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Post-operative cognitive dysfunction at 3 months in adults after non-cardiac surgery: a qualitative systematic review

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BACKGROUND:

Post-operative cognitive dysfunction is defined as a decline in cognitive functions that occurs after surgery, but different diagnostic criteria and incidences have been reported in medical literature. Our aim was to determine incidence of post-operative cognitive dysfunction 3 months after non-cardiac surgery in adults.

METHODS:

A Systematic Review of available evidence was performed by PRISMA guidelines. A search was done in May-July 2015 on PubMed, EMBASE, CINAHL, LILACS, Scielo, Clinical Trials and Grey Literature Reports. Inclusion criteria were prospective design studies with patients over 18 years old, surgery under general or regional anesthesia, follow up for 3 months, and use of a neurocognitive battery for diagnosis. We excluded studies made on cardiac or brain surgery patients. Risk of bias was assessed using tools from National Heart Lung and Blood Institute.

RESULTS:

We selected 24 studies. Average age was 68 years. Only 5 studies reported incidence of cognitive decline for a non-surgical control group. Median number of tests used was 5 (range 3 – 13). Pooled incidence of post-operative cognitive dysfunction at 3 months was 11.7% [95% CI 10.9 - 12.5] but with several methodological differences between studies. Increasing age was the most consistent risk factor identified (7 studies).

CONCLUSIONS:

Post-operative cognitive dysfunction in patients is frequent, especially in patients over 60 years old. Limitations include methodological differences in studies. Efforts must be made to reach a consensus in definition and diagnosis for future research.

Editorial Comment

This systematic review focused on 24 studies where detailed neuropsychological testing was done prior to non-cardiac surgery and then again after at least 3 months. The overall incidence of postoperative cognitive dysfunction was 10%. Risk factors identified in more than one study included increasing age, low level of education, postoperative delirium, and use of sedatives. Future studies should be based on a more standardised approach.

Introduction

As the population ages and medical progress is made, many elderly patients that previously would not have been candidates for surgery are now presenting for operations. According to the National Institute on Aging ¹ in 2010 approximately 8% of the world's population was 65 years or older; and it is anticipated that by 2050, this will rise to 16%.

In this group of older patients, brain dysfunction after anesthesia and surgery is well recognized and with two distinct clinical entities that have been identified². Delirium, is an acute and fluctuating deterioration in attention accompanied by either a change in cognition or arousal³ and is often diagnosed by criteria established in the Confusion Assessment Method (CAM)⁴. Advanced age and previous disease are a well-known risk factors, and surgery is often a precipitant.⁵

Post-Operative Cognitive Dysfunction (POCD), is a term used to describe subtle changes in cognition, such as memory and executive function⁶. It is often subclinical, but it may be noticed by patients and their families. In severe cases it can lead to inability to perform daily living functions. POCD is not classified in the International Classification of Diseases (ICD) and lacks a clear uniform definition. The diagnosis relies on the use of neuropsychological tests, but there is no consensus about which tests are more sensitive and specific to use⁷.

Studies on animal models have linked isoflurane with calcineurin activation (a protein involved in apoptosis)⁸, sevoflurane with tau protein phosphorylation⁹ and inflammatory mediators activation¹⁰, and propofol or isoflurane in altered hippocampal cell proliferation¹¹ among many other theories, but the exact pathogenesis of POCD has not been clarified.

Moreover, it has been hypothesized that POCD is the result of multiple variables that encompass the surgical process and not just anesthesia. For example, in a study done in rat models of metabolic syndrome this was associated with a reduction in learning capacity at postoperative day 7 and 5 month later compared to rats without metabolic syndrome¹². Postoperative inflammation has also been linked to the development of POCD in a rat model of tibial fracture surgery with disruption of the brain-blood barrier and macrophage migration via release of Tumor Necrosis Factor- α (TNF- α) and Nuclear Factor- $\kappa\beta$ (NF- $\kappa\beta$) signaling¹³. Stimulation of the cholinergic nicotinic receptor in this study prevented this inflammatory response and attenuated cognitive decline (anti-inflammatory cholinergic pathway).

In order to make progress on research about POCD it is necessary to know its true incidence. However, clinical studies have given different results for incidence of this condition after non-cardiac surgery. A systematic review published in 2007 by Newman et al.¹⁴ reported a POCD incidence for 22 days up to 6 months assessment that ranged between 6.2% and 56%, an interval too wide to be used as a reference incidence for this condition in subsequent studies. This is mainly due to the fact that the studies included used different time intervals to assess cognition, ranging from 7 days up to a year. In a consensus panel in 1995¹⁵ it was established that evaluation should ideally be at 3 months after surgery to avoid confounding factors such as use of drugs and hospitalization, assuming that patients are already in their home and evaluation would correspond to their real cognition status.

Apart from the timing of the postoperative assessment, the type of test, the number of tests administered, the characteristics of the control group, and method of calculation, have all led to the highly variable incidence of POCD reported.

The main objective of this systematic review (SR) was to estimate the incidence of POCD at 3 months in adult patients over 18 years old after non-cardiac surgery under general or regional anesthesia. This would inform on the current standing of POCD and help direct future research.

Methods

This SR was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement¹⁶. An internet search was done in May – July 2015, every study we found that was published before this date was included in the reviewing process. PubMed database was searched using the strings (Figure 1).

Excerpta Medica database (EMBASE), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Literatura Latinoamericana en Ciencias de la Salud (LILACS), Clinical Trials, Scielo and Grey Literature Report databases were searched using the key words “cognition” AND “surgery”. A grey literature search was performed on Grey Literature Report for any paper that covered the topic “cognition” and “surgery” or “anesthesia”. Clinical Trials database was searched for results of studies not yet published.

Eligibility criteria

Studies that evaluated cognition in patients older than 18 years old who underwent any kind of anesthesia for a surgical procedure were selected.

Follow up in included studies had to be no less than 3 months. Neuropsychological testing had to be used at least once before surgery and at a minimum of 3 months to establish a diagnosis of POCD. We chose this timing in accordance to the “Statement of consensus

on assessment of neurobehavioral outcomes after cardiac surgery” issued in 1995¹⁵. This time frame would allow any effect of drugs or hospitalization to wear off. There was no limit to number of tests used.

Prospective studies were included, whether observational or controlled trials. Language had to be English or Spanish.

Exclusion criteria

Studies that focused on cardiac surgery or brain surgery patients (including vascular surgery involving intracranial or extracranial circulation) were excluded because physiopathology underlying a decline in cognition may have been attributable to other characteristics, such as direct brain damage or vascular affections. We did not exclude studies on vascular surgery patients, such as abdominal aortic aneurysm.

Studies that used only Mini-Mental Status Examination (MMSE) for evaluating cognitive dysfunction were excluded. The reason for excluding studies that only used this tool is that it was not designed to be applied repeatedly as decreases its sensitivity for detecting cognitive deficits, thus it is not suitable to be applied as a test for POCD¹⁷.

Reviews and letters to the editor were excluded.

Risk of bias and quality assessment

Bias was assessed by two blind independent reviewers using quality assessment tools for observational and controlled studies from the National Heart, Lung and Blood Institute (NHLBI). Each tool is comprised of 14 points that have to be answered “Yes”, “No” or “Other (cannot determine, not reported or not applicable)”. Global evaluation is subjective as there are no defined limits, it is intended

as an aid in evaluating bias and not to exclude studies. If discrepancies between reviewers were found, the lowest score achieved was used as global score. We arbitrarily considered an individual score over 9 to be a good quality study. If achieved score was 6 or below in a study, it was excluded from analysis.

Data extraction

Data extraction was made by one of the reviewers. Independent tables were made for observational studies and controlled studies. Selection of variables was done based on reviews that have been made about this topic^{6,18}. Missing data was calculated from available information. If this was not possible, we tried to contact authors. Results are presented as percentages and 95% confidence interval if reported by authors.

Statistical analysis

Total incidence was calculated as pooled number of patients with POCD divided by total patients in studies, multiplied by 100. We calculated confidence intervals (CI) with 95% precision. Agreement among observers was assessed by calculating weighted *kappa* estimator using R program (available from <https://www.r-project.org/>).

Results

Studies

Our search yielded 2610 studies of which twenty-four papers were selected for final reading, published between year 1990 and May 2015 (Figure 2). Patients included, number of tests used, interventions and comparisons and outcome assessment for prospective observational studies and controlled trials are described in Tables 1 and 2, respectively.

Eleven papers were rated as good quality, eleven were rated as fair quality and two rated as poor quality evidence. Disagreement was present in five papers, one observational study and four controlled trials. Median scores for quality assessment was 10 (IQR 9 – 11) deemed as a good overall rating. No study was excluded due to low quality (6 or below). Overall agreement was substantial according to weighted kappa estimator with a value of 0.73 (CI 95% 0.5 – 0.96).

Tables 3 and 4 present a summary of findings in each study for cohort studies and controlled studies, respectively. Bias assessment details are presented in Tables 5 for prospective cohort studies and Table 6 for controlled studies

Patients and risk factors

In total, there were 8314 patients in 24 studies who underwent a surgical procedure and 1797 non-surgical control patients.

Seventeen studies focused exclusively on patients who were aged over 60 years old. Average age across the studies was 68 years. Increasing age was a risk factor for developing POCD at 3 months in seven studies. Other significant risk factors were years of education found in three studies^{19–21}, use of sedative drugs in two studies^{22,23}, postoperative delirium in three studies^{19,21,24}. Presence of a mood disorder (depression), history of previous stroke, infectious or respiratory postoperative complication, POCD at discharge, time of bispectral index level below 40, and presence of leukoaraiosis or lacunae on brain imaging were identified as risk factors for 3 months-POCD, but only in one study each and not a consistent finding across studies.

Eleven studies focused on orthopedic surgery, mainly knee or hip replacement surgery. Fourteen studies included patients with regional anesthesia, thirteen of them with intravenous sedation used. In one study²⁵ sedation during epidural anesthesia was not used, but patient enrolling was compromised because of reluctance of patients to undergo a procedure without sedation.

Evaluation of cognition

Fifteen papers used a control group to evaluate cognition and four sub-studies from the ISPOCD group used the same group of non-surgical controls²². Sixteen studies used the reliable change index or Z-score described by Moller et al. in ISPOCD1 study²². This approach uses a standardized score to adjust for changes in score due to practice effects in neurocognitive tests and cognitive dysfunction is diagnosed if a change of 2 or more standard deviations (SD) exists in two or more neurocognitive tests or if a global score is below 2 SD compared to the control group. Other methods used to diagnose POCD were comparing raw scores between groups or deterioration of less than 2 SD in scores.

Median number of tests used was 5 (range 3 – 13) and two studies used a computerized program for neurocognitive testing. Timing of evaluation ranged among discharge from hospital up to 1 year after surgery.

Presence of a mood disorder was the most assessed confounding variable (13 studies). Intellectual quotient (IQ) was measured in 7 studies. Other confounding variables assessed were anxiety, