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CAM: Confusion Assessment Method; **CI:** confidence interval; **DRS:** Delirium Rating Scale; **MAP:** mean arterial pressure; **MD:** mean difference; **MMSE:** Mini-Mental State Examination; **OR:** odds ratio; **PACU:** postanaesthesia care unit

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GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] We downgraded by one level for study limitations; we noted few included studies for this outcome had sufficiently reported methods of randomization and we were concerned by high risk of attrition bias in two studies and high risk of selective outcome reporting bias in one study. We downgraded by two levels for inconsistency; we could not be certain whether measurements of delirium, and time points of measurement, were equivalent between studies, and we used sensitivity analysis to show that choice of time point in one study may influence direction of this result

[b] We downgraded by one level for study limitations; we noted that some studies had insufficiently reported methods of randomization and we were concerned by high risk of attrition bias in one study. We downgraded by one level for inconsistency; we noted a moderate level of statistical heterogeneity (I^2 = 41%) which we were unable to explain in subgroup analysis

[c] We downgraded by one level for study limitations; we noted that some studies had insufficiently reported methods of randomization. Analysis included few studies with few participants and, because deaths due to anaesthesia are rare we would require a large sample size to show evidence of a difference; we downgraded by two levels for imprecision.

[d] We downgraded by one level for study limitations; we noted some studies reported insufficient methods of randomization. We downgraded by one level for inconsistency because of statistical heterogeneity (I^2 = 63%) and noted differences in visual inspection of results; this could be explained by possible variation in clinical management and medication used to manage hypotension in each study

[e] We downgraded by one level for study limitations; we noted some studies reported insufficient methods of randomization. We downgraded by two levels for inconsistency; we noted substantial statistical heterogeneity (I^2 = 94%) and differences in visual inspection of results which may be explained by likely differences in study designs related to definitions of time points of measurement for this outcome

[f] Few studies with few participants; we downgraded by two levels for imprecision. We noted a moderate level of statistical heterogeneity (I^2 = 41%) and noted differences in visual inspection of results; we downgraded by one level for inconsistency

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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 (> 60 years of age) 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 (Rundshagen 2014). 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 following surgery (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 (which may be given at high or low initial concentrations; Boonmak 2016), 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 ventilation and increased cardiovascular stability. In many patients, anaesthesia is maintained by the inhalation of volatile agents (typically sevoflurane, desflurane, or isoflurane, historically also enflurane and halothane). 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, with or without nitrous oxide (Hounsome 2016), (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 minimum alveolar concentration (MAC). In order to prevent awareness, it is suggested that the end-tidal volatile concentration should exceed 0.7 MAC (Pandit 2013). 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 2005). 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 may be calculated

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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).

Monitors of anaesthetic depth have been widely available for some years. They enable titration of dose of general anaesthetic both to avoid unnecessarily high doses and also the risk of accidental awareness if too little anaesthetic is given (Chhabra 2016; Messina 2016; Punjasawadwong 2014). The use of EEG-based depth of anaesthesia monitoring in the elderly population, in order to minimize 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 new technologies 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 optimize the use of healthcare resources and reduce the overall healthcare costs.

OBJECTIVES

To compare maintenance of general anaesthesia for elderly people undergoing non-cardiac surgery using propofol-based TIVA or inhalational anaesthesia on postoperative cognitive function, mortality, risk of hypotension, length of stay in the postanaesthesia care unit (PACU), and hospital stay.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomized controlled trials (RCTs), and aimed to include 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 therefore included participants aged 60 years and above, undergoing surgery under general anaesthesia. We excluded 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 included participants less than 60 years of age, we included the study if it was possible to identify the ratio of participants who were more than 60 years of age; if the ratio was more than 75%, and this was distributed evenly between intervention groups, we included these studies.

Types of interventions

We included studies that compared maintenance of anaesthesia with propofol-based TIVA versus inhalational anaesthesia. Comparisons of inhalational maintenance anaesthesia included both inhalational and IV induction of anaesthesia.

Types of outcome measures

We aimed 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.

We excluded studies that did not measure any of the review outcomes. See Differences between protocol and review.

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.

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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 (measured as minutes).
4. Length of hospital stay (measured as days).

Search methods for identification of studies

Electronic searches

We identified RCTs through literature searching with systematic and sensitive search strategies as outlined in Chapter 6.4 of the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011). We applied no restrictions to language or publication status.

We searched the following databases for relevant trials.

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 11)
2. MEDLINE (Ovid SP, 1946 to 20 November 2017)
3. Embase (Ovid SP, 1974 to 20 November 2017)
4. PsycINFO (EBSCO, 1887 to 21 November 2017)

We developed a subject-specific search strategy in MEDLINE and used that as the basis for the search strategies in the other listed databases. The search strategy was developed in consultation with the Information Specialist. Search strategies can be found in Appendix 1, Appendix 2, Appendix 3, Appendix 4.

We scanned the following trials registries for ongoing and unpublished trials (20 November 2017).

1. The World Health Organization International Clinical Trials Registry Platform (WHOICTRP) (who.int/ictrp/network/en)
2. https://clinicaltrials.gov/

Searching other resources

We carried out citation searching of identified included studies in Web of Science (apps.webofknowledge.com), and Google Scholar (scholar.google.co.uk), on 23 November 2017 and conducted a search of grey literature through 'Opengrey' (www.opengrey.eu./), on 5 December 2017. We carried out backward citation searching of key reviews identified from the searches.

Data collection and analysis

Two review authors (SRL and DM, OSR, or MP) independently assessed trial quality and extracted data. Consensus was reached through discussion. We used standard Cochrane methodological procedures, including assessment of risk of bias for all studies.

Selection of studies

We used reference management software to collate the results of the searches and to remove duplicates (Endnote 2011). We used 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 sourced the full texts of all those potentially relevant studies and considered whether they met the inclusion criteria. We included abstracts at this stage. However, we only included these in the review if they contained sufficient information and relevant results that included denominator figures for each intervention/comparison group. We recorded the number of papers retrieved at each stage and reported this using a PRISMA flow chart (Moher 2009). We reported brief details of closely-related, but excluded papers in the review.

Data extraction and management

We used 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 adapted the template to include the following information.

1. Methods: type of study design, setting, dates of study, funding sources.
2. Participants: number randomized to each group, baseline characteristics (age, urgency of surgery, American Society of Anesthesiologists (ASA) grade and type of surgery).
3. 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. minimum 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).
4. Outcomes: data for all reported review outcomes to include study author definitions, measurement tools, and time points.

We considered 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 were associated publications from the same study, we created a composite data set from all the eligible publications.

Assessment of risk of bias in included studies

We assessed study quality, study limitations, and the extent of potential bias using the Cochrane 'Risk of bias' tool (Higgins 2011). We considered 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).

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6. Other - use of concomitant drugs.

It is not 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. In addition to the standard risk of bias domains, we also collected data on the use of concomitant drugs such as opiate analgesics, anticholinergics, antiemetics, and benzodiazapines, which are known or suspected to increase the risk of delirium (Clegg 2011).

For each domain, two review authors (SRL and DM, OSR, or MP) judged whether study authors made sufficient attempts to minimize bias in their study design. We made judgements using three measures - high, low, or unclear risk of bias. We recorded this in 'Risk of bias' tables and presented a summary 'Risk of bias' figure.

Measures of treatment effect

We collected dichotomous data for 30-day mortality. We anticipated that postoperative delirium and postoperative cognitive dysfunction would be measured using a scale, either validated (e.g. CAM) or determined by the study authors. We planned to establish an appropriate cut-off on such scales (delirium versus no delirium), so that the data could be recorded as dichotomous. We recorded data for hypotension as dichotomous using cut-offs defined by the study authors. We collected length of recovery in the PACU and length of hospital stay as continuous data.

Unit of analysis issues

It was possible that studies may have compared 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 combined the two comparison groups for comparison with TIVA. In subgroup analysis, however, we analysed these comparison groups separately against TIVA, and used the 'halving' method for the TIVA group to ensure that no double-counting occurred (Higgins 2011).

Dealing with missing data

In the event that study authors reported loss of participants during follow-up, we did not impute values but reported data as analysed by study authors. We used sensitivity analysis to explore the effect of including studies with high risk of attrition bias. See Differences between protocol and review, and sensitivity analysis in Effects of interventions.

Assessment of heterogeneity

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

As well as looking at the statistical results, we considered 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 therefore interpreted heterogeneity with caution (Guyatt 2011a).

Assessment of reporting biases

We attempted to source published protocols for each of our included studies using clinical trials registers. We compared published protocols with published study results to assess the risk of selective reporting bias. If there were sufficient studies, i.e. more than 10 (Higgins 2011), we planned to 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 completed a meta-analysis for outcomes for which we had comparable effect measures from more than one study, and where measures of heterogeneity indicated that pooling of results was appropriate. We used the statistical calculator in Review Manager 5 (Review Manager 2014).

For dichotomous outcomes, for example, mortality rate, we calculated the odds ratio (OR) using the summary data presented in each trial. We used the Mantel-Haenszel effects model, unless events were extremely rare (1 per 1000), in which case we planned to use the Peto method (Higgins 2011). For continuous outcomes, for example, length of hospital stay, we used mean difference (MD). We used a random-effects statistical model which allowed for differences between studies (for example, because of different types of surgery (Borenstein 2010).

We calculated CIs at 95% and used a P value of 0.05 or below to judge if a result was statistically significant. We considered whether there was imprecision in the results of analysis by assessing the CI around the relative effects measure; a wide CI suggested 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 undertook a subgroup analysis when there were sufficient studies that reported the relevant characteristic (Higgins 2011). We

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used RevMan 5 to calculate differences in subgroups, based on the test for heterogeneity Chi^2 statistics (Review Manager 2014); we used a P value $\geq$ 0.05 to indicate a statistically significant difference between subgroups.

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 80 years of age 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 also used subgroup analysis to explore differences in results for the inhalational maintenance group, in which induction was undertaken using either inhalational or IV agents. We only conducted a subgroup analysis based on information presented in the written paper. In summary, subgroups were:

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 explored the potential effects of decisions made as part of the review process in the following way.

1. We excluded all studies that we judged to be at high or unclear risk of selection bias.
2. We excluded studies that we judged to have a high risk of attrition bias because of missing data for a large number of participants that were unevenly distributed or unclearly reported between groups. See Differences between protocol and review.
3. We conducted a meta-analysis using the alternate meta-analytic effects model (fixed-effect or random-effects).

We compared effect estimates from the above results with effect estimates from the main analysis. We reported differences that altered interpretation of the effect.

'Summary of findings' tables and GRADE

The GRADE Working Group approach incorporates assessment of indirectness, study limitations, inconsistency, publication bias, and imprecision (Atkins 2004). We made 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 used 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. We assessed the certainty of the evidence using one of four judgements (high, moderate, low, and very low).

One review author (SL) used the GRADEpro software to create a 'Summary of findings' table for each comparison (GRADEpro GDT). Consensus was reached with a second author (MP) who checked the table and approved judgements.

RESULTS

Description of studies

Results of the search

We screened 12,313 titles and abstracts from database searches, results from clinical trials register searches, grey literature searches, and forward and backward citation searches. We carried out full-text review of 440 articles. We excluded 397 studies, and reported details of 46 of these excluded studies. We identified 28 eligible studies, and 11 ongoing studies. We found four studies awaiting classification; we had insufficient information to assess review eligibility for these studies. See Figure 1.

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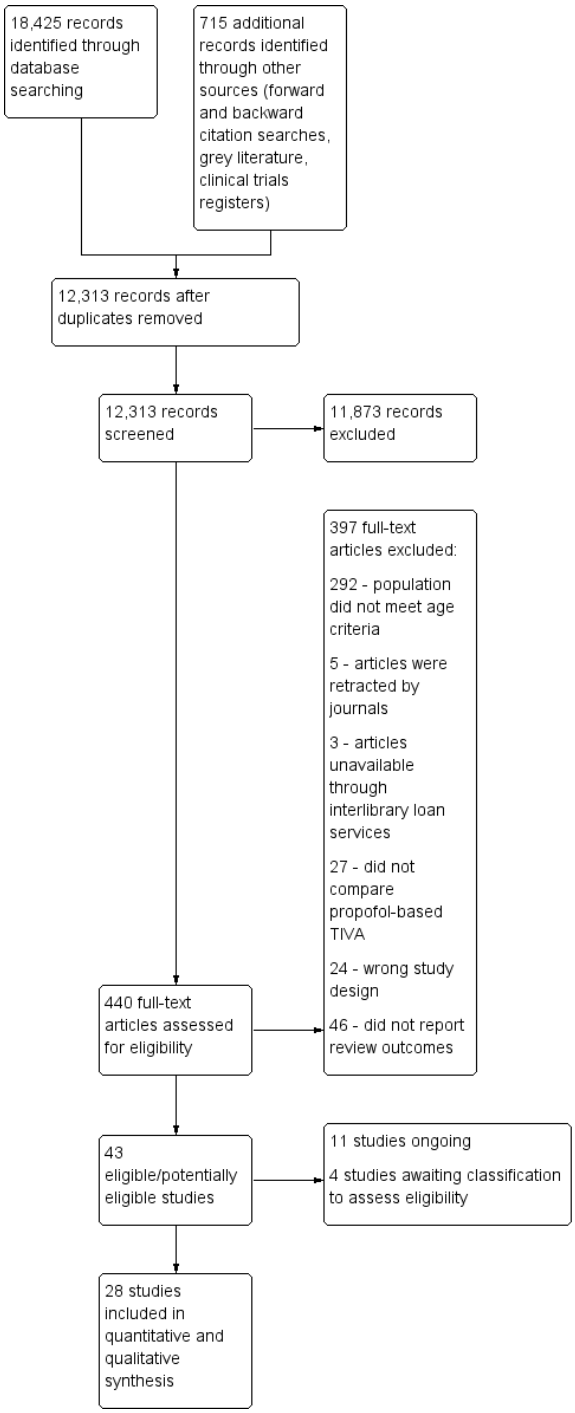
Figure 1. Study flow diagram



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Included studies

We included 28 parallel design randomized controlled trials (Ammar 2016; Biboulet 2012; Cai 2012a; Celik 2011; Chan 1996; Demeere 2006; Egawa 2016; Epple 2001; Geng 2017; Gursoy 2015; Ishii 2016; Jellish 2003; Juvin 1997; Kim 2015a; Lindholm 2013; Liu 2013; Longas 2004; Luntz 2004; Micha 2016; Moffat 1995; Nishikawa 2004; Rohan 2005; Tan 2009; Tanaka 2017; Tang 2014; Trembach 2012; Tylman 2011; Zhang 2015). We sourced no quasi-randomized studies. Included studies had an assumed total of 4507 randomized participants; two studies reported number of participants unclearly and we assumed totals from other data in the study reports (Jellish 2003; Longas 2004). One included study was an abstract with sufficient information regarding number of participants in each group and relevant outcome data (Trembach 2012). See Characteristics of included studies.

Study population and setting

Twenty-one studies specifically included elderly participants (Biboulet 2012; Cai 2012a; Celik 2011; Chan 1996; Epple 2001; Geng 2017; Gursoy 2015; Ishii 2016; Juvin 1997; Kim 2015a; Liu 2013; Luntz 2004; Micha 2016; Moffat 1995; Nishikawa 2004; Rohan 2005; Tan 2009; Tanaka 2017; Tang 2014; Trembach 2012; Zhang 2015). Seven studies did not report inclusion of elderly participants and we used mean ages reported in the baseline characteristics table to ascertain that more than 75% of participants were > 60 years of age (Ammar 2016; Demeere 2006; Egawa 2016; Jellish 2003; Lindholm 2013; Longas 2004; Tylman 2011). All participants were undergoing surgery which were typical of elderly patients. Surgery types were:

1. vascular surgery: abdominal aortic aneurysm (AAA) (Ammar 2016); open abdominal aortic surgery (Lindholm 2013); carotid endarterectomy (Jellish 2003; Longas 2004);
2. laparoscopic surgery: laparoscopic surgery (choledocholithotomy, colectomy, sigmoidectomy) (Nishikawa 2004); laparoscopic cholecystectomy (Geng 2017; Trembach 2012);
3. abdominal surgery: abdominal surgery (Tan 2009); laparotomy (Gursoy 2015); radical rectal resection surgery (Tang 2014); colorectal surgery (Tylman 2011); gastrectomy, colectomy, or rectectomy (Ishii 2016);
4. orthopaedic surgery: total hip replacement (Biboulet 2012; Chan 1996; Demeere 2006); hip arthroplasty, knee arthroplasty, laminectomy, other orthopaedic surgery (Juvin 1997); hip replacement, knee replacement, long bone fracture fixation, spinal surgery (Kim 2015a); spinal surgery (Liu 2013); total knee arthroplasty (Tanaka 2017);
5. ophthalmic surgery: cataract surgery (Epple 2001), cataract extraction and lens implantation (Moffat 1995); ophthalmic surgery (Luntz 2004); and
6. mixed surgery to include: oesophagectomy, gastrectomy, nephrectomy and fracture reduction (Cai 2012a); urological surgery (Celik 2011); one-lung surgery (Egawa 2016); minor urological or gynaecological surgery (Rohan 2005); tumour resection (Micha 2016); radical surgery (Zhang 2015).

We noted American Society of Anesthesiologists (ASA) status reported in studies. Four studies recruited participants with ASA I to II and did not report breakdown per group (Ammar 2016; Ishii 2016; Liu 2013; Tan 2009). Four studies recruited participants with ASA I to II (Juvin 1997; Kim 2015a; Nishikawa 2004; Zhang 2015), and most participants in these studies were ASA II. Eight studies recruited participants with ASA I to III; in four studies most participants were ASA II (Celik 2011; Chan 1996; Egawa 2016; Epple 2001), in one study most participants were ASA II and III (Micha 2016), and four studies did not report breakdown per group (Gursoy 2015; Luntz 2004; Moffat 1995; Tang 2014). One study recruited participants who were ASA II and III; in one study most participants were ASA II (Geng 2017), and in one study ASA status was evenly distributed (Tanaka 2017). Three studies recruited participants who were all ASA III (Jellish 2003; Longas 2004; Trembach 2012), and one study recruited participants who were ASA II, III, and IV, and most were ASA III (Lindholm 2013). One study recruited participants who were ASA III and IV, and most were ASA III (Biboulet 2012); this study recruited participants > 75 years of age. Four studies reported no ASA status (Cai 2012a; Demeere 2006; Rohan 2005; Tylman 2011). One study recruited participants with a body mass index (BMI) > 30 kg/m². Whilst some studies excluded patients who had existing neurological, psychiatric or cognitive disorders, or had dementia symptoms (Cai 2012a; Egawa 2016; Geng 2017; Gursoy 2015; Kim 2015a; Lindholm 2013; Micha 2016; Nishikawa 2004; Rohan 2005; Tan 2009; Tanaka 2017), we noted two studies included only participants who had existing mild cognitive impairment (Liu 2013; Tang 2014).

Interventions and comparators

All studies compared total intravenous anaesthesia (TIVA) using propofol versus maintenance anaesthesia using inhalational agents. Six studies were multi-arm studies and included additional TIVA groups or additional inhalational maintenance or both (Demeere 2006; Geng 2017; Juvin 1997; Longas 2004; Luntz 2004; Zhang 2015).

Ten studies described propofol anaesthesia using target-controlled infusion (TCI) (Biboulet 2012; Demeere 2006; Egawa 2016; Geng 2017; Kim 2015a; Moffat 1995; Nishikawa 2004; Rohan

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2005; Tylman 2011; Zhang 2015).

Nineteen studies compared TIVA versus maintenance using sevoflurane (Ammar 2016; Biboulet 2012; Celik 2011; Demeere 2006; Egawa 2016; Geng 2017; Gursoy 2015; Ishii 2016; Kim 2015a; Lindholm 2013; Liu 2013; Longas 2004; Luntz 2004; Micha 2016; Nishikawa 2004; Rohan 2005; Tang 2014; Tylman 2011; Zhang 2015). Eight studies compared TIVA versus maintenance using isoflurane (Cai 2012a; Chan 1996; Epple 2001; Geng 2017; Jellish 2003; Juvin 1997; Moffat 1995; Tan 2009). Three studies compared TIVA versus maintenance using desflurane (Demeere 2006; Juvin 1997; Tanaka 2017). One study described the comparator as volatile induction and maintenance anaesthesia (VIMA) and did not report details of the anaesthetic agents (Trembach 2012).

Seven studies used inhalation agents during induction of participants in the inhalational maintenance groups (Biboulet 2012; Nishikawa 2004; Rohan 2005; Tang 2014; Trembach 2012; Tylman 2011; Zhang 2015). Twenty studies used intravenous agents during induction of participants in the inhalational maintenance groups (Ammar 2016; Cai 2012a; Celik 2011; Chan 1996; Demeere 2006; Egawa 2016; Epple 2001; Geng 2017; Gursoy 2015; Ishii 2016; Jellish 2003; Juvin 1997; Lindholm 2013; Liu 2013; Longas 2004; Luntz 2004; Micha 2016; Moffat 1995; Tan 2009; Tanaka 2017). Two studies used propofol and inhalation agents during induction of participants in the inhalational maintenance groups (Kim 2015a; Luntz 2004); Luntz 2004 was a multi-arm study that included a group that used only inhalation agents during induction.

Six studies reported use of epidural for anaesthesia and postoperative analgesia in addition to general anaesthesia (Ammar 2016; Egawa 2016; Ishii 2016; Lindholm 2013; Nishikawa 2004; Zhang 2015). We noted 13 studies administered fentanyl (Ammar 2016; Cai 2012a; Chan 1996; Egawa 2016; Ishii 2016; Juvin 1997; Longas 2004; Micha 2016; Rohan 2005; Tan 2009; Tanaka 2017; Tang 2014; Zhang 2015), and three studies administered remifentanil (Biboulet 2012; Celik 2011; Luntz 2004) during induction or maintenance or both. One study administered fentanyl at induction, and remifentanil during maintenance (Geng 2017). Two studies administered remifentanil in only the TIVA group (Gursoy 2015; Kim 2015a), and one study administered fentanyl in only the TIVA group (Trembach 2012). Two studies administered remifentanil to participants in the TIVA group, and fentanyl to participants in the inhalational maintenance group (Epple 2001; Jellish 2003), and two studies administered fentanyl and remifentanil in the TIVA group and only fentanyl in the inhalational maintenance group (Lindholm 2013; Tylman 2011). Two studies administered sufentanil (Demeere 2006; Liu 2013). We have included details of other analgesics and agents as part of routine anaesthetic management in Characteristics of included studies.

Fourteen studies described use of bispectral index (BIS) for monitoring of depth of anaesthesia (Ammar 2016; Biboulet 2012; Cai 2012a; Demeere 2006; Egawa 2016; Geng 2017; Ishii 2016; Kim 2015a; Lindholm 2013; Liu 2013; Longas 2004; Micha 2016; Tang 2014; Zhang 2015), and one study used Sedline for monitoring of depth of anaesthesia (Tanaka 2017). Other studies used standard care (e.g. clinical assessment, vital signs, and end-tidal concentration of anaesthetic agent (for inhalational agents) or calculated concentrations of anaesthetic agent (for TCI TIVA)), or did not describe monitoring and we assumed standard care was used.

We noted that one study (Cai 2012a) used anaesthetic methods that differed from standard practice. Participants were exposed to a disproportionately high dose of isoflurane (2% to 3% end-tidal concentration; equivalent to 2.06 to 3.09 minimum alveolar concentration (MAC) at age 70 years) compared to propofol (target concentration 3 µg/mL; a conventional dose for this age group (Al-Rifai 2016)). This methodological criticism was raised by Deiner 2012, who postulated that participants in Cai 2012a had been exposed to a toxic dose of isoflurane; this was not disputed in the study authors' subsequent response (Cai 2012b).

Funding sources

Ten studies reported department funding or external funding sources that we assumed to be independent (Ammar 2016; Biboulet 2012; Cai 2012a; Egawa 2016; Geng 2017; Kim 2015a; Lindholm 2013; Liu 2013; Rohan 2005; Tang 2014). Four studies reported support from pharmaceutical companies (Epple 2001; Juvin 1997; Luntz 2004; Tanaka 2017). The remaining 14 studies reported no details of funding sources (Celik 2011; Chan 1996; Demeere 2006; Gursoy 2015; Ishii 2016; Jellish 2003; Longas 2004; Micha 2016; Moffat 1995; Nishikawa 2004; Tan 2009; Trembach 2012; Tylman 2011; Zhang 2015).

Excluded studies

We excluded 397 articles following review of full texts where available. See Figure 1.

We excluded 24 articles because they were not RCTs (for example: commentaries; editorials; observational or cohort studies). Many studies did not report participant age within the abstract and therefore, we considered participant age from full texts. We excluded 292 studies in which participants had a mean age less than 60 years, or the study inclusion criteria was 18 to 65 years of age (in which case, these studies had participants with a mean age less than 60 years), or we calculated that fewer than 75% of participants were more than 60 years of age. We excluded five articles that reported details of retracted studies and three studies for which we were unable to access full texts and information in abstracts was insufficient. We excluded 27 studies that did not compare a propofol-based TIVA versus an inhalational maintenance anaesthetic agent. We did not include references for these studies in the review.

We excluded 46 RCTs that compared propofol-based TIVA versus an inhalational maintenance anaesthetic agent and did not

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measure any of our review outcomes (Arar 2005; Arnaoutoglou 2007; But 2003; Carles 2008; Doe 2016; Filipovic 2007; Fredman 2002; Gasowska 1999; Gauger 2008; Guedes 1988; Halberg 1996; Holst 1993; Hosseinzadeh 2013; Ionescu 2009; Ito 2012; Kadoi 2009a; Kim 2015b; Konstantopoulos 2013a; Kvarnstrom 2012; Malcharek 2015; Manolescu 2012; Mets 1992; Murray 1994; Mutch 1995; Ohe 2014; Oikkonen 1992; Passot 2005; Pirttikangas 1996; Polarz 1995; Sal'nikov 2003; Schäfer 2002; Schilling 2007; Schilling 2011; Shao 2013; Sohn 2008; Sugata 2012; Trifu 2011; Tufano 2000; Ueda 1999; Wakabayashi 2014; Weilbach 2005; Wen 2010; Wormald 2005; Yu 2010a; Zabolotskikh 2013; Zhang 2014). It was a post-hoc decision to exclude studies that did not measure the review outcomes and we have included references and additional details for these 46 studies in Characteristics of excluded studies.

Awaiting classification

We found four studies for which we had insufficient information to assess eligibility or extract data (IRCT2015112925277N1; McDonagh 2012; NCT02766062; Shen 2011). Two studies were described as completed in clinical trials registers; study results were not posted in the register and we were unable to source a published full-text reports for these studies (IRCT2015112925277N1; NCT02766062). One study was published as an abstract and reported insufficient information to assess eligibility (McDonagh 2012). One study requires translation from Chinese to assess eligibility (Shen 2011). See Characteristics of studies awaiting classification.

Ongoing studies

We found 11 ongoing studies from clinical trials register searches, with an estimated 3704 participants. All studies compare TIVA with inhalation anaesthetic agents. Eight studies specifically include older participants (ChiCTR-IOR-16009851; NCT01809041; NCT01995214; NCT02133638; NCT02301676; NCT02458547; NCT02662257; NCT03165396); remaining studies do not specify age and we will ascertain mean age of participants once the studies are completed. Nine studies aim to report data for our postoperative delirium or postoperative cognitive dysfunction (POCD) (ChiCTR-IOR-16009851; NCT01809041; NCT01995214; NCT02107170; NCT02133638; NCT02301676; NCT02662257; NCT03165396; NCT03194074). See Characteristics of ongoing studies.

Risk of bias in included studies

See Figure 2 and Figure 3, and Characteristics of included studies.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

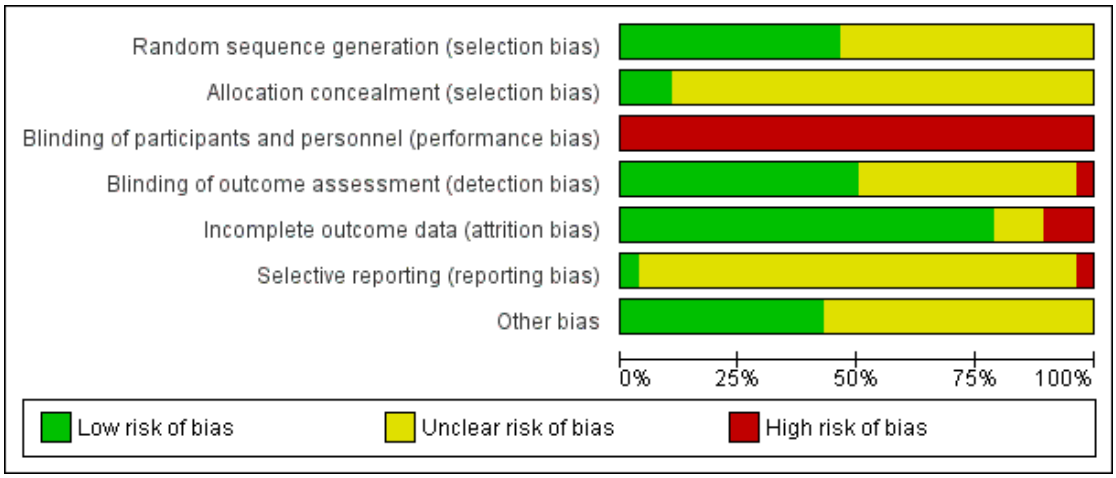

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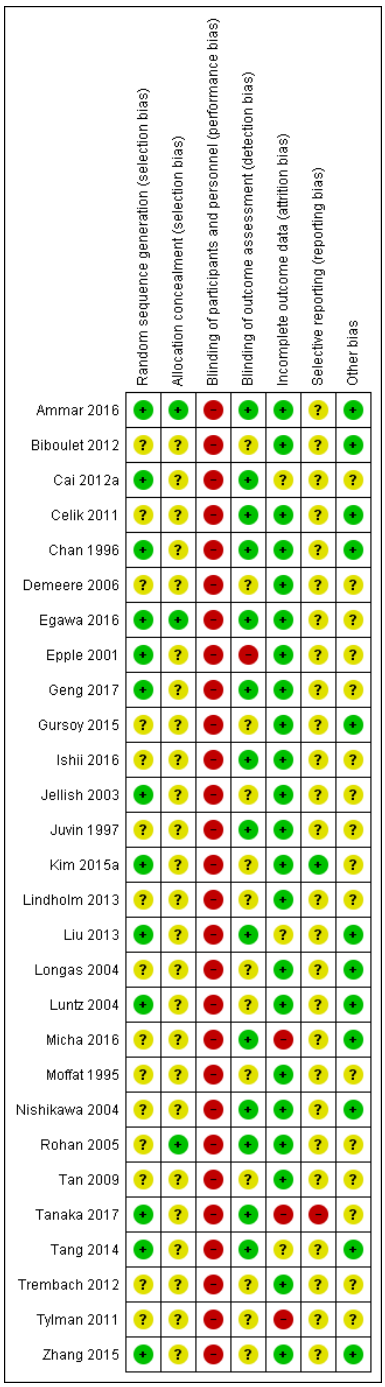
Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



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Allocation

Thirteen studies reported adequate randomization methods and we judged these studies to have low risk of selection bias (Ammar 2016; Cai 2012a; Chan 1996; Egawa 2016; Epple 2001; Geng 2017; Jellish 2003; Kim 2015a; Liu 2013; Luntz 2004; Tanaka 2017; Tang 2014; Zhang 2015). Remaining studies reported insufficient details of randomization methods to judge risk of selection bias.

