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Regional versus general anaesthesia for improved cognitive function after procedures other than cardiac surgery or neurosurgery in adult and paediatric patients

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Abstract

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

The objective of this review is to compare the effects of regional versus general anaesthesia on cognitive function after procedures other than cardiac surgery or neurosurgery in adult and in paediatric patients.

BACKGROUND

Description of the condition

Cognitive function refers to a range of high-level brain functions including perception, memory, thinking and capacity for judgement (Kirshner 2004). Postoperative cognitive dysfunction (POCD) is defined as 'deterioration of intellectual function presenting as impaired memory or concentration' that occurs in the postoperative period (Rasmussen 2001). This complication occurs commonly after cardiac, and also after non-cardiac, surgery. The consequences of POCD are far-reaching and alter the quality of life of both patients and families by reducing physical, psychological and social functioning (Hogue 2008). Among children, potential impairment of subsequent postoperative cognitive development is a matter of concern (DiMaggio 2009). The etiology of POCD is multi-

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factorial and includes drug effects, pain, preoperative neurocognitive status and metabolic disturbances (Cully 2007; Hanning 2005). The elderly are especially at risk of POCD, and evidence suggests that infants and young children may also be vulnerable to cognitive dysfunction after general anaesthesia (Wilder 2009; Williams-Russo 1995).

It is important to differentiate POCD from delirium. Postoperative delirium is an acute, temporary confusional state that may occur shortly after surgery (within hours to days) and typically follows a short-lived course. Postoperative cognitive dysfunction occurs as a long-term decrease in mental abilities that persists long after surgery (Newman 2007). Strictly speaking, POCD can be diagnosed only when a decrement in neurocognitive function is noted in a comparison of postoperative and preoperative testing (Kirshner 2004).

Cognitive impairment after surgery has been reported for over a century, especially among the elderly. Concern about cognitive development in children has flared up more recently (Ing 2012). Concern about this problem is increasing, particularly among patients and relatives who are affected by POCD. Several studies have investigated preventive strategies for use against POCD (Rasmussen 2006). However, we are still a long way from reaching a satisfactory solution. An international study on postoperative cognitive dysfunction (ISPOCD) revealed that 25% of elderly patients developed cognitive impairment one week after surgery and use of a general anaesthetic (Moller 1998). Moreover, nearly 10% of patients still had a decline in cognitive function three months postoperatively (Moller 1998). Contributing factors to POCD include advanced age, higher American Society of Anesthesiologists (ASA) physical status, more complicated surgery and longer hospital stay (Monk 2008).

Description of the intervention

Regional anaesthesia (RA) uses local anaesthetics to block nerve conduction in only a part of the body and may be accomplished with or without sedation.

How the intervention might work

Regional anaesthesia may prevent postoperative cognitive dysfunction in three ways.

1. Regional anaesthesia may provide superior analgesia, thus reducing the interference of pain with cognition.
2. Regional anaesthesia may decrease the use of certain medications including opioid analgesics, sedatives and anaesthetic agents, all of which may lead to POCD.
3. Regional anaesthesia may blunt inflammatory and stress responses after surgery; this is associated with POCD.

A wealth of basic science studies in rodent models have demonstrated that when anaesthetic and sedative agents are administered to rodents during synaptogenesis or rapid brain growth, widespread neuronal apoptosis, neurodegeneration and changes in neuronal growth and cell structure ensue (Jevtovic-Todorovic 2003; Rappaport 2015). Behavioural studies of these rodents have shown learning and behavioural abnormalities in adulthood. Studies done in non-human primates, although limited, also demonstrate widespread neurodegeneration and

neuronal death when commonly used anaesthetics are administered during vulnerable periods of rapid brain growth (Slikker 2007). Although robust, the clinical applicability of these animal studies to humans remains unclear (Loepke 2008). Retrospective observational studies performing secondary analyses on pre-existing data have found variable associations between clinical anaesthetic exposure and cognitive dysfunction in infants and young children, but no synthesis of evidence from prospective, randomized trials is available to date (Sinner 2014).

Why it is important to do this review

Regional anaesthesia avoids exposure to drugs that affect the central nervous system and blunts inflammatory and stress responses, either or both of which may be expected to decrease the incidence of POCD. Some randomized controlled trials (RCTs) have suggested that regional anaesthesia improves postoperative cognitive function, and others have found no statistically significant effect or were underpowered (Anwer 2006; Rasmussen 2003; Williams-Russo 1995). Research on cognitive outcomes in children has intensified recently, but we are not aware of any completed randomized trials to date (Ramsay 2012). Most reviews on impaired cognitive development after anaesthesia in children are based on retrospective data and animal studies (Ing 2012).

