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Post-operative cognitive function following general versus regional anesthesia, a systematic review

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Abstract

The effect of anesthetic technique on post-operative outcomes remains in question. This systematic review compares the role of regional versus general anesthesia, with a particular focus on post-operative cognitive function. Potentially relevant articles were identified by searching publicly available computerized databases for this systematic review. Any surgical procedure was accepted with the exception of cardiac, carotid, and neurosurgical procedures. Any regional anesthetic technique was accepted unless combined with a general anesthetic or in conjunction with propofol as a sedative. Any measure of post-operative cognitive function was accepted as long as it was performed no sooner than seven days post-operatively. Sixteen studies met inclusion criteria and were included in the final analysis. Three studies showed some difference in cognitive function between regional and general anesthesia, while the remaining thirteen showed no difference between regional and general anesthesia on postoperative cognitive function.

Keywords

cognitive function; regional anesthesia; general anesthesia

INTRODUCTION

Cognitive dysfunction following surgery is a complication that can have a significant impact on a patient's quality of life and remains an increasing source of concern for adult and pediatric patients and their families.[1]

In adults, postoperative cognitive dysfunction is described as an impairment in concentration, memory, language, learning, and/or daily functioning that develops after surgery, and can persist for weeks, months, or more with varying severity. In most cases,

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cognitive dysfunction can be quite mild and only diagnosed through assessment using specific neuropsychological tests.[1] Postoperative cognitive decline occurs more frequently in the elderly population with an incidence as high as 26% in patients older than 60 years of age and persisting more than one week after non-cardiac surgery.[2] Factors that have been implicated in increasing this risk after surgery include pain, preoperative impairment in neurocognitive function, metabolic disturbances, duration/type of surgery, hypoxemia, old age, and use of certain anesthetics.[3]

In pediatric patients, the possible association between long-term neurocognitive impairment and anesthesia has been raised from both animal and recent clinical epidemiological studies.[4] In animal studies, exposure of the developing brain to general anesthetic agents in both rodents and non-human primates have been shown to induce neurotoxic effects at the cellular level, and neurobehavioral deficits in these same animals as adults. Over the past five years, several clinical studies have also reported an association between neurodevelopmental impairment and anesthesia in very young children.[5–7] Due to concern about cognitive dysfunction from anesthesia and surgery, several studies have attempted to evaluate whether the avoidance of exposure to general anesthetics and adoption of regional anesthetic techniques reduce the risk of cognitive dysfunction or impairment in patients.

The goal of this paper is to conduct a systematic review of studies that have specifically compared the risk of postoperative cognitive dysfunction following general versus regional anesthesia in patients without pre-existing neurologic diagnoses undergoing non-cardiac and non-carotid surgery. Although much of the data on postoperative cognitive dysfunction has been from adults, we expanded our search to include both pediatric and adult patients.

We defined cognitive dysfunction as an abnormal change in concentration, memory, language, learning, and/or daily functioning that may be diagnosed by neuropsychological tests and persists after postoperative day seven, and regional anesthesia as spinal, epidural, peripheral nerve blocks with minimal sedation (i.e. midazolam, fentanyl). We chose to review studies that avoided the use of propofol with regional anesthesia in order to further differentiate the two anesthetic techniques.

To date, all of the published studies comparing cognitive dysfunction between general versus regional anesthesia have been conducted in adults.[5–8] In pediatric patients, an ongoing study, the GAS study, specifically compares the long-term neurodevelopmental outcome between infants undergoing inguinal hernia repair under general anesthesia with sevoflurane and regional anesthesia. The results of the GAS study are still pending.[9]

MATERIALS AND METHODS

Protocol

The study protocol was developed to review both randomized control trials and observational studies that compared post-operative cognitive function following regional anesthesia (includes spinal, epidural, combined spinal/epidural, peripheral nerves blocks, and Bier blocks) and general anesthesia. The primary outcome was measurement of cognitive function no sooner than seven days post-operatively. This time frame was chosen to eliminate any possible direct effects of surgery and anesthesia, as well as to avoid outcomes that might be due to post-operative delirium. Any measure of cognitive function was accepted. Patients of any age were included. Excluded in the review well are patients who underwent cardiac, carotid, or neurosurgical procedures, or with pre-existing neurologic deficits or diagnoses. Also excluded were those patients who received combined regional and general anesthetics, as well as those who received propofol for sedation during their regional anesthesia. No secondary outcomes were reviewed.