Only three studies reported adequate methods to conceal allocation and we judged these to have low risk of allocation bias (Ammar 2016; Egawa 2016; Rohan 2005). Remaining studies reported no details and we were unable to judge risk of selection bias.

Blinding

It was not feasible to blind personnel to anaesthetic management and we judged all studies to have high risk of performance bias.

For studies that reported data for more than one outcome we judged risk of detection bias for our primary outcomes. For studies that did not report our primary outcomes, we judged risk of detection bias on our secondary outcomes. Thirteen studies had adequately reported whether personnel responsible for outcome assessment were blinded to the intervention and we judged these studies to have low risk of detection bias (Ammar 2016; Cai 2012a; Celik 2011; Chan 1996; Egawa 2016; Geng 2017; Ishii 2016; Juvin 1997; Micha 2016; Nishikawa 2004; Rohan 2005; Tanaka 2017; Tang 2014). Attempts to blind assessors was not described in Liu 2013; the only review outcome of interest was mortality and we believed assessment of this outcome had low risk of detection bias.

One study reported that assessment of discharge from PACU was completed by personnel aware of group allocation and we judged this study to have high risk of detection bias (Epple 2001).

Remaining studies reported insufficiently whether outcome assessors were blinded to group allocation.

Incomplete outcome data

Twenty-two studies reported no losses or few losses that were clearly reported and balanced between groups and we judged these studies to have a low risk of bias (Ammar 2016; Biboulet 2012; Celik 2011; Chan 1996; Demeere 2006; Egawa 2016; Epple 2001; Geng 2017; Gursoy 2015; Ishii 2016; Jellish 2003; Juvin 1997; Kim 2015a; Lindholm 2013; Longas 2004; Luntz 2004; Moffat 1995; Nishikawa 2004; Rohan 2005; Tan 2009; Trembach 2012; Zhang 2015). We noted a large number of losses (> 10%) in three studies and were unclear whether risk of attrition bias could influence outcome data (Cai 2012a; Liu 2013; Tang 2014).

We judged three studies to have high risk of attrition bias (Micha 2016; Tanaka 2017; Tylman 2011). Micha 2016 reported loss of participants at nine months but did not include data for these participants at an earlier time point of seven days. Tanaka 2017 reported a large number of losses and reasons for losses were not clearly reported by group. Tylman 2011 reported a post-hoc decision to exclude participants due to particular conditions; these lost participants belonged to only the inhalational maintenance group.

Selective reporting

Three studies reported retrospective clinical trials registration (Ammar 2016; Geng 2017; Tanaka 2017). It was not feasible to assess risk of selective outcome reporting bias from these documents. We judged Ammar 2016 and Geng 2017 to have unclear risk of bias. In Tanaka 2017, however, we noted that one outcome was listed in the methods section but not reported in the results, and some outcome data were inconsistently reported; therefore, we judged this study to have high risk of selective outcome reporting bias.

Two studies reported prospective clinical trials registration (Kim 2015a; Lindholm 2013). We judged Kim 2015a to have a low risk of selective reporting bias, although we noted that secondary outcomes were not reported as described in the clinical trials register documents (i.e. MAP was reported, rather than hypotension). It was not feasible to assess risk of selective outcome reporting bias in Lindholm 2013 because the clinical trials registration documents did not report intended outcomes.

Remaining studies did not report clinical trials registration or prospectively published study protocols and it was not feasible to assess risk of selective reporting bias for these studies.

Other potential sources of bias

We noted no other sources of bias in 12 studies and judged these to have low risk of other biases (Ammar 2016; Biboulet 2012; Celik 2011; Chan 1996; Gursoy 2015; Liu 2013; Longas 2004; Luntz 2004; Micha 2016; Nishikawa 2004; Tang 2014; Zhang 2015).

Six studies reported differences between groups in administration of fentanyl or remifentanil and it is unclear whether these differences may influence outcome data (Epple 2001; Jellish 2003; Kim 2015a; Lindholm 2013; Trembach 2012; Tylman 2011). We noted baseline imbalances between groups, or differences in length of surgery or duration of anaesthesia in five studies (Demeere 2006; Egawa 2016; Geng 2017; Juvin 1997; Tanaka 2017).

Four full-text study reports and one abstract contained limited information in the report and it is unclear whether other sources of bias were present (Demeere 2006; Ishii 2016; Rohan 2005; Tan 2009; Trembach 2012).

We noted differences in study design in Moffat 1995, which used a different airway management technique in each group. This

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difference was related to the study aim which compared the use of neuromuscular blockade in addition to anaesthetic agents for maintenance. We were uncertain whether this may influence data.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings TIVA versus inhalational maintenance of anaesthesia

Primary outcomes

1. Postoperative delirium

Five studies reported postoperative delirium (Chan 1996; Ishii 2016; Micha 2016; Nishikawa 2004; Tanaka 2017).

Chan 1996 did not report the diagnostic tool used to assess delirium which was reported nine hours postoperatively in one participant (associated with a transient episode of cerebral ischaemia), on the second postoperative day in one participant,and on the fourth postoperative day in one participant (associated with pneumonia).

Three studies used the Confusion Assessment Method (CAM) to diagnose postoperative delirium (Ishii 2016; Micha 2016; Tanaka 2017). Micha 2016 made assessments at 48 hours postoperatively, and Ishii 2016 did not report the time point of assessment. Tanaka 2017 made assessments at one, six, 24, and 48 hours postoperatively, although time points for reported data are not clear. We noted differences in data between the published report for Tanaka 2017, and outcome data in the clinical trials register documents; for primary analysis we used the data as reported in the published study report. Nishikawa 2004 used the Delirium Rating Scale (DRS) on the first, second, and third postoperative day; in order to avoid risk of double-counting participants in this study, we included data only for the third postoperative day.

We noted no difference in postoperative delirium according to whether total intravenous anaesthesia (TIVA)or inhalational maintenance of anaesthesia was used (odds ratio (OR) 0.59, 95% confidence interval (CI) 0.15 to 2.26; 321 = participants; I^2 = 17%; Analysis 1.1).

We used the GRADE approach to judge the certainty of the evidence for postoperative delirium to be very low. We downgraded by one level for study limitations; we noted few included studies for this outcome had sufficiently reported the methods of randomization and we were concerned by high risk of attrition bias in two studies and high risk of selective outcome reporting bias in one study. We downgraded by two levels for inconsistency; we could not be certain whether measurements of delirium, and time points of measurement, were equivalent between studies, and we used sensitivity analysis to show that choice of time point in one study may influence direction of this result. See Summary of findings for the main comparison.

2. Postoperative cognitive dysfunction (POCD)

Thirteen studies reported on POCD (Cai 2012a; Egawa 2016; Geng 2017; Gursoy 2015; Juvin 1997; Lindholm 2013; Liu 2013; Micha 2016; Moffat 1995; Rohan 2005; Tan 2009; Tanaka 2017; Tang 2014). Nine studies used the Mini-Mental State Examination (MMSE) or Mini Mental Test (MMT) (Cai 2012a; Egawa 2016; Geng 2017; Gursoy 2015; Juvin 1997; Liu 2013; Micha 2016; Rohan 2005; Tan 2009); two of these studies used additional tools, which are reported in Characteristics of included studies (Egawa 2016; Geng 2017). Tanaka 2017 assessed postoperative cognitive function with the Digit Symbol Substitution Test (DSST), Digit Span, and Trail Making tests.The remaining studies did not report diagnostic tools used to measure POCD.

Seven studies (2869 participants) reported data as number of participants who had POCD: Cai 2012a at three days postoperatively; Egawa 2016 at five days postoperatively; Geng 2017 at one and three days postoperatively, and we used data at three days; Lindholm 2013 up to 30 days postoperatively; Micha 2016 and Tanaka 2017 at 48 hours postoperatively; Rohan 2005 on the day following surgery; Tang 2014 at seven days postoperatively. Geng 2017 reported data for two inhalational maintenance arms (isoflurane and sevoflurane) and we combined data for these groups. In Tanaka 2017, we used data provided from study authors (following email communication) for Trail Making (part A). Owing to concern about methodology in Cai 2012a, in particular that participants may have been exposed to a toxic dose of inhalational agent, we did not include this large study in the primary analysis. We found fewer incidences of POCD in participants following use of TIVA (OR 0.52, 95% CI 0.31 to 0.87; 869 participants; I^2 = 41%; Analysis 1.2).

Three studies (160 participants) reported data as mean (standard deviation (SD)), or mean (range), scores for POCD and we reported these data in Table 1; we used time points at 24 hours postoperatively (Gursoy 2015; Tan 2009), and two hours postoperatively (Moffat 1995). We noted no apparent differences in these scores from visual inspection.

One study reported data in a figure, which we were unable to interpret for this outcome; study authors reported that postoperative psychometric evaluations were similar in each groups (Juvin 1997).

One study included participants with amnesic mild cognitive impairment (aMCI) and assessed progression at two years postoperatively using the MMSE; we did not include data for this study in the analysis because this time point was not comparable to other included studies (Liu 2013). Study authors reported that 30/55 participants in the sevoflurane group had aMCI at two years, and 17/52 participants in the propofol group had aMCI.

We used the GRADE approach to judge the certainty of the evidence for POCD to be low. We downgraded by one level for study limitations; we noted that some studies had insufficiently reported methods of randomization and we were concerned by high risk of attrition bias in one study. We downgraded by one level for incon-

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sistency; we noted a moderate level of statistical heterogeneity (I^2 = 41%) which we could not explain. See Summary of findings for the main comparison.

Secondary outcomes

1. Mortality at 30 days

Four studies reported on mortality (Ammar 2016; Biboulet 2012; Lindholm 2013; Liu 2013). Liu 2013 reported the number of participants who were lost to follow-up because of death; three participants died but these deaths were not reported by group.

We included Ammar 2016, Biboulet 2012 and Lindholm 2013 in the analysis which demonstrated no difference in the number of deaths at 30 days according to whether TIVA or inhalational maintenance of anaesthesia was used (OR 1.21, 95% CI 0.33 to 4.45; 271 participants; I^2 = 0%; Analysis 1.3).

We used the GRADE approach to judge certainty of the evidence for mortality to be very low. We downgraded by one level for study limitations because we noted that some studies had insufficiently reported methods of randomization. We downgraded by two levels for imprecision because the analysis included only three studies with few participants and, because deaths due to anaesthesia are rare, we would require a large sample size to show evidence of a difference. See Summary of findings for the main comparison.

2. Intraoperative hypotension

Twelve studies reported data for intraoperative hypotension (Biboulet 2012; Chan 1996; Geng 2017; Jellish 2003; Lindholm 2013; Longas 2004; Luntz 2004; Micha 2016; Nishikawa 2004; Tang 2014; Trembach 2012; Zhang 2015). We included data for 11 studies in the analysis; one study (Lindholm 2013), reported data as median number of episodes lasting more than two minutes and we reported these data in Table 1.

We included hypotension as defined by study authors, which was reported as a change from baseline in mean arterial pressure.

We included three multi-arm studies in analysis (Longas 2004; Luntz 2004; Zhang 2015). For Luntz 2004, we combined data from the two inhalational maintenance groups (one that used total sevoflurane anaesthesia, and one that used propofol induction with sevoflurane maintenance). For Longas 2004, we combined data from the two inhalational maintenance groups (one used sevoflurane 1 MAC, and one used sevoflurane 1.5 MAC). For Zhang 2015, we combined the two TIVA groups (one used additional epidural anaesthesia) versus combined data for the two sevoflurane groups (one used additional epidural anaesthesia).

We noted a high level of statistical heterogeneity (I^2 = 63%), and because we expected that studies had clinical variation in the management strategy and medication used to manage hypotension, we did not combine data in a meta-analysis. Visual inspection of data demonstrated inconsistencies in results and we could not be certain whether TIVA or inhalational maintenance anaesthesia reduces episodes of intraoperative hypotension. Unpooled data for 11 studies (945 participants) are presented in Analysis 1.4.

We used the GRADE approach to judge certainty of the evidence for intraoperative hypotension to be low. We downgraded by one level for study limitations; we noted some studies reported insufficient methods of randomization. We downgraded by one level for inconsistency because of possible variation in clinical management of participants in each study. See Summary of findings for the main comparison.

3. Length of stay in the postoperative anaesthesia care unit (PACU)

Eight studies reported the length of stay in the PACU (Celik 2011; Chan 1996; Demeere 2006; Epple 2001; Jellish 2003; Juvin 1997; Kim 2015a; Tanaka 2017). Two of these studies were multi-arm studies and reported data for TIVA versus maintenance using sevoflurane and TIVA versus maintenance using desflurane (Demeere 2006), and TIVA versus maintenance using isoflurane and TIVA versus maintenance using desflurane (Juvin 1997). For the primary analysis, we included data for the sevoflurane and isoflurane groups; we assessed this decision in a sensitivity analysis using data for the desflurane groups in each study. Data for length of stay in the PACU were not clearly reported in Tanaka 2017, and we noted discrepancies between the published study report and the clinical trials registration documents; we did not report data for this study.

We noted a substantial level of statistical heterogeneity between studies (I^2 = 94%), and we expected that there were differences in study methods for this outcome (e.g. whether length of stay in the PACU was reported as time until ready for discharge or time until discharge occurred). We did not conduct meta-analysis for this outcome because of these differences. Visual inspection of data demonstrated inconsistencies in results and we could not be certain whether TIVA or inhalational maintenance anaesthesia reduces length of time in the PACU. Unpooled data for seven studies (467 participants) are presented in Analysis 1.5.

We used the GRADE approach to judge the certainty of the evidence for length of time in the PACU to be very low. We downgraded the evidence by one level for study limitations; we noted some studies reported insufficient methods of randomization. We downgraded the evidence by two levels because of inconsistency; we expected likely differences in study methods related to definitions of time points of measurement of this outcome. See Summary of findings for the main comparison.

4. Length of hospital stay

Six studies reported length of hospital stay (Ammar 2016; Demeere 2006; Jellish 2003; Juvin 1997; Lindholm 2013; Tylman 2011). Two of these studies were multi-arm studies and reported

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data for TIVA versus maintenance using sevoflurane and TIVA versus maintenance using desflurane (Demeere 2006), and TIVA versus maintenance using isoflurane and TIVA versus maintenance using desflurane (Juvin 1997). For the primary analysis we included data for the sevoflurane and isoflurane groups; we assessed this decision in sensitivity analysis using data for the desflurane groups in each study. Two studies reported data as median values with little or no difference between median number of days in each group, therefore we did not include these data in analysis (Lindholm 2013; Tylman 2011); data for these studies are reported in Table 1.

We included four studies in meta-analysis and noted no difference between participants given TIVA and participants given inhalational maintenance anaesthesia in length of hospital stay (mean difference (MD) -0.00, 95% CI -1.32 to 1.32; participants = 175; I^2 = 41%; Analysis 1.6).

We used the GRADE approach to judge the certainty of the evidence for length of hospital stay to be very low. We downgraded by two levels for imprecision because we included few studies with few participants, and we downgraded by one level for inconsistency because we noted moderate statistical heterogeneity and visual differences in the results. See Summary of findings for the main comparison.

Subgroup analysis

We performed pre-planned subgroup analysis as follows.

1. Elderly (60 to 79 years of age) versus late elderly (80 years of age or older)

We included no studies recruiting participants who were > 80 years of age.

2. Elective versus non-elective surgery

We identified no studies that described surgery as non-elective.

3. Inhalational induction versus intravenous (IV) induction (as a subgroup of inhalational maintenance only)

Postoperative delirium: one study used inhalational agents at induction (Nishikawa 2004), and four studies used propofol at induction (Chan 1996; Ishii 2016; Micha 2016; Tanaka 2017). We noted little or no difference in postoperative delirium in participants who had anaesthesia with TIVA versus anaesthesia induction with propofol and inhalational maintenance (OR 0.42, 95% CI 0.11 to 1.67; 271 participants; 4 studies; Analysis 2.1). We noted little or no difference between subgroups according to agents used during induction (P = 0.27).

POCD: two studies used inhalational agents at induction (Rohan 2005; Tang 2014), and this analysis showed little or no difference in incidences of POCD between groups (OR 0.87, 95% CI 0.50 to 1.50; 230 participants). Five studies used intravenous agents at induction and we found less POCD in participants when IV agents had been used (OR 0.38, 95% CI 0.20 to 0.75; 639 participants). We noted little or no difference between subgroups according to agents used during induction (P = 0.07). See Analysis 2.2.

Mortality: one study used inhalational agents at induction (Biboulet 2012) and two studies used propofol for induction (Ammar 2016; Lindholm 2013). We noted little or no difference between subgroups according to agents used during induction (P = 0.53). See Analysis 2.3.

Intraoperative hypotension: we noted visual inconsistencies in the data during our primary assessment of this outcome, which we expected could be explained by differences in the clinical management of hypotension between studies and we did not conduct meta-analysis. We used pre-planned subgroup analysis to assess whether induction agents may explain inconsistencies in data between studies. However, we noted visual inconsistencies in one of the subgroups (when induction was given with inhalational agents), and expected that differences in clinical management between studies continued to affect the data such that subgroup analysis was not appropriate. See Analysis 2.4.

Length of stay in the PACU: we could not perform subgroup analysis because we included no studies using inhalational agents for induction.

Length of hospital stay: we could not perform subgroup analysis because we included no studies using inhalational agents for induction.

4. Target-controlled infusion (TCI) versus non-TCI maintenance of anaesthesia (as a subgroup of TIVA only)

Postoperative delirium: one study used TCI (Nishikawa 2004), and four studies did not report use of TCI for maintenance of TIVA (Chan 1996; Ishii 2016; Micha 2016; Tanaka 2017). We noted no difference in postoperative delirium when TCI had not been used (OR 0.42, 95% CI 0.11 to 1.67; 271 participants; Analysis 2.1). We noted little or no difference between subgroups according to whether TCI had been used (P = 0.27).

POCD: we noted little or no difference between subgroups (P = 0.38). Whilst effect estimates in each subgroup favoured use of TIVA, we found little or no difference in POCD when studies used TCI (OR 0.31, 95% CI 0.07 to 1.38; 294 participants), or when studies did not use TCI (OR 0.63, 95% CI 0.36 to 1.10; 575 participants). We noted a high level of statistical heterogeneity (I^2 = 71%) between the studies that used TCI which we could not explain. See Analysis 2.5.

Mortality: one study used TCI for maintenance of anaesthesia (Biboulet 2012). We noted no difference between subgroups according to whether TCI had been used (P = 0.53). See Analysis 2.3.

Intraoperative hypotension: we noted visual inconsistencies in the data during our primary assessment of this outcome, which we

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expected could be explained by differences in the clinical management of hypotension between studies and therefore, we did not conduct meta-analysis. We used pre-planned subgroup analysis to assess whether use of TCI maintenance may explain inconsistence in data between studies. However, we noted visual inconsistencies in each subgroup (TCI, and non-TCI) and expected that differences in clinical management between studies continued to affect the data such that subgroup analysis was not appropriate. See Analysis 2.6.

Length of stay in the PACU: we noted visual inconsistencies in the data during our primary assessment of this outcome, which we expected could be explained by differences in the definition of time point for length of stay in PACU between studies and we did not conduct meta-analysis. We used pre-planned subgroup analysis to assess whether use of TCI maintenance may explain inconsistence in data between studies. However, we noted visual inconsistencies in one of the subgroups (non-TCI) and expected that possible differences in time point definitions between studies continued to affect the data such that subgroup analysis was not appropriate. See Analysis 2.7.

Length of hospital stay: no studies used TCI for maintenance of anaesthesia.

5. Use of depth of anaesthesia monitoring

We considered the use of any processed electroencephalogram (EEG) for depth of monitoring. Fourteen studies described use of bispectral index (BIS) for monitoring of depth of anaesthesia (Ammar 2016; Biboulet 2012; Cai 2012a; Demeere 2006; Egawa 2016; Geng 2017; Ishii 2016; Kim 2015a; Lindholm 2013; Liu 2013; Longas 2004; Micha 2016; Tang 2014; Zhang 2015), and one study used Sedline for monitoring of depth of anaesthesia (Tanaka 2017). We compared studies that reported use any processed EEG versus studies that used standard care for monitoring (e.g. clinical assessment, vital signs, and end-tidal concentration of anaesthetic agent (for inhalational agents) or calculated concentrations of anaesthetic agent (for TCI TIVA)).

Postoperative delirium: three studies used processed EEG (Ishii 2016; Micha 2016; Tanaka 2017) and when combined, we noted little or no difference in whether anaesthesia was maintained with TIVA or inhalation agents (OR 0.56, 95% CI 0.04 to 7.44; 211 participants). Two studies used standard care (Chan 1996; Nishikawa 2004) and when combined we noted little or no difference in whether anaesthesia was maintained with TIVA or inhalation agents (OR 1.00, 95% CI 0.14 to 7.06; 110 participants). We noted no differences between subgroups (P = 0.73). See Analysis 3.1.

POCD: one study used standard care (Rohan 2005); this single study showed no difference in POCD depending on whether anaesthesia was maintained with TIVA or inhalation agents (OR 1.00, 95% CI 0.24 to 4.20; 30 participants). Six studies used processed EEG or Sedline for depth of monitoring and when combined we noted that fewer participants had experiences of POCD when TIVA was used (OR 0.47, 95% CI 0.27 to 0.84; 839 participants). We noted little or no difference between subgroups (P = 0.35). See Analysis 3.2.

Mortality: all included studies used processed EEG for depth of anaesthesia monitoring.

Intraoperative hypotension: we noted visual inconsistencies in the data during our primary assessment of this outcome, which we expected could be explained by differences in the clinical management of hypotension between studies and we did not conduct meta-analysis. We used pre-planned subgroup analysis to assess whether use of processed EEG may explain inconsistence in data between studies. However, we noted visual inconsistencies in each subgroup and expected that differences in clinical management between studies continued to affect the data such that subgroup analysis was not appropriate. See Analysis 3.3.

Length of stay in the PACU: we noted visual inconsistencies in the data during our primary assessment of this outcome, which we expected could be explained by differences in the definition of time point for length of stay in PACU between studies and we did not conduct meta-analysis. We used pre-planned subgroup analysis to assess whether use of processed EEG may explain inconsistence in data between studies. However, we noted visual inconsistencies in one of the subgroups (use of processed EEG) and expected that possible differences in time point definitions between studies continued to affect the data such that subgroup analysis was not appropriate. See Analysis 3.4.

Length of hospital stay: one study used processed EEG, and for studies which used standard care; we noted little or no difference in length of hospital stay depending on whether anaesthesia was maintained with TIVA or inhalation agents (OR -0.27 minutes, 95% CI -1.40 to 0.86; 138 participants; Analysis 3.5). We noted little or no difference between subgroups (P = 0.10).

Sensitivity analysis

1. Risk of bias judgements. In sensitivity analysis, we excluded studies that we judged to be at high or unclear risk of selection bias. We performed sensitivity analysis on studies that were pooled in primary analysis.

1. Postoperative delirium: we excluded three studies from the analysis, which did not alter interpretation of the effect (Ishii 2016; Micha 2016; Nishikawa 2004).
2. POCD: we excluded three studies from analysis, which did not alter interpretation of the effect (Lindholm 2013; Micha 2016; Rohan 2005).
3. Mortality: we excluded two studies from analysis (Biboulet 2012; Lindholm 2013), the remaining study reported no deaths in either group.
4. Length of hospital stay: we excluded two studies (Demeere 2006; Juvin 1997). We noted that the effect remained the same but statistical heterogeneity was reduced (I^2 = 0%).

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2. Decisions made for missing data. In sensitivity analysis, we excluded studies that we judged to be at high risk of attrition bias.

1. Postoperative delirium: we excluded two studies which did not alter interpretation of the effect (Micha 2016; Tanaka 2017).

2. POCD: we excluded one study from analysis which did not alter interpretation of the effect (Micha 2016).

3. Effects model. In sensitivity analysis, we used the alternate meta-analytic effects model for those outcomes in which we pooled data.

1. Postoperative delirium: we used a fixed-effect model which did not alter interpretation of the result.

2. POCD: we used a fixed-effect model which did not alter interpretation of the result.

3. Length of hospital stay: we used a fixed-effect model which did not alter interpretation of the result.

Additional sensitivity analysis

We made decisions during the review process that may have influenced our review results. In sensitivity analysis, we assessed the following decisions for each outcome.

1. In primary analysis, we included studies in which we used mean ages reported in the baseline characteristics table to ascertain that > 75% of participants were > 60 years of age (Ammar 2016; Demeere 2006; Egawa 2016; Jellish 2003; Lindholm 2013; Longas 2004; Tylman 2011). It was feasible that some participants in these studies were not elderly.

1. Postoperative delirium: we included no studies in primary analysis that may have included participants that were not elderly.

2. POCD: in sensitivity analysis, we removed Egawa 2016 and Lindholm 2013 from analysis and this did not alter interpretation of the effect.

3. Mortality: in sensitivity analysis, we removed Ammar 2016 and Lindholm 2013. One remaining study reported one death in the TIVA group.

4. Length of hospital stay: in sensitivity analysis, we removed three studies (Ammar 2016; Demeere 2006; Jellish 2003); it was not possible to pool data because only one study remained.

2. In primary analysis, we included studies in which participants had an existing neurological impairment at baseline (Liu 2013; Tang 2014).

1. Postoperative delirium: we included no studies in primary analysis that recruited participants with an existing neurological impairment.

2. POCD: in sensitivity analysis, we removed Tang 2014 from analysis. This did not alter our interpretation of the effect.

3. Mortality: we included no studies in primary analysis that recruited participants with an existing neurological impairment.

4. Length of hospital stay: we included no studies in primary analysis that recruited participants with an existing neurological impairment.

3. In primary analysis, we made decisions to include data for one time point when the study reported different time points (Nishikawa 2004 reported postoperative delirium for the first and second postoperative day, which we did not include in primary analysis; Geng 2017 reported POCD for the first postoperative day that we did not include in analysis).

1. Postoperative delirium: in sensitivity analysis, we used data for the first postoperative day in Nishikawa 2004 and, whilst we found no statistically significant difference in incidences of delirium between groups, we noted a change in the direction of effect and a reduced level of statistical heterogeneity (OR 0.41, 95% CI 0.13 to 1.29; 321 participants; 5 studies; I^2 = 11%). This result was similar when we used data for the second postoperative day in Nishikawa 2004 (OR 0.54, 95% CI 0.19 to 1.50; participants = 321; studies = 5; I^2 = 17%).

2. POCD: in sensitivity analysis, we used data for the first postoperative day in Geng 2017.This did not alter interpretation of the effect.

3. Mortality: we included no studies in which different time points were reported.

4. In primary analysis, we made decisions to manage data for multi-arm studies. We combined groups for POCD and intraoperative hypotension (Geng 2017; Longas 2004; Luntz 2004; Zhang 2015), and we used one inhalational maintenance group for length of PACU stay, and length of hospital stay (sevoflurane in Demeere 2006; isoflurane in Juvin 1997).

1. Postoperative delirium: we included no multi-arm studies in analysis of this outcome.

2. POCD: in sensitivity analysis, we included data separately for each inhalational maintenance group for Geng 2017. This did not alter interpretation of the effect.

3. Mortality: we included no multi-arm studies in analysis of this outcome.

4. Length of hospital stay: in sensitivity analysis, we included data for the desflurane groups in Demeere 2006 and Juvin 1997. We noted a change in the effect estimate which showed that participants who had anaesthesia maintained with inhalational agents had a shorter length of hospital stay (MD 0.10 days, 95% CI 0.00 to 0.20; 175 participants; I^2 = 9%). However, this result demonstrated only a small change in time and is unlikely to be clinically important.

5. In primary analysis, we excluded one large study (because of methodological differences that were inconsistent with usual anaesthetic practice) in analysis of POCD (Cai 2012a).

1. POCD: in sensitivity analysis, we included Cai 2012a. This increased statistical heterogeneity from I^2 = 41% to I^2 = 90%. The direction of effect was not altered by including this study in analysis (OR 0.32, 95% CI 0.11 to 0.93; 2869 participants; I^2 = 90%).

DISCUSSION

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Summary of main results

We included 28 studies with 4507 randomized participants. Four studies are awaiting classification because we had insufficient information to assess eligibility. All included studies compared maintenance with propofol-based total intravenous anaesthesia (TIVA) versus inhalational maintenance of anaesthesia.

We found little or no evidence of a difference in incidences of postoperative delirium according to type of anaesthetic maintenance agents from five studies (Chan 1996; Ishii 2016; Micha 2016; Nishikawa 2004; Tanaka 2017). We used sensitivity analysis to explore including different time points of outcome assessment reported by one study (Nishikawa 2004), which may influence direction of effect for postoperative delirium. We found that fewer people may experience postoperative cognitive dysfunction (POCD) with propofol-based TIVA in seven studies. We excluded one large study from analysis for POCD because study investigators had used a non-standard method of anaesthetic management. Five additional studies reported data for POCD, which we were unable to pool and we noted little or no difference in scores of POCD in five of these studies, and in the remaining study the time point was not comparable to other studies.

We found little or no evidence of a difference in mortality from three studies (Ammar 2016; Biboulet 2012; Lindholm 2013). We did not combine data in meta-analysis for intraoperative hypotension or length of stay in the postanaesthesia care unit (PACU); we noted visual inconsistencies in the data and expected that these might be explained by clinical differences between studies in the management of hypotension and methodological differences in definition of time points before discharge from the PACU. We found little or no evidence of a difference in length of hospital stay according to type of anaesthetic maintenance agent from four studies.

Overall completeness and applicability of evidence

We included studies that recruited participants who were more than 60 years of age, and studies in which we calculated that more than 75% participants were more than 60 years of age.

The included studies recruited people scheduled for non-cardiac surgery under general anaesthesia. The surgery types were typical of elderly patients but varied between studies to include: cardiovascular, laparoscopic, abdominal, orthopaedic, ophthalmic, and mixed surgery (oesophagectomy, gastrectomy, nephrectomy, urological surgery, one-lung surgery, gynaecological surgery, tumour resection, and radical surgery). The ASA status differed between the included studies. Most studies included a majority of participants who were classed as ASA II; however, some studies included only participants who were ASA III, and two studies also included participants with an ASA status up to ASA IV (Biboulet 2012; Lindholm 2013).

Anaesthetic management differed between studies, for example with use of different intraoperative and postoperative analgesic management, use of epidurals, or use of premedication. We also noted differences in studies that used target-controlled infusion (TCI) for TIVA, that used processed electroencephalogram (EEG) for monitoring of depth of anaesthesia (bispectral index (BIS) or Sedline), and that used inhalation agents only for induction and maintenance.

These differences may introduce inconsistency and reduce the overall applicability of the evidence.

Quality of the evidence

We found insufficient reporting of randomization methods in many studies and all studies were at high risk of performance bias because it was not feasible to blind anaesthetists for this study design. Thirteen studies had described blinding of outcome assessors. Three studies had a high of risk of attrition bias, and we noted differences in use of analgesics between groups in six studies, and differences in baseline characteristics, which may have influenced results in five studies. Few studies reported clinical trials registration and we could not assess risk of selective outcome reporting bias.