Neither long-term effects of general anaesthetic drugs on specific components of cognition nor long-term cognitive effects of intra-operative haemodynamic fluctuations and consequent changes in cerebral perfusion have been studied to date. These aspects of general anaesthesia may also contribute to POCD. Avoiding these two situations, by avoiding general anaesthesia and by subjecting the patient to regional anaesthesia when feasible, may prevent POCD.

However, we plan to focus on the hypothesis that regional anaesthesia might attenuate the inflammatory stress response, improve pain control or reduce administration of opioids and other adjuvant sedative medications intraoperatively and postoperatively, thereby reducing the risk of POCD.

We hypothesize that general anaesthesia is more often associated with POCD than is regional anaesthesia. A larger number of studies have been conducted in adults, but outcomes and methods vary, and conclusions remain uncertain. A definitive answer to this question would assist anaesthesia providers in advising patients on the best choice of anaesthetic technique and may prove helpful to patients and their families.

OBJECTIVES

The objective of this review is to compare the effects of regional versus general anaesthesia on cognitive function after procedures other than cardiac surgery or neurosurgery in adult and in paediatric patients.

METHODS

Criteria for considering studies for this review

Types of studies—We will include published and unpublished randomized controlled trials (RCTs) that investigate the effects of regional anaesthesia on postoperative cognitive dysfunction (POCD).

Types of participants—We will include adult and paediatric participants receiving general or regional anaesthesia for any procedures other than cardiac or carotid procedures or neurosurgery. We will exclude these procedures because they can by themselves affect cognitive function (Bo 2005; Gao 2005; Newman 2001).

We will include children from 29 days to 21 years of age, thus excluding neonates, as testing modalities are very different from those used in older children, and because a review focusing on this topic has already been conducted under the umbrella of the Cochrane Neonatal Group (Jones 2015).

We will also exclude studies including participants with pre-existing neurological disorders, for example, seizure or stroke.

We will analyse studies on the paediatric population separately from those investigating adults.

Types of interventions—We will include studies that compare regional anaesthesia versus a non-regional anaesthesia alternative, given intraoperatively or postoperatively. We will include studies comparing general anaesthesia versus general anaesthesia plus regional anaesthesia. We will include all types of regional or local anaesthesia, and we define regional anaesthesia as any technique that uses local anaesthetics or similar agents to achieve a conduction block centrally, peripherally or locally.

We will apply the following specific exclusion criteria.

1. Studies examining carotid, cardiac or neurosurgical procedures.
2. Studies including patients with pre-existing neurological disorders.
3. Cross-over studies.

Types of outcome measures

Primary outcomes: Our primary outcome is postoperative cognitive dysfunction. We will accept any report of postoperative cognitive decline after surgery as assessed using preoperative and postoperative neuropsychological assessments and when an outcome is defined as POCD or no POCD. We will accept only reports in which postoperative measurement of cognitive function was performed at least seven days after surgery to eliminate the effects of anaesthesia and to avoid confusion with postoperative delirium. We will also include longer periods of follow-up.

We will collapse adjacent time periods, for example, we will pool together data from separate studies at four, five, six and seven weeks, or data at three and four months.

Secondary outcomes

1. If outcome data employing specific tests of cognitive function are sufficient, we will use these secondary outcomes (the various dimensions of cognition that can be tested, such as attention, perception, language, memory, reasoning and motor skills) and will attempt an evidence synthesis.
2. We will record any adverse effects of therapy reported in the included studies.
3. We will record any other reported *cognitive* outcomes, ranging from mild cognitive impairment to postoperative (but not emergence) delirium. Hence, we define postoperative delirium in accordance with Deiner and Silverstein, and we will use the tests described in their review (Deiner 2009), including the Confusion Assessment Method (CAM), the Delirium Rating Scale Revised-98 and the Delirium Symptom Interview and NEECHAM Confusion Scale, as well as the Estimation of Physiologic Ability and Surgical Stress (E-PASS). For mild cognitive impairment, we will employ similar outcome measures as for the primary outcome. As a secondary analysis, we will investigate the influence of pain on cognitive function using individual patient data meta-analysis.

Search methods for identification of studies

Electronic searches—We will search the Cochrane Central Register of Controlled Trials (CENTRAL) (current issue); MEDLINE & MEDLINE In Process & Non-indexed Citations (Ovid) (1950 to present); EMBASE (Ovid) (1980 to present); the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EbscoHost) (1982 to present); and PsycINFO (Ovid) (from 1806 to present). We will revise the search strategy and will use a combination of controlled vocabulary and free text searches adapted for each database (CENTRAL: Appendix 1; MEDLINE: Appendix 2; EMBASE: Appendix 3; CINAHL: Appendix 4; PsycINFO: Appendix 5).

We will combine MEDLINE and EMBASE search strategies with the Cochrane highly sensitive search strategy phases one and two, as provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will not impose a language restriction.