Search methods

Potentially relevant articles were identified by searching publicly available computerized databases. The electronic databases searched were: Ovid MEDLINE, The Cochrane Database of Systematic Reviews, CENTRAL, DARE, HTA Database, CINAHL, and Scopus. Dates searched were from database inception to April 2014. The searches were conducted on April 22, 2014. All relevant subject headings and free-text terms were used to represent anesthesia and cognitive function, and the sets of terms were combined with AND. Terms for MEDLINE included the following: Anesthesia, General/, Anesthesia, Conduction/, Anesthesia, Epidural/, Anesthesia, Local/, Anesthetics/, ((local or regional or general) adj an?esth$).ti,ab., Postoperative Complications/, exp Cognition Disorders/, (cognitive adj (function or dysfunction or decline or status)).ti,ab., pocd.ti,ab., exp Memory/, attention/, memory loss.ti,ab., and (reduc$ adj attention).ti,ab. These terms were adapted for the other databases. Studies were also sought by searching clinical trial registries and by scanning the reference lists of relevant studies and reviews and by using the Related Articles feature in PubMed and the Cited Reference Search in ISI Web of Science. Appendix 1 summarizes the results and the strategies of each of the databases searched.

Two authors reviewed all titles and abstracts. When a discrepancy in whether studies met inclusion criteria was noted between the two reviewers, a third reviewer was added to adjudicate the decision of inclusion or exclusion of the study for the review.

RESULTS

A total of 5201 titles and abstracts were screened, 45 were found to be potentially relevant and possibly filled our search criteria and were reviewed. Twenty-four of the 45 reviewed studies were excluded for not fulfilling study criteria. An additional five studies could not be fully analyzed due to inability to locate full text or English translations of the study. The final number of studies included for the review was sixteen. Of the studies in our analysis, one (Riis et al[10]) had an additional combined general/regional anesthetic group, but also had distinct GA and RA groups for comparison. The remaining fifteen studies compared general anesthesia to spinal, epidural, or local anesthesia (Figure 1). Both randomized control studies and observational studies were acceptable based on the criteria of this systematic review. However, in the final analysis, no observational studies met criteria.

A summary of the randomized control trials included is below (Table 1, Table 2). Of the sixteen studies, twelve showed no difference in cognitive function between general and regional anesthesia at seven days post-operatively. Four studies (Hole et al[20], Jones et al[21], Karhunen et al[22], Mandal et al[23]) did show a difference between regional and general anesthesia. Hole et al[20] compared general anesthesia to epidural anesthesia in patients undergoing hip arthroplasty. Of the thirty-one patients in the general anesthesia group, seven experienced mental changes post-operatively, with five continuing to experience significant post-operative decline several months following the procedure by self-report. None of the twenty-nine patients in the regional anesthesia group had a measurable decline in cognitive function.

Jones et al[21] randomized patients to receive either general anesthesia or a spinal anesthetic for their orthopedic procedure. 129 patients completed testing at the three-month follow-up. Seven cognitive function tests were performed, with significant improvement favoring general anesthesia on the choice reaction time test ($p<0.05$).

Karhunen et al[22] compared general anesthesia to local anesthesia in patients undergoing cataract surgery. While there was no difference in most cognitive testing results between the two groups, there was a statistically significant difference favoring general anesthesia over local in one subset of memory testing (the Luria test). Karhunen et al[22] did show a generalized reduction in memory performance across both anesthetic groups.

Mandal et al[23] compared general anesthesia to epidural anesthesia in patients undergoing hip and knee surgery. They observed a gross difference at seven days favoring regional anesthesia in the mini-mental status exam only.

A sampling of excluded studies is presented in Table 3.

Studies that report outcomes related to cognitive functions during the first postoperative seven days do not meet the criteria of this systematic review and are not included in the analysis. However, of note, several studies have found small differences related to changes in cognitive function during this very early post-operative period. Table 4 summarizes the findings in these studies, as well as adjuncts used during regional anesthesia (Table 4).

DISCUSSION

The etiology of cognitive dysfunction following surgery, sometimes reported as postoperative cognitive dysfunction (POCD), has been a source of discussion and research for years. While it seems likely that the origins of POCD are multifactorial, there remains the question of whether the effects of exposure to general anesthesia and alteration of consciousness might contribute to its severity. Thus, there may exist possible beneficial effects of the use of a regional anesthesia technique. Multiple clinical trials have attempted to differentiate the effect of regional versus general anesthesia on POCD. While the majority of the studies showed no difference in cognitive function between regional and general anesthesia, some earlier trials did show a significant difference in post-operative cognitive outcomes (Hole et al[20], Jones et al[21], Karhunen et al[22], Mandal et al[23]).