We used the GRADE approach and considered study limitations noted during 'Risk of bias' assessment which may influence the certainty of the evidence for each outcome. In addition, we identified few studies with few participants for two outcomes (mortality, and length of hospital stay) which introduced imprecision. We noted visual differences in some results which might be explained by differences in clinical management or methodological designs which prevented pooling of data in meta-analysis and introduced inconsistency. We judged evidence for postoperative delirium, mortality, length of stay in the PACU, and length of hospital stay to be very low certainty, and evidence for POCD, and intraoperative hypotension to be low certainty.

We explored potential explanations for this heterogeneity in subgroup analysis, in particular with consideration of whether intravenous agents were used during induction in the inhalational maintenance group, whether TIVA was given using TCI, and whether depth of anaesthesia was monitored. Results of subgroup analyses did not appear to explain heterogeneity and we noted that high levels of statistical heterogeneity remained in one or both subgroups in each analysis. We were not confident that these subgroups alone could explain the differences between studies and the levels of heterogeneity that prevented meta-analysis; we did not explore this in additional subgroup analyses.

Potential biases in the review process

We conducted our review using Cochrane methodology, using two review authors to select studies, extract data, and assess risk of bias

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according to our published protocol (Miller 2016). We conducted a thorough search that included clinical trials registers, forward and backward citation searching, and grey literature.

We reported changes from the protocol in Differences between protocol and review. In particular, we found that studies did not always define 'elderly' using a cut-off of 60 years (according to WHO 2016b), and studies typically used an included age category of 18 to 65 years. We excluded studies that used an age category of 18 to 65 years, but we found that these studies had a mean age for participants of less than 60 years and therefore this decision did not affect choice of included studies for this review.

We made a post-hoc decision to exclude studies that did not measure our review outcomes. We included references for these studies in the review in order to inform readers of other studies that compare intravenous versus inhalational maintenance anaesthesia for different purposes.

We were cautious to assess the impact of decisions that we made during the review process and used sensitivity analysis for this purpose.

In particular, some studies may have included participants that were younger than 60 years of age. When sufficient studies allowed sensitivity analysis, we considered whether results differed if we excluded these studies; we found no differences in the interpretation of effect estimates. In addition, we considered the effect of including studies in which participants had an existing cognitive impairment, and, again, found excluding relevant studies did not alter the effect.

We considered the effect of decisions regarding which time point to use in studies that reported more than one time point. For delirium, we noted that, whilst there remained no statistical evidence of a difference according to type of anaesthetic maintenance agent, direction of effect changed when we used different time points reported in one study. We believed that our decisions on which time point to use may have the potential to affect interpretation of the data and we used GRADE to downgrade the certainty of the evidence for postoperative delirium.

We noted one large study which had methodological differences in anaesthetic management that were not consistent with standard anaesthetic management (Cai 2012a). For this reason, we excluded Cai 2012a from analysis of POCD. We assessed this decision during sensitivity, by including the study in analysis of POCD. The direction of effect was not altered and we believed that the decision to exclude Cai 2012a from primary analysis did not affect the conclusion of the review.

Also, we were unable to assess eligibility of four studies (see Studies awaiting classification); inclusion of these studies may have influenced the results (IRCT2015112925277N1; McDonagh 2012; NCT02766062; Shen 2011).

Agreements and disagreements with other studies or reviews

We found no reviews that specifically looked at intravenous versus inhalational maintenance of anaesthesia in elderly surgical patients.

One Cochrane Review considered intravenous versus inhalation agents for transabdominal robotic assisted laparoscopic surgery (Herling 2017). This review did not specifically include elderly patients and no included randomized controlled trials measured cognitive function, mortality, or length of stay. Another Cochrane Review compared the two types of anaesthetic for emergence from anaesthesia after brain tumour surgery (Prabhakar 2016). Again, the patients were not specifically elderly and the review authors did not seek the outcomes specified in our review. Another Cochrane Review considered general anaesthesia versus regional anaesthesia for hip fracture (a surgery which would typically include an older patient population), however this review did not measure outcomes related to cognitive function (Guay 2016). This review does serve to remind us, however, that general anaesthesia is not the only option and can be avoided for many operations (Lewis 2015).

AUTHORS' CONCLUSIONS

Implications for practice

We are uncertain whether maintenance with propofol-based total intravenous anaesthesia (TIVA) or with inhalational agents affect incidences of postoperative delirium, mortality, or length of hospital stay. We identified 28 studies which assessed the effects of propofol-based TIVA versus inhalational maintenance in elderly surgical patients. Few of the included studies reported the effect on postoperative delirium.

We found no evidence of a difference in postoperative delirium according to type of anaesthetic agents used and we judged this evidence to be very low certainty. We found low-certainty evidence that propofol-based TIVA may reduce postoperative cognitive dysfunction (POCD). We were unable to ascertain any effects on length of stay in postanaesthesia care unit (PACU); we judged this evidence to be very low certainty, and we were unable to ascertain any effects on intraoperative hypotension for which we judged the evidence to be low certainty. We found little or no evidence of a difference in mortality and length of hospital stay, but this evidence was very low certainty.

Implications for research

We identified a large number of ongoing studies (11), which assess the effects of propofol-based TIVA versus inhalational agents in elderly surgical patients. This demonstrates continuing interest in this research field and including these studies in future review updates would increase certainty of the effect. The studies included in this review did not separate data for participants that were frail

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elderly (or more than 80 years of age), and no studies specifically included non-elective surgical patients. These are important subgroups and evidence for these groups of patients in future research would be useful. We focused our review outcomes on postoperative cognitive outcomes and length of stay; however we propose that future review updates consider postoperative nausea and vomiting as an additional relevant outcome.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ammar 2016

Methods	RCT, parallel design, single-centre
Participants	**Total number of randomized participants:** 50 **Inclusion criteria** 1. People who were ASA II or III, and scheduled for elective infrarenal AAA repair **Exclusion criteria** 1. Needed concomitant procedures other than AAA repair 2. Had experienced an acute coronary syndrome within 3 months 3. > 85 years of age **Type of surgery:** elective infrarenal AAA repair **Baseline characteristics** **TIVA group** 1. Age, median (range): 70 (65 to 79) years 2. Gender, M/F: 20/5 3. NYHA score, median (range): 1 (1 to 2) **Inhalational maintenance group** 1. Age, median (range): 71 (67 to 79) years 2. Gender, M/F: 19/6 3. NYHA score, median (range): 1 (1 to 2) **Country:** Egypt **Setting:** hospital
Interventions	**TIVA group** Participants: n = 25; 0 losses Induction details: propofol 1.5 mg/kg to 2 mg/kg, fentanyl 3 µg/kg, cisatracurium 0.1 mg/kg Maintenance details: continuous infusion of propofol 4 mg/kg/hour to 6 mg/kg/hour, and cisatracurium 2 µg/kg/min. BIS kept between 45 and 55 Additional regional anaesthesia: epidural analgesia before starting anaesthesia at T8-T10. Epidural block with 12 mL bupivacaine hydrochloride 0.25%. 4 mL bupivacaine injected 2 hours later as maintenance and every hour thereafter for postoperative epidural analgesia Other information: fluid loading was performed with 1.0 L of 6% 130/0.4 hydroxyethyl starch (Voluven) infusion. Fluid and blood replacements were adjusted to maintain participant haematocrit value above 30%. Norepinephrine and nicardipine were used if required (if MAP changed by > 20%) to maintain haemodynamic stability. Normothermia maintained. Acetaminophen IV postoperatively if required **Inhalational maintenance group** Participants: n = 25; 0 losses Induction details: propofol 1.5 mg/kg to 2 mg/kg, fentanyl 3 µg/kg, cisatracurium 0.1 mg/kg Maintenance details: sevoflurane 1 MAC, cisatracurium 2 µg/kg/min. BIS kept between 45 and 55 Additional regional anaesthesia and other information: epidural analgesia, epidural block

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	and all other fluid management etc. was the same as the TIVA group
Outcomes	1. Kidney specific proteins 2. Serum creatinine and cystatin 3. Serum pro-inflammatory cytokines 4. Blood loss 5. Blood transfusion 6. Length of ICU and hospital stay 7. 30-day mortality
Notes	**Funding/declarations of interest:** university funding. No conflicts of interest **Study dates:** February 2012 to April 2014

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Use of a computer-generated random number table
Allocation concealment (selection bias)	Low risk	Quote: "an independent statistician was assigned to perform central randomization to ensure proper concealment of the study management from the patients and investigators until the release of the final statistical results."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind anaesthetists to intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "one analyst was blinded in respect to the drug under study during the procedure by covering the lines, infusion pump, gas analyzer, and by numeric codes during the whole process of data evaluation. Furthermore, physicians who were charged for postoperative care of patients and for their discharges from intensive care unit (ICU) and hospital were effectively blinded to the study design."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent loss of study participants
Selective reporting (reporting bias)	Unclear risk	Retrospective registration with clinical trials register (PACTR201505001095139). Not feasible to assess risk of selective outcome reporting bias with these documents
Other bias	Low risk	No other sources of bias identified

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Biboulet 2012

Methods	RCT, parallel design, single-centre
Participants	**Total number of randomized participants:** 30 **Inclusion criteria** 1. > 75 years of age, ASA III or IV with severe cardiac comorbidities, presenting for hip fracture and undergoing hip nailing or partial hip replacement **Exclusion criteria** 1. Contraindication to spinal anaesthesia 2. Allergy to any of the anaesthetic drugs used 3. Existing total hip replacement **Type of surgery:** total hip replacement **Baseline characteristics:** **TIVA group** (characteristics for 14 participants) 1. Age, mean (SD): 86 (± 6) years 2. Gender, M/F: 4/10 3. ASA grade: ASA III: 8; ASA IV: 6 **Inhalational maintenance group** (characteristics for 15 participants) 1. Age, mean (SD): 85 (± 6) years 2. Gender, M/F: 5/10 3. ASA grade: ASA III: 10; ASA IV: 5 **Country:** France **Setting:** hospital
Interventions	**TIVA group** Participants: n = 15; 1 loss (change to surgical technique which warranted study exclusion) ; 14 analysed Induction details: initial target plasma concentration 1.5 µg/mL propofol, gradually increased by increments of 0.5 µg/mL every 2 minutes until BIS of 50. Remifentanil 0. 25 µg/kg for 2 minutes, with repeated boluses if required to maintain BIS of 50 or HR and MAP no more than 20% of baseline Maintenance details: after intubation, propofol TCI decreased to 0.5 µg/mL, and titrated to maintain BIS of 50. Remifentanil infusion 0.1 µg/kg/min, preceded by bolus of 0.25 µg/kg for 2 minutes Other information: femoral nerve block with 30 mL ropivacaine 0.5% on arrival in operating theatre **Inhalational maintenance group** Participants: n = 15; 1 loss (cardiac arrest during induction); 14 analysed Induction details: sevoflurane, initially at 6%, decreased to 3% when BIS fell to 50. Remifentanil 0.25 µg/kg for 2 minutes, with repeated boluses if required to maintain BIS of 50 or HR and MAP no more than 20% of baseline Maintenance details: after intubation, sevoflurane decreased to FiO_2 0.5%, to maintain BIS of 50. Remifentanil infusion 0.1 µg/kg/min, preceded by bolus of 0.25 µg/kg for 2 minutes Other information: femoral nerve block with 30 mL ropivacaine 0.5% on arrival in operating theatre. 1 g paracetamol given in recovery room, and, if score on VAS > 3, 1 mg IV morphine given every 5 minutes up to 10 mg
Outcomes	1. Biological data (serum urea nitrogen, creatinine, haemoglobin, troponin) 2. Stroke 3. Acute heart failure (after 1 month)

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Biboulet 2012 (*Continued*)

	4. MI (after 1 month) 5. Mortality (after 1 month) 6. Times for anaesthesia 7. Haemodynamic data (to include number of participants given ephedrine for hypotension - defined as 30% decrease in MAP from baseline value, lasting > 1 minute)
Notes	**Funding/declarations of interest:** Department of Anaesthsia and Critical Care Unit, Lapeyronie University Hospital, France. Study authors declare no conflicts of interest **Study dates:** not reported **Note:** study includes a group with continuous spinal anaesthesia. We have not included data for this group in the review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants were randomly divided into groups; no additional details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind anaesthetists to intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	Few losses, unlikely to influence outcome data
Selective reporting (reporting bias)	Unclear risk	Study authors do not report clinical trials registration. Not feasible to judge risk of selective outcome reporting
Other bias	Low risk	No other sources of bias identified

Cai 2012a

Methods	RCT, parallel design, single-centre
Participants	**Total number of randomized participants:** 2216 **Inclusion criteria** 1. Elderly Han patients (Chinese ethnic group) scheduled to undergo general anaesthesia **Exclusion criteria** 1. Did not consent to be enrolled 2. Dementia symptoms

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Cai 2012a (*Continued*)

	3. Hepatic dysfunction 4. Renal dysfunction 5. Heart disease 6. Lung disease 7. Participants who required postoperative intensive care (because of bleeding, inflammation, respiratory failure, heart failure, anastomotic leaks etc.) or required postoperative sedation were excluded from analysis **Type of surgery:** oesophagectomy, gastrectomy, nephrectomy, fracture reduction **Baseline characteristics** **TIVA group** 1. Age, mean (SD): 71.2 (± 3.8) years 2. Gender, M/F: 570/430 3. ASA grade: not reported Inhalational maintenance group 1. Age, mean (SD): 69.3 (± 5.1) years 2. Gender, M/F: 570/430 3. ASA grade: not reported **Country:** China **Setting:** hospital
Interventions	**TIVA group** Participants: n = 1106; 106 losses (anastomotic leaks, bleeding, respiratory failure, heart failure, inflammation); 1106 analysed using ITT: 1000 analysed PP Induction details: loading doses of fentanyl 4 μg/kg, propofol 3 mg/kg and vecuronium 0.08 mg/kg Maintenance details: fentanyl continuous infusion 0.03 μg/kg/min, propofol continuous infusion at a rate of 53.8 μg/kg/min injected with gradual increases in concentration of 0.4 μg/mL with initial target level of 1 μg/mL. Continuous infusion of vecuronium 0.5 μg/kg/min. BIS maintained at 40 to 60 Other information: premedication with 10 mg diazepam, 0.5 mg atropine im 30 minutes before GA **Inhalational maintenance group** Participants: n = 1110; 110 losses (anastomotic leaks, bleeding, respiratory failure, heart failure, inflammation); 1110 analysed using ITT; 1000 analysed PP Induction details: loading doses of fentanyl 4 μg/kg, propofol 3 mg/kg and vecuronium 0.08 mg/kg Maintenance details: continuous inhalation 2% to 3% end-tidal concentration isoflurane. Continuous infusion of vecuronium 0.5 μg/kg/min. BIS maintained at 40 to 60 Other information: premedication same as TIVA group
Outcomes	1. MMSE (tested every day for 10 days) 2. Frequency distribution of ApoE alleles and genotypes
Notes	**Funding/declarations of interest:** supported by grants from National Nature Science Foundation of China, and by Doctor funding **Study dates:** 2005 to 2010
Risk of bias	

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Cai 2012a (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Use of a computerized random number generator and block randomization
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind anaesthetists to intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Postoperative assessment of MMSE was carried out by psychiatrists who were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reasons for losses are described and balanced between group but number of losses is large (> 10%) and we were unclear whether this could influence outcome data
Selective reporting (reporting bias)	Unclear risk	Study authors do not report clinical trials registration. Not feasible to judge risk of selective outcome reporting
Other bias	Unclear risk	We noted a discrepancy between table 2 and the text in results section of the study report. Table 2 reports a big difference in MMSE scores at baseline, with very low scores in the inhalation group, and text reports no difference at baseline. We have assumed that table 2 has a typo, because baseline MMSE score is unusually low. We noted that data in this study differed from other studies. We did not identify any differences that could explain this, and we could not be certain whether other sources of unidentified bias were present

Celik 2011

Methods	RCT, parallel design, single-centre
Participants	**Total number of randomized participants:** 100 **Inclusion criteria** 1. ASA I to III, aged 65 to 80 years, scheduled for elective urological surgery estimated to last > 1.5 hours **Exclusion criteria** 1. Routine use of sedative drugs 2. Requirement of dialysis 3. Emergency surgery

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	4. Cardiac and respiratory failure **Type of surgery:** urological surgery **Baseline characteristics** **TIVA group** 1. Age, mean (SD): 69.2 (± 4.8) years 2. Gender, M/F: 38/12 3. ASA grade: ASA I: 18; ASA II: 24; ASA III: 8 **Inhalational maintenance group** 1. Age, mean (SD): 69.8 (± 3.9) 2. Gender, M/F: 36/14 3. ASA grade: ASA I: 18; ASA II: 25; ASA III: 7 **Country:** Turkey **Setting:** hospital
Interventions	**TIVA group** Participants: n = 50; 0 losses Induction details: premedicated with 0.06 mg/kg midazolam 45 minutes before surgery. Prior to induction 5 mL/kg of IV fluid. Bolus dose 1 µg/kg remifentanil (over 30 to 60 seconds), and infusion of remifentanil at rate of 0.5µg/kg/min added simultaneously. Propofol starting dose of 0.5 mg/kg and titrated thereafter at 10 mg every 10 seconds until participant was unresponsive to verbal commands. Rocuronium 0.6 mg/kg Maintentance details: remifentanil 0.25 µg/kg/min. Propofol 2 mg/kg/hour to 8 mg/kg/hour. Fresh gas flow with 4 L/min oxygen 35% in air. Depth of anaesthesia adjusted according to haemodynamic parameters Other: tramadol 2 mg/kg administered for hyperalgesia 30 minutes before end of surgery **Inhalational maintenance group** Participants: n = 50; 0 losses Induction details: premedicated with 0.06 mg/kg midazolam 45 minutes before surgery. Prior to induction 5 mL/kg of IV fluid. Bolus dose 1 µg/kg remifentanil (over 30 to 60 seconds), and infusion of remifentanil at rate of 0.5µg/kg/min added simultaneously. Propofol starting dose of 0.5 mg/kg and titrated thereafter at 10 mg every 10 seconds until participant was unresponsive to verbal commands. Rocuronium 0.6 mg/kg Maintenance details: remifentanil 0.25 µg/kg/min. Sevoflurane end expiratory levels 0 to 4% and MAC values at 0.5 to 1. Fresh gas flow with 4 L/min oxygen 35% in air. Depth of anaesthesia adjusted according to haemodynamic parameters Other: tramadol 2 mg/kg administered for hyperalgesia 30 minutes before end of surgery
Outcomes	1. Doses of remifentanil 2. Emergence and recovery times (to include length of stay in the PACU) 3. Cognitive tests (TDT and DSST) 4. Pain (VAS) 5. PONV 6. Shivering
Notes	**Funding/declarations of interest:** not reported **Study dates:** not reported
Risk of bias	

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Celik 2011 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomly divided into groups; no additional details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind anaesthetists to intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants assessed in recovery room by an investigator who was blinded to group allocations
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent losses
Selective reporting (reporting bias)	Unclear risk	Study authors do not report clinical trials registration. Not feasible to judge risk of selective outcome reporting
Other bias	Low risk	No other sources of bias identified

Chan 1996

Methods	RCT, parallel design, single-centre
Participants	**Total number of randomized participants:** 60 **Inclusion criteria** 1. ASA I, II, and III, 65 to 85 years of age, scheduled for total hip replacement surgery **Exclusion criteria** 1. Significant cardiovascular, respiratory, hepatic, or renal disease **Type of surgery:** total hip replacement **Baseline characteristics** **TIVA group** 1. Age, mean (SD): 68.6 (± 8) years; 15 participants were > 70 years of age 2. Gender, M/F: 9/20 3. ASA grade: ASA I: 1; ASA II: 22; ASA III: 6 **Inhalational maintenance group** 1. Age, mean (SD): 70.2 (± 8) years; 15 participants were > 70 years of age 2. Gender, M/F: 8/23 3. ASA grade: ASA I: 1; ASA II: 23; ASA III: 7 **Country:** Canada **Setting:** hospital

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Interventions	**TIVA group** Participants: n = 29; 0 losses Induction details: propofol at 0.75 mg/kg/min via electronic pump. Succinylcholine 1. 0 mg/kg to 1.5 mg/kg to facilitate tracheal intubation Maintenance details: 60% N_2O in O_2. Propofol increased/decreased by 50% in response to 25% change in baseline BP or HR. Fentanyl 1 µg/kg (to a maximum of 4 µg/kg) with increase of propofol. Intraoperative muscle relaxation maintained with vecuronium. Propofol discontinued 5 minutes before end of surgery, N_2O and O_2 continued until end of surgery. Postoperative pain management with IV morphine as required. Use of clinical parameters (HR and BP) to monitor depth of anaesthesia Other information: evening before surgery, participants were given triazolam 0.125 mg to 0.25 mg, if required. Participants usual medication was withheld on morning of surgery. Then as premedication given 10 mL/kg IV crystalloid, then vecuronium 1 mg, and fentanyl 0.75 µg/kg **Inhalational maintenance groups** Participants: n = 31; 0 losses Induction details : bolus of 2 mg/kg thiopental, titrated to 4 mg/kg within 60 seconds as necessary. Succinylcholine 1.0 mg/kg to 1.5 mg/kg to facilitate tracheal intubation Maintenance details: 60% N_2O in O_2. 0.5% to 1.5% isoflurane end-tidal concentration increased/decreased by 50% in response to 25% change in baseline BP or HR. Fentanyl 1 µg/kg (to a maximum of 4 µg/kg) with increase of propofol. Intraoperative muscle relaxation maintained with vecuronium. Isoflurane discontinued 5 minutes before end of surgery, N_2O and O_2 continued until end of surgery. Postoperative pain management with IV morphine as required Other information: premedication etc. same as TIVA group
Outcomes	1. Dose requirement 2. Duration of anaesthesia 3. Haemodynamics (to include hypotension) 4. Myocardial ischemias 5. Recovery (to include time in PACU) 6. Mental alertness 7. Adverse effects (PONV)
Notes	**Funding/declarations of interest:** not reported **Study dates:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Use of a computer-generated random number list
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind anaesthetists to intervention groups

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Chan 1996 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Discharge from the PACU was assessed by a blinded independent investigator. Study authors do not report whether assessment of hypotension was done by a blinded investigator
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent loss of study participants
Selective reporting (reporting bias)	Unclear risk	Study authors do not report clinical trials registration. Not feasible to judge risk of selective outcome reporting
Other bias	Low risk	N_2O in O_2 used in both groups in addition to other agents. However, unlikely to affect results

Demeere 2006

Methods	RCT, parallel design, single-centre
Participants	**Total number of randomized participants:** 60 **Inclusion criteria** 1. undergoing hip replacement under GA **Exclusion criteria** 1. Not reported **Type of surgery:** total hip replacement surgery **Baseline characteristics** (table reported by study authors appears to include data for number analysed not number randomized) **TIVA group** 1. Age, mean (SD): 68.6 (± 10.9) years 2. Gender: 50% male 3. ASA grade: not reported **Inhalational maintenance group (sevoflurane)** 1. Age, mean (SD): 72.8 (± 6.9) years 2. Gender: 11% male 3. ASA grade: not reported **Inhalational maintenance group (desflurane)** 1. Age, mean (SD): 70.7 (± 8.7) years 2. Gender: 24% male 3. ASA grade: not reported **Country:** Belgium **Setting:** hospital
Interventions	**TIVA group** Participants: n = 20; 1 loss (reasons for losses described only as 'methodological problems') ; 19 analysed Induction details: propofol 1% 50 mL, TCI 4 µg/mL via a Diprivusor, 3 µg/kg sufentanil. Atracurium 0.5 µg/kg

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	Maintenance details: 50% N_2O and 50% O_2. Propofol TCI, 10 mL atracurium, and 10 µg sufentanil as necessary. To maintain BIS 'around 40' Other information: oral premedication with 0.25 or 0.5 mg alprazolam. BP maintained above 80 mmHg with ephedrine as required **Inhalational maintenance group (sevoflurane)** Participants: n = 20; 2 losses (reasons for losses described only as 'methodological problems'); 18 analysed Induction details: propofol 1% 20 mL (1 mg/kg/body weight to 2 mg/kg/body weight) , 3 µg/kg sufentanil. Atracurium 0.5 µg/kg Maintenance details: 50% N_2O and 50% O_2. 10 mL atracurium, and 10 µg sufentanil as necessary. Sevoflurane to maintain BIS 'around 40' Other information: oral premedication with 0.25 mg or 0.5 mg alprazolam. BP maintained above 80 mmHg with ephedrine as required **Inhalational maintenance group (desflurane)** Participants: n = 20; 0 losses Induction details: propofol 1% 20 mL (1 mg/kg/body weight to 2 mg/kg/body weight) , 3 µg/kg sufentanil. Atracurium 0.5 µg/kg Maintenance details: 50% N_2O and 50% O_2. 10 mL atracurium, and 10 µg sufentanil as necessary. Desflurane to maintain BIS 'around 40' Other information: oral premedication with 0.25 mg or 0.5 mg alprazolam. BP maintained above 80 mmHg with ephedrine as required
Outcomes	1. Cost-effectiveness data 2. Length of stay in PACU 3. Length of hospital stay
Notes	**Funding/declarations of interest:** not reported **Study dates:** not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants were randomized to groups; no additional details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind anaesthetists to intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	Although reasons for losses are not well described, loss is small and unlikely to influence outcome data

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Demeere 2006 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Study authors do not report clinical trials registration. Not feasible to judge risk of selective outcome reporting
Other bias	Unclear risk	Limited detail in paper - does not include inclusion/exclusion criteria. We noted a difference in gender balance between groups

Egawa 2016

Methods	RCT, parallel design, single-centre
Participants	**Total number of randomized participants:** 148 **Inclusion criteria** 1. Scheduled for one-lung surgery, 20 to 85 years of age, ASA I to III, fluency in Japanese, ability to read, and absence of serious hearing or visual impairments that would preclude neuropsychological testing **Exclusion criteria** 1. Interstitial lung disease or lung fibrosis 2. Pregnancy or possibility of pregnancy 3. History of neurological or mental illness 4. Baseline MMSE score < 24 5. Renal insufficiency 6. Active liver disease 7. Documented coagulopathy **Type of surgery:** one-lung surgery **Baseline characteristics** **TIVA group** 1. Age, median (IQR): 69 (63 to 73) years 2. Gender, M/F: 48/23 3. ASA grade: ASA I: 25; ASA II: 42; ASA III: 5 **Inhalational maintenance group** 1. Age, median (IQR): 72 (63 to 72) years 2. Gender, M/F: 39/33 3. ASA grade: ASA I: 29; ASA II: 40; ASA III: 3 **Country:** Japan **Setting:** hospital
Interventions	**TIVA group** Participants: n = 74; 2 losses (1 withdrew prior to surgery; 1 had surgery cancelled); 72 analysed (at 5 days postoperatively) Induction details: propofol TCI 3 µg/mL to 4 µg/mL, bolus of fentanyl 2.0 µg/kg, to 2.5 µg/kg, Rocuronium 0.6 mg/kg to 0.9 mg/kg Maintenance details: TCI propofol, plus fentanyl, and epidural Other information: epidural inserted between thoracic 5 to 6 and 7 to 8 intervertebral spaces. No additional details **Inhalational maintenance groups** Participants: n = 74; 2 losses (1 withdrew prior to surgery; 1 had unsuccessful jugular

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	vein cannulation); 72 analysed (at 5 days postoperatively) Induction details : propofol 1 mg/kg to 2 mg/kg and fentanyl 2.0 µg/kg to 2.5 µg/kg Maintenance details: sevoflurane, plus fentanyl and epidural. To maintain BIS 40 to 60 Other information: epidural same as TIVA group
Outcomes	1. POCD (defined as a decline of > 20% from baseline) at baseline, 5 days postoperatively, and 3 months postoperatively using MMSE, Trail Making Test (Parts A and B), Digit Span (forward and backward), and Grooved Pegboard Test (dominant and non-dominant hands) 2. Oxygen saturation measures 3. Cerebral desaturation measures
Notes	**Funding/declarations of interest:** department funding. Study authors declared no conflicts of interest **Study dates:** March 2007 to January 2013

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Use of a computer-generated randomization list
Allocation concealment (selection bias)	Low risk	Allocation concealment was assured by the use of numbered sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind anaesthetists to intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome was assessed by the same anaesthesiologist blinded to group allocation and not involved in intraoperative management
Incomplete outcome data (attrition bias) All outcomes	Low risk	Few losses which were well reported
Selective reporting (reporting bias)	Unclear risk	Study authors report that clinical trials registration was not required in Japan at the time of the start of the study. Not feasible to judge risk of selective reporting bias
Other bias	Unclear risk	Participants in the sevoflurane groups appeared to have shorter duration of surgery and anaesthesia

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Epple 2001

Methods	RCT, parallel design, single-centre
Participants	**Total number of randomized participants:** 124 **Inclusion criteria** 1. Geriatric participants > 65 years of age, ASA I, II, or III, scheduled for elective cataract surgery under GA **Exclusion criteria** 1. History of allergic reaction to one of the study drugs **Type of surgery:** cataract surgery **Baseline characteristics** **TIVA group** 1. Age, mean (SD): 77 (± 6) years; participants described as 'geriatric' 2. Gender, M/F: 17/45 3. ASA grade: ASA I: 3; ASA II: 40; ASA III: 19 **Inhalational maintenance group** 1. Age, mean (SD): 76 (± 6) years; participants described as 'geriatric' 2. Gender, M/F: 17/45 3. ASA grade: ASA I: 1; ASA II: 39; ASA III: 22 **Country:** Germany **Setting:** PACU in hospital
Interventions	**TIVA group** Participants: n = 62; 0 losses Induction details: propofol 1.5 mg/kg and remifentanil 1.5 µg/kg over 3 minutes, 0.15 mg/kg mivacurium Maintenance details: continuous infusion of propofol 0.05 mg/kg/min to 0.1 mg/kg/min and remifentanil 0.15 µg/kg/min to 0.3 µg/kg/min. Haemodynamic parameters used to monitor depth of anaesthesia Other information: received no medication before surgery **Inhalational maintenance group** Participants: n = 62; 0 losses Induction details: etomidate 0.1 mg/kg to 0.3 mg/kg and fentanyl 1.5 µg/kg, 0.15 mg/kg mivacurium Maintenance details: isoflurane 0.8 to 2.5 MAC and bolus of 0.1 mg fentanyl. Haemodynamic parameters used to monitor depth of anaesthesia
Outcomes	1. Cost-benefit analysis 2. Anaesthetic and surgical time intervals 3. Emergence times 4. Time to discharge from PACU 5. Postanaesthetic adverse events (to include hypertension, PONV, shivering, pain requiring intervention) 6. Patient satisfaction
Notes	**Funding/declarations of interest:** supported by a grant from Glaxo Wellcome GmbH Co., Hamburg, Germany **Study dates:** not reported **Note:** we identified an associated reference for this study (Kubitz 2001)

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Epple 2001 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Use of a computer-generated randomization list
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind anaesthetists to intervention groups
Blinding of outcome assessment (detection bias) All outcomes	High risk	Discharge from the PACU judged by unblinded anaesthetist
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent loss of study participants
Selective reporting (reporting bias)	Unclear risk	Study authors do not report clinical trials registration. Not feasible to judge risk of selective outcome reporting
Other bias	Unclear risk	Use of remifentanil and fentanyl differs between groups