Searching other resources—We will handsearch reference lists of identified published trials, reference lists of other relevant articles and abstracts of relevant conference proceedings to identify additional clinical trials. We will contact relevant trial authors to identify additional studies and will search the following clinical trial registries for relevant ongoing trials.

1. International Standard Randomized Controlled Trial Number (ISRCTN) Registry (www.controlled-trials.com).
2. ClinicalTrials.gov (clinicaltrials.gov).
3. Clinical Trials and Medical Research – Clinical trials – NHS Choices (<http://www.nhs.uk/Conditions/Clinical-trials/Pages/clinical-trial.aspx>).

Data collection and analysis

Selection of studies—Three review authors (AA, SS, JC) will independently scan the titles and abstracts of reports retrieved by electronic searching and by handsearching. We will select trials for inclusion using a checklist designed in advance for that purpose. A third review author (MHA) will settle disagreements.

Data extraction and management—Three review authors (AA, SS, JC) will independently extract data using a data extraction form designed for this review (Appendix 6), amended to work with the online systematic review Software DestillerSR®. This may lead to a slightly revised electronic data extraction form, specifically documenting additional details on the precise intervention and control provided. Extracted data will include information regarding participants, interventions, outcomes and study quality. We will resolve disagreements by discussion with the fourth review author (MHA). Data extracted will include the following: study eligibility, participant characteristics, methodological criteria, inclusion and exclusion criteria, trial setting, neurocognitive test used, criteria used to diagnose POCD, all relevant outcome measures and length of follow-up.

Assessment of risk of bias in included studies—Three review authors (AA, SS, JC) will independently assess and document the quality of each included trial using the 'Risk of bias' tables provided in RevMan 5. Specifically, we will consider the following criteria (Higgins 2011).

1. Adequacy of random sequence generation.
2. Adequacy of allocation concealment.
3. Completeness of follow-up and handling of incomplete outcome data.
4. Blinding of participants and of care providers (including surgeons, nurses and the anaesthetist performing regional anaesthesia block, as well as the person administering cognitive tests).
5. Validity, reliability, objectivity of outcome measurement.
6. Evidence of conflicts of interest or undue sponsor influence.

We will categorize each item as having unclear, low or high risk of bias and will cite the reasons for our judgement based on extracted data.

We will settle differences with assistance of a third review author (MHA) and will seek further information from study authors when possible.

Measures of treatment effect—We will use the standardized mean difference (SMD) as a summary statistic because assessment of the outcome measure will be based on a variety of scoring systems. Our primary effect measure will be global change, but when this is not reported nor measured, we will consider converting the reported score or domain into the global change score. We will reconsider our summary statistic after we complete study selection but before we extract data, in other words, when we know which scores were used but are still blinded to study results.

Unit of analysis issues—We will check for duplicate publications and will count only once studies described in separate reports. We will include in our analysis any trial in which individual participants are randomly allocated to therapy. If we encounter any trials in which randomization has been achieved on any other basis (e.g. groups of participants randomized together), we will discuss these results separately. If individuals are subjected to repeated measurements over time, we will analyse each time period separately with no individual included more than once in any individual analysis. As a secondary analysis, we will consider analysing all longitudinal data in one coherent model to investigate, for example, change points after which effects of regional anaesthesia are diminished.

We will exclude cross-over studies, which are unlikely to be found in this search.

Dealing with missing data—We will base quantitative analyses of outcomes on intention-to-treat (ITT) analysis, if possible. If most study authors report only a per-protocol analysis, we will report our evidence synthesis accordingly, while emphasizing this methodological shortcoming in the discussion. For studies in which trial authors have used ITT analysis by imputing data for missing cases (such as the last observation carried forward method or assumed no changes), we will contact study authors for available case analysis or individual patient data. If correspondence with the principal investigator(s) is unsuccessful, depending on the case, we might exclude the trial from the pooled analysis, or we might include it while performing a sensitivity analysis to determine study quality. We will evaluate the effect of missing data on the estimate of effect by performing sensitivity analysis.

We will contact study authors and will ask them for individual patient data (IPD) when published aggregate data are insufficient for evidence synthesis. If too many studies report data in disparate ways that make traditional meta-analysis difficult, we will consider an IPD meta-analysis.

Assessment of heterogeneity—We will address clinical heterogeneity, when relevant, by:

1. analysing separately paediatric and adult patients;
2. analysing separately studies comparing regional alone versus general alone, and studies comparing a combination of regional and general anaesthesia versus general anaesthesia alone; and
3. performing subgroup analyses as described below (subgroup analysis and investigation of heterogeneity).

We will use the Q statistic to test statistical heterogeneity between trials. We will use the I^2 statistic to assess the proportion of variability between trials that is due to heterogeneity rather than to chance, and we will accept $I^2 > 50\%$ as an indication of important heterogeneity (Higgins 2002). We will explore and discuss reasons for observed heterogeneity.