Hole et al[20] reported five out of thirty-one patients who underwent a general anesthetic for total hip replacement had significant cognitive decline several months following surgery. This study did have several limitations, however, most notably that the study was not blinded and that the psychometric assessment was subjective--the prolonged post-operative decline was self-reported. Jones et al[21] performed seven separate cognitive function tests on patients undergoing hip and knee surgery. They found a significant difference favoring general anesthesia on the choice reaction time test, though no difference in the other testing components. Karhunen et al[22] used several techniques to assess cognitive function, and did find a significant difference favoring a general technique on one test of memory (the Luria test). Of note, however, there was a higher score at baseline on this test in the general anesthesia group, and a similar final score when compared to the regional group. This study also noted a general decline in memory testing scores across both groups. Mandal et al[23] saw a gross difference at seven days favoring regional anesthesia in the mini-mental status exam only. There also appeared to be a difference favoring regional anesthesia in verbal fluency testing, though this difference was not significant after correction for multiple comparisons. The remaining thirteen studies included in this systematic review showed no difference in cognitive outcomes between regional and general anesthetic techniques.

Although we included studies of patients of all ages, there were no studies in the pediatric age group. Therefore, our systematic review does not provide any information that can contribute to the discussion of anesthetic technique and anesthetic neurotoxicity in the very young. The GAS study is an ongoing international randomized control trial comparing general and regional anesthesia during infancy on neurocognitive development at ages 2 and 5 years. Updates of the study were reported at both the Third and Fourth PANDA symposium.[32] However, results of the study will not be available until 2015.

A serious limitation in interpreting the results of these studies includes the use of a wide range of modalities to assess cognitive function. It is possible many of these tests may not be sufficiently sensitive to detect subtle changes in cognitive function. This combined with the confounding factor of sedative adjuncts often used during regional anesthetics makes it difficult to specifically compare whether there are differences between general anesthesia and regional anesthesia alone on POCD.

Our review suggests that currently there remains no definitive comparative data showing that either general or regional anesthesia is associated with a reduced risk for the development of cognitive dysfunction following surgery.

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Appendix 1: Database search strategy

Database	Dates searched	Number of references retrieved	Number after de-duplication
MEDLINE (Ovid) and Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations	1946 to April Week 2 2014 April 22, 2014	4072	4011
Cochrane Database of Systematic Reviews	All databases accessed April 23, 2014	9	9
CENTRAL		1017	17
DARE		15	15
HTA Database All databases are part of *The Cochrane Library*. www.thecochranelibrary.com		1	1
CINAHL (EBSCOHost)	1981 to April 2014	539	265
Scopus	Accessed April 23, 2014	1088	874
Clinicaltrials.gov	Accessed April 23, 2014	0 relevant out of 111 retrieved	0
International Clinical Trials **Registry Platform** http://www.who.int/ictrp/en/	Accessed April 23, 2014	6 relevant out of 15 retrieved	6
All databases		**6747**	**5198**

MEDLINE

1. Anesthesia, General/
2. Anesthesia, Conduction/
3. Anesthesia, Epidural/
4. Anesthesia, Local/
5. Anesthetics/
6. ((local or regional or general) adj an?esth$).ti,ab.
7. or/1–6
8. Postoperative Complications/
9. exp Cognition Disorders/
10. exp cognition/
11. (cognitive adj (function or dysfunction or decline or status)).ti,ab.
12. pocd.ti,ab.
13. exp Memory/
14. exp Memory Disorders/
15. attention/
16. memory loss.ti,ab.
17. (reduc$ adj attention).ti,ab.
18. or/8–16
19. 7 and 18
20. randomized controlled trial.pt.
21. controlled clinical trial.pt.
22. randomized.ab.
23. placebo.ab.
24. drug therapy.fs.
25. randomly.ab.
26. trial.ab.
27. groups.ab.
28. or/20–27
29. exp animals/not humans.sh.
30. 28 not 29