Geng 2017

Methods	RCT, parallel design, single-centre
Participants	**Total number of randomized participants:** 150 **Inclusion criteria** 1. ASA II to III, ≥ 65 years of age, sufficient level of education to be capable of completing neuropsychological tests **Exclusion criteria** 1. History of allergy to anaesthetics 2. Dialysis-dependent renal failure 3. Liver transaminase level < 1.5 times the normal value 4. MMSE score ≤ 26 5. Pre-existing diagnosis of schizophrenia or dementia 6. Recent stroke 7. Known disorder affecting cognition 8. Mental dysfunction 9. History of cerebral surgery 10. Severe anxiety 11. Recent history of alcohol abuse 12. History of chronic opioid or other psychotropic drug use

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	Type of surgery: laparoscopic cholecystectomy **Baseline characteristics** **TIVA group** 1. Age: not reported 2. Gender, M/F: 20/30 3. ASA grade: ASA II: 35; ASA III: 15 **Inhalational maintenance group (isoflurane)** 1. Age: not reported 2. Gender, M/F: 18/32 3. ASA grade: ASA II: 33; ASA III: 17 **Inhalational maintenance group (sevoflurane)** 1. Age: not reported 2. Gender, M/F: 22/28 3. ASA grade: ASA II: 31; ASA III: 19 **Country:** China **Setting:** hospital
Interventions	**TIVA group** Participants: n = 50; 0 losses Induction details: 5 minutes of pre-oxygenation, then midazolam 0.05 mg/kg, fentanyl 4 μg/kg, rocuronium 0.6 mg/kg. TCI 3.0 μg/kg propofol Maintenance details: propofol with target concentration 2.5 μg/mL to 3.0 μg/mL. Remifentanil 0.2 μg/kg/min to 0.3 μg/kg/min. To maintain BIS 40 to 50 Other information: all patients given crystalloids as required. All patients were given flurbiprofen 100 mg and granisetron 3 mg at beginning of operation, and 0.25% ropivacaine via local infiltration for postoperative analgesia **Inhalational maintenance groups** Participants: n = 50; 0 losses Induction details: 5 minutes of pre-oxygenation, then midazolam 0.05 mg/kg, fentanyl 4 μg/kg, rocuronium 0.6 mg/kg. TCI 3.0 μg/kg propofol Maintenance details: isoflurane 1.0 MAC to 1.5 MAC. Remifentanil 0.2 μg/kg/min to 0.3 μg/kg/min. To maintain BIS 40 to 50 Other information: fluids and analgesics same as TIVA group **Inhalational maintenance groups** Participants: n = 50; 0 losses Induction details: 5 minutes of pre-oxygenation, then midazolam 0.05 mg/kg, fentanyl 4 μg/kg, rocuronium 0.6 mg/kg. TCI 3.0 μg/kg propofol Maintenance details: sevoflurane 1.0 MAC to 1.5 MAC. Remifentanil 0.2 μg/kg/min to 0.3 μg/kg/min. To maintain BIS 40 to 50 Other information: fluids and analgesics same as TIVA group
Outcomes	1. POCD on postoperative day 1 and 3 (using MMSE, vision test, the Digit Symbol Substitution Test, the Cumulative test, digit span, forward and backward, Trail Making Test Part A, the RAVLT, Grooved Pegboard Test (dominant and non-dominant hand)). POCD defined as decline > 20% in at least 2 tests compared to baseline 2. Plasma concentrations or protein biomarkers of POCD 3. Proinflammatory markers 4. Duration of anaesthesia and emergence times 5. Use of vasoconstrictors

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Geng 2017 (*Continued*)

	6. Hypotension (number of participants, number of episodes, and duration)
Notes	**Funding/declarations of interest:** no funding and authors declare no conflicts of interest **Study dates:** December 2010 to June 2011

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Use of a computer-generated random number table
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind anaesthetists to intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	A blinded anaesthetist evaluated cognitive scores
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses
Selective reporting (reporting bias)	Unclear risk	Retrospective clinical trials registration (ChiCTR-OCC-11001411). Not feasible to assess risk of selective reporting bias
Other bias	Unclear risk	Some differences in duration of anaesthesia, surgery times, and time to emergence from anaesthesia. We were not certain whether these differences were clinically significant. Also note that no ages were reported in baseline characteristics

Gursoy 2015

Methods	RCT, parallel group, single-centre
Participants	**Total number of participants:** 60 **Inclusion criteria** 1. > 65 years of age, ASA I to III, scheduled for laparotomy **Exclusion criteria** 1. Neurological or psychiatric illnesses 2. Alcohol or substance misuse 3. Significant fluid loss or electrolyte impairment. 4. Participants were excluded during the study if they had respiratory or cardiac arrest, ischaemia, cerebral haemorrhage or long-lasting episodes of hypotension

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Gursoy 2015 (*Continued*)

	Type of surgery: laparotomy **Baseline characteristics** **TIVA group** 1. Age, mean (SD): 73.17 (± 6.35) years 2. Gender, M/F: 15/15 3. ASA grade: not reported **Inhalational maintenance group** 1. Age, mean (SD): 73.27 (± 6.15) years 2. Gender, M/F: 13/17 3. ASA grade: not reported **Country:** Turkey **Setting:** hospital
Interventions	**TIVA group** Participants: n = 30; 0 reported losses (study authors report use of ITT analysis) Induction details: propofol 3 mg/kg to 6 mg/kg, remifentanil 1 µg/kg, vecuronium 0.1 mg/kg Maintenance details: propofol infusion of 12 mg/kg/hour, then 9 mg/kg/hour, then 6 mg/kg/hour over 10 minutes. Remifentainil 0.15 µg/kg/hour to 0.30 µg/kg/hour. 67% air and 33% O_2 **Inhalational maintenance group** Participants: n = 30; 0 reported losses (study authors report use of ITT analysis) Induction details: thiopentone 3 mg/kg to 5 mg/kg, vecuronium 0.1 mg/kg IV Maintenance details: 2% sevoflurane, with 67% N_2O/33% O_2
Outcomes	1. Changes in MAP 2. Cognitive dysfunction (measured at 1, 6, 12, 24 hours postoperatively with MMT)
Notes	**Funding/declarations of interest:** study authors report no conflict of interest **Study dates:** not reported Note: study report in Turkish. Review authors used Google translate to assist with translation of key paragraphs

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomized to groups; no additional details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind anaesthetists to intervention groups

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Gursoy 2015 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent loss of study participants
Selective reporting (reporting bias)	Unclear risk	Study authors do not report clinical trials registration. Not feasible to judge risk of selective outcome reporting
Other bias	Low risk	No other sources of bias identified

Ishii 2016

Methods	RCT, parallel design, single-centre
Participants	**Total number of randomized participants:** 59 **Inclusion criteria** 1. ASA I to II, ≥ 70 years of age **Exclusion criteria** 1. History of dementia, depression, alcoholism, and liver cirrhosis 2. History of using benzodiazepine, major tranquillizers, or steroids 3. An ineffective postoperative analgesia via epidural anaesthesia 4. Allergic reactions to local anaesthetics **Type of surgery:** elective gastrectomy, colectomy, or rectectomy **Baseline characteristics** **TIVA group** 1. Age, mean (SD): 77.3 (± 4.6) years 2. Gender, M/F: 20/9 3. ASA grade: not reported **Inhalational maintenance group** 1. Age, mean (SD): 76.5 (± 4.5) years 2. Gender, M/F: 20/10 3. ASA grade: not reported **Country:** Japan **Setting:** single-centre
Interventions	**TIVA group** Participants: n = 29; 0 losses Induction details: insertion of epidural catheter, then induction with propofol 1 mg/kg to 1.5 mg/kg Maintenance details: propofol to maintain BIS 40 to 60 Other information: intraoperative analgesia given with injection of fentanyl or continuous infusion of 0.25% ropivacaine (6 mL/hour) **Inhalational maintenance groups** Participants: n = 30; 0 losses Induction details: insertion of epidural catheter, then induction with propofol 1 mg/kg

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Ishii 2016 (*Continued*)

	to 1.5 mg/kg Maintenance details: sevoflurane to maintain BIS 40 to 60 Other information: analgesia same as TIVA group
Outcomes	1. Incidence of postoperative delirium (using CAM)
Notes	**Funding/declarations of interest:** not reported **Study dates:** July 2009 to December 2010

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants were randomized to groups; no additional details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind anaesthetists to intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessment done by ICU nurses blinded to group assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent losses
Selective reporting (reporting bias)	Unclear risk	Study authors do not report clinical trials registration. Not feasible to judge risk of selective outcome reporting
Other bias	Unclear risk	No other sources of bias noted. However, report is short with limited detail on anaesthetic regimen

Jellish 2003

Methods	RCT, parallel design, single-centre
Participants	**Total number of randomized participants:** 60 (unclearly reported in paper, possibly 59 randomized participants) **Inclusion criteria** 1. Undergoing unilateral carotid endarterectomy **Exclusion criteria** 1. Undergoing emergency surgery 2. In atrial fibrillation 3. Significant renal or hepatic disease

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	Type or surgery: carotid endarterectomy **Baseline characteristics** **TIVA group** 1. Age, mean (SD): 72.1 (± 1.5) years 2. Gender: 55% male 3. ASA grade: all patients were ASA III **Inhalational maintenance group** 1. Age, mean (SD): 69.2 (± 1.7) years 2. Gender: 62% male 3. ASA grade: all patients were ASA III **Country:** USA **Setting:** single-centre
Interventions	**TIVA group** Participants: n = 30; 0 losses Induction details : propofol 1.0 mg/kg to 1.5 mg/kg IV. Remifentanil infusion started at 0.25 µg/kg/min. Additional propofol 25 mg to 50 mg IV given if necessary to maintain MAP within 10 % pre-induction values during intubation Maintenance details: propofol 50 µg/kg/min to 75 µg/kg/min. Remifentanil 0.125 µg/kg/min to 0.5 µg/kg/min. Adjusted to maintain haemodynamic parameters within 15% pre-induction. N_2O in O_2 mix 60/40 Other information: hypertension non-responsive to anaesthesia treated with sodium nitroprusside 0.5 µg/kg/min. Hypotension non-responsive to anaesthesia treated with phenylephrine 40 µg to 80 µg IV. Tachycardia unresponsive to anaesthesia treated with esmolol 10 mg to mg 20 mg IV, bradycardia treated with glycopyrrolate 0.2 mg IV **Inhalational maintenance group** Participants: number of randomized participants is unclearly reported. We have assumed that 30 participants were randomized, with 1 loss (owing to technical difficulties with transoesophageal probe), and 29 participants were analysed Induction details: propofol 1.5 mg/kg to 2 mg/kg IV, fentanyl 2 µg/kg. Additional propofol 25 mg to 50 mg IV given if necessary to maintain MAP within 10 % pre-induction values during intubation Maintenance details: isoflurane 0.5% to 2% end-tidal. Titrated to maintain MAP 15% pre-induction values. N_2O in O_2 mix 60/40 Other information: other drugs to maintain stability same as TIVA group
Outcomes	1. Haemodynamic variables (hypertension, hypotension, tachycardia, bradycardia) 2. Emergence and recovery data to include length of time in PACU, time to hospital discharge, cardiac performance (using TEE)
Notes	**Funding/declarations of interest:** not reported **Study dates:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Use of computer generated randomization

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Jellish 2003 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind anaesthetists to intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant lost from inhalation group, which is unclearly reported. We have assumed that 30 participants were randomized to the inhalation group, with one loss. We were not concerned by risk of attrition bias because losses were few and unlikely to influence outcome data
Selective reporting (reporting bias)	Unclear risk	Study authors do not report clinical trials registration. Not feasible to judge risk of selective outcome reporting
Other bias	Unclear risk	Study includes comparison of remifentanil with fentanyl, which introduces methodological differences between groups. Also note differences in amount of propofol given at induction

Juvin 1997

Methods	RCT, parallel design, single-centre
Participants	**Total number of randomized participants:** 45 **Inclusion criteria** 1. ASA I or II, > 70 years of age, scheduled for major orthopedic surgery expected to last > 60 minutes. No participants had any clinical condition that might influence the assessment of variables used for the study and/or comparisons among groups **Excluded criteria** 1. Clinical conditions to contraindicate rapid extubation 2. Preoperative haematocrit 25% 3. Significant coronary disease 4. ß-blocker treatment 5. Chronic pulmonary disease 6. Previous neurologic insult 7. Chronic alcohol or drug abuse 8. Renal failure or hepatic dysfunction 9. Previous personal or family history of malignant hyperthermia **Type of surgery:** hip arthroplasty, knee arthroplasty, laminectomy, other orthopaedic surgery **Baseline characteristics**

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	TIVA group 1. Age, mean (SD): 75.6 (± 4.2) years 2. Gender, M/F: 3/11 3. ASA grade: ASA I: 1: ASA II: 13 **Inhalational maintenance group (isoflurane)** 1. Age, mean (SD): 77.3 (± 5) years 2. Gender, M/F: 3/12 3. ASA grade: ASA 1: 2; ASA II: 13 **Inhalational maintenance group (desflurane)** 1. Age, mean (SD): 77.4 (± 5.1) years 2. Gender, M/F: 4/10 3. ASA grade: ASA I: 1; ASA II: 13 **Country:** France **Setting:** hospital
Interventions	**TIVA group** Participants: n = 15; 1 loss (excluded owing to intraoperative complication); 14 analysed Induction details: propofol 1 mg/kg to 2 mg/kg, fentanyl 1 µg/kg to 2 µg/kg, vecuronium 0.1 mg/kg Maintenance details: 60% N_2O in O_2. Propofol titrated to maintain HR and BP within 20% of baseline. Study authors report mean (SD) infusion rates at 2.18 (± 1.24) mg/kg/hour Other information: premedication with oral hydroxyzine 100 mg. Additional fentanyl at 1 µg/kg at 40-minute intervals depending on length of surgery **Inhalational maintenance group (isoflurane)** Participants: n = 15; 0 losses Induction details: propofol 1 mg/kg to 2 mg/kg, fentanyl 1 µg/kg to 2 µg/kg, vecuronium 0.1 mg/kg Maintenance details: 60% N_2O in O_2. Isoflurane titrated to maintain HR and BP within 20% of baseline. Fresh gas flow of 1.5 L/min. Study authors report mean (SD) concentration isoflurane at 0.33% (± 0.21%) Other info: premedication and use of fentanyl same as TIVA group **Inhalational maintenance group (desflurane)** Participants: n = 15; 1 loss (owing to sudden vaporizer failure); 14 analysed Induction details: propofol 1 mg/kg to 2 mg/kg, fentanyl 1 µg/kg to 2 µg/kg, vecuronium 0.1 mg/kg Maintenance details: 60% N_2O in O_2. Desflurane titrated to maintain HR and BP within 20% of baseline. Fresh gas flow of 1.5 L/min. Study authors report mean (SD) concentration desflurane 1.59% (± 1.02) Other information: premedication and use of fentanyl same as TIVA group
Outcomes	1. Psychometric evaluation (recovery of cognitive function, assessed with MMSE at time points up to 24 hours) 2. Sedation scores 3. Pain measurement 4. PONV 5. Postoperative analgesic requirements 6. Time to discharge from PACU (using Aldrete; minutes) 7. Time to hospital discharge (days)

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Juvin 1997 (*Continued*)

Notes	**Funding/declarations of interest:** supported by Pharmacia and Upjohn **Study dates:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomly allocated to groups; no additional information
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind anaesthetists to intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes assessed by a single investigator who was blinded to participants' group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Few participants losses (1 participant in desflurane group, and 1 in propofol group); unlikely to influence outcome data
Selective reporting (reporting bias)	Unclear risk	Study authors do not report clinical trials registration. Not feasible to judge risk of selective outcome reporting
Other bias	Unclear risk	Some differences between groups in numbers for each type of surgery. Note balance of gender, with more female participants; balanced between groups and not a risk of bias within the study

Kim 2015a

Methods	RCT, parallel design, single-centre
Participants	**Total number of randomized participants:** 60 **Inclusion criteria** 1. ASA I to II, > 65 years of age, scheduled for elective orthopaedic surgery **Exclusion criteria** 1. Severe heart disease (NYHA class > III) 2. Severe arrhythmia 3. Uncontrolled hypotension 4. Haemodynamic instability 5. Drug hypersensitivity 6. Any cognitive deficiency, hepatic or renal compromise 7. Infectious disease

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	8. Surgery lasting > 3 hours **Type of surgery:** orthopaedic surgery (hip replacement, knee replacement, long bone fracture fixation, spinal surgery) **Baseline characteristics** **TIVA group** 1. Age, mean (SD): 73.5 (± 7.2) years 2. Gender, M/F: 8/22 3. ASA grade: ASA I: 11; ASA II: 19 **Inhalational maintenance group** 1. Age, mean (SD): 72.3 (± 6.2) years 2. Gender, M/F: 8/20 3. ASA grade: ASA I: 8; ASA II: 20 **Country:** South Korea **Setting:** hospital
Interventions	**TIVA group** Participants: n = 30; 0 losses Induction details: premedication with midazolam 0.05 mg/kg im. Remifentanil and propofol based on Minto and Marsh pharmacokinetic model using TCI. Target effect-site concentration 3 µg/mL propofol, 2.5 ng/mL remifentanil. Rocuronium 1.0 mg/kg Maintenance details: propofol-remifentanil with 50% O_2 and 50% air mix. Target effect-site concentration 3 µg/mL propofol, 2.5 ng/mL remifentanil. Rocuronium 1.0 mg/kg. To maintain BIS near 50 (range 40 to 60) Other information: after surgery fentanyl administration using PCI **Inhalational maintenance group** Participants: n = 30; 2 losses (owing to surgery lasting more than 2 hours); 27 analysed Induction details: premedication with midazolam 0.05 mg/kg im. Propofol 1.5 mg/kg to 2.0 mg/kg, 3% to 4 % sevoflurane and 50% O_2- air mixture. Rocuronium 1.0 mg/kg Maintenance details: sevoflurane with 50% O_2 and 50% air mix. Adjusted to maintain BIS near 50 (range 40 to 60) Other information: fentanyl after surgery same as TIVA group
Outcomes	1. Pain score 2. PONV 3. Duration of time in recovery
Notes	**Funding/declarations of interest:** grants from Chosun University Medical Research Institute. Study authors declare no competing interests **Study dates:** not reported **Note:** study has four comparison groups - sevoflurane vs TIVA, with and without dexmedetomidine. For the review, we have only used the comparison groups without dexmedetomidine

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Use of computer-generated randomization

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Kim 2015a (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind anaesthetists to intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss of 2 participants in the inhalation group; few losses unlikely to influence outcome data
Selective reporting (reporting bias)	Low risk	Prospective trial registration (NCT01851005). Most outcomes were reported, although we noted that adverse events (secondary outcomes) were not included in the written report. For the purpose of our review, MAP was reported but not in terms of hypotension
Other bias	Unclear risk	Differences between groups in use of remifentanil and fentanyl. Also, a higher ratio of female to male participants; however, this is balanced between groups

Lindholm 2013

Methods	RCT, parallel design, single-centre
Participants	**Total number of randomized participants:** 200 **Inclusion criteria** 1. People with AAA or aortic arteriosclerosis obliterans, or both, scheduled for open abdominal aortic surgery **Excluded criteria** 1. < 18 years of age 2. Included in other pharmaceutical studies 3. Abuse of opioids, benzodiazepines, antiepileptic drugs, alcohol, or alpha2-agonists 4. Pregnant and breastfeeding women 5. Family history of malignant hyperthermia 6. Known hypersensitivity for opioids, propofol, or volatile anaesthetics 7. Serious arrhythmias, ventricular fibrillation/tachycardia or tachycardia > 100 beats/min 8. Severe valvular diseases requiring surgical repair before major noncardiac surgery 9. Uncontrolled hypertension 10. Serious psychiatric disease 11. Unstable angina pectoris or MI 30 days before inclusion 12. Acute abdominal aortic surgery 13. Planned laparoscopic AAA surgery

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	Type of surgery: open abdominal aortic surgery **Baseline characteristics** **TIVA group** 1. Age, mean (SD): 67 (± 9) years 2. Gender, M/F: 72/24 3. ASA grade: ASA II: 34; ASA III: 49; ASA IV: 13 **Inhalational maintenance group** 1. Age, mean (SD): 69 (± 9) years 2. Gender, M/F: 73/24 3. ASA grade: ASA II: 36; ASA III: 47; ASA IV: 14 **Country:** Norway **Setting:** hospital
Interventions	**TIVA group** Participants: n = 100; losses unclearly reported; 96 analysed (PP) Induction details : premedication with paracetamol. Fentanyl 0.1 mg to 0.3 mg IV, and propofol 1 mg/kg to 2 mg/kg IV. Vecuronium 0.1 mg/kg, and 0.01 mg/kg to 0.02 mg/kg based on train-of-four Maintenance details: propofol 1 mg/kg/hour to 10 mg/kg/hour IV, and remifentanil 0.1 mg/kg/min to 0.7 mg/kg/min. Aim to maintain BIS 40 to 60 Additional regional anaesthesia: epidural 3 mL/hour to 12 mL/hour (bupivacaine 1 mg/mL, fentanyl 2 µg/mL, adrenaline 2 µg/mL) Other information: morphine 1 mg to 10 mg IV as rescue analgesia **Inhalational maintenance group** Participants: n = 100; losses unclearly reported; 97 analysed (PP) Induction details : premedication with paracetamol as for TIVA. Fentanyl 0.1 mg to 0.3 mg IV and thiopental sodium 3 mg/kg to 6 mg/kg IV. Vecuronium as for TIVA Maintenance details: balanced anaesthesia with sevoflurane at 0.7 MAC to 1.5 MAC, and repeated doses of fentanyl 0.05 mg to 0.1 mg IV. Aim to maintain BIS 40 to 60 Additional regional anaesthesia: epidural 3 mL/hour to 12 mL/hour (bupivacaine 1 mg/mL, fentanyl 2 µg/mL, adrenaline 2 µg/mL) Other information: morphine same as TIVA group
Outcomes	1. Troponin T levels on first postoperative day 2. Postoperative complications, to included cognitive dysfunction (at 30 days) 3. Non-fatal coronary events including acute MI 4. Non-thrombotic troponin increase 5. Mortality (at 30 days) 6. Use of inotropic-, vasodilator- , and anaesthetic drugs 7. Bleeding, urine output, tachycardia, bradycardia, hypotensive and hypertensive episodes during surgery 8. Ischaemic events 9. Arrhythmias 10. Fluids and transfusions 11. Postoperative pain 12. Nausea and vomiting 13. SOFA scores at 8 hours and first and second postoperative days 14. Length of ward or ICU stay 15. Length of hospital stay

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Lindholm 2013 (*Continued*)

Notes	**Funding/declarations of interest:** institution or department funding. One author received fees for presentations at Baxter AS Norway **Study dates:** February 2008 to February 2012

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomized to groups; no additional details
Allocation concealment (selection bias)	Unclear risk	Quote: "after informed consent was given, patients selected a blank envelope with the randomization code inside from a box containing envelopes for all remaining patients to be included." Study does not report if envelopes were opaque and sealed. Unclear if this is a sufficient method to conceal group allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind anaesthetists to intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Postoperative care was blinded. However, study authors do not report who collected data for POCD
Incomplete outcome data (attrition bias) All outcomes	Low risk	Small loss of participant data. Reasons for losses are unclearly reported, however loss is < 10% and balanced between groups
Selective reporting (reporting bias)	Unclear risk	Prospective registration with clinical trials register (NCT00538421). However, outcomes are not reported in trials register documents; not feasible to assess risk of selective outcome reporting bias
Other bias	Unclear risk	Groups differ in use of fentanyl and remifentanil which presents methodological differences between groups

Liu 2013

Methods	RCT, parallel design, single-centre
Participants	**Total number of randomized participants:** 120 **Inclusion criteria** 1. People with aMCI, history of spinal surgery, ASA I to II, aged 65 to 75 years **Exclusion criteria**

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	1. History of general anaesthetic exposure or surgery 2. Neurological diseases that may affect cognitive function (e.g. subdural haematoma, vascular dementia, frontotemporal dementia) 3. Hypothyroidism 4. Alcoholic dementia 5. Vitamin B12 deficiency 6. Encephalitis 7. Cerebral infarction 8. Brain tumour 9. Insufficient education to complete the tests **Type of surgery:** spinal surgery **Baseline characteristics** **TIVA group** 1. Age, mean (SD): 69.33 (± 2.90) years 2. Gender, M/F: 24/28 3. ASA grade: all ASA I to II **Inhalational maintenance group** 1. Age, mean (SD): 69.56 (± 2.99) years 2. Gender, M/F: 27/28 3. ASA grade: all ASA I to II **Country:** China **Setting:** hospital
Interventions	**TIVA group** Participants: n = 60; 8 losses (reasons reported overall, not by group, to include: 'lost to follow-up', death, other surgeries before 2-year follow-up time point); 52 analysed Induction details: midazolam 0.05 mg/kg, sufentanil 0.5 μg/kg, vecuronium 0.5 μg/kg, propofol 1.0 mg/kg Maintenance details: propofol 4 mg/kg/hour to 6 mg/kg/hour continuously, intermittent vecuronium 0.5 mg/kg. To maintain BIS 40 to 50 Other information: during surgery, patients given lactated Ringer's solution and hetastarch. Continuous infusion of sufentanil 0.6 μg/kg/hour, tropisetron 6 μg/kg/hour, single bolus of sufentanil 0.015 μg/kg and tropisetron 1.5 μg/kg over a 15-minute interval for postoperative pain relief **Inhalational maintenance group** Participants: n = 60; 5 losses (reasons reported overall, not by group, to include: 'lost to follow-up', death, other surgeries before 2-year follow-up time point); 55 analysed Induction details: midazolam 0.05 mg/kg, sufentanil 0.5 μg/kg, vecuronium 0.5 μg/kg, propofol 1.0 mg/kg Maintenance details: sevoflurane 2% to 3 % in pure O_2. Adjusted to maintain BIS 40 to 50 Other information: fluids and analgesic management etc. same as TIVA group
Outcomes	1. Progression of aMCI. Measured at follow-up of 2 years
Notes	**Funding/declarations of interest:** supported by the Department of Anesthesiology, Beijing Military General Hospital. The authors have no financial or other conflicts of interest to disclose **Study dates:** January 2007 to January 2009

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Liu 2013 (*Continued*)

	Note: study has 3 arms: propofol vs sevoflurane vs lidocaine epidural. We have not included data for the lidocaine comparison arm

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Use of computer-generated randomization
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind anaesthetists to intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only review outcome of interest is mortality. Blinding of assessors is not described but lack of blinding is unlikely to influence mortality data
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	High number of losses, which are reported with reasons. We have used this as data for mortality outcome
Selective reporting (reporting bias)	Unclear risk	Study authors do not report clinical trials registration. It is not feasible to assess risk of selective outcome reporting
Other bias	Low risk	No other sources of bias identified

Longas 2004

Methods	RCT, parallel design, single-centre
Participants	**Total number of randomized participants:** 60 **Inclusion criteria** 1. Male participants, ASA III **Exclusion criteria** 1. Autoimmune deficiency diseases 2. Existing treatment with immunosuppressants or corticosteroids which may affect the basal immunology profile 3. NYHA III to IV 4. Renal insufficiency 5. Transfusion within the last 3 months or perioperative transfusion 6. Infections prior to intervention **Type of surgery:** carotid endarterectomy **Baseline characteristics** **TIVA group**

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	1. Age, mean (SD): 66 (± 7.1) years 2. Gender, M/F: not reported 3. ASA grade: all patients ASA III **Inhalational maintenance group (sevoflurane MAC 1.0)** 1. Age, mean (SD): 65 (7.2) years 2. Gender: not reported 3. ASA grade: all patients ASA III **Inhalational maintenance group (sevoflurane MAC 1.5)** 1. Age, mean (SD): 64 (8.1) years 2. Gender: not reported 3. ASA grade: all patients ASA III **Country:** Spain **Setting:** hospital
Interventions	**TIVA group** Participants: n = 20; 0 losses Induction details: premedication the night before surgery with diazepam 10 mg given orally, then 30 minutes before surgery with midazolam 0.1 mg/kg im. Induction with propofol 2 mg/kg, cisatracurium 0.2 mg/kg, and fentanyl 3 µg/kg to 4 µg/kg Maintenance details: mix of O_2 and air, FiO_2 of 0.4. Fentanyl 0.05 mg, cisatracurium 0.1 mg/kg IV. Propofol 5 mg/kg/hour. To maintain a BIS 40 to 60 Other information: for postoperative analgesia methadone 0.1 mg/kg, and metamizole in doses of 2 g IV every 8 hours. Analgesia started 30 minutes before end of surgery **Inhalational maintenance group (sevoflurane MAC 1.0)** Participants: n = 20; 0 losses Induction details: premedication the night before surgery with diazepam 10 mg given orally, then 30 minutes before surgery with midazolam 0.1 mg/kg im. Then induction with propofol 2 mg/kg, cisatracurium 0.2 mg/kg, and fentanyl 3 µg/kg to 4 µg/kg Maintenance details: mix of O_2 and air, FiO_2 of 0.4. Fentanyl 0.05 mg, cisatracurium 0.1 mg/kg IV. Sevoflurane MAC 1.0. To maintain a BIS 40 to 60 Other information: postoperative analgesia same as TIVA group **Inhalational maintenance group (sevoflurane MAC 1.5)** Participants: n = 20; 0 losses Induction details: premedication the night before surgery with diazepam 10 mg given orally, then 30 minutes before surgery with midazolam 0.1 mg/kg im. Then induction with propofol 2 mg/kg, cisatracurium 0.2 mg/kg, and fentanyl 3 µg/kg to 4 µg/kg Maintenance details: mix of O_2 and air, FiO_2 of 0.4. Fentanyl 0.05 mg, cisatracurium 0.1 mg/kg IV. Sevoflurane MAC 1.5. To maintain a BIS 40 to 60 Other information: postoperative analgesia same as TIVA group
Outcomes	1. Haemodynamic variable 2. Hypertension 3. Hypotension (30% reduction from baseline) 4. Treatment with ephedrine for hypotension 5. Postoperative pain (on VAS) 6. Amnesia in PACU
Notes	**Funding/declarations of interest:** not reported **Study dates:** not reported

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Longas 2004 (*Continued*)

	Note: the study included a 4th comparison group of remifentanil. We did not include this group in the review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomly allocated to groups; no additional details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind anaesthetists to intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent loss of study participants
Selective reporting (reporting bias)	Unclear risk	Study authors do not report clinical trials registration. Not feasible to assess risk of selective outcome reporting
Other bias	Low risk	No other sources of bias identified

Luntz 2004

Methods	RCT, parallel design, single-centre
Participants	**Total number of randomized participants:** 96 **Inclusion criteria** 1. Scheduled for elective, unilateral ophthalmic surgery, ≥ 65 years of age, ASA I to III **Exclusion criteria** 1. Obvious cardiovascular complaints (NYHA III to IV) 2. Previous adverse reactions to one of the study drugs 3. Participating in another study 4. History of GA in last 3 months 5. Less than 60% vision in the contralateral eye **Type of surgery:** ophthalmic surgery **Baseline characteristics** **TIVA group** 1. Age, (assumed) mean (SD): 74 (± 7) years 2. Gender: not reported