We will use the random-effects model regardless of the result of our investigation of between-study heterogeneity.

Assessment of reporting biases—We will address publication bias by using a funnel plot to identify signs of asymmetry, if the number of studies is sufficient (more than 10) to make use of a funnel plot or Egger's test meaningful.

Data synthesis—For continuous outcomes, we will use mean differences (MDs), and when outcomes are measured on different scales, we will calculate standardized mean differences (SMDs). For binary data, we will use odds ratios (ORs) and 95% confidence intervals (95% CIs), and we will calculate the number needed to treat for an additional beneficial outcome (NNTB) by using the statistical software environment R (R 2015). We will use the random-effects model to account for diversity of settings and cognitive outcome assessment instruments. We will extract data by performing an ITT analysis and will use the Cochrane statistical software Review Manager (RevMan 5.3), presenting results in a 'Summary of findings' table.

We found in previous systematic reviews and meta-analyses (Andreae 2012; Andreae 2015; Carter 2015) that studies that are otherwise homogeneous enough to justify their synthesis may report their outcome of interest slightly differently, which may preclude simple data synthesis with RevMan (RevMan 5.3) (e.g. reporting pain outcomes as continuous outcomes in one study, but as dichotomous outcomes in another). If outcome reporting is too disparate and varied for pooling of aggregated data in a classic meta-analysis using RevMan (RevMan 5.3), we will consider alternative statistical approaches, including IPD meta-analysis (Stewart 2011) and Bayesian evidence synthesis (Carter 2015; Sutton 2000), or a combination thereof (Andreae 2015; Young 2008). In particular, we may estimate the SMD from dichotomous published data or outcomes in different cognitive domains when relevant data are not available from primary study authors and will feed these study level estimates into a comprehensive hierarchical model to estimate the overall pooled effect, for example, in the update of Andreae 2012, as often, study authors were not able to provide individual data for all studies, precluding a meta-analysis based only on IPD from all studies. Hence we will also build a single coherent hierarchical Bayesian model in which we have pooled IPD (study A), dichotomous aggregate data (studies B and C) and continuous aggregate data (studies D, E and F) and compared the results by performing a classical analysis.

Subgroup analysis and investigation of heterogeneity—We are deciding a priori to stratify the analysis into broad surgical categories, such as major joint surgery, thoracic surgery, abdominal surgery, gynaecological surgery and limb amputation, as between these subgroups, populations and co-morbidities are likely clinically significantly different. When we find evidence of significant clinical or statistical heterogeneity (as evidenced by $I^2 > 50\%$

or by clinical differences between populations included in the various studies to be pooled), we will consider subgroup analyses based on the following.

1. Age (children from 29 days to one year, children from one year to 18 years, adults 18 to 75 years, elderly participants (> 75 years)).
2. ASA physical status (1 and 2; 3, 4 and 5).
3. Type of surgery (emergency or elective).
4. Site of surgery (extremities, chest, abdomen, etc.).
5. Duration of surgery (more than or less than two hours).
6. Different agents used (sedation medication or different volatile anaesthetic agents employed).
7. Duration of regional block (single-shot vs perioperative extended nociceptive blockade).

We will include children from 29 days to 21 years of age, thus excluding neonates, for the reasons detailed in the Types of participants section. If we find a sufficient number of studies, we may decide to analyse data as stratified in subgroups by age group or may perform a sensitivity analysis that excludes older or younger children to test for changes in effect measures related to age. We may decide to do a meta-regression to investigate the relation of age and effect (e.g. by ordering included RCTs in the forest plot according to the median age of included research participants).

Sensitivity analysis—If appropriate, we will perform sensitivity analysis for missing data by using best-case, worst-case scenarios and by examining effects on the direction and magnitude of our results. We will consider sensitivity analysis based on study quality.

Summary of findings—We will employ the GRADE (Grades of Recommendation, Assessment, Development and Evaluation Working Group) approach to interpret findings (Langendam 2013) and the GRADE profiler (GRADEPRO) to import data from Review Manager 5.3 (RevMan 5.3) to create 'Summary of findings' tables. These tables will provide outcome-specific information concerning the overall quality of evidence derived from studies included in the comparison, the magnitude of effect of the interventions examined and the sum of available data on the outcomes that we considered.

1. Our primary outcome is postoperative cognitive dysfunction. We will collapse adjacent time periods, for example, we will pool together data from separate studies at four, five, six and seven weeks, or data from three and four months. If data are sufficient, we will break down the outcome into various dimensions of cognition that can be tested, such as attention, perception, language, memory, reasoning and motor skills. We will analyse adults and children separately, and if data are sufficient, we will analyse separately different paediatric age groups.
2. We will populate the 'Assumed risk' column using data from the literature for the relevant outcome in the respective age group.

3. We will use the GRADE approach to assess the quality of the body of evidence. For assessments of overall quality of evidence for each outcome that will include pooled data from RCTs only, we will downgrade the evidence from 'high quality' by one level for serious (or by two levels for very serious) study limitations (risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias).

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Internal sources

- No sources of support supplied

External sources

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Appendix 1. CENTRAL search strategy

1. anesthesia, conduction/
2. anesthesia, epidural/
3. Anesthesia, Caudal/
4. anesthesia, local/
5. anesthesia, spinal/
6. nerve block/
7. Analgesia, Epidural/
8. exp Anesthetics, Local/
9. (an?esth* adj2 (local or regional or general or conduction or epidural)).ti,ab.
10. (block* adj2 (spinal or epidural or plexus or bier)).ti,ab.
11. Ropivacaine.ti,ab.
12. Lidocaine.ti,ab.
13. Bupivacaine.ti,ab.

14. Tetracaine.ti,ab.
15. Mepivacaine.ti,ab.
16. Prilocaine.ti,ab.
17. levobupivacaine.ti,ab.
18. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. anesthesia, general/
20. anesthesia, inhalation/
21. balanced anesthesia/
22. anesthesia, intratracheal/
23. anesthesia, intravenous/
24. exp Anesthetics, Intravenous/
25. (an?esth* adj2 general).ti,ab.
26. 19 or 20 or 21 or 22 or 23 or 24 or 25
27. Postoperative Complications/
28. Delirium, Dementia, Amnestic, Cognitive Disorders/
29. Amnesia/
30. Cognition Disorders/
31. Cognition Disorders/
32. Mild Cognitive Impairment/
33. Dementia/
34. exp Aphasia, Primary Progressive/
35. exp Cognition/
36. exp Memory/
37. exp Neuropsychological Tests/
38. exp Psychomotor Performance/
39. exp Speech Disorders/
40. exp confusion/
41. exp memory disorders/
42. exp perceptual disorders/
43. exp psychomotor disorders/
44. Attention/

45. ((mental or memory or speech or concentrat* or attention) adj5 (function or dysfunction or disability or loss or deficit or effect? or impair* or outcome or flawed)).ti,ab.
46. delirium.ti,ab.
47. cogniti*.ti,ab.
48. neurocogniti*.ti,ab.
49. neuropsycholog*.ti,ab.
50. Postoperative cognitive dysfunction.ti,ab.
51. confusion.ti,ab.
52. POCD.ti,ab.
53. 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52
54. randomized controlled trial.pt.
55. controlled clinical trial.pt.
56. randomized.ab.
57. placebo.ab.
58. drug therapy.fs.
59. randomly.ab.
60. trial.ab.
61. groups.ab.
62. 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61
63. exp animals/ not humans.sh.
64. 62 not 63

Appendix 2. MEDLINE & MEDLINE In Process & Non-indexed Citations search strategy

1. anesthesia, conduction/
2. anesthesia, epidural/
3. Anesthesia, Caudal/
4. anesthesia, local/
5. anesthesia, spinal/
6. nerve block/

7. Analgesia, Epidural/
8. exp Anesthetics, Local/
9. (an?esth* adj2 (local or regional or general or conduction or epidural)).ti,ab.
10. (block* adj2 (spinal or epidural or plexus or bier)).ti,ab.
11. Ropivacaine.ti,ab.
12. Lidocaine.ti,ab.
13. Bupivacaine.ti,ab.
14. Tetracaine.ti,ab.
15. Mepivacaine.ti,ab.
16. Prilocaine.ti,ab.
17. levobupivacaine.ti,ab.
18. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. anesthesia, general/
20. anesthesia, inhalation/
21. balanced anesthesia/
22. anesthesia, intratracheal/
23. anesthesia, intravenous/
24. exp Anesthetics, Intravenous/
25. (an?esth* adj2 general).ti,ab.
26. 19 or 20 or 21 or 22 or 23 or 24 or 25
27. Postoperative Complications/
28. Delirium, Dementia, Amnestic, Cognitive Disorders/
29. Amnesia/
30. Cognition Disorders/
31. Auditory Perceptual Disorders/
32. Mild Cognitive Impairment/
33. Dementia/
34. exp Aphasia, Primary Progressive/
35. exp Cognition/
36. exp Memory/

37. exp Neuropsychological Tests/
38. exp Psychomotor Performance/
39. exp Speech Disorders/
40. exp confusion/
41. exp memory disorders/
42. exp perceptual disorders/
43. exp psychomotor disorders/
44. Attention/
45. ((mental or memory or speech or concentrat* or attention) adj5 (function or dysfunction or disability or loss or deficit or effect? or impair* or outcome or flawed)).ti,ab.
46. delirium.ti,ab.
47. cogniti*.ti,ab.
48. neurocogniti*.ti,ab.
49. neuropsycholog*.ti,ab.
50. Postoperative cognitive dysfunction.ti,ab.
51. confusion.ti,ab.
52. POCD.ti,ab.
53. 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52
54. randomized controlled trial.pt.
55. controlled clinical trial.pt.
56. randomized.ab.
57. placebo.ab.
58. drug therapy.fs.
59. randomly.ab.
60. trial.ab.
61. groups.ab.
62. 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61
63. exp animals/ not humans.sh.
64. 62 not 63
65. 18 and 26 and 53 and 64

Appendix 3. EMBASE search strategy

1. regional anesthesia/
2. epidural anesthesia/
3. caudal anesthesia/
4. local anesthesia/
5. spinal anesthesia/
6. nerve block/
7. exp Anesthetics, Local/
8. (an?esth* adj2 (local or regional or general or conduction or epidural)).ti,ab.
9. (block* adj2 (spinal or epidural or plexus or bier)).ti,ab.
10. Ropivacaine.ti,ab.
11. Lidocaine.ti,ab.
12. Bupivacaine.ti,ab.
13. Tetracaine.ti,ab.
14. Mepivacaine.ti,ab.
15. Prilocaine.ti,ab.
16. levobupivacaine.ti,ab.
17. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. general anesthesia/
19. inhalation anesthesia/
20. balanced anesthesia/
21. intravenous anesthesia/
22. exp intravenous anesthetic agent/
23. (an?esth* adj2 general).ti,ab.
24. 18 or 19 or 20 or 21 or 22 or 23
25. postoperative complication/
26. cognitive defect/
27. amnesia/
28. perception deafness/
29. mild cognitive impairment/

30. dementia/
31. exp primary progressive aphasia/
32. exp Cognition/
33. exp Memory/
34. exp Neuropsychological Test/
35. exp Psychomotor Performance/
36. exp Speech Disorder/
37. exp confusion/
38. exp memory disorder/
39. exp perceptual disorder/
40. exp psychomotor disorder/
41. Attention/
42. ((mental or memory or speech or concentrat* or attention) adj5 (function or dysfunction or disability or loss or deficit or effect? or impair* or outcome or flawed)).ti,ab.
43. delirium.ti,ab.
44. cogniti*.ti,ab.
45. neurocogniti*.ti,ab.
46. neuropsycholog*.ti,ab.
47. Postoperative cognitive dysfunction.ti,ab.
48. confusion.ti,ab.
49. POCD.ti,ab.
50. 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49
51. random\$.mp.
52. factorial\$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
53. crossover\$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
54. cross over\$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

55. cross-over\$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
56. placebo\$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
57. (doubl\$ adj blind\$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
58. (singl\$ adj blind\$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
59. assign\$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
60. allocat\$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
61. volunteer\$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
62. crossover-procedure/
63. double-blind procedure/
64. randomized controlled trial/
65. single-blind procedure/
66. 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65
67. 17 and 24 and 50 and 66

Appendix 4. CINAHL search strategy

S98 S66 AND S72 AND S97

S97 S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81 OR S82 OR S83 OR S84 OR S85 OR S86 OR S87 OR S88 OR S89 OR S90 OR S91 OR S92 OR S93 OR S94 OR S95 OR S96

S96 POCD

S95 confusion

S94 "Postoperative cognitive dysfunction"

S93 neuropsycholog*
 S92 neurocogniti*
 S91 cogniti*
 S90 delirium
 S89 ((mental OR memory OR speech OR concentrat* OR attention) N5
 (function OR dysfunction OR disability OR loss OR deficit OR effect? OR
 impair* OR outcome OR flawed))
 S88 (MH "Psychomotor Disorders+")
 S87 (MH "Perceptual Disorders+")
 S86 (MH "Memory Disorders+")
 S85 (MH "Confusion+")
 S84 (MH "Speech Disorders+")
 S83 (MH "Psychomotor Performance+")
 S82 (MH "Neuropsychological Tests")
 S81 (MH "Memory+")
 S80 (MH "Cognition+")
 S79 (MH "Aphasia")
 S78 (MH "Dementia")
 S77 (MH "Auditory Perceptual Disorders")
 S76 (MH "Cognition Disorders")
 S75 (MH "Amnesia")
 S74 (MH "Delirium, Dementia, Amnestic, Cognitive Disorders+")
 S73 (MH "Postoperative Complications")
 S72 S67 OR S68 OR S69 OR S70 OR S71
 S71 anesth* N2 general
 S70 (MH "Anesthetics, Intravenous+")
 S69 (MH "Anesthesia, Intravenous")
 S68 (MH "Anesthesia, Inhalation")
 S67 (MH "Anesthesia, General+")
 S66 S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58
 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65
 S65 levobupivacaine
 S64 Prilocaine

S63 Mepivacaine

S62 Tetracaine

S61 Bupivacaine

S60 Lidocaine

S59 Ropivacaine

S58 block* N2 (spinal OR epidural OR plexus OR Bier)

S57 anesth* N2 (local OR regional OR general OR conduction OR epidural)

S56 (MH "Anesthetics, Local+")

S55 (MH "Analgesia, Epidural")

S54 (MH "Nerve Block+")

S53 (MH "Anesthesia, Spinal")

S52 (MH "Anesthesia, Local")

S51 (MH "Anesthesia, Epidural")

S50 (MH "Anesthesia, Conduction+")

S49 S17 AND S23 AND S48

S48 S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32
OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41
OR S42 OR S43 OR S44 OR S45 OR S46 OR S47

S47 POCD

S46 confusion

S45 "Postoperative cognitive dysfunction"

S44 neuropsycholog*

S43 neurocogniti*

S42 cogniti*

S41 delirium

S40 ((mental OR memory OR speech OR concentrat* OR attention) N5
(function OR dysfunction OR disability OR loss OR deficit OR effect? OR
impair* OR outcome OR flawed))

S39 (MH "Psychomotor Disorders+")

S38 (MH "Perceptual Disorders+")

S37 (MH "Memory Disorders+")

S36 (MH "Confusion+")

S35 (MH "Speech Disorders+")

S34 (MH "Psychomotor Performance+")
 S33 (MH "Neuropsychological Tests")
 S32 (MH "Memory+")
 S31 (MH "Cognition+")
 S30 (MH "Aphasia")
 S29 (MH "Dementia")
 S28 (MH "Auditory Perceptual Disorders")
 S27 (MH "Cognition Disorders")
 S26 (MH "Amnesia")
 S25 (MH "Delirium, Dementia, Amnestic, Cognitive Disorders+")
 S24 (MH "Postoperative Complications")
 S23 S18 OR S19 OR S20 OR S21 OR S22
 S22 an?esth* N2 general
 S21 (MH "Anesthetics, Intravenous+")
 S20 (MH "Anesthesia, Intravenous")
 S19 (MH "Anesthesia, Inhalation")
 S18 (MH "Anesthesia, General+")
 S17 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR
 S11 OR S12 OR S13 OR S14 OR S15 OR S16
 S16 levobupivacaine
 S15 Prilocaine
 S14 Mepivacaine
 S13 Tetracaine
 S12 Bupivacaine
 S11 Lidocaine
 S10 Ropivacaine
 S9 block* N2 (spinal OR epidural OR plexus OR bier)
 S8 an?esth* N2 (local OR regional OR general OR conduction OR epidural)
 S7 (MH "Anesthetics, Local+")
 S6 (MH "Analgesia, Epidural")
 S5 (MH "Nerve Block+")
 S4 (MH "Anesthesia, Spinal")

S3 (MH “Anesthesia, Local”)
 S2 (MH “Anesthesia, Epidural”)
 S1 (MH “Anesthesia, Conduction+”)

Appendix 5. PsycINFO Search Strategy

1. exp local anesthetics/
2. (an?esth* adj2 (local or regional or general or conduction or epidural)).ti,ab.
3. (block* adj2 (spinal or epidural or plexus or bier)).ti,ab.
4. Ropivacaine.ti,ab.
5. Lidocaine.ti,ab.
6. Bupivacaine.ti,ab.
7. Tetracaine.ti,ab.
8. Mepivacaine.ti,ab.
9. Prilocaine.ti,ab.
10. levobupivacaine.ti,ab.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. exp General Anesthetics/
13. (an?esth* adj2 general).ti,ab.
14. 12 or 13
15. Postsurgical Complications/
16. Amnesia/
17. Cognitive Impairment/
18. Dementia/
19. exp Aphasia/
20. exp Cognition/
21. exp Memory/
22. exp Neuropsychological Assessment/
23. exp Motor Performance/
24. exp Speech Disorders/
25. exp memory disorders/
26. exp Perceptual Motor Processes/

27. Attention/
28. ((mental or memory or speech or concentrat* or attention) adj5 (function or dysfunction or disability or loss or deficit or effect? or impair* or outcome or flawed)).ti,ab.
29. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. 11 and 14 and 29

Appendix 6. Data extraction form

CARG 187: Data extraction form

First study author	Journal/Conference proceedings, etc.	Year

Study eligibility

RCT/Quasi/CCT	Relevant participants	Relevant interventions	Relevant outcomes
Yes/No/Unclear	Yes/No/Unclear	Yes/No/Unclear	Yes/No [*] /Unclear

* Issue relates to selective reporting ? when authors may have taken measurements for particular outcomes but did not report these within the paper(s). Review authors should contact study authors for information on possible non-reported outcomes and reasons for exclusion from publication. Study should be listed in 'Studies awaiting assessment' until clarified. If no clarification is received after three attempts, study should be excluded.

Do not proceed if any of the above answers is 'No'. If study is to be included in 'Excluded studies' section of the review, record below information to be inserted in the 'Table of excluded studies'

Freehand space for comments on study design and treatment:

References to trial

Check other references identified in searches. If further references to this trial are available, link the papers now and list below. All references to a trial should be linked under one Study ID in RevMan.

Code each paper	Study author(s)	Journal/Conference proceedings, etc.	Year
A	<i>Paper listed above</i>		
B	<i>Other papers</i>		

Participants and trial characteristics

Participant characteristics

	Additional details
Age (mean, median, range, etc.)	
Sex of participants (numbers/%, etc.)	
ASA	
Surgery	
Type of surgery: emergency/elective	
Site of surgery (extremities, chest, abdomen, etc.)	
Duration of surgery	
Other	

Trial characteristics: See Appendix 7, usually completed by just one review author.

Assessment of risk of bias

1. Adequate sequence generation?	Low risk/High risk/Unclear risk
Method used to generate allocation and reasons for grading:	
2. Allocation concealment?	Low risk/High risk/Unclear risk
Method used to conceal allocation and reasons for grading:	
3. Blinding: person responsible for participant care	Low risk/High risk/Unclear risk
4. Blinding: participant	Low risk/High risk/Unclear risk
5. Blinding: outcome assessor	Low risk/High risk/Unclear risk
6. Incomplete outcome data addressed?	Low risk/High risk/Unclear risk
7. Free of selective reporting?	Low risk/High risk/Unclear risk
8. Free of other bias?	Low risk/High risk/Unclear risk

Intention-to-treat

An intention-to-treat analysis is one in which all participants in a trial are analysed according to the intervention to which they were allocated, whether or not they received it

All participants entering trial	Yes/No
Participants excluded	15% or less/More than 15%
Analysed as	intention-to-treat/per protocol/unspecified

Were withdrawals described? Yes ? No ? Not clear ?

Discuss if appropriate.

Data extraction

Outcomes relevant to your review

Copy and paste from 'Types of outcome measures'

	Reported in paper (circle)
Postoperative cognitive decline	Yes/No
Hospital length of stay	Yes/No
ICU length of stay	Yes/No
Mortality within 30 days	Yes/No

Other	Yes/No

For continuous data

Code of paper	Outcomes	Unit of measurement	Treatment group 1		Treatment group 2		Details if outcome described only in text
			N	Mean (SD)	N	Mean (SD)	
A etc.	Postoperative cognitive decline						
	Hospital length of stay	Days					
	ICU length of stay	Days					
	Mortality within 30 days	Per cent					

For dichotomous data

Code of paper	Outcomes	Character	Treatment group 1		Treatment group 2		Details if outcome described only in text
			n	%	n	%	

Other information that you believe is relevant to the results

Indicate if: any data were obtained from the primary study author; if results were estimated from graphs, etc, or were calculated by you using a formula (this should be stated and the formula given). In general, if results not reported in paper(s) are obtained, this should be made clear here to be cited in the review

Freehand space for writing actions such as contact with study authors and changes**References to other trials**

Did this report include any references to published reports of potentially eligible trials not already identified for this review?

First author	Journal/Conference	Year of publication

Did this report include any references to unpublished data from potentially eligible trials not already identified for this review? If yes, list contact names and details

Trial characteristics

	Further details
Single centre/Multi-centre	
Country/Countries	

How was participant eligibility defined?	
How many people were randomized?	
Number of participants in each intervention group	
Number of participants who received intended treatment	
Number of participants who were analysed	
Surgery	
Type of surgery: emergency/elective	
Site of surgery (extremities, chest, abdomen, etc.)	
Duration of surgery	
Number and timing of assessment	
Length of follow-up	
Time points when measurements were taken during the study	
Time points reported in the study	
Time points you are using in RevMan	
Trial design (e.g. parallel/cross-over*)	
Other	

CONTRIBUTIONS OF AUTHORS

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Undertaking manual searches: AMMC, AA, SS, JC.

Screening search results: AMMC, AA, SS, JC.

Organizing retrieval of papers: AMMC, AA, SS, JC.

Screening retrieved papers against inclusion criteria: AMMC, AA, SS, MHA, JC.

Appraising quality of papers: AMMC, AA, SS, MHA, JC.

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Performing previous work that formed the foundation of the present study: MHA, AA.

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NOTES

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The Cochrane Anaesthesia, Critical and Emergency Care Group asked Drs. Andreae and Achabedian to take over this review and to revise the previously published protocol (Raksamani 2010). We enlisted the help of two cognitive outcome specialists (RL, S Shinnar), a biostatistician (CH), a medical librarian and several anaesthesiologists to complete this review. We updated the search, clarified inclusion criteria and focused the review on comparison of regional versus non-regional techniques. We will consider Bayesian evidence synthesis to help us pool study outcomes that we predict to be heterogeneously reported.

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* Indicates the major publication for the study

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