31. 19 and 30
32. Epidemiologic studies/
33. Observational study.pt.
34. exp case control studies/
35. exp cohort studies/
36. Case control.tw.
37. (cohort adj (study or studies)).tw.
38. Cohort analy$.tw.
39. (Follow up adj (study or studies)).tw.
40. (observational adj (study or studies)).tw.
41. Longitudinal.tw.
42. Retrospective.tw.
43. Cross sectional.tw.
44. Cross-sectional studies/
45. or/32–44
46. exp animals/not humans.sh.
47. 45 not 46
48. 19 and 47
49. 31 or 48

The Cochrane Library

#1 MeSH descriptor: [Anesthesia, General] this term only

#2 MeSH descriptor: [Anesthesia, Conduction] this term only

#3 MeSH descriptor: [Anesthesia, Epidural] this term only

#4 MeSH descriptor: [Anesthesia, Local] this term only

#5 MeSH descriptor: [Anesthetics] this term only

#6 ((local or regional or general) next an?esth*):ti,ab

#7 #1 or #2 or #3 or #4 or #5 or #6

#8 MeSH descriptor: [Postoperative Complications] this term only

#9 MeSH descriptor: [Cognition Disorders] explode all trees

#10 MeSH descriptor: [Cognition] explode all trees

#11 (cognitive next (function or dysfunction or decline or status)):ti,ab

#12	pocd:ti,ab
#13	MeSH descriptor: [Memory] explode all trees
#14	MeSH descriptor: [Memory Disorders] explode all trees
#15	MeSH descriptor: [Attention] this term only
#16	“memory loss”:ti,ab
#17	(reduc* next attention):ti,ab
#18	#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
#19	#7 and #18

Scopus

#1	TITLE-ABS-KEY(local anesth*) OR TITLE-ABS-KEY(local anaesth*)
#2	TITLE-ABS-KEY(regional anesth*) OR TITLE-ABS-KEY(regional anaesth*)
#3	TITLE-ABS-KEY(general anesth*) OR TITLE-ABS-KEY(general anaesth*)
#4	#1 OR #2 OR #3
#5	TITLE-ABS-KEY(cognitive function) OR TITLE-ABS-KEY(cognitive dysfunction) OR TITLE-ABS-KEY(cognitive decline) OR TITLE-ABS-KEY(cognitive status)
#6	TITLE-ABS-KEY(pocd)
#7	TITLE-ABS-KEY(memory loss)
#8	TITLE-ABS-KEY(reduc* attention)
#9	#5 OR #6 OR #7 OR #8
#10	#4 AND #9

CINAHL

S1	(MH “Anesthesia, General”)
S2	(MH “Anesthesia, Conduction”)
S3	(MH “Anesthesia, Epidural”)
S4	(MH “Anesthesia, Local”)
S5	(MH “Anesthetics”)
S6	TI local anesth* OR TI local anaesth* OR AB local anesth* OR AB local anaesth* OR TI regional anesth* OR TI regional anaesth* OR AB regional anesth* OR AB regional anaesth* OR TI general anesth* OR TI general anaesth* OR AB general anesth* OR AB general anaesth*
S7	S1 OR S2 OR S3 OR S4 OR S5 OR S6

S8 (MH “Postoperative Complications”)

S9 (MH “Cognition Disorders+”)

S10 (MH “Cognition+”)

S11 TI cognitive function OR AB cognitive function OR TI cognitive dysfunction OR AB cognitive dysfunction OR TI cognitive decline OR AB cognitive decline OR TI cognitive status OR AB cognitive status

S12 TI pocd OR AB pocd

S13 (MH “Memory+”)

S14 (MH “Memory Disorders+”)

S15 (MH “Attention”)

S16 TI memory loss OR AB memory loss

S17 TI reduc* attention OR AB reduc* attention

S18 S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17

S19 S7 AND S18 Limiters - Publication Type: Clinical Trial, Meta Analysis, Meta Synthesis, Randomized Controlled Trial, Research, Systematic Review

Clinicaltrials.gov

Advanced Search:

Completed | Studies With Results | “Anesthetics, General”

International Clinical Trials Registry Platform

Advanced Search:

(Anesthes* OR anaesth*) in Intervention

AND (cognit* OR memory OR attention) in Title

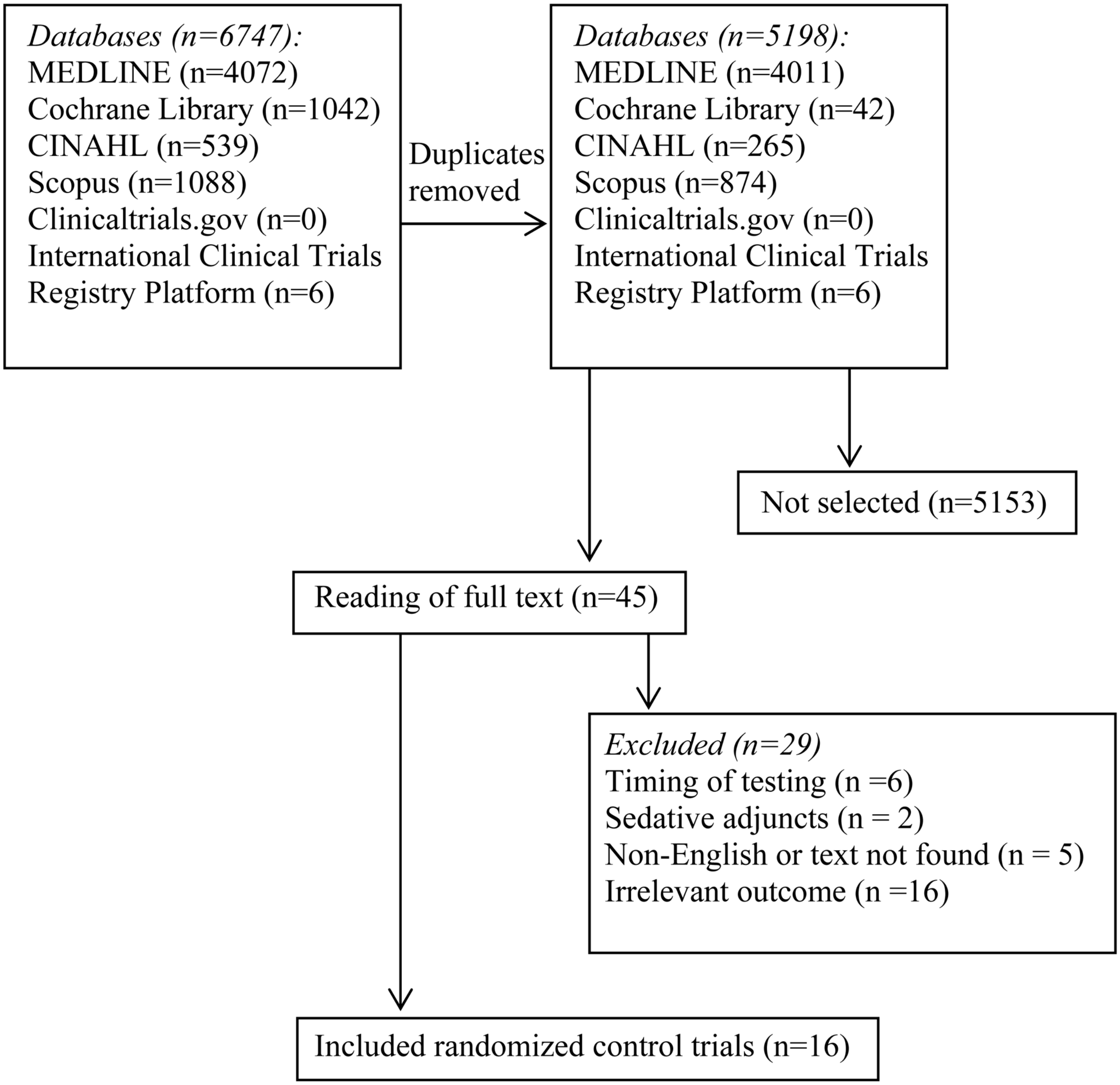

Figure 1.
Flow diagram detailing process of study selection from database to inclusion

Table 1

Summary of Randomized Control Trials Included in Systematic Review

Study (year)	Anesthetic Techniques	Sample Size	Cognitive Function Testing Performed	Time of Assessment	Type of surgery
Asbjorn et al (1989) [11]	GA EA	20 20	other	4 days, 3 weeks	TURP
Berggren et al (1987) [12]	GA EA	29 28	OBS	1 day, 7 days	Femoral neck fracture repair
Bigler et al (1985) [13]	GA SA	20 20	AMT	7 days, 3 months	Hip fracture surgery
Campbell et al (1993) [14]	GA LA	77 80	PRT, FOMTL, FPU, HAI, NART, other	24h, 2 weeks, 3 months	Cataract surgery
Chung et al (1987) [15]	GA SA	24 20	MMS, GEMS	6h, 1 day, 3 days, 5 days, 1 month	TURP or pelvic floor repair
Chung et al (1989) [16]	GA SA	22 22	MMS, GEMS	6h, 1 day, 3 days, 5 days, 1 month	TURP
Crul et al (1992) [17]	GA SA	27 33	HOL, SLC	1 day, 3 days, 4 weeks	Urologic surgery
Ghoneim et al (1988) [18]	GA SA EA	53 38 14	SIP, SCL-90-R, MMQ, MMS, other	1 day, 3 months	Hysterectomy, prostatectomy, joint replacement
Haan et al (1991) [19]	GA SA	22 27	MMS, WAIS, other	4 days, 3 months	TURP
Hole et al (1980) [20]	GA EA	31 29	other	1 day, 3 days, 7 days, 12 days, 4 months	Hip arthroplasty
Jones et al (1990) [21]	GA SA	72 74	NART, FLS, CDS, other	3 months	Hip or knee replacement
Karhunen et al (1982) [22]	GA LA	30 30	WMS, LMS	7 days	Cataract surgery
Mandal et al (2011) [23]	GA EA	30 30	MMS, KCSB	7 days	Hip or knee surgery
Nielson et all (1990) [24]	GA SA	39 25	WAIS, WMS, other	3 months	Knee arthroplasty
Riis et al (1983) [10]	GA EA GEA	10 10 10	WAIS, other	2 days, 4 days, 7 days, 3 months	Hip arthroplasty
Williams-Russo et al (1995) [25]	GA EA	128 134	WAIS, BNT, BVR, MKVRR	1 week, 6 months	Total knee replacement

GA: general anesthesia, EA: epidural anesthesia, SA: spinal anesthesia, LA: local anesthesia, GEA: combined general and epidural anesthesia, OBS: Organic brain syndrome scale, AMT: abbreviated mental test from Roth Hopkins test, PRT: Rivermead behavioral memory test, FOMTL: Fuld object memory test, FPU: Felix post unit questionnaire, HAI: Holbrook activity index, NART: national adult reading test, MMS: mini-mental status test, GEMS: geriatric mental status exam, HOL: hospital observation list, SLC: subjective loss of condition, SIP: sickness impact profile, SCL-90-R: symptom checklist-90-revised, MMQ: metamemory questionnaire, WAIS: Wechsler adult intelligence scale, FLS: functional life scale, CDS: cognitive difficulties scale, WMS: Wechsler memory scale, LMS: Luria memory test, KCSB: Kolkata cognitive screening battery, BNT: Boston naming test, BVR: Benton visual retention, MKVRR: Mattis-Kovner verbal recall and recognition, “other” indicates different modes of psychometric testing

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Table 2

Outcomes of Randomized Control Trials Included in Systematic Review

Study (year)	**Anesthetic Techniques**	**Outcomes at ≥POD 7**
Asbjorn et al (1989) [11]	GA v. EA	No difference in standard (Z) scores on psychological tests involving short-term, long-term, verbal, and visual memory, $p>0.05$
Berggren et al (1987) [12]	GA v. EA	50% of EA group and 38% of GA group experienced mental status change, no significant difference, $p> 0.05$
Bigler et al (1985) [13]	GA v. SA	No difference on abbreviated mental test between GA and SA groups, student's t-test, $p>0.05$
Campbell et al (1993) [14]	GA v. LA	No evidence of a change in the relationship between the LA and GA groups with time for all tests performed, analyzed using multivariate analysis of variance
Chung et al (1987) [15]	GA v. SA	No difference in mini-mental status exam score or geriatric mental exam score between or within groups, $p>0.05$
Chung et al (1989) [16]	GA v. SA	No difference in mini-mental status exam score or geriatric mental exam score between or within groups, $p>0.05$
Crul et al (1992) [17]	GA v. SA	No difference in three cognitive function tests using multivariate analysis of variance, $p>0.05$
Ghoneim et al (1988) [18]	GA v. SA v. EA	No difference in seventeen cognitive function tests using multivariate analysis of variance, $p>0.05$
Haan et al (1991) [19]	GA v. SA	No difference in three cognitive function tests using multivariate analysis of variance, $p>0.05$
Hole et al (1980) [20]	GA v. EA	0/29 patient in EA and 7/31 patients in GA with persistent mental changes, two-sided Student's t-test or chi-square test, $p<0.01$
Jones et al (1990) [21]	GA v. SA	Of seven cognitive function tests, significant difference in recognition and response times on choice reaction time test (improved in general anesthesia group, $p<0.05$)
Karhunen et al (1982) [22]	GA v. LA	Two tests of memory were performed, patient in LA group scored significantly worse on Luria memory test, $p<0.01$
Mandal et al (2011) [23]	GA v. EA	Two cognitive function tests performed, gross difference at seven days favoring regional anesthesia in the mini-mental status exam, $p<0.01$
Nielson et all (1990) [24]	GA v. SA	No difference in eight cognitive function tests, $p>0.05$
Riis et al (1983) [10]	GA v. EA v. GEA	No difference in thirteen cognitive function tests, data comparison via Z-scores, $p>0.05$
Williams-Russo et al (1995) [25]	GA v. EA	No difference in ten cognitive function tests, comparison via Student's t-test, $p>0.005$

POD: post-operative day, GA: general anesthesia, EA: epidural anesthesia, SA: spinal anesthesia, LA: local anesthesia, GEA: combined general and epidural anesthesia

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Table 3

Sample of studies excluded from systematic review

Study (year)	Anesthetic Techniques	Trial précis and reason for exclusion
Boos et al (2005) [26]	GA v. RA	100 patients undergoing orthopedic, urologic, general, or vascular surgery received GA or RA (not specified) at discretion of anesthesiologist, cognitive testing performed between 3 and 7 days post-operatively, propofol possibly used for sedation in some regional patients
Krier et al (1993) [27]	GA v. LA	101 patient undergoing ophthalmological procedures randomized to either GA or LA, cognitive function testing performed less than seven days post-operatively
O'Hara et al (2000) [28]	GA v. SA/EA	Retrospective study of 9,425 patient receiving either GA or SA/EA, outcome of change in mental status not differentiated well from post-operative delirium
Rasmussen et al (2003) [29]	GA v. EA/SA	340 patients undergoing non-cardiac surgery randomized to either GA or EA/SA, propofol sedation permitted in regional group
Somprakit et al (2002) [30]	GA v. EA/SA	120 patients undergoing orthopedic, gynecologic, or urologic surgery with either GA or EA/SA, mental status assessment performed less than seven days post-operatively
White et al (1980) [31]	GA v. SA v. psoas block	60 patient undergoing repair of fractured femoral neck randomized to GA, SA, or psoas compartment block, SA group received "light general anesthesia" with 50% nitrous oxide and alfaxolone/alfadolone

GA: general anesthesia, RA: regional anesthesia, EA: epidural anesthesia, SA: spinal anesthesia, LA: local anesthesia

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Table 4

Cognitive Functions Reported Before Postoperative Day 7 and Documented Use of Adjuncts

Study (year)	Outcomes Reported Before POD 7	Adjuncts Used in Regional Techniques
Asbjorn et al (1989) [11]	No difference	Fentanyl, dihydrobenzperidol
Berggren et al (1987) [12]	No difference	Meperidine
Bigler et al (1985) [13]	Not reported	Diazepam
Campbell et al (1993) [14]	No difference	None
Chung et al (1987) [15]	Significant impairment at 6h in GA, slight decline at 3 days	None
Chung et al (1989) [16]	Decrease in MMS score in both groups at 6h post-op, no other changes	Fentanyl, droperidol, diazepam
Crul et al (1992) [17]	No difference	None
Ghoneim et al (1988) [18]	Slight decline in cognitive function immediately post-op in both groups	Midazolam, fentanyl
Haan et al (1991) [19]	No difference	Temazapam, lorazepam
Hole et al (1980) [20]	7 patients with POCD in GA group on early testing, 2 with persistent POCD	Atropine, diazepam
Jones et al (1990) [21]	Not reported	Midazolam
Karhunen et al (1982) [22]	Not reported	Fentanyl, diazepam
Mandal et al (2011) [23]	Not reported	Diazepam
Nielson et all (1990) [24]	Not reported	Diazepam, lorazepam
Riis et al (1983) [10]	No difference	Not mentioned
Williams-Russo et al (1995) [25]	Not reported	Midazolam, fentanyl

POD: post-operative day, GA: general anesthesia, MMS: mini-mental status exam, POCD: post-operative cognitive decline