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	3. ASA grade: not reported **Inhalational maintenance group (propofol/sevoflurane)** 1. Age, (assumed) mean (SD): 76 (± 6) years 2. Gender: not reported 3. ASA grade: not reported **Inhalational maintenance group (total sevoflurane)** 1. Age, (assumed) mean (SD): 77 (± 7) years 2. Gender: not reported 3. ASA grade: not reported **Note:** table of baseline characteristics is not reported. Study authors report "There were no significant differences between the patient groups with regard to age, gender, height, weight and ASA physical status" **Country:** Germany **Setting:** hospital
Interventions	**TIVA group** Participants: n = 32; 0 losses Induction details: propofol 2 mg/kg, continuous infusion of remifentanil 20 µg/ kg/ hour. Atracurium 0.3 mg/kg to 0.5 mg/kg Maintenance details: continuous infusion of propofol 4 mg/kg/hour to 8 mg/kg/hour. Remifentanil at 10 µg/kg/hour **Inhalational maintenance group (propofol/sevoflurane)** Participants: n = 32; 0 losses Induction details: propofol 2 mg/kg, continuous infusion of remifentanil 20 µg/ kg/ hour. Atracurium 0.3 mg/kg to 0.5 mg/kg Maintenance details: sevoflurane end-tidal concentration 0.6% to 1.2%. Remifentanil 10µg/kg/hour **Inhalational maintenance group (total sevoflurane)** Participants: n = 32; 0 losses Induction details : continuous infusion of remifentanil 20 µg/ kg/hour. Atracurium 0.3 mg/kg to 0.5 mg/kg. After 1 minute pre-oxygenation, vaporizer adjusted stepwise up to 8% sevoflurane until eyelash reflex was abolished, then reduced to 5% Maintenance details: sevoflurane end-tidal concentration 0.6% to 1.2%. Remifentanil 10µg/kg/hour
Outcomes	1. Clinical outcomes (MAP and hypotension, shivering, pain, PONV, duration of induction and maintenance of anaesthesia, and time to emergence) 2. Psychomotor recovery 3. Participant satisfaction 4. Cost analysis
Notes	**Funding/declarations of interest:** supported in part by a grant from Abbott Laboratories, Wiesbaden, Germany **Study dates:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement

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Luntz 2004 (*Continued*)

Random sequence generation (selection bias)	Low risk	Use of computer-generated randomization
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind anaesthetists to intervention group
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Relevant reported outcome is for hypotension. Study authors do not report who collected this data and whether they were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent loss of study participants
Selective reporting (reporting bias)	Unclear risk	Study authors do not report clinical trials registration. Not feasible to judge risk of selective outcome reporting
Other bias	Low risk	Baseline characteristics table not reported, but study authors reported no differences. No other sources of bias identified

Micha 2016

Methods	RCT, parallel design, single-centre
Participants	**Total number of randomized participants:** 80 **Inclusion criteria** 1. 60 to 74 years of age, native Greek speakers, of at least preliminary educational status, tumour resection of > 2 hours duration **Exclusion criteria** 1. Not competent in writing 2. Severe impairment of hearing or vision 3. Preoperative cognitive dysfunction (MMSE $\leq$ 23) 4. Central nervous system (dementia, Parkinson's, Alzheimer disease) or psychiatric disease 5. Antidepressant therapy 6. Abuse of drugs or alcohol 7. Assessment with psychometric tests in the past 8. Participants required reoperation during the study period **Type of surgery:** tumour resection (non-cardiovascular or neurosurgical) **Baseline characteristics** **TIVA group** 1. Age, median (IQR): 64 (62 to 67) years 2. Gender, M/F: 19/17 3. ASA grade: ASA I: 3; ASA II & III: 33

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Micha 2016 (*Continued*)

	Inhalational maintenance group 1. Age, median (IQR): 65.62 (62 to 68) years 2. Gender, M/F: 20/17 3. ASA grade: ASA I: 3; ASA II & III: 34 **Country:** Greece **Setting:** hospital
Interventions	**TIVA group** Participants: n = 40; 4 losses (2 patients had operations cancelled; 2 were haemodynamically unstable); 36 analysed Induction details: propofol 2 mg/kg, and fentanyl 2 μg/kg Maintenance details: propofol 6 mg/kg/hour to 10 mg/kg/hour. To maintain BIS 40 to 60 Other information: postoperative analgesia with morphine to achieve a VAS score ≤ 3 **Inhalational maintenance groups** Participants: n = 40; 3 losses (no data available at 9 months); 37 analysed = 37 Induction details: propofol 2 mg/kg, and fentanyl 2 μg/kg Maintenance details: sevoflurane 2% to 3%. To maintain BIS 40 to 60 Other information: postoperative analgesia same as TIVA group
Outcomes	1. Hypotension (MAP ≤ 60 mmHg for > 30 mins) 2. Oxygen saturation ≤ 80% for > 30 mins 3. MMSE (48 hrs postoperatively) with a decrease of ≥ 2 units 4. Delirium using CAM Notes 1. MMSE was evaluated only when participants' performance in CAM proved absence of delirium 2. Cognitive function and BDI also evaluated at 9 months postoperatively
Notes	**Funding/declarations of interest:** not reported **Study dates:** June 2010 to July 2013

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomly allocated to groups; no additional details
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes used; no additional details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind anaesthetists to intervention group
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessment of cognitive function completed by personnel blinded to study groups

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Micha 2016 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	Reason for losses in sevoflurane group owing to loss of data at 9 months; however, data time points are at 7 days as well as 9 months postoperatively
Selective reporting (reporting bias)	Unclear risk	Clinical trials registration not reported. Not feasible to assess risk of selective outcome reporting bias
Other bias	Low risk	No other sources of bias identified

Moffat 1995

Methods	RCT, parallel design, single-centre
Participants	**Total number of randomized participants:** 40 **Inclusion criteria** 1. ASA I to III, > 60 years of age, undergoing cataract extraction and lens implantation under GA **Exclusion criteria** 1. Not reported **Type of surgery:** cataract extraction and lens implantation **Baseline characteristics** **TIVA group** 1. Age, mean (range): 72 (60 to 86) years 2. Gender: not reported 3. ASA grade: not reported **Inhalational maintenance group** 1. Age, mean (range): 77 (64 to 88) years 2. Gender: not reported 3. ASA grade: not reported **Country:** Scotland, UK **Setting:** hospital
Interventions	**TIVA group** Participants: n = 20; 0 losses Induction details: premedication with metoclopramide 10 mg 1 hour before surgery. Topical anaesthesia (1% amethocaine) applied to non-operative eye. Propofol with initial plasma concentration of 6 µg/mL reducing to 4 µg/mL after 10 minutes. Mix of 70% N_2O in O_2 throughout the procedure Maintenance details: 4 µg/mL propofol TCI Other information: topical anaesthesia with 1% amethocaine in operative eye before surgical incision. Airway maintained with LMA **Inhalational maintenance group** Participants: n = 20; 0 losses Induction details: premedication with metoclopramide 10 mg 1 hour before surgery. Topical anaesthesia (1% amethocaine) applied to non-operative eye. Induction with etomidate 0.25 mg/kg and vecuronium 0.075 mg/kg Maintenance details: Mix of 70% N_2O in oxygen, and 0.5% to 1% isoflurane

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	Other information: topical anaesthesia with 1% amethocaine in operative eye before surgical incision. Airway maintained with intubation
Outcomes	1. Haemodynamic measures 2. Recovery times from anaesthesia 3. PONV 4. Ability to converse normally, walk unaided and retain oral fluids 5. Cognitive function assessed using MMSE
Notes	**Funding/declarations of interest:** not reported **Study dates:** not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants were randomly allocated to groups; no additional details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind anaesthetists to intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent loss of study participants
Selective reporting (reporting bias)	Unclear risk	Study authors do not report clinical trials registration. Not feasible to judge risk of selective outcome reporting
Other bias	Unclear risk	We noted use of different types of airway management which was because of the study aim to assess anaesthetic management using neuromuscular blockade vs no neuromuscular blockade for intraocular pressure

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Nishikawa 2004

Methods	RCT, parallel design, single-centre
Participants	**Total number of randomized participants:** 50 **Inclusion criteria** 1. ASA I or II, > 65 years of age, scheduled for elective laparoscope-assisted surgical procedures which would last > 3 hours, under combined GA and epidural anaesthesia **Exclusion criteria** 1. People with anticoagulation, symptomatic coronary artery disease, cardiac valvular regurgitation or stenosis, central nervous system or neuromuscular disorders 2. Major or minor tranquillizer medication 3. Psychotic symptoms or cognitive impairment as judged by a psychiatrist **Type of surgery:** laparoscopic surgery (choledocholithotomy, colectomy, sigmoidectomy) **Baseline characteristics** **TIVA group** 1. Age, mean (SD): 71 (± 8) years 2. Gender, M/F: 13/12 3. ASA grade: ASA I: 7; ASA II: 18 **Inhalational maintenance group** 1. Age, mean (SD): 71 (± 7) years 2. Gender, M/F: 12/13 3. ASA grade: ASA I: 6; ASA II: 19 **Country:** Japan **Setting:** hospital
Interventions	**TIVA group** Participants: n = 25; 0 losses Induction details: 100% O_2 via face mask for 3 minutes prior to induction. Induction with propofol using 4 µg/mL TCI. Use of 2% lidocaine solution for injection pain Maintenance details: 4 µg/mL propofol TCI. Study authors report mean (SD) range of 1.2 (± 0.2) µg/mL to 2.7 (± 0.2) µg/mL propofol. Use of clinical signs to maintain anaesthesia Additional regional anaesthesia: epidural anaesthesia: 6 mL to 8 mL of 1.5% lidocaine, followed by continuous epidural administration at a rate of 4 mL/hour to 6 mL/hour throughout surgery **Inhalational maintenance group** Participants: n = 25; 0 losses Induction details: 100% oxygen via face mask for 3 minutes prior to induction. 5% sevoflurane and 100% oxygen at 6 L/min until inspired limb-drug concentration was > 4%. Vecuronium 0.1 mg/kg Maintenance details: sevoflurane with O_2/air mix at total gas flow of 3 L/min. Vecuronium 1 mg to 2 mg IV boluses as required. Study authors report mean (SD) range of 0.9% (± 0.1%) to 1.7% (± 0.4%) sevoflurane
Outcomes	1. Duration of anaesthesia 2. Duration of surgery 3. Intraoperative complications (hypotension, bradycardia, hypertension, tachycardia, increased salivation) 4. Postoperative delirium (using DRS) 5. Pain (using VAS)

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Notes	**Funding/declarations of interest:** not reported **Study dates:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were "randomly assigned by a sealed envelope technique". Insufficient information
Allocation concealment (selection bias)	Unclear risk	Described as "randomly assigned by a sealed envelope technique". Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind anaesthetists to intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Delirium was assessed by a psychiatrist blinded to intervention group. Data on emergence times was assessed by a nurse who was blinded to intervention group
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent loss of study participants
Selective reporting (reporting bias)	Unclear risk	Study authors do not report clinical trials registration. Not feasible to judge risk of selective outcome reporting
Other bias	Low risk	No other source of bias identified

Rohan 2005

Methods	RCT, parallel design, single-centre
Participants	**Total number of randomized participants:** 30 **Inclusion criteria:** 1. Elderly patients (> 65 years of age) presenting for minor urological (rigid cystoscopy, transurethral resection of bladder mucosal tumour) or gynaecological surgery (hysteroscopy), requiring GA, and with an anticipated hospital stay of one night postoperatively **Exclusion criteria** 1. Diseases of the central nervous system including pre-existing cognitive dysfunction (defined as a MMSE < 24) 2. Consumption of phenothiazines or antidepressants 3. Cardiac or neurosurgery 4. Previous neuropsychological testing

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	5. Poor comprehension of the language used in processing the tests 6. Patients with alcoholism or addictive drug dependence **Type of surgery:** minor urological or gynaecological surgery **Baseline characteristics** **TIVA group** 1. Age, mean (range): 72.9 (65 to 83) years 2. Gender, M/F: 12/3 3. ASA grade: not reported **Inhalational maintenance group** 1. Age, mean (range): 73.8 (67 to 86) years 2. Gender M/F: 11/4 3. ASA grade: not reported **Country:** Ireland **Setting:** hospital
Interventions	**TIVA group** Participants: n = 15; 0 losses Induction details: 500 mL crystalloid solution, fentanyl 1 µg/kg IV, propofol TCI using a Deprifusor Maintenance details: TCI propofol adjusted to maintain adequate depth of anaesthesia, at discretion of attending anaesthetist. 50% O_2 and 50% air **Inhalational maintenance group** Participants: n = 15; 0 losses Induction details: 500 mL crystalloid solution, fentanyl 1 µg/kg IV. Incremental dose of sevoflurane by tidal volume inhalation induction technique Maintenance details: 50% O_2 and 50% air. No additional information for maintenance
Outcomes	1. Cognitive dysfunction on the day following surgery 2. S-100β and neuron-specific enolase levels
Notes	**Funding/declarations of interest:** funded entirely from the resources of the Department of Anesthesia, Critical Care and Pain Medicine, Mater Misericordiae Hospital ***Study dates:*** not reported **Note:** study also includes an age-matched control group of participants which we did not include in the review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants were randomized to groups; no additional details
Allocation concealment (selection bias)	Low risk	Use of sequentially numbered sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind anaesthetists to intervention groups

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Rohan 2005 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the investigator who undertook patient enrolment, neuropsychological tests and blood tests did not deliver anaesthesia to the patient and, therefore, was unaware of study group allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent loss of study participants
Selective reporting (reporting bias)	Unclear risk	Study authors do not report clinical trials registration. Not feasible to assess risk of selective outcome reporting
Other bias	Unclear risk	No detail on doses of anaesthetic drugs. Unable to assess whether groups were equivalent

Tan 2009

Methods	RCT, parallel design, single-centre
Participants	**Total number of randomized participants:** 60 **Inclusion criteria** 1. Undergoing abdominal surgery, > 60 years of age, ASA I to II **Exclusion criteria** 1. Neurological abnormalities 2. Regularly taking medication for neuropsychiatric disorders **Type of surgery:** abdominal surgery **Baseline characteristics** **TIVA group** 1. Age, range: 60 to 81 years 2. Gender: not reported 3. ASA grade: not reported **Inhalational maintenance group** 1. Age, range: 60 to 81 years 2. Gender: not reported 3. ASA grade: not reported **Note:** Study authors do not report a baseline characteristics table. Study authors report no differences between group in age, weight, height and general condition **Country:** China **Setting:** hospital
Interventions	**TIVA group** Participants: n = 30; 0 losses Induction details: propofol IV 1.5 mg/kg to 2 mg/kg, fentanyl 2 μg/kg to 4 μg/kg, vecuronium 0.1 mg/kg Maintenance details: propofol IV 100 μg/kg/min to 150 μg/kg/min, fentanyl and vecuronium as required **Inhalational maintenance group** Participants: n = 30; 0 losses

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Tan 2009 (*Continued*)

	Induction details: propofol IV 1.5 mg/kg to 2 mg/kg, fentanyl 2 μg/kg to 4 μg/kg, vecuronium 0.1 mg/kg Maintenance details: 1% to 2 % isoflurane, fentanyl and vecuronium as required
Outcomes	1. POCD, using MMSE before and after surgery (1, 6, 12, 24 and 48 hours after surgery) 2. Intraoperative stress response 3. HR 4. MAP 5. BIS
Notes	**Funding/declarations of interest:** not reported **Study dates:** not reported **Note:** study report is in Chinese. We have used Google translate for essential paragraphs. We noted that this study was reported by a single author and may not be the original study report; we checked the study details against other included studies for duplication but found no duplication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomized to groups; no additional details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind anaesthetists to intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent loss of study participants
Selective reporting (reporting bias)	Unclear risk	Study authors do not report clinical trials registration. Not feasible to judge risk of selective outcome reporting
Other bias	Unclear risk	No baseline characteristics table. Limited information in short report, and we noted that this study was reported by a single author

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Tanaka 2017

Methods	RCT, parallel design, single-centre
Participants	**Total number of randomized participants:** 100 **Inclusion criteria** 1. > 65 years of age, scheduled for TKA, ASA II or III, BMI > 30 kg/m^2 **Exclusion criteria** 1. Refusal of or failure of regional block 2. Pre-existing neurocognitive disorders (MMSE ≤ 23) 3. Known intolerance to any of drugs used in the study **Type of surgery:** total knee arthroplasty **Baseline characteristics** **TIVA group** 1. Age, mean (SD): 71 (± 5.8) years (taken from clinical trials register documents) 2. Gender, M/F: 16/34 (taken from clinical trials register documents) 3. ASA grade: ASA II: 22; ASA III: 23 (calculated from study report for 45 participants) **Inhalational maintenance group** 1. Age, mean (SD): 70 (± 4.0) years (taken from clinical trials register documents) 2. Gender, M/F: 29/21 (taken from clinical trials register documents) 3. ASA grade: ASA II: 26; ASA III: 19 (calculated from study report for 45 participants) **Country:** US **Setting:** hospital
Interventions	**TIVA group** Participants: n = 50; 11 losses (3 withdrawn; other reasons include early hospital discharge, oversedation, respiratory distress, PONV, and pain - not reported by group); 39 analysed Induction details: femoral nerve block with initial bolus of 30 mL 0.25% ropivacaine as well as placement of indwelling catheter. Sedation with fentanyl and midazolam provided for femoral nerve block at discretion of regional anaesthesia team. Induction with propofol 1 mg/kg, fentanyl 1 µg/kg to 2 µg/kg, rocuronium 0.4 mg/kg, all dosed according to lean body weight Maintenance details: propofol. Use of Sedline to maintain PSI 30 to 50 Other information: after surgery, a continuous infusion of 0.2% ropivacaine at 6 mL/hour was initiated in recovery room and adjusted to maximum of 10 mL/hour for next 48 hours. PCA device to administer IV hydromorphone with standardized dosing and lock-out period **Inhalational maintenance groups** Participants: n = 50; 10 losses (1 withdrawn; other reasons include early hospital discharge, oversedation, respiratory distress, PONV, and pain - not reported by group); 40 analysed Induction details: femoral nerve block with initial bolus of 30 mL 0.25% ropivacaine as well as placement of indwelling catheter. Sedation with fentanyl and midazolam provided for femoral nerve block at discretion of regional anaesthesia team. Induction with propofol 1 mg/kg, fentanyl 1 µg/kg to 2 µg/kg, rocuronium 0.4 mg/kg, all dosed according to lean body weight Maintenance details: desflurane. Use of Sedline to maintain PSI 30 to 50 Other information: after surgery, a continuous infusion of 0.2% ropivacaine at 6 mL/

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	hour was initiated in recovery room and adjusted to maximum of 10 mL/hour for next 48 hours. PCA device to administer IV hydromorphone with standardized dosing and lock-out period
Outcomes	1. Postoperative delirium (using CAM) at baseline 1, 6, 24 and 48 hours after surgery 2. Cognitive function (20% decrease from baseline to indicate cognitive decline) using DSST (day 1), Digit Span (day 2), and Trail Making Test (part A and part B; day 2) 3. Wake-up times 4. Length of stay in PACU 5. Pain scores 6. PONV Note: we interpreted bar charts provided by study authors (from email communication) for cognitive function tests. In meta-analysis, we used data for Trail Making part A
Notes	**Funding/declarations of interest:** research grant from Baxter Healthcare Corporation **Study dates:** October 2010 to August 2014 Note: all participants are obese

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Use of computer-generated random numbers
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind anaesthetists to intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Nurses who administered CAM assessment were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Study authors do not report reasons for losses by each group, and data is reported inconsistently between clinical trials register documents and published study report. Overall losses are high
Selective reporting (reporting bias)	High risk	Retrospectively registered with clinical trials register (NCT01270620). Not feasible to assess risk of selective reporting bias from this document. However, we noted that MMSE was an outcome in the methods section of the published report but was not reported in results. In addition, we noted a difference in data for postoperative delirium, and length of stay was reported for a different number

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Tanaka 2017 (*Continued*)

		of participants. Overall, we judged risk of selective reporting bias as high
Other bias	Unclear risk	We noted a difference in gender balance between groups; unclear if this is clinically important

Tang 2014

Methods	RCT, parallel design, single-centre
Participants	**Total number of randomized participants:** 220 **Inclusion criteria** 1. Elderly patient with MCI, ≥ 60 years of age, ASA I to III, scheduled for radical rectal resection surgery **Exclusion criteria** 1. Current diagnosis of dementia (pre-operative MMSE score 23) 2. Current or past psychiatric illness; current use of antidepressant of antianxiety medication 3. History of drug dependence or alcohol abuse 4. History of coronary artery, peripheral arterial or cerebrovascular disease 5. Severe visual, auditory, or motor disability 6. Acute infection 7. Preoperative haemoglobin 85 g/L **Type of surgery:** radical rectal resection surgery **Baseline characteristics** **TIVA group** 1. Age, mean (SD): 69.6 (± 4.8) years; 41 patients were ≥ 70 years of age 2. Gender, M/F: 26/75 3. ASA grade: not reported **Inhalational maintenance group** 1. Age, mean (SD): 70.0 (± 4.3) years; 41 patients were ≥ 70 years of age 2. Gender, M/F: 32/67 3. ASA grade: not reported **Country:** China **Setting:** hospital
Interventions	**TIVA group** Participants: n = 110; 9 losses (declined to participate in follow-up at day 7); 101 analysed Induction details: midazolam 0.03 mg/kg to 0.04 mg/kg IV, fentanyl 0.002 mg/kg to 0.003 mg/kg IV, vecuronium 0.15 mg/kg to 0.2 mg/kg. Then propofol 1.5 mg/kg to 2 mg/kg IV Maintenance details: propofol 6 mg/kg/hour to 10 mg/kg/hour. To maintain BIS 30 to 60. Remifentanil 9 µg/kg/hour to 12 µg/kg/hour continuous IV infusion, vecuronium intermittent IV infusion Other information: all patients had PCI 150 mL saline with fentanyl 1.5 mg, tropisetron 12 mg, infusion rate 2 mL/hour, with 15-minute lockout **Inhalational maintenance group** Participants: n = 110; 11 losses (declined to participate in follow-up at day 7); 99 analysed

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	Induction details: midazolam 0.03 mg/kg to 0.04 mg/kg IV, fentanyl 0.002 mg/kg to 0.003 mg/kg IV, vecuronium 0.15 mg/kg to 0.2 mg/kg. Then 8% sevoflurane (fresh gas flow 6 L/min, decreased to 3% to 4% after loss of consciousness with fresh gas flow 1 L/min to 2 L/min) Maintenance details: sevoflurane 2% to 3%. To maintain BIS 30 to 60. Remifentanil 9 μg/kg/hour to 12 μg/kg/hour continuous IV infusion, vecuronium intermittent IV infusion Other information: analgesics same as TIVA group
Outcomes	1. POCD 2. Anaesthesia duration 3. Dose of remifentanil and atropine 4. Hypotension 5. Haemodynamic variables 6. Pain (using VAS) 7. Wound infection 8. Pneumonia
Notes	**Funding/declarations of interest:** study authors report that authors received no specific grant from any funding agency in the public, commercial or not-for-profit sectors **Study dates:** January 2010 to November 2013

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Use of computer-generated, blocked random-allocation sequence
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind anaesthetist to intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "to ensure blinding, neuropsychological assessment work was carried out by a physician trained in psychology. Neither the physician nor the patient knew which anaesthetic had been used during surgery"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Some loss of participant data at about 10%. It is unclear whether this loss could influence outcome data
Selective reporting (reporting bias)	Unclear risk	Study authors do not report clinical trials registration. Not feasible to judge risk of selective outcome reporting

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Tang 2014 (*Continued*)

Other bias	Low risk	No other sources of bias identified.

Trembach 2012

Methods	RCT, parallel design, single-centre
Participants	**Total number or randomized participants:** 99 **Included criteria** 1. ASA III patients with acute cholecystitis undergoing laparoscopic cholecystectomy **Excluded criteria** 1. Not reported (abstract only) **Type of surgery:** laparoscopic cholecystectomy Baseline characteristics not reported (abstract only) **Country:** not reported **Setting:** hospital
Interventions	**TIVA group** Participants: n = 45; 0 reported losses Described as propofol-fentanyl TIVA. No additional details in abstract **Inhalational maintenance group** Participants: n = 44; 0 reported losses Described a VIMA. No additional details in abstract
Outcomes	1. Hypotension (requiring support with phenylephrine) 2. Induction time 3. Time to intubation 4. Time to recovery of consciousness 5. Time to extubation 6. Time to full orientation 7. PONV 8. Participant satisfaction 9. Cost 10. Cardiovascular events
Notes	**Funding/declarations of interest:** not reported **Study dates:** not reported Very limited detail in abstract

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants were randomly assigned to groups; no additional details
Allocation concealment (selection bias)	Unclear risk	No details. Abstract only

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Trembach 2012 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind anaesthetists to intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details. Abstract only
Incomplete outcome data (attrition bias) All outcomes	Low risk	No details. Abstract only. We have assumed there were no losses
Selective reporting (reporting bias)	Unclear risk	Study authors do not report clinical trials registration. Not feasible to judge risk of selective outcome reporting
Other bias	Unclear risk	Limited detail in abstract, unable to assess risk of other biases. Description of inhalational maintenance does not include fentanyl/remifentanil

Tylman 2011

Methods	RCT, parallel design, single-centre
Participants	**Total number of randomized participants:** 50 **Inclusion criteria** 1. Scheduled for elective colorectal surgery **Exclusion criteria** 1. Study authors report that participants with ulcerative colitis and Crohn's disease were excluded after randomization. No other exclusion criteria reported **Types of surgery:** colorectal surgery for rectal or colon cancer **Baseline characteristics** **TIVA group** 1. Age, median (25 to 75% range): 63 (59 to 72) years 2. Gender, M/F: 15/10 3. ASA grade: not reported **Inhalational maintenance group** 1. Age, median (25 to 75% range): 70 (59 to 78) years 2. Gender, M/F: 16/9 3. ASA grade: not reported **Country:** Sweden **Setting:** hospital
Interventions	**TIVA group** Participants: n = 25; 0 losses Induction details : propofol TCI 3 µg/mL. Continuous infusion of remifentanil 0.25 µg/kg/min Maintenance details: propofol 2 µg/mL. Remifentanil 0.15 µg/kg/min Additional regional anaesthesia: epidural anaesthesia of 5 mg/mL bupivacaine, and 5

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	µg/mL epinephrine at rate of 4 mL to 5 mL during surgery. Postoperatively participants epidural changed to 1 mg/mL bupivacaine, 2 µg/mL fentanyl, 2 µg/mL epinephrine at rate of 5 mL/hour to 12 mL/hour Other information: before induction of anaesthesia participants given 1 µg/kg to 2 µg/kg fentanyl IV, and standard dose of rocuronium **Inhalational maintenance group** Participants: n = 25; 4 losses (did not meet study inclusion criteria); 21 analysed Induction/maintenance details: sevoflurane with 60% O_2 throughout surgery. Concentration not reported. We assume that induction was also with sevoflurane Additional regional anaesthesia: epidural anaesthesia of 5 mg/mL bupivacaine, and 5 µg/mL epinephrine at rate of 4mL to 5 mL during surgery. Postoperatively participants epidural changed to 1 mg/mL bupivacaine, 2 µg/mL fentanyl, 2 µg/mL epinephrine at rate of 5 mL/hour to 12 mL/hour Other information: fentanyl and rocuronium same as TIVA group
Outcomes	1. Inflammatory markers 2. Blood loss 3. Body temperature 4. Blood glucose levels 5. Length of hospital stay
Notes	**Funding/declarations of interest:** not reported **Study dates:** not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants were randomly assigned to groups; no additional details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind anaesthetist to intervention groups.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss of participants (all in inhalation group) after randomization because these participants were diagnosed with additional conditions (ulcerative colitis and Crohn's disease). Decision to remove these participants was to avoid confounding. Post-hoc decision which is imbalanced between groups

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Tylman 2011 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Study authors do not report clinical trials registration. Not feasible to judge risk of selective outcome reporting
Other bias	Unclear risk	Differences in groups in use of remifentanil and fentanyl. Also, study authors do not report concentration of sevoflurane. Note limited information in baseline characteristics table, and lack of inclusion/exclusion criteria

Zhang 2015

Methods	RCT, parallel design, single-centre
Participants	**Total number of randomized participants:** 80 **Inclusion criteria** 1. Senile gastric cancer patients receiving selective radical surgery **Exclusion criteria** 1. Mental health disorder 2. Severe dysfunction of heart, lung, liver, or kidney 3. Spinal deformity 4. Contraindications of epidural anaesthesia 5. History of severe trauma 6. Surgical treatment **Type of surgery:** radical surgery for gastric cancer **Baseline characteristics** **TIVA group (without epidural)** 1. Age, mean (SD): 71.4 (± 5.6) years 2. Gender, M/F: 15/5 3. ASA grade: ASA I: 4; ASA II: 16 **Inhalational maintenance group (without epidural)** 1. Age, mean (SD): 67.9 (± 7.2) years 2. Gender, M/F: 16/4 3. ASA grade: ASA I: 5; ASA II: 15 **TIVA group (with epidural)** 1. Age, mean (SD): 69.0 (± 6.6) years 2. Gender, M/F: 15/5 3. ASA grade: ASA I: 3; ASA II: 17 **Inhalational maintenance group (with epidural)** 1. Age, mean (SD): 70.4 (± 5.9) years 2. Gender, M/F: 14/6 3. ASA grade: ASA I: 4; ASA II: 16 **Country:** China **Setting:** hospital
Interventions	**TIVA group (without epidural)** Participants: n = 20; 0 losses Induction details: TCI propofol 4.0 μg/mL, 3 μg/kg to 4 μg/kg fentanyl and 0.2 mg/kg

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	cisatracurium IV Maintenance details: fentanyl IV 0.15 μg/kg/min to 0.35 μg/kg/min, TCI propofol 1.5 μg/mL to 3.0 μg/mL. To maintain BIS 40 to 60 Other information: 30 minutes before end of surgery, 0.6 μg to μg 1 μg fentanyl IV **Inhalational maintenance group (without epidural)** Participants: n = 20; 0 losses Induction details: 8% sevoflurane at high-flow rate, 8 L/min to 10 L/min. After loss of consciousness, adjusted to 2 L/min to achieve end-tidal concentration of 2% Maintenance details: continuous inhalation end-tidal concentration of 1.5% to 3.5%. Cisastracurium 0.05 mg/kg to 0.1 mg/kg. To maintain BIS 40 to 60 Other info: 30 minutes before end of surgery, 0.6 μg to 1 μg fentanyl IV **TIVA group (with epidural)** Participants: n = 20; 0 losses Induction details: TCI propofol 4.0 μg/mL, 3 μg/kg to 4 μg/kg fentanyl and 0.2 mg/kg cisatracurium IV Maintenance details: fentanyl IV 0.15 μg/kg/min to 0.35 μg/kg/min, TCI propofol 1.5 μg/mL to 3.0 μg/mL. 30 minutes before skin incision: 10 mL ropivacaine and 2 μg/mL, fentanyl injected into epidural space Other info: once epidural puncture was performed, a test dose of 3 mL 2% lidocaine to confirm level and absence of adverse reactions. 30 minutes before end of surgery, 10 mL mixed anaesthesia solution **Inhalational maintenance group (with epidural)** Participants: n = 20; 0 losses Induction details: 8% sevoflurane at high-flow rate, 8 L/min to 10 L/min. After loss of consciousness, adjusted to 2 L/min. to achieve end-tidal concentration of 2% Maintenance details: 30 minutes before skin incision: 10 mL ropivacaine and 2 μg/mL fentanyl injected into epidural space. Continuous inhalation end-tidal concentration of 1.5% to 3.5% sevoflurane. Cisastracurium 0.05 mg/kg to 0.1 mg/kg. BIS 40 to 60 Other info: once epidural puncture was performed, a test dose of 3 mL 2% lidocaine to confirm level and absence of adverse reactions. 30 minutes before end of surgery, 10 mL mixed anaesthesia solution
Outcomes	1. Dose of remifentanil 2. Incidence of hypotension (defined as SBP ≤ 90 mmHg or reduction ≥ 20% or baseline for ≥ 5 minutes) 3. Time to awakening 4. Time to endotracheal tube removal 5. Time to orientation 6. Time to achieve modified Aldrete scores ≥ 9 7. Emergence agitation
Notes	**Funding/declarations of interest:** not reported **Study dates:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement

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Zhang 2015 (*Continued*)

Random sequence generation (selection bias)	Low risk	Use of a random number table
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible to blind anaesthetists to intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent loss of study participants
Selective reporting (reporting bias)	Unclear risk	Study authors do not report clinical trials registration. Not feasible to judge risk of selective outcome reporting
Other bias	Low risk	No other sources of bias identified

AAA: abdominal aortic aneurysm
aMCI: amnesic mild cognitive impairment
ApoE: apoliproprotein E
ASA: American Society of Anesthesiologists
BDI: Beck Depression Inventory
BIS: bispectral index
BMI: body mass index
BP: blood pressure
CAM: confusion assessment method
DRS: delirium rating scale
DSST: Digit Symbol Substitution Test
FiO_2: fraction of inspired oxygen
GA: general anaesthesia
HR: heart rate
ICU: intensive care unit
im: intramuscular
IV: intravenous(ly)
IQR: interquartile range
ITT: intention to treat
LMA: laryngeal mask airway
MAC: minimum alveolar concentration
MAP: mean arterial pressure
MCI: mild cognitive impairment
M/F: male/female
MI: myocardial infarction
MMSE: Mini-Mental State Examination

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MMT: Mini Mental Test
n: number of randomized participants per group
N_2O: nitrous oxide
NYHA: New York Heart Association
O_2: oxygen
PACU: postanaesthesia care unit
PCA: patient controlled analgesia
PCI: percutaneous coronary intervention
POCD: postoperative cognitive dysfunction
PONV: postoperative nausea and vomiting
PP: per protocol
PSI: patient state index
RAVLT: Rey Auditory Verbal Learning test
RCT: randomized control trial
SBP: systolic blood pressure
SD: standard deviation
SOFA: Sequential Organ Failure Assessment
T8-T10: epidural given between the 8th and 9th, or the 9th and 10th thoracic vertebrae
TCI: target-controlled infusion
TDT: Trieger Dot Test
TEE: transoesophageal echocardiography
TIVA: total intravenous anaesthesia
TKA: total knee arthroplasty
VAS: visual analogue scale
VIMA: volatile induction and maintenance anaesthesia
vs: versus

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Arar 2005	RCT, measuring effects of sevoflurane versus isoflurane versus propofol infusions on postoperative recovery criteria in geriatric participants. Outcomes measured: time to spontaneous eye opening, extubation, response to verbal stimuli, and orientation. Post-hoc decision to exclude studies that did not measure review outcomes
Arnaoutoglou 2007	RCT, measuring effects of propofol versus sevoflurane on the production of free oxygen radicals during total knee arthroplasty in elderly participants. Outcomes measured: MDA levels. Post-hoc decision to exclude studies that did not measure review outcomes
But 2003	Unclear if this is an RCT. Measures effects of sevoflurane versus propofol on hepatic and renal functions in participants > 65 years of age. Post-hoc decision to exclude studies that did not measure review outcomes
Carles 2008	RCT, measuring effects of sevoflurane versus propofol versus spinal anaesthesia on levels of interstitial glycolysis metabolites in elderly participants. Post-hoc decision to exclude studies that did not measure review outcomes

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(*Continued*)

Doe 2016	RCT, measuring effects of sevoflurane versus propofol on jugular venous bulb oxygenation (SjO2) and regional oxygen saturation in participants undergoing robotic-assisted laparoscopic prostatectomy. Post-hoc decision to exclude studies that did not measure review outcomes
Filipovic 2007	RCT, measuring effects of anaesthetics on left ventricular diastolic function in participants aged between 18 and 75. Outcomes measured: haemodynamic parameters. Post-hoc decision to exclude studies that did not measure review outcomes
Fredman 2002	RCT, measuring the effects of propofol verses sevoflurane on postanaesthesia recovery in geriatric participants. Outcomes measured: emergence time, time to orientation, postanaesthesia recovery scores, and therapeutic interventions. Post-hoc decision to exclude studies that did not measure review outcomes
Gasowska 1999	RCT, measuring effects of halothane versus isoflurane versus propofol on venous admixture in participants between 28 to 72 years of age. Post-hoc decision to exclude studies that did not measure review outcomes
Gauger 2008	RCT, measuring effects of propofol on postoperative nausea and vomiting in participants undergoing thyroid and parathyroid operations. Outcomes measured: occurrences of nausea and vomiting. Post-hoc decision to exclude studies that did not measure review outcomes
Guedes 1988	RCT, measuring effects of propofol versus enflurane on intraocular pressure in elderly participants. Outcomes measured: haemodynamic parameters. Post-hoc decision to exclude studies that did not measure review outcomes
Halberg 1996	Unclear if this is an RCT. A pharmaco-economic evaluation of anaesthesia in ambulatory surgery comparing desflurane verses isoflurane and propofol. Unable to source full text. Post-hoc decision to exclude studies that did not measure review outcomes. Decision made from information in the abstract
Holst 1993	Unclear if this is an RCT. A comparison of the intraoperative sympatho-adrenergic response and the postoperative vigilance of a propofol/alfentanil anaesthesia to a conventional isoflurane anaesthesia. Unable to source full text. Post-hoc decision to exclude studies that did not measure review outcomes. Decision made from information in the abstract
Hosseinzadeh 2013	RCT, measuring effects of propofol versus isoflurane on incidence of postoperative nausea and vomiting in participants between 16 to 65 year of age. Post-hoc decision to exclude studies that did not measure review outcomes
Ionescu 2009	Unclear if this is an RCT. Effects of TIVA versus isoflurane on postoperative nausea and vomiting, and patient satisfaction, in participants undergoing laparoscopic cholecystectomy. Unable to source full text. Post-hoc decision to exclude studies that did not measure review outcomes. Decision made from information in the abstract
Ito 2012	RCT, measuring effects of TIVA versus desflurane on postoperative emergence in elderly participants. Outcomes measured: presence of spontaneous speech, early recovery time, time to extubation, eye opening, and squeezing fingers on command. Post-hoc decision to exclude studies that did not measure review outcomes
Kadoi 2009a	RCT, measuring effects of propofol versus sevoflurane on cerebrovascular carbon dioxide reactivity in elderly participants. Outcomes measured: cerebral circulation. Post-hoc decision to exclude studies that did not measure review outcomes

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Kim 2015b	RCT, measuring effects of propofol versus desflurane on postoperative spirometry in elderly after knee surgery. Outcomes measured: spirometry parameters. Post-hoc decision to exclude studies that did not measure review outcomes
Konstantopoulos 2013a	RCT, measuring effects of sevoflurane versus propofol on recovery characteristics in older participants. Outcomes measured: haemodynamic stability, recovery characteristics, postoperative nausea and vomiting, and pain intensity. Post-hoc decision to exclude studies that did not measure review outcomes
Kvarnstrom 2012	RCT, measuring effects of sevoflurane versus propofol on complement activation and the release of inflammatory interleukins in participants undergoing major abdominal surgery. Post-hoc decision to exclude studies that did not measure review outcomes
Malcharek 2015	RCT, measuring effects of desflurane versus propofol on tcMEP amplitudes in participants without PMDs undergoing CEA. Post-hoc decision to exclude studies that did not measure review outcomes
Manolescu 2012	Unclear if this is an RCT. Evaluation of cardioprotective effects of sevoflurane versus propofol in patients with cardiac risk, undergoing noncardiac surgery. Unable to source full text. Post-hoc decision to exclude studies that did not measure review outcomes. Decision made from information in the abstract
Mets 1992	RCT, measuring effects of propofol versus isoflurane in elderly participants undergoing ophthalmic surgery. Outcomes measured: haemodynamic parameters. Post-hoc decision to exclude studies that did not measure review outcomes
Murray 1994	RCT, measuring effects of isoflurane versus propofol on hepatic glutathione-S-transferase concentrations. Post-hoc decision to exclude studies that did not measure review outcomes
Mutch 1995	RCT, measuring effects of propofol versus isoflurane in older patients undergoing carotid endarterectomy. Outcomes measured: haemodynamic parameters. Post-hoc decision to exclude studies that did not measure review outcomes
Ohe 2014	Unclear if this is an RCT. Compares effects of sevoflurane versus propofol on preventing intraoperative hypothermia. Post-hoc decision to exclude studies that did not measure review outcomes
Oikkonen 1992	RCT, measuring effects of isoflurane versus alfentanil-methohexitone verses propofol on arterial pressure or heart rate in geriatric participants. Post-hoc decision to exclude studies that did not measure review outcomes
Passot 2005	RCT, measuring effects of target- versus manually-controlled infusion of propofol and desflurane in elderly participants undergoing hip fracture surgery. Outcomes measured: haemodynamic parameters. Post-hoc decision to exclude studies that did not measure review outcomes
Pirttikangas 1996	RCT, measuring effects of propofol versus combined isoflurane in elderly participants undergoing ophthalmic surgery. Outcomes measured: immune responses. Post-hoc decision to exclude studies that did not measure review outcomes
Polarz 1995	RCT, measuring effects of isoflurane versus propofol on participants undergoing ophthalmic surgery. Outcomes measured: intraocular pressure. Unable to source full text. Post-hoc decision to exclude studies that did not measure review outcomes

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Sal'nikov 2003	Unclear if this is an RCT. A comparative evaluation of "cerebral oximetry" during anaesthesia with xenon and other anaesthetics. Unable to source full text. Post-hoc decision to exclude studies that did not measure review outcomes
Schilling 2007	RCT, measuring effects of propofol versus desflurane in older participants undergoing open thoracic surgery. Outcomes measured: alveolar inflammatory response to one-lung ventilation. Post-hoc decision to exclude studies that did not measure review outcomes
Schilling 2011	RCT, measuring effects of propofol versus desflurane versus sevoflurane in older participants undergoing open thoracic surgery. Outcomes measured: alveolar inflammatory response. Post-hoc decision to exclude studies that did not measure review outcomes
Schäfer 2002	RCT, measuring effects of propofol versus sevoflurane in participants aged over 50 undergoing cataract surgery. Outcomes measured: intraocular pressure. Post-hoc decision to exclude studies that did not measure review outcomes
Shao 2013	RCT, measuring effects of propofol versus sevoflurane in elderly participants. Outcomes measured: quality of neuromuscular blockade with cisatracurium. Post-hoc decision to exclude studies that did not measure review outcomes
Sohn 2008	RCT, measuring effects of propofol versus sevoflurane in elderly participants undergoing total knee arthroplasty. Outcomes measured: haemodynamic parameters. Post-hoc decision to exclude studies that did not measure review outcomes
Sugata 2012	RCT, measuring effects of propofol versus sevoflurane in participants undergoing prone spine surgery. Outcomes measured: intraocular pressure. Unable to source full text. Post-hoc decision to exclude studies that did not measure review outcomes
Trifu 2011	RCT, measuring effects of propofol versus sevoflurane in participants aged between 16 and 76 undergoing elective neurosurgery. Unable to source full text. Outcomes measured: cardiovascular stability, recovery characteristics, and side effects. Post-hoc decision to exclude studies that did not measure review outcomes
Tufano 2000	RCT, measuring effects of propofol versus sevoflurane in participants aged between 18 and 70. Outcomes measured: drug consumption, intraoperative responses, and times of recovery. Post-hoc decision to exclude studies that did not measure review outcomes
Ueda 1999	RCT, measuring effects of sevoflurane versus propofol combined with thoracic epidural anaesthesia on arterial oxygenation during one-lung ventilation for thoracotomy. Unable to source full text. Outcomes measured: haemodynamic parameters. Post-hoc decision to exclude studies that did not measure review outcomes. Decision made from information in the abstract
Wakabayashi 2014	RCT, measuring effects of sevoflurane versus propofol in older participants undergoing oesophagectomy. Outcomes measured: levels of cytokine and chemokine at the airway epithelium. Post-hoc decision to exclude studies that did not measure review outcomes
Weilbach 2005	RCT, measuring effects of TIVA versus BA in elderly participants undergoing a cataract operation. Outcomes measured: patient satisfaction. Post-hoc decision to exclude studies that did not measure review outcomes

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Wen 2010	RCT, measuring effects of sevoflurane versus propofol on neuromuscular blockade produced by continuous cisatracurium infusion. Post-hoc decision to exclude studies that did not measure review outcomes
Wormald 2005	RCT, measuring effects of sevoflurane versus propofol on the surgical field. Post-hoc decision to exclude studies that did not measure review outcomes
Yu 2010a	RCT, measuring effects of sevoflurane versus propofol in elderly patients undergoing abdominal surgery. Outcomes measured: haemodynamic parameters. Post-hoc decision to exclude studies that did not measure review outcomes
Zabolotskikh 2013	Unclear if this is an RCT. Measuring effects of sevoflurane versus propofol on intracerebral and cerebral perfusion pressure. Post-hoc decision to exclude studies that did not measure review outcomes
Zhang 2014	RCT, measuring effects of propofol versus propofol and sevoflurane versus sevoflurane on immune responses in patients undergoing surgery for tongue cancer. Post-hoc decision to exclude studies that did not measure review outcomes

BA: balanced anaesthesia
CEA: carotid endarterectomy
MDA: malondialdehyde
PMDs: pre-existing motor deficits
RCT: randomized control trial
SjO^2: jugular venous bulb oxygenation saturation
tcMEP: transcranial electrical motor evoked potential
TIVA: total intravenous anaesthesia

Characteristics of studies awaiting assessment *[ordered by study ID]*

IRCT2015112925277N1

Methods	RCT, parallel design
Participants	**Target number of randomized participants:** 100 **Inclusion criteria** 1. Not reported **Exclusion criteria** 1. History of allergic reaction to the drug used in this study 2. Pregnancy 3. Drug addiction 4. Pain relief medications 24 hours before surgery 5. Persistent hypertension 6. Cardiovascular disease 7. Renal failure **Type of surgery:** inguinal herniorrhaphy **Country:** Iran **Setting:** hospital

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IRCT2015112925277N1 (*Continued*)

Interventions	**TIVA group** Maintenance details: 100 mg /kg/minute propofol **Inhalational maintenance group** Maintenance details: 1 mg/kg/minute isoflurane
Outcomes	1. Pain 2. Temperature 3. Blood pressure 4. Heart rate 5. Respiratory rate 6. Recovery times 7. Intubation time 8. Dose of diclofenac postoperatively
Notes	Study is completed, but study results are not posted. Study does not specifically recruit elderly participants. Once published, we would need to ascertain whether mean age of participants is > 60 years of age

McDonagh 2012

Methods	RCT, parallel design
Participants	**Number of randomized participants**: 200 **Inclusion criteria** 1. ≥ 65 years of age, after obtaining IRB approval and informed consent **Exclusion criteria** 1. Not fluent in English 2. Severe visual or auditory deficits 3. Diagnosis of dementia 4. Score 18 on the MMSE **Type of surgery:** orthopaedic **Country:** not reported **Setting:** hospital
Interventions	**TIVA group** Induction details: pre-medicated with midazolam. Induction with propofol; no additional details Maintenance details: propofol TIVA to maintain BIS 40 to 60 **Inhalational maintenance group** Induction details: pre-medicated with midazolam Induction with propofol; no additional details Maintenance details: isoflurane to maintain BIS 40 to 60
Outcomes	1. Cognitive function at 3 months postsurgery using GDS. Cognitive testing using standardized cognitive measures
Notes	We only have an abstract for this study. No denominator figures for each group. Not clear whether outcome data is available for immediate postoperative period

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NCT02766062

Methods	RCT, parallel design
Participants	**Target number of participants:** 94 **Inclusion criteria** 1. ≥ 60 years of age, with ASA II or III, scheduled for noncardiac and non-neural surgery **Exclusion criteria** 1. MMSE score which is too low 2. Chronic alcohol and drug abuse 3. Disturbed renal and liver function 4. History of a cerebrovascular accident 5. Permanent ventricular pacing 6. Preoperative cognitive deficits 7. Lack of co-operation **Type of surgery:** noncardiac and non-neural surgery **Country:** China **Setting:** General Hospital of Ningxia Medical University
Interventions	**TIVA group** Maintenance details: propofol **Inhalational maintenance group** Maintenance details: sevoflurane
Outcomes	1. Number of participants with POCD as assessed by MMSE score up to 7 days postoperatively
Notes	Study is completed, but study results are not posted

Shen 2011

Methods	RCT, parallel design
Participants	**Total number of randomized participants:** 60 **Inclusion criteria:** requires translation **Exclusion criteria:** requires translation **Type of surgery:** thoracic **Country:** China **Setting:** hospital
Interventions	**TIVA group** Induction details: requires translation Maintenance details: propofol and fentanyl **Inhalational maintenance group** Induction details: requires translation Maintenance details: sevoflurane and fentanyl
Outcomes	1. Durations of operation and one-lung ventilation 2. Volume of blood loss during operation 3. Time of spontaneous eye opening 4. Extubation 5. Cognitive function (assessed before operation and at various times after operation using MMSE)

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Notes	Unable to extract detailed data due to paper being written in Chinese. All data extracted from abstract

ASA: American Society of Anesthesiologists
BIS: bispectral index
GDS: Geriatric Depression scale
IRB: institutional review board
MMSE: Mini-Mental State Examination
RCT: randomized control trial
POCD: postoperative cognitive dysfunction
TIVA: total intravenous anaesthesia

Characteristics of ongoing studies *[ordered by study ID]*

ChiCTR-IOR-16009851

Trial name or title	Impact of postoperative cognitive function after sevoflurane- or propofol-anaesthesia in aged cancer patients: a double-blinded randomized controlled trial
Methods	RCT, parallel design
Participants	**Target number of randomized participants:** 220 **Inclusion criteria** 1. ≥ 65 years and < 86 years of age, male or female of any nationality 2. Presenting for major abdominal malignant tumour resection under GA with estimated duration of operation > 2 hours 3. Primary malignant tumour 4. Patient and relatives agree to participate and sign informed consents. **Exclusion criteria** 1. Refusal to join the study 2. History of depression, schizophrenia, or epilepsy 3. Parkinsons disease, or myasthenia gravis 4. Serious Alzheimers disease 5. Any severe visual or auditory disorders 6. Unable to understand the language used 7. Coma 8. End-stage diseases 9. Emergency operation 10. In a critical condition (ASA status IV or V before surgery) 11. History of neurological surgery 12. MMSE < 24 13. History of alcoholism, or drug dependence **Type of surgery:** major abdominal malignant tumour resection **Country:** China **Setting:** hospital

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ChiCTR-IOR-16009851 (*Continued*)

Interventions	**TIVA group** Details: propofol; no details **Inhalational maintenance group** Details: sevoflurane; no details
Outcomes	1. POCD (at 7 days and 3 months postoperatively) 2. Quality of recovery 3. Complications after surgery 4. Length of hospital stay 5. EORCT 6. QLQ-C30
Starting date	11 July 2016
Contact information	Liang Guo (1159398818@qq.com) or Ling-Hui Pan (plinghui@hotmail.com)
Notes	

EUCTR2014-004604-29-DK

Trial name or title	Sevoflurane versus standard general anaesthesia in elective open abdominal aortic aneurism surgery
Methods	RCT, parallel design
Participants	**Target number of randomized participants:** 24 **Inclusion criteria** 1. Enrolled for abdominal infrarenal aortic aneurism repair surgery **Exclusion criteria** 1. < 18 years of age 2. Included in other pharmaceutical studies 3. Abuse of opioids, benzodiazepines, anti-epileptic drugs, alcohol or alpha 2-agonists 4. pregnant and breastfeeding women 5. Family history of malignant hyperthermia 6. Known hypersensitivity for opioids, propofol or volatile anaesthetics 7. Serious arrhythmia, ventricular tachycardia or tachycardia > 120 beats/min 8. Severe valvular diseases requiring surgical repair before major noncardiac surgery 9. Uncontrolled hypertension 10. Unstable angina pectoris or MI within 30 days of inclusion 11. Requiring acute abdominal aortic aneurysm surgery, or endovascular abdominal aortic aneurysm surgery 12. Severe uncontrolled psychiatric disease **Type of surgery:** aortic aneurysm repair **Country:** Denmark **Setting:** hospital
Interventions	**TIVA group** Details: propofol; no details **Inhalational maintenance group**

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EUCTR2014-004604-29-DK (*Continued*)

	Details: sevoflurane; no details
Outcomes	1. Biochemical measurements 2. Need for inotropic support 3. MI 4. Intestinal ischaemia diagnosed with endoscopy, laparoscopy or angiograph during admission 5. Postoperative incidences of ARDS and need for dialysis 6. Need for postoperative respiratory support 7. Days until discharge 8. Days in ICU 9. 30-day mortality
Starting date	Not clear from the clinical trials register documents
Contact information	Peder Bach (pedebach@rm.dk)
Notes	Study does not specifically recruit elderly participants. Once completed, we would need to ascertain whether mean age of participants is > 60 years of age

NCT01809041

Trial name or title	Comparison of intravenous anesthetics to volatile anesthetics on postoperative cognitive dysfunction
Methods	RCT, parallel design
Participants	**Target number of randomized participants:** 684 **Inclusion criteria** 1. Major elective gastrointestinal, gynaecological, prostate or bladder surgery patients, ≥ 60 years of age 2. Laparoscopic surgery expected to last for ≥ 2 hours under GA and the patient will stay in hospital for ≥ 7 days after surgery 3. Lack of serious hearing and vision impairment and be able to read so that neurobehavioral tests can be performed **Exclusion criteria** 1. Not expected to be alive for > 3 months 2. MMSE score ≤ 23 3. History of dementia, psychiatric illness or any diseases of central nervous system 4. Current use of sedatives or antidepressant, alcoholism and drug dependence 5. Previously included in this study (for participants who have second intra-abdominal surgery during the study period) 6. Difficult to follow up or participants with poor compliance 7. Uncontrolled hypertension (> 180/100 mmHg) **Type of surgery:** intra-abdominal and intrapelvic surgery **Country:** China **Setting:** hospital
Interventions	**TIVA group** Maintenance details: propofol (50 - 150 μg/kg/min) and remifentanil (0.1 - 0.5 μg/kg/min) **Inhalational maintenance group**

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NCT01809041 (*Continued*)

	Maintenance details: sevoflurane at 0.5 to 1.5 MAC plus remifentanil (0.1 - 0.5 μg/kg/min)
Outcomes	Number of participants with POCD (at 7 days and 3 months) Time for bowel function return after surgery Degree of increase of stress hormones Length of hospital stay
Starting date	March 2013
Contact information	Yujuan Li, MD, PhD (yujuan_04@hotmail.com); or Shulin Peng (pslmzk@yahoo.com.cn)
Notes	

NCT01995214

Trial name or title	Sevoflurane and propofol anaesthesia on postoperative delirium
Methods	RCT, parallel design
Participants	**Target number of randomized participants:** 500 **Inclusion criteria** 1. ASA I to III, ≥ 60 years of age, elective major surgery under GA **Exclusion criteria** 1. ASA ≥ IV, < 60 years of age 2. BMI > 30 3. Neurologic disease 4. Cardiac surgery or neurologic surgery 5. Anticonvulsant drugs 6. Chronic analgesics intake 7. Participating in another study **Type of surgery:** not specified **Country:** China **Setting:** hospital
Interventions	**TIVA group** Maintenance details: propofol and remifentanil guided by Narcotrend index monitoring **Inhalational maintenance group** Maintenance details: sevoflurane and remifentanil guided by Narcrotrend index monitoring
Outcomes	1. Postoperative delirium (using CAM at 24 hours, and at 2, 3, and 7 days postoperatively) 2. Length of PACU stay 3. Haemodynamic parameters 4. PONV 5. Quality of recovery (using QOR-40) 6. Postoperative stroke (at 1, 2, 3, and 7 days postoperatively)
Starting date	June 2013

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NCT01995214 (*Continued*)

Contact information	Yuke Tian, MD, PhD
Notes	

NCT02107170

Trial name or title	Effects of anesthetics on postoperative cognitive function of patients undergoing endovascular repair of aortic aneurysm and endovascular treatment of arteriosclerosis obliterans of lower extremities
Methods	RCT, parallel design
Participants	**Target number of randomized participants:** 400 **Inclusion criteria** 1. 18 to 100 years of age, patients presenting for endovascular repair of aortic aneurysm and endovascular treatment of arteriosclerosis obliterans of lower extremities **Exclusion criteria** 1. Pre-existing delirium 2. Inability to converse **Type of surgery:** endovascular repair of aortic aneurysm, endovascular treatment of arteriosclerosis obliterans of lower extremities **Country:** China **Setting:** hospital
Interventions	**TIVA group** Details: propofol (50 to 150 μg/kg/min) plus remifentanil (0.1 to 0.5 μg/kg/min) during the surgery **Inhalational maintenance group** Details: sevoflurane at 0.5 to 1.5 MAC plus remifentanil (0.1 to 0.5 μg/kg/min) during the surgery
Outcomes	1. Number of participants with POCD (at 7 days and 3 months postoperatively) 2. Changes in plasma levels of VEGF, TGF-1, TNF-α, IL-1β, and IL-6 (a composite outcome measure, at 3 days postoperatively)
Starting date	February 2014
Contact information	Tao Zhang, Master of Medicine (zhtao98@aliyun.com)
Notes	Study does not specifically recruit elderly participants. Once completed, we would need to ascertain whether mean age of participants is > 60 years of age

NCT02133638

Trial name or title	Sevoflurane decreases the risk of postoperative delirium after cerebral hypoxemia during surgery
Methods	RCT, parallel design

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NCT02133638 (*Continued*)

Participants	**Target number of randomized participants:** 130 **Inclusion criteria** 1. ASA III to IV, history of arterial vascular disease (arterial hypertension, myocardial ischaemia and/or cerebral vascular disease), undergoing elective non-cardiac surgery (hemicolectomy, hernioplasty, laparoscopic cholecystectomy and laparoscopic hysterectomy), 65 to 80 years of age **Exclusion criteria** 1. Dementia 2. Stroke or myocardial infarction ≤ 6 months before surgery 3. Oncological disease of T2-4N3M1 stage **Type of surgery:** elective non-cardiac surgery (hemicolectomy, hernioplasty, laparoscopic cholecystectomy and laparoscopic hysterectomy) **Country:** Russia **Setting:** hospital
Interventions	**TIVA group** Induction details: propofol 2 mg/kg and fentanyl 4 µg/kg Maintenance details: infusion of propofol 8 mg/kg/hour and boluses of fentanyl 3 µg/kg **Inhalational maintenance group** Induction details: fentanyl 2 µg/kg and a bolus inhalation of 8% sevoflurane in an 8 L/min fresh gas flow Maintenance details: 1 MAC sevoflurane at a low fresh gas flow of 0.6 to 0.8 L/min in a 60% air-oxygen mixture supplemented with boluses of fentanyl
Outcomes	1. Regional cerebral oxygenation 2. Peripheral tissue oxygen saturation 3. Non-invasive blood pressure 4. Postoperative delirium (using CAM 24 and 48 hours postoperatively) 5. Plasma concentration of S100b protein
Starting date	May 2014
Contact information	Yuri V Iljin, Negovsky Reanimatology Research Institute, Moscow, Russia
Notes	

NCT02301676

Trial name or title	Long term postoperative cognitive dysfunction in the elderly patients
Methods	RCT, parallel design
Participants	**Target number of randomized participants:** 190 **Inclusion criteria** 1. ≥ 60 years of age, scheduled for laparoscopic cholecystectomy under GA **Exclusion criteria** 1. Diseases of the central nervous system, including dementia (MMSE < 24) 2. Consumption of major tranquillizers or antidepressants 3. Previous neuropsychological testing 4. Inability to comply and follow procedures or poor comprehension of the language used in the study

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NCT02301676 (*Continued*)

	5. Parkinson's disease 6. Severe visual or auditory disability 7. Illiteracy 8. Alcoholism (intake of > 5 units of alcohol daily during the last 3 months) 9. Drug dependence 10. Not expected to complete the postoperative tests **Type of surgery:** laparoscopic cholecystectomy under GA **Country:** South Korea **Setting:** hospital
Interventions	**TIVA group** Details: no details **Inhalational maintenance group** Details: sevoflurane; no details
Outcomes	1. POCD (at 2 years postoperatively)
Starting date	December 2014
Contact information	Seung-Hoon Baek, Pusan National University Yangsan Hospital
Notes	

NCT02458547

Trial name or title	Effect of anaesthesia technique on outcome after hip fracture surgery in elderly adult patients
Methods	RCT, parallel design
Participants	**Target number of randomized participants:** 186 **Inclusion criteria** 1. > 65 years scheduled for elective or emergency hip fracture surgery **Exclusion criteria** 1. Participant refusal 2. Inflammation or wound at puncture site 3. Increased intracranial pressure 4. Bleeding diathesis 5. Allergies to propofol or its ingredients, soybeans or peanuts 6. Participants with altered mental status 7. Illiterate 8. From another country **Type of surgery:** elective or emergency hip fracture surgery **Country:** South Korea **Setting:** hospital
Interventions	**TIVA group** Details: propofol TCI **Inhalational maintenance group**

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NCT02458547 (*Continued*)

	Details: desflurane at age-adjusted MAC of 0.8 to 1.0
Outcomes	1. Measures of pro-inflammatory cytokines
Starting date	May 2015
Contact information	Not reported
Notes	Study may not report outcomes of interest. Because the study includes elderly surgical patients and compares the anaesthetic agents of interest, we have included this study in our list of ongoing studies

NCT02662257

Trial name or title	Impact of anaesthesia maintenance methods on incidence of postoperative delirium
Methods	RCT, parallel design
Participants	**Target number of randomized participants:** 1200 **Inclusion criteria** 1. ≥ 65 years and < 90 years of age 2. Primary malignant tumour 3. Not receiving radiation therapy or chemotherapy before surgery 4. Scheduled to undergo surgery for the treatment of tumours, with an expected duration of ≥ 2 hours, under GA 5. Agree to participate, and give signed written informed consent **Exclusion criteria:** 1. Preoperative history of schizophrenia, epilepsy, parkinsonism or myasthenia gravis 2. Inability to communicate in the preoperative period (coma, profound dementia, language barrier, or end-stage disease) 3. Critical illness (preoperative ASA ≥ IV) 4. Severe hepatic dysfunction (Child-Pugh class C) 5. Severe renal dysfunction (undergoing dialysis before surgery) 6. Neurosurgery 7. Other reasons that are considered unsuitable for participation by the responsible surgeons or investigators **Type of surgery:** treatment of tumour **Country:** China **Setting:** hospital
Interventions	**TIVA group** Details: propofol adjusted to maintain BIS 40 to 60, with or without 50% nitrous oxide. Remifentanil (administered by continuous infusion), sufentanil (administered by intermittent injection/continuous infusion) , or fentanyl (administered by intermittent injection). Towards the end of surgery, propofol infusion rate will be decreased and fentanyl/sufentanil will be administered when necessary **Inhalational maintenance group** Details: sevoflurane adjusted to maintain BIS 40 to 60, with or without 50% nitrous oxide. Remifentanil (administered by continuous infusion), sufentanil (administered by intermittent injection/continuous infusion) , or fentanyl (administered by intermittent injection). Towards the end of surgery, sevoflurane inhalational

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NCT02662257 (*Continued*)

	concentration will be decreased and fentanyl/sufentanil will be administered when necessary
Outcomes	1. Delirium (using CAM or CAM-ICU, at 7 days postoperatively) 2. Length of hospital stay (up to 30 days) 3. Incidence of non-delirium complications (up to 30 days) 4. Cognitive function (using TICS-m at 30 days) 5. All-cause 30-day mortality 6. Pain score (during first 3 days postoperatively) 7. Cognitive function at 7 days postoperatively
Starting date	April 2015
Contact information	Dong-Xin Wang, MD, PhD, Peking University FIrst Hospital
Notes	Also registered as ChiCTR-IPR-15006209

NCT03165396

Trial name or title	Appropriate compatibility of propofol and sevoflurane for orthopaedic surgery of patients with MCI
Methods	RCT, parallel design
Participants	**Target number of randomized participants:** 100 **Inclusion criteria** 1. Scheduled for elective orthopaedic surgery, ASA II, 50 to 75 years **Exclusion criteria** 1. Neurological diseases that may affect cognitive function (e.g. subdural haematoma) 2. Hypothyroidism 3. Alcoholic dementia **Type of surgery:** orthopaedic surgery **Country:** China **Setting:** hospital
Interventions	**TIVA group** Details: propofol TCI 2.0 to 2.5 μg/mL **Inhalational maintenance group** Details: 1.3 MAC sevoflurane
Outcomes	1. Evidence of clinically cognitive function decline (using ApoJ, at 7 days; soluble CD14, at 7 days) 2. Cognitive function (using MMSE, at 24 hours and 7 days postoperatively; and MoCA, at 24 hours and 7 days postoperatively)
Starting date	10 May 2016
Contact information	Haiyun Wang (why@126.com) or Yimeng Chen (chenyimeng5525@163.com)
Notes	Compares two additional groups using propofol at different doses combined with sevoflurane

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NCT03194074

Trial name or title	Early cognitive function in elderly patients after laser laryngeal surgery: des vs prop
Methods	RCT, parallel design
Participants	**Target number of randomized participants:** 70 **Inclusion criteria** 1. Scheduled for laser laryngeal surgery under GA **Exclusion criteria** 1. Cardiac, pulmonary, hepatic, or renal dysfunction 2. Epilepsy 3. Uncontrolled hypertension 4. Taking medications that influence the central nervous system 5. Showing obvious alteration of mental status 6. Refusal to participate **Type of surgery:** laser laryngeal surgery **Country:** China **Setting:** hospital
Interventions	**TIVA group** Maintenance details: propofol at a rate 75 to 150 µg/kg/min and remifentanil at 0.1 to 0.3 µg/kg/min maintained throughout surgery **Inhalational maintenance group** Maintenance details: desflurane at end-tidal concentration at 0.7 to 1.0 MAC and remifentanil 0.1 to 0.3 µg/kg/min
Outcomes	1. Change of MMSE (day before surgery and 30min postoperatively) 2. MMSE scores at 1, 3, and 24 hours postoperatively
Starting date	15 August 2017
Contact information	Xia Shen, MD (zlsx@yahoo.com) or Hui Qiao, MD (theyellow@163.com)
Notes	Study does not specifically recruit elderly participants. Once completed, we would need to ascertain whether mean age of participants is > 60 years of age

ApoJ: Apolipoprotein J
ARDS: acute respiratory distress syndrome
ASA: American Society of Anesthesiologists
BIS: Bispectral Index
BMI: body mass index
CAM: confusion assessment method
CD: cluster of differentiation
EORCT QLQ-C30: (quality of life questionnaire for cancer patients)
GA: general anaesthesia
ICU: intensive care unit
IL: interleukin
MAC: minimum alveolar concentration
MCI: mild cognitive impairment

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MI: myocardial infarction
MMSE: Mini-Mental State Examination
MoCA: Montreal Cognitive Assessment
PACU: postanaesthesia care unit
POCD: postoperative cognitive dysfunction
PONV: postoperative nausea and vomiting
QOR-40: quality of recovery questionnaire
RCT: randomized control trial
TGF: transforming growth factor
TCI: target-controlled infusion
TICS-m: Telephone Interview for Cognitive Status-Modified
TIVA: total intravenous anaesthesia
TNF: tumour necrosis factor
VEGF: vascular endothelial growth factor

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DATA AND ANALYSES

Comparison 1. TIVA vs Inhalational maintenance

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Postoperative delirium	5	321	Odds Ratio (M-H, Random, 95% CI)	0.59 [0.15, 2.26]
2 Postoperative cognitive dysfunction	7	869	Odds Ratio (M-H, Random, 95% CI)	0.52 [0.31, 0.87]
3 Mortality	3	271	Odds Ratio (M-H, Random, 95% CI)	1.21 [0.33, 4.45]
4 Intraoperative hypotension	11		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
5 Length of stay in PACU	7		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Length of hospital stay	4	175	Mean Difference (IV, Random, 95% CI)	-0.00 [-1.32, 1.32]

Comparison 2. TIVA vs inhalational maintenance: subgroup analysis (induction agents; and TCI vs non-TCI)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Postoperative delirium (induction agents; and TCI vs non-TCI)	5	321	Odds Ratio (M-H, Random, 95% CI)	0.59 [0.15, 2.26]
1.1 Induction with inhalational agents, and TCI	1	50	Odds Ratio (M-H, Random, 95% CI)	3.12 [0.12, 80.39]
1.2 Induction with intravenous agents, and non-TCI	4	271	Odds Ratio (M-H, Random, 95% CI)	0.42 [0.11, 1.67]
2 Postoperative cognitive dysfunction (induction agents)	7	869	Odds Ratio (M-H, Random, 95% CI)	0.52 [0.31, 0.87]
2.1 Induction with inhalational agents	2	230	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.50, 1.50]
2.2 Induction with intravenous agents	5	639	Odds Ratio (M-H, Random, 95% CI)	0.38 [0.20, 0.75]
3 Mortality (induction agents; and TCI vs non-TCI)	3	271	Odds Ratio (M-H, Random, 95% CI)	1.21 [0.33, 4.45]
3.1 Induction with inhalational agents, and TCI	1	28	Odds Ratio (M-H, Random, 95% CI)	3.22 [0.12, 86.09]
3.2 Induction with intravenous agents, and non-TCI	2	243	Odds Ratio (M-H, Random, 95% CI)	1.01 [0.25, 4.16]
4 Intraoperative hypotension (induction agents)	11		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Induction with inhalational agents	5		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Induction with intravenous agents	6		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

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5 Postoperative cognitive dysfunction (TCI vs non-TCI)	7	869	Odds Ratio (M-H, Random, 95% CI)	0.52 [0.31, 0.87]
5.1 TCI	2	294	Odds Ratio (M-H, Random, 95% CI)	0.31 [0.07, 1.38]
5.2 non-TCI	5	575	Odds Ratio (M-H, Random, 95% CI)	0.63 [0.36, 1.10]
6 Intraoperative hypotension (TCI vs non-TCI)	11		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
6.1 TCI	4		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 non-TCI	7		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Length of stay in the PACU (TCI vs non-TCI)	7		Mean Difference (IV, Random, 95% CI)	Totals not selected
7.1 TCI	2		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 non-TCI	5		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 3. TIVA vs inhalational maintenance: subgroup analysis, monitoring with processed EEG vs standard care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Postoperative delirium	5	321	Odds Ratio (M-H, Random, 95% CI)	0.59 [0.15, 2.26]
1.1 Monitoring with processed EEG	3	211	Odds Ratio (M-H, Random, 95% CI)	0.56 [0.04, 7.44]
1.2 Monitoring with standard care	2	110	Odds Ratio (M-H, Random, 95% CI)	1.00 [0.14, 7.06]
2 Postoperative cognitive dysfunction	7	869	Odds Ratio (M-H, Random, 95% CI)	0.52 [0.31, 0.87]
2.1 Monitoring with processed EEG	6	839	Odds Ratio (M-H, Random, 95% CI)	0.47 [0.27, 0.84]
2.2 Monitoring with standard care	1	30	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.24, 4.20]
3 Intraoperative hypotension	11		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Monitoring with processed EEG	6		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Monitoring with standard care	5		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Length of stay in PACU	7		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.1 Monitoring with processed EEG	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Monitoring with standard care	6		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5 Length of hospital stay	4	175	Mean Difference (IV, Random, 95% CI)	-0.00 [-1.32, 1.32]
5.1 Monitoring with processed EEG	1	37	Mean Difference (IV, Random, 95% CI)	2.30 [-0.50, 5.10]
5.2 Monitoring with standard care	3	138	Mean Difference (IV, Random, 95% CI)	-0.27 [-1.40, 0.86]

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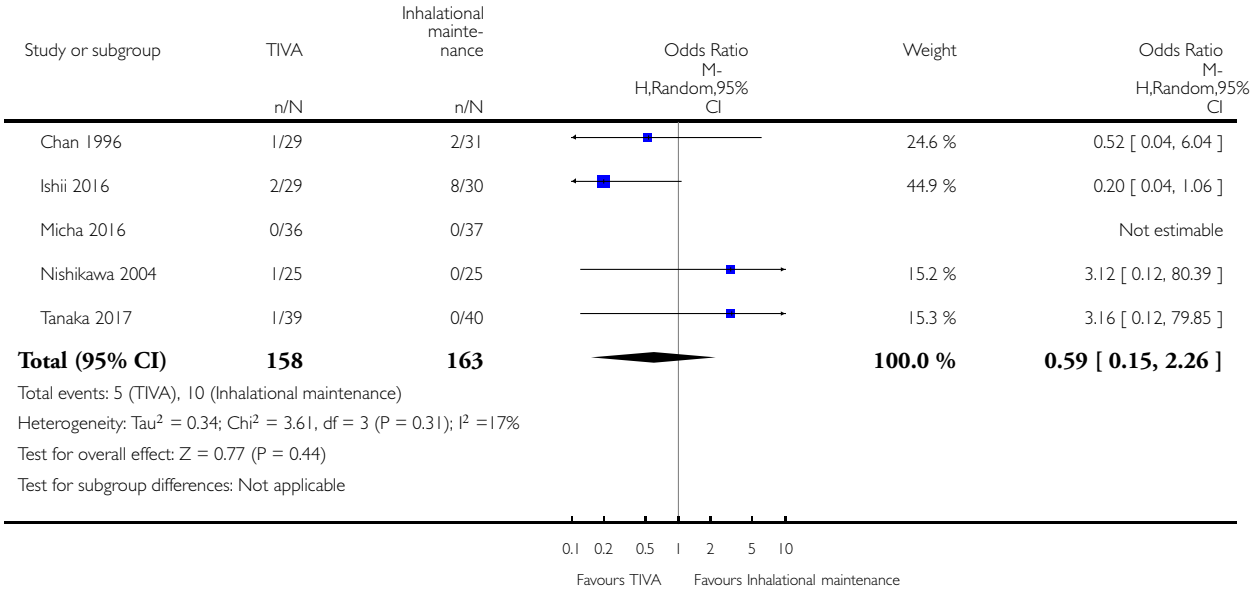
Analysis 1.1. Comparison 1 TIVA vs Inhalational maintenance, Outcome 1 Postoperative delirium.

Review: Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery

Comparison: 1 TIVA vs Inhalational maintenance

Outcome: 1 Postoperative delirium



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Analysis 1.2. Comparison 1 TIVA vs Inhalational maintenance, Outcome 2 Postoperative cognitive dysfunction.

Review: Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery

Comparison: 1 TIVA vs Inhalational maintenance

Outcome: 2 Postoperative cognitive dysfunction

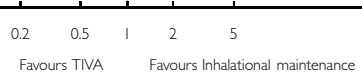
Study or subgroup	TIVA n/N	Inhalational maintenance n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Egawa 2016	16/72	24/72		21.5 %	0.57 [0.27, 1.20]
Geng 2017 (1)	2/50	25/100		9.3 %	0.13 [0.03, 0.55]
Lindholm 2013	4/96	6/97		11.3 %	0.66 [0.18, 2.41]
Micha 2016	1/36	10/37		5.2 %	0.08 [0.01, 0.64]
Rohan 2005	7/15	7/15		9.8 %	1.00 [0.24, 4.20]
Tanaka 2017	19/39	26/40		17.7 %	0.51 [0.21, 1.26]
Tang 2014	30/101	33/99		25.3 %	0.85 [0.47, 1.54]
Total (95% CI)	**409**	**460**		**100.0 %**	**0.52 [0.31, 0.87]**

Total events: 79 (TIVA), 131 (Inhalational maintenance)

Heterogeneity: $Tau^2 = 0.18$; $Chi^2 = 10.12$, df = 6 (P = 0.12); $I^2 = 41\%$

Test for overall effect: Z = 2.47 (P = 0.014)

Test for subgroup differences: Not applicable



(1) Combined data for isoflurane and sevoflurane groups

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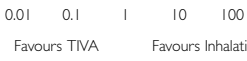
Analysis 1.3. Comparison 1 TIVA vs Inhalational maintenance, Outcome 3 Mortality.

Review: Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery

Comparison: 1 TIVA vs Inhalational maintenance

Outcome: 3 Mortality

Study or subgroup	TIVA	Inhalational maintenance	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
	n/N	n/N			
Ammar 2016	0/25	0/25			Not estimable
Biboulet 2012	1/14	0/14		15.7 %	3.22 [0.12, 86.09]
Lindholm 2013	4/96	4/97		84.3 %	1.01 [0.25, 4.16]
Total (95% CI)	**135**	**136**		**100.0 %**	**1.21 [0.33, 4.45]**
Total events: 5 (TIVA), 4 (Inhalational maintenance)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.40$, df = 1 (P = 0.52); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.29 (P = 0.77)					
Test for subgroup differences: Not applicable					



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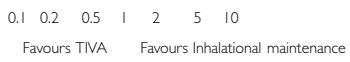
Analysis 1.4. Comparison 1 TIVA vs Inhalational maintenance, Outcome 4 Intraoperative hypotension.

Review: Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery

Comparison: 1 TIVA vs Inhalational maintenance

Outcome: 4 Intraoperative hypotension

Study or subgroup	TIVA n/N	Inhalational maintenance n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
Biboulet 2012	14/14	11/14		8.83 [0.41, 188.73]
Chan 1996	8/29	5/31		1.98 [0.56, 6.96]
Geng 2017 (1)	3/50	9/100		0.65 [0.17, 2.50]
Jellish 2003	28/30	26/29		1.62 [0.25, 10.45]
Longas 2004 (2)	15/20	33/40		0.64 [0.17, 2.33]
Luntz 2004	17/32	33/64		1.06 [0.46, 2.49]
Micha 2016	0/36	0/37		Not estimable
Nishikawa 2004	1/25	3/25		0.31 [0.03, 3.16]
Tang 2014	26/101	35/99		0.63 [0.35, 1.16]
Trembach 2012	26/45	9/44		5.32 [2.08, 13.64]
Zhang 2015 (3)	11/40	2/40		7.21 [1.48, 35.07]



(1) combined data for isoflurane and sevoflurane groups

(2) hypotension defined as MAP < 30% baseline. Data also available for hypotension requiring vasopressors

(3) combined TIVA groups vs combined inhalational maintenance groups

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Analysis 1.5. Comparison 1 TIVA vs Inhalational maintenance, Outcome 5 Length of stay in PACU.

Review: Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery

Comparison: 1 TIVA vs Inhalational maintenance

Outcome: 5 Length of stay in PACU

Study or subgroup	TIVA		Inhalational maintenance		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
Celik 2011	50	20.4 (2.7)	50	24.2 (3.8)		-3.80 [-5.09, -2.51]
Chan 1996	29	116.4 (28)	31	131.6 (44)		-15.20 [-33.74, 3.34]
Demeere 2006	19	53.8 (60.6)	18	44.3 (47.1)		9.50 [-25.37, 44.37]
Epple 2001	62	77.3 (31)	62	93.9 (47.6)		-16.60 [-30.74, -2.46]
Jellish 2003	30	79.1 (8.4)	29	63.2 (6.8)		15.90 [12.01, 19.79]
Juvin 1997	14	213 (87)	15	252 (71)		-39.00 [-97.03, 19.03]
Kim 2015a	30	42 (7.3)	28	42.1 (6.7)		-0.10 [-3.70, 3.50]

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Analysis 1.6. Comparison 1 TIVA vs Inhalational maintenance, Outcome 6 Length of hospital stay.

Review: Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery

Comparison: 1 TIVA vs Inhalational maintenance

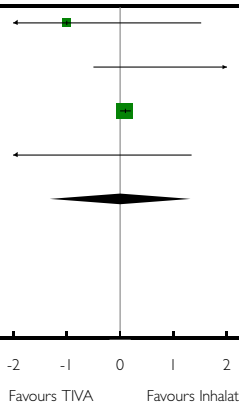
Outcome: 6 Length of hospital stay

Study or subgroup	TIVA N	Mean(SD)	Inhalational maintenance N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Ammar 2016	25	10 (4)	25	11 (5)		18.7 %	-1.00 [-3.51, 1.51]
Demeere 2006	19	12.3 (4.7)	18	10 (3.99)		16.0 %	2.30 [-0.50, 5.10]
Jellish 2003	30	1.4 (0.2)	29	1.3 (0.2)		57.3 %	0.10 [0.00, 0.20]
Juvin 1997	14	12 (3)	15	15 (8)		8.0 %	-3.00 [-7.34, 1.34]
Total (95% CI)	**88**		**87**			**100.0 %**	**0.00 [-1.32, 1.32]**

Heterogeneity: $Tau^2 = 0.79$; $Chi^2 = 5.06$, df = 3 (P = 0.17); $I^2 = 41\%$

Test for overall effect: Z = 0.00 (P = 1.0)

Test for subgroup differences: Not applicable



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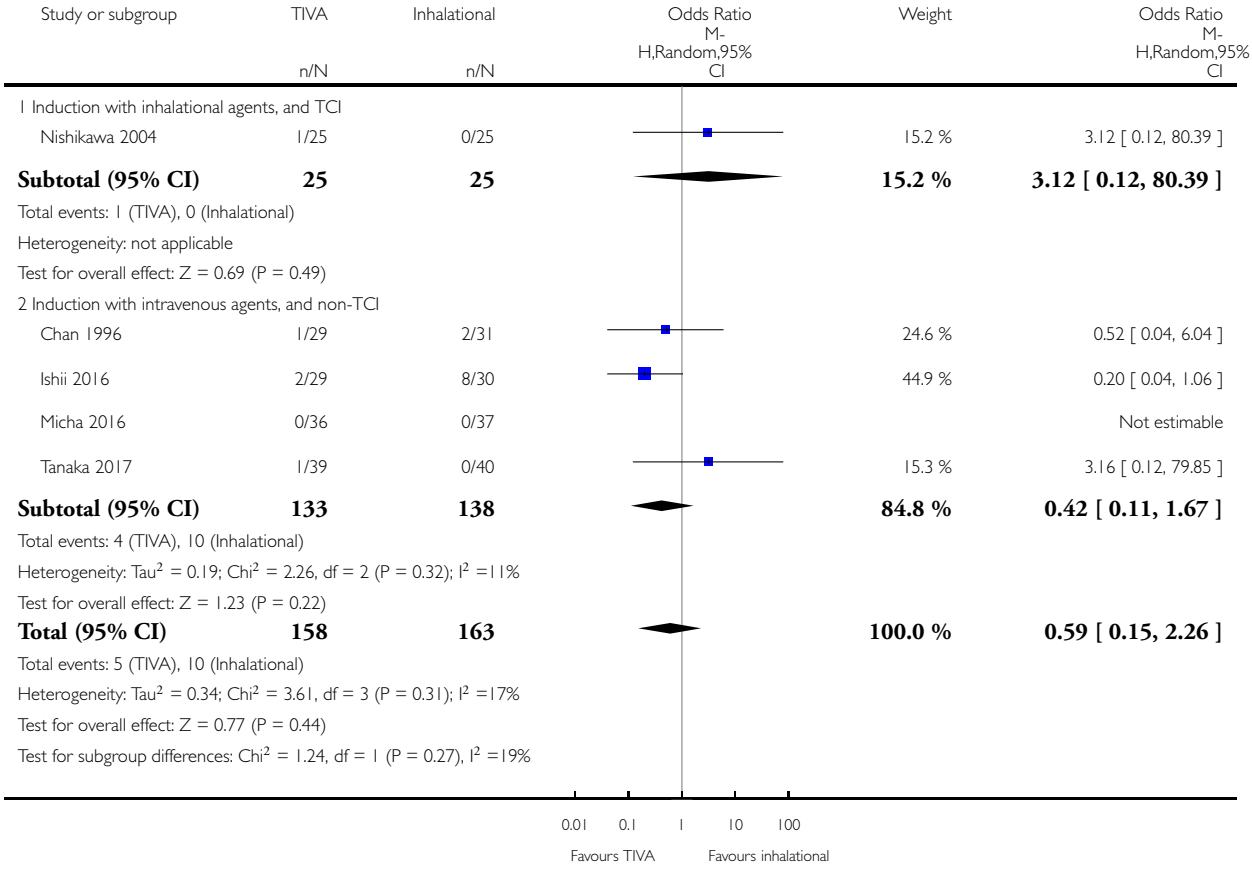
Analysis 2.1. Comparison 2 TIVA vs inhalational maintenance: subgroup analysis (induction agents; and TCI vs non-TCI), Outcome 1 Postoperative delirium (induction agents; and TCI vs non-TCI).

Review: Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery

Comparison: 2 TIVA vs inhalational maintenance: subgroup analysis (induction agents; and TCI vs non-TCI)

Outcome: 1 Postoperative delirium (induction agents; and TCI vs non-TCI)



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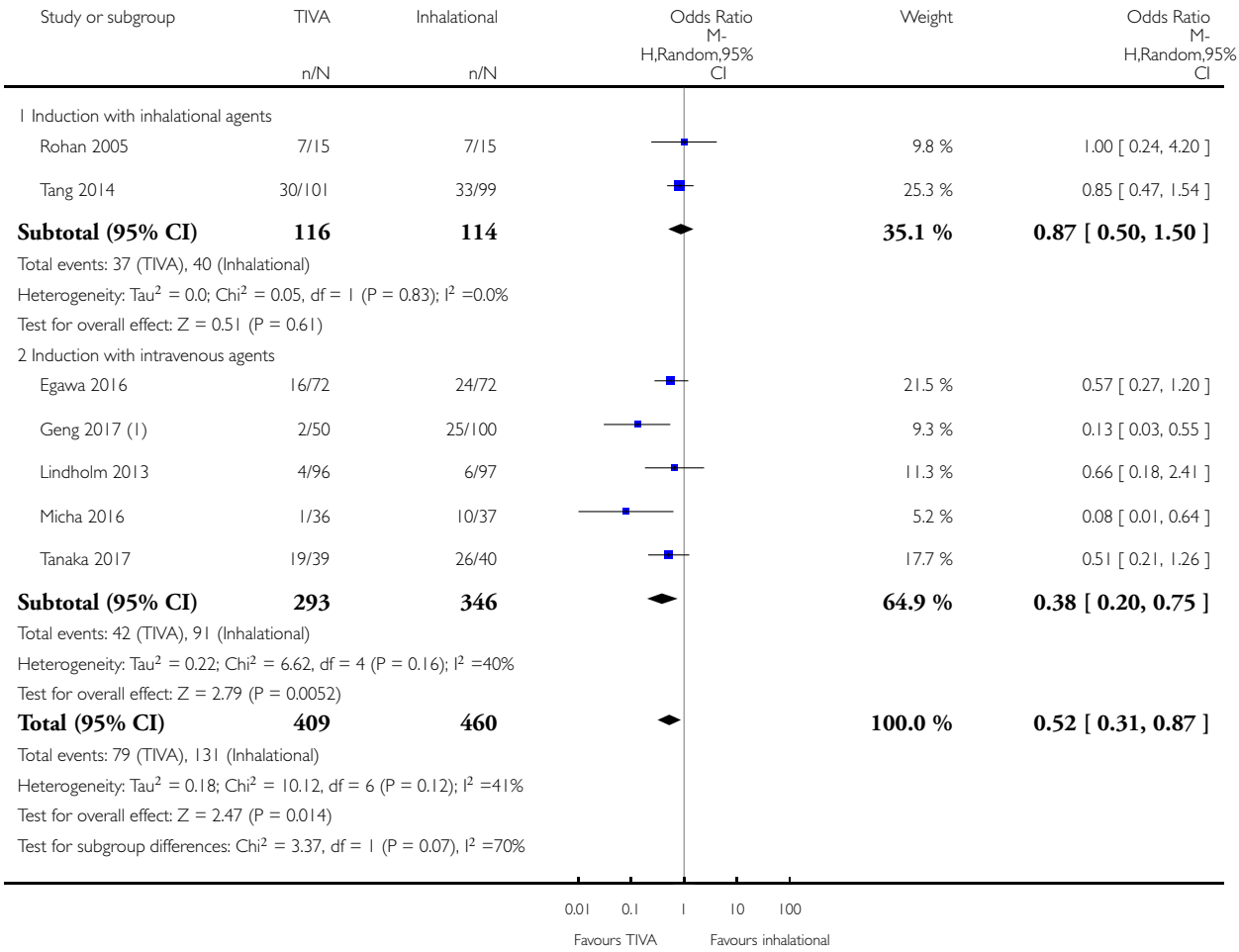
Analysis 2.2. Comparison 2 TIVA vs inhalational maintenance: subgroup analysis (induction agents; and TCI vs non-TCI), Outcome 2 Postoperative cognitive dysfunction (induction agents).

Review: Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery

Comparison: 2 TIVA vs inhalational maintenance: subgroup analysis (induction agents; and TCI vs non-TCI)

Outcome: 2 Postoperative cognitive dysfunction (induction agents)



(1) Combined data for isoflurane and sevoflurane groups

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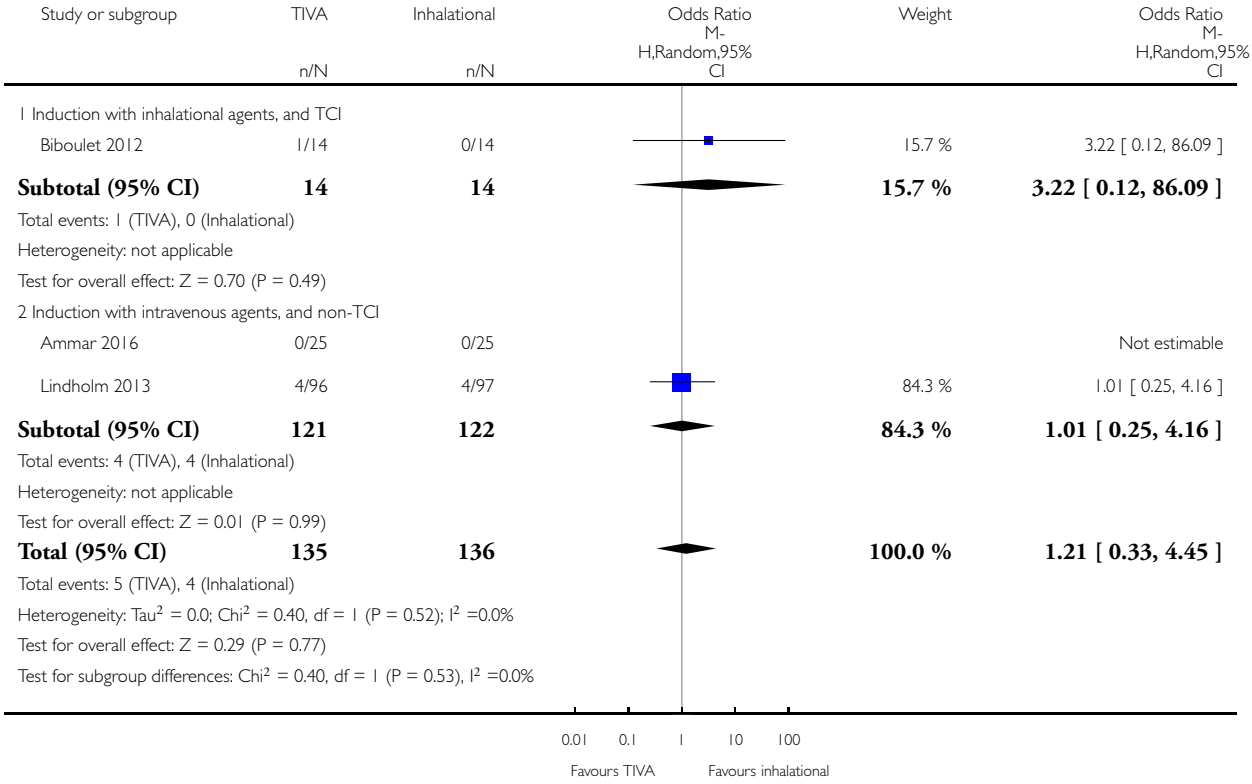
Analysis 2.3. Comparison 2 TIVA vs inhalational maintenance: subgroup analysis (induction agents; and TCI vs non-TCI), Outcome 3 Mortality (induction agents; and TCI vs non-TCI).

Review: Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery

Comparison: 2 TIVA vs inhalational maintenance: subgroup analysis (induction agents; and TCI vs non-TCI)

Outcome: 3 Mortality (induction agents; and TCI vs non-TCI)



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Analysis 2.4. Comparison 2 TIVA vs inhalational maintenance: subgroup analysis (induction agents; and TCI vs non-TCI), Outcome 4 Intraoperative hypotension (induction agents).

Review: Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery

Comparison: 2 TIVA vs inhalational maintenance: subgroup analysis (induction agents; and TCI vs non-TCI)

Outcome: 4 Intraoperative hypotension (induction agents)

Study or subgroup	TIVA n/N	Inhalational n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
1 Induction with inhalational agents				
Biboulet 2012	14/14	11/14		8.83 [0.41, 188.73]
Nishikawa 2004	1/25	3/25		0.31 [0.03, 3.16]
Tang 2014	26/101	35/99		0.63 [0.35, 1.16]
Trembach 2012	26/45	9/44		5.32 [2.08, 13.64]
Zhang 2015 (1)	11/40	2/40		7.21 [1.48, 35.07]
2 Induction with intravenous agents				
Chan 1996	8/29	5/31		1.98 [0.56, 6.96]
Geng 2017 (2)	3/50	9/100		0.65 [0.17, 2.50]
Jellish 2003	28/30	26/29		1.62 [0.25, 10.45]
Longas 2004 (3)	15/20	33/40		0.64 [0.17, 2.33]
Luntz 2004	17/32	33/64		1.06 [0.46, 2.49]
Micha 2016	0/36	0/37		Not estimable

(1) combined TIVA groups vs combined inhalational maintenance groups

(2) combined data for isoflurane and sevoflurane groups

(3) hypotension defined as MAP < 30% baseline. Data also available for hypotension requiring vasopressors

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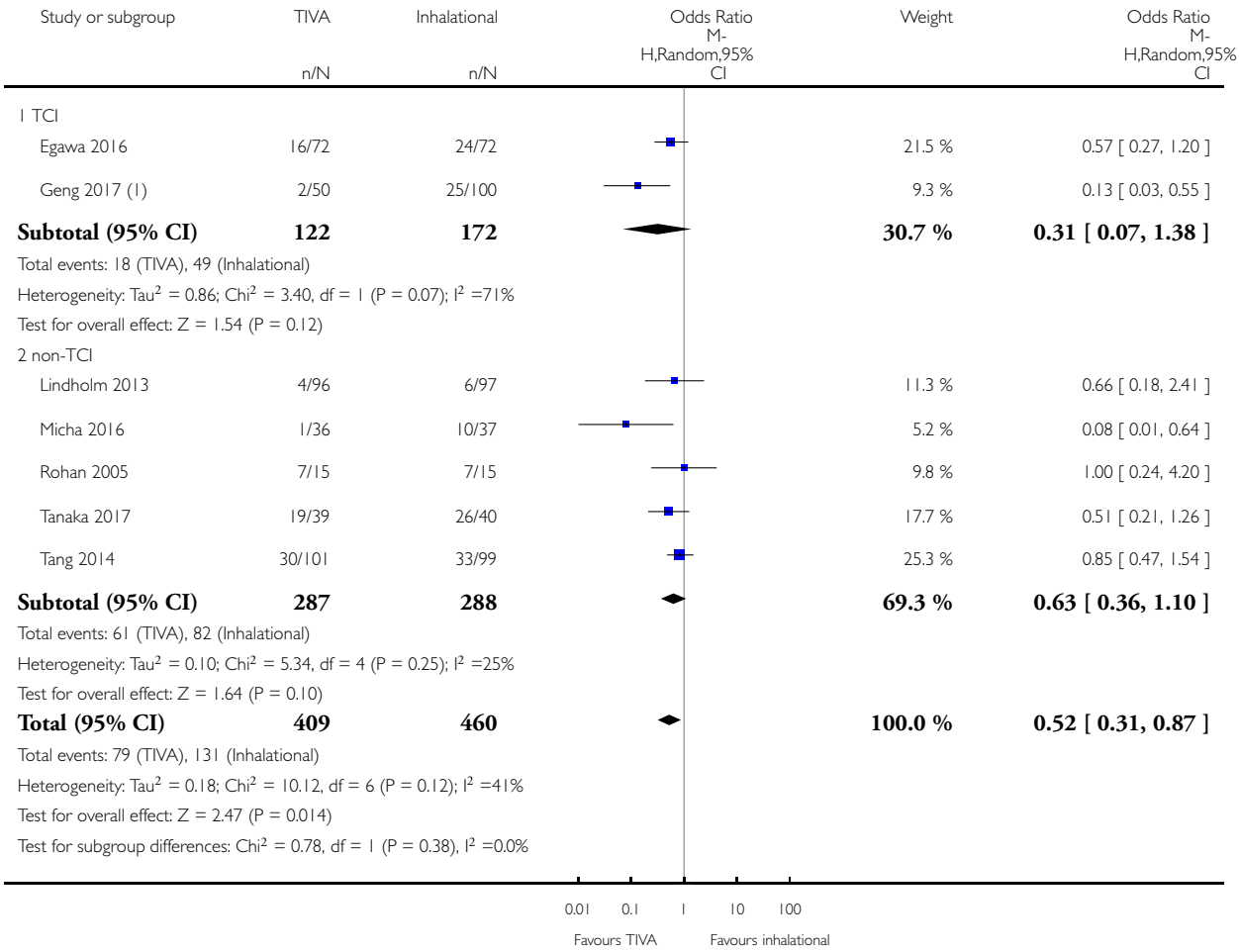
Analysis 2.5. Comparison 2 TIVA vs inhalational maintenance: subgroup analysis (induction agents; and TCI vs non-TCI), Outcome 5 Postoperative cognitive dysfunction (TCI vs non-TCI).

Review: Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery

Comparison: 2 TIVA vs inhalational maintenance: subgroup analysis (induction agents; and TCI vs non-TCI)

Outcome: 5 Postoperative cognitive dysfunction (TCI vs non-TCI)



(1) Combined data for isoflurane and sevoflurane groups

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Analysis 2.6. Comparison 2 TIVA vs inhalational maintenance: subgroup analysis (induction agents; and TCI vs non-TCI), Outcome 6 Intraoperative hypotension (TCI vs non-TCI).

Review: Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery

Comparison: 2 TIVA vs inhalational maintenance: subgroup analysis (induction agents; and TCI vs non-TCI)

Outcome: 6 Intraoperative hypotension (TCI vs non-TCI)

Study or subgroup	TIVA n/N	Inhalational n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
1 TCI				
Biboulet 2012	14/14	11/14		8.83 [0.41, 188.73]
Geng 2017 (1)	3/50	9/100		0.65 [0.17, 2.50]
Nishikawa 2004	1/25	3/25		0.31 [0.03, 3.16]
Zhang 2015 (2)	11/40	2/40		7.21 [1.48, 35.07]
2 non-TCI				
Chan 1996	8/29	5/31		1.98 [0.56, 6.96]
Jellish 2003	28/30	26/29		1.62 [0.25, 10.45]
Longas 2004 (3)	15/20	33/40		0.64 [0.17, 2.33]
Luntz 2004	17/32	33/64		1.06 [0.46, 2.49]
Micha 2016	0/36	0/37		Not estimable
Tang 2014	26/101	35/99		0.63 [0.35, 1.16]
Trembach 2012	26/45	9/44		5.32 [2.08, 13.64]

(1) combined data for isoflurane and sevoflurane groups

(2) combined TIVA groups vs combined inhalational maintenance groups

(3) hypotension defined as MAP < 30% baseline. Data also available for hypotension requiring vasopressors

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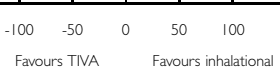
Analysis 2.7. Comparison 2 TIVA vs inhalational maintenance: subgroup analysis (induction agents; and TCI vs non-TCI), Outcome 7 Length of stay in the PACU (TCI vs non-TCI).

Review: Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery

Comparison: 2 TIVA vs inhalational maintenance: subgroup analysis (induction agents; and TCI vs non-TCI)

Outcome: 7 Length of stay in the PACU (TCI vs non-TCI)

Study or subgroup	TIVA		Inhalational		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
1 TCI						
Demeere 2006	19	53.8 (60.6)	18	44.3 (47.1)		9.50 [-25.37, 44.37]
Kim 2015a	30	42 (7.3)	28	42.1 (6.7)		-0.10 [-3.70, 3.50]
2 non-TCI						
Celik 2011	50	20.4 (2.7)	50	24.2 (3.8)		-3.80 [-5.09, -2.51]
Chan 1996	29	116.4 (28)	31	131.6 (44)		-15.20 [-33.74, 3.34]
Epple 2001	62	77.3 (31)	62	93.9 (47.6)		-16.60 [-30.74, -2.46]
Jellish 2003	30	79.1 (8.4)	29	63.2 (6.8)		15.90 [12.01, 19.79]
Juvin 1997	14	213 (87)	15	252 (71)		-39.00 [-97.03, 19.03]



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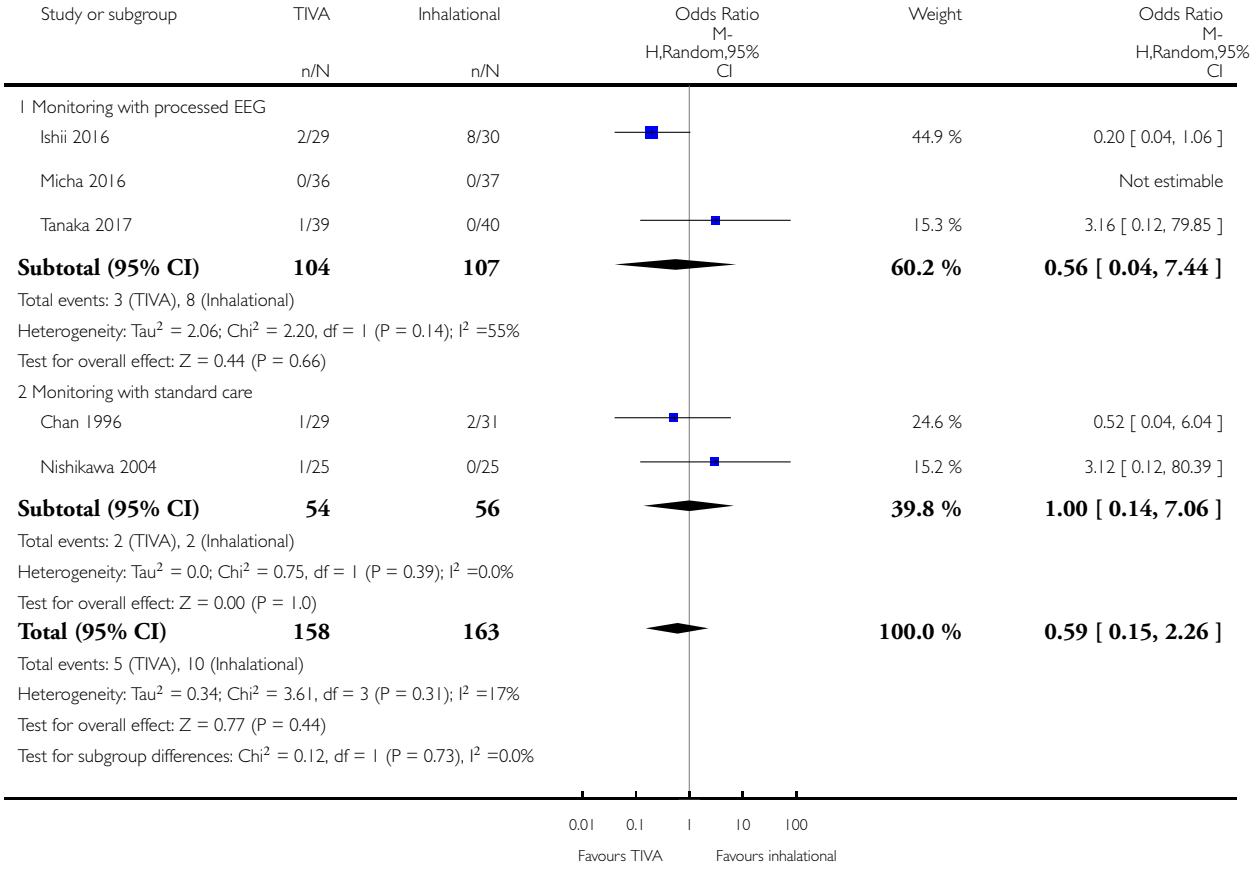
Analysis 3.1. Comparison 3 TIVA vs inhalational maintenance: subgroup analysis, monitoring with processed EEG vs standard care, Outcome 1 Postoperative delirium.

Review: Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery

Comparison: 3 TIVA vs inhalational maintenance: subgroup analysis, monitoring with processed EEG vs standard care

Outcome: 1 Postoperative delirium



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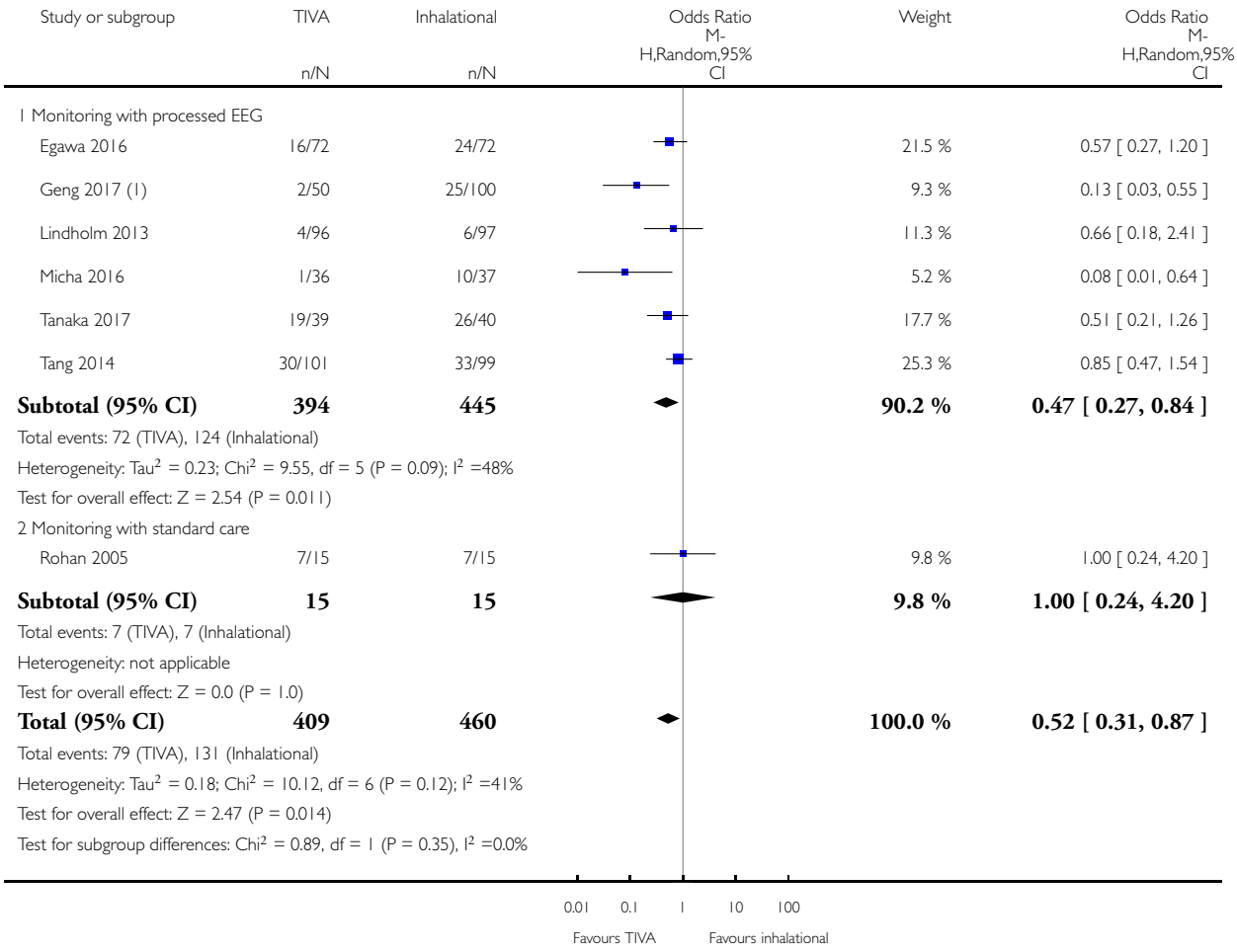
Analysis 3.2. Comparison 3 TIVA vs inhalational maintenance: subgroup analysis, monitoring with processed EEG vs standard care, Outcome 2 Postoperative cognitive dysfunction.

Review: Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery

Comparison: 3 TIVA vs inhalational maintenance: subgroup analysis, monitoring with processed EEG vs standard care

Outcome: 2 Postoperative cognitive dysfunction



(1) Combined data for isoflurane and sevoflurane groups

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Analysis 3.3. Comparison 3 TIVA vs inhalational maintenance: subgroup analysis, monitoring with processed EEG vs standard care, Outcome 3 Intraoperative hypotension.

Review: Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery

Comparison: 3 TIVA vs inhalational maintenance: subgroup analysis, monitoring with processed EEG vs standard care

Outcome: 3 Intraoperative hypotension

Study or subgroup	TIVA n/N	Inhalational n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
1 Monitoring with processed EEG				
Biboulet 2012	14/14	11/14		8.83 [0.41, 188.73]
Geng 2017 (1)	3/50	9/100		0.65 [0.17, 2.50]
Longas 2004 (2)	15/20	33/40		0.64 [0.17, 2.33]
Micha 2016	0/36	0/37		Not estimable
Tang 2014	26/101	35/99		0.63 [0.35, 1.16]
Zhang 2015 (3)	11/40	2/40		7.21 [1.48, 35.07]
2 Monitoring with standard care				
Chan 1996	8/29	5/31		1.98 [0.56, 6.96]
Jellish 2003	28/30	26/29		1.62 [0.25, 10.45]
Luntz 2004	17/32	33/64		1.06 [0.46, 2.49]
Nishikawa 2004	1/25	3/25		0.31 [0.03, 3.16]
Trembach 2012	26/45	9/44		5.32 [2.08, 13.64]

(1) combined data for isoflurane and sevoflurane groups

(2) hypotension defined as MAP < 30% baseline. Data also available for hypotension requiring vasopressors

(3) combined TIVA groups vs combined inhalational maintenance groups

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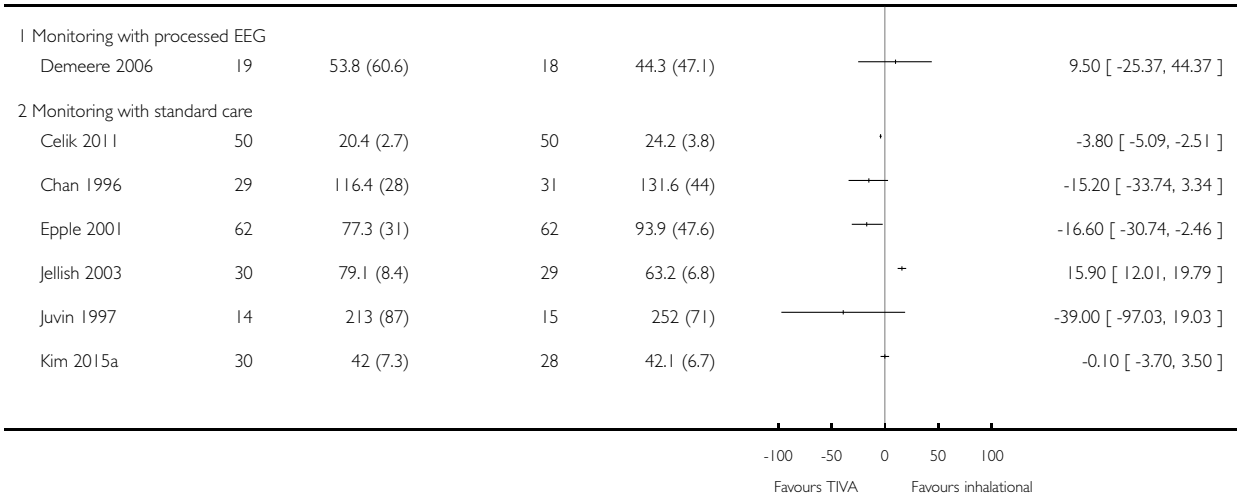
Analysis 3.4. Comparison 3 TIVA vs inhalational maintenance: subgroup analysis, monitoring with processed EEG vs standard care, Outcome 4 Length of stay in PACU.

Review: Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery

Comparison: 3 TIVA vs inhalational maintenance: subgroup analysis, monitoring with processed EEG vs standard care

Outcome: 4 Length of stay in PACU

Study or subgroup	TIVA N	Mean(SD)	Inhalational N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Monitoring with processed EEG						
Demeere 2006	19	53.8 (60.6)	18	44.3 (47.1)		9.50 [-25.37, 44.37]
2 Monitoring with standard care						
Celik 2011	50	20.4 (2.7)	50	24.2 (3.8)		-3.80 [-5.09, -2.51]
Chan 1996	29	116.4 (28)	31	131.6 (44)		-15.20 [-33.74, 3.34]
Epple 2001	62	77.3 (31)	62	93.9 (47.6)		-16.60 [-30.74, -2.46]
Jellish 2003	30	79.1 (8.4)	29	63.2 (6.8)		15.90 [12.01, 19.79]
Juvin 1997	14	213 (87)	15	252 (71)		-39.00 [-97.03, 19.03]
Kim 2015a	30	42 (7.3)	28	42.1 (6.7)		-0.10 [-3.70, 3.50]



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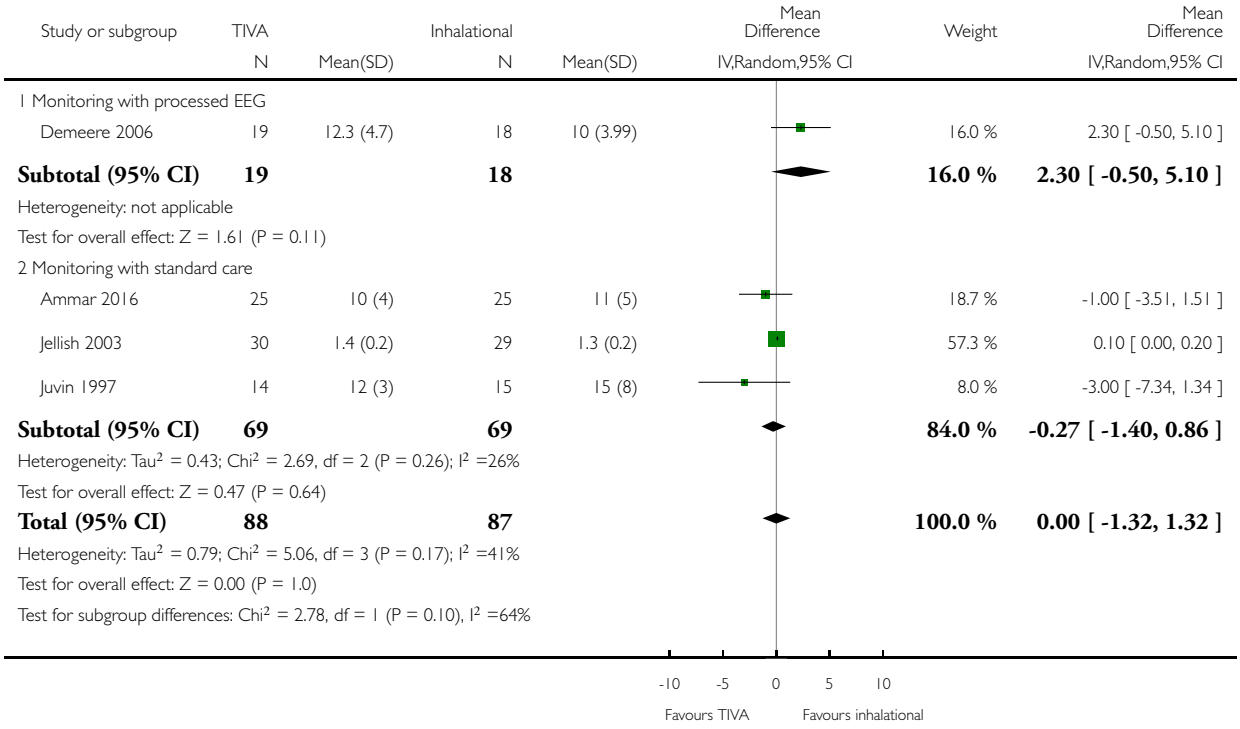
Analysis 3.5. Comparison 3 TIVA vs inhalational maintenance: subgroup analysis, monitoring with processed EEG vs standard care, Outcome 5 Length of hospital stay.

Review: Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery

Comparison: 3 TIVA vs inhalational maintenance: subgroup analysis, monitoring with processed EEG vs standard care

Outcome: 5 Length of hospital stay



ADDITIONAL TABLES

Table 1. Study data reported in different formats

Outcome: postoperative cognitive dysfunction			
Study	**Measurement**	**Data* TIVA group**	**Data* Inhalational maintenance group**
Gursoy 2015	Using MMT (higher scores indicate improved cognitive function); 24 hours	Mean (SD): 24.5 (± 2.4); n = 30	Mean (SD): 23.7 (± 3.1); n = 30

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Table 1. Study data reported in different formats (*Continued*)

Moffat 1995	Using MMSE (higher scores indicate improved cognitive function); 2 hours	Mean (range): 28 (25 to 30); n = 20	Mean (range): 27 (25 to 30); n = 20
Tan 2009	Using MMSE (higher scores indicate improved cognitive function); 24 hours	Mean (SD): 26.2 (± 2.9); n = 30	Mean (SD): 25.8 (± 3.7); n = 30
Outcome: intraoperative hypotension			
Study	**Measurement**	**Data* TIVA group**	**Data* Inhalational maintenance group**
Lindholm 2013	Episodes lasting > 2 minutes	Median (25 to 75% percentiles) : 4 (2 to 6)	Median (25 to 75% percentiles) : 5 (2 to 6)
Outcome: length of hospital stay			
Study	**Measurement**	**Data* TIVA group**	**Data* Inhalational maintenance group**
Lindholm 2013	Number of days	Median (25 to 75% percentiles) : 9 (8 to 12) days; n = 96	Median (25 to 75% percentiles) : 9 (8 to 12) days; n = 97
Tylman 2011	Number of days	Median (25 to 75% percentiles) : 8 (6 to 12) days; n = 25	Median (25 to 75% percentiles) : 8 (6 to 10) days; n = 21

*data as reported by study authors;
n: number of analysed participants
MMSE: mini-mental state examination
MMT: mini-mental test
SD: standard deviation
TIVA: total intravenous anaesthesia

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APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Anesthesia, Intravenous] explode all trees
#2 MeSH descriptor: [Anesthesia, Inhalation] explode all trees
#3 MeSH descriptor: [Anesthetics, Inhalation] explode all trees
#4 MeSH descriptor: [Anesthetics, Intravenous] explode all trees
#5(an?esthe* near/2 (iv or intravenous or inhalation* or volatile)) or (TIVA or propofol or halothane or enflurane or isoflurane or desflurane)
#6 #1 or #2 or #3 or #4 or #5
#7 MeSH descriptor: [Geriatrics] explode all trees
#8 MeSH descriptor: [Aged] explode all trees
#9 (Geriatric* or Elder* or old-age or pensioner*) or ((aging or aged or elderly or senior or old) near/2 (wom?n or m?n or lady or ladies or adult* or citizen* or population* or people or person))
#10 #7 or #8 or #9
#11 #6 and #10

Appendix 2. MEDLINE (Ovid) 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

Appendix 3. Embase (Ovid) search strategy

1. intravenous anesthesia/ or inhalation anesthesia.mp. 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. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
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. aged/ or geriatrics/
5. 2 or 3 or 4
6. 1 and 5
7. ((crossover procedure or double blind procedure or single blind procedure).sh. or (crossover* or cross over*).ti,ab. or placebo*.ti,ab,sh. or (doubl* adj blind*).ti,ab. or (controlled adj3 (study or design or trial)).ti,ab. or allocat*.ti,ab. or trial*.ti,ab. or randomized controlled trial.sh. or random*.ti,ab.) not ((exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.))
8. 6 and 7

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Appendix 4. PsycINFO (EBSCO) search strategy

S1 MM "Anesthesiology"
S2 ((an?esthe* N2 (iv or intravenous or inhalation* or volatile))
S3 TIVA or propofol or halothane or enflurane or isoflurane or desflurane
S4 S1 OR S2 OR S3
S5 MM "Geriatrics"
S6 Geriatric* or Elder* or old-age or pensioner*
S7 ((aging or aged or elderly or senior or old) N2 (wom?n or m?n or lady or ladies or adult* or citizen* or population* or people or person))
S8 S5 OR S6 OR S7
S9 ((MM "Randomized Controlled Trials") OR (MM "Random Assignment") OR (MH "Clinical Trials") OR (MH "Placebos")) OR (random* or (trial* and (clinical or controlled)) or multicenter or prospective)
S10 S4 AND S8 AND S9

WHAT'S NEW

Last assessed as up-to-date: 20 November 2017.

Date	Event	Description
4 October 2018	Amended	Acknowledgement section amended to include Sign-off Editor

CONTRIBUTIONS OF AUTHORS

David Miller (DM), Sharon R Lewis (SRL), Michael W Pritchard (MP), Oliver Schofield-Robinson (OSR), Cliff Shelton (CS), Phil Alderson (PA), Andrew F Smith (AS)

Conceiving the review: SRL, PA, AS

Writing the protocol: CS, DM, SRL

Co-ordinating the review: SRL

Undertaking manual searches: SRL, OSR, MP

Screening search results: DM, SRL, OSR, MP

Organizing retrieval of papers: SRL, OSR

Screening retrieved papers against inclusion criteria: DM, SRL, OSR, MP

Appraising quality of papers: DM, SRL, OSR, MP

Extracting data from papers: DM, SRL, OSR, MP

Data management for the review: SRL

Entering data into Review Manager (Review Manager 2014): SRL, MP

RevMan statistical data: SRL

Interpretation of data: SRL, DM

Statistical inferences: SRL

Writing the review: SRL, MP, DM, CS, PA, AS

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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

DECLARATIONS OF INTEREST

David Miller: Funded Health Education England internship for the clinical academic programme. This was a six month part time funded post, 30 days in total, to allow an introduction into all aspects and roles across clinical academic research. The internship is designed to provide dedicated time to gain an understanding of the world of health research (Sources of support)

Cliff Shelton has received an NIHR award (DRF-2015-08-208) to fund a qualitative research project investigating anaesthesia for hip fracture surgery as part of his doctoral research fellowship at Lancaster University

Sharon R Lewis see Sources of support

Michael Pritchard: see Sources of support

Oliver Schofield-Robinson see Sources of support.

Phil Alderson: work on this review is funded, in part, by a UK NIHR Cochrane programme grant for the preparation of reviews relevant to recovery from critical illness (Sources of support)

Andrew F Smith: see Sources of support

See Sources of support

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NIHR Cochrane Collaboration Programme Grant, UK. 'Back to normal': speed and quality of recovery after surgery, major injury and critical care. Project ref. 13/89/16, UK.
- NIHR/HEE Integrated academic programme internship, UK.

North West, North East and Yorkshire and the Humber internship programme

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes to the published protocol (Miller 2016).

1. Authors: we added additional authors during the review, Michael W Pritchard and Oliver J Schofield Robinson.

2. Title: we edited it to make it clear that our inclusion criteria was 'non cardiac' surgery.

3. Objectives: we edited the wording of our review objective to reflect our intention at protocol to only include interventions that were propofol-based TIVA.

4. Inclusion criteria: we excluded studies in which the inclusion criteria specified a participant age range of 18 to 65 years because we believed these studies were not aiming to specifically recruit elderly patients; we found that these studies had a mean age for participants of < 60 years and therefore this decision did not affect choice of included studies. We found a large number of studies that compared intravenous versus inhalational anaesthetic agents, but only measured outcomes which were outside the scope of this

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review, e.g. biochemical parameters. We therefore added an exclusion criteria to the review: to exclude studies that did not measure our review outcomes. We reported these studies in Characteristics of excluded studies.

5. In the protocol, we stated that our final choice of fixed-effect or random-effects statistical model was influenced by the level of identified heterogeneity and the number of studies. We selected to use a random-effects statistical model; this decision was made because a random-effects model is more appropriate for analysis of studies in which differences (for example, in types of surgery) were most likely.

6. Dealing with missing data: we did not contact authors to request missing data (except for in Tanaka 2017). In the case that study participants were lost at follow-up, we included data as analysed by study authors. We did not impute missing values with replacement values. In the case of missing statistics, we did not impute missing values with replacement values. We reported data in the format presented by study authors, and if it was in a format that was not comparable to other data that could be pooled (e.g. median values), we reported these data separately in additional tables. We found high statistical heterogeneity in included studies and noted inconsistencies in visual inspection of results; imputing appropriate values was not appropriate because of heterogeneity. We used sensitivity analysis to explore the effect of including studies in which attrition was high and unbalanced between groups.

7. 'Summary of findings' table and GRADE: only one review author used GRADEpro software to create a 'Summary of findings' table. This was checked and approved by a second review author.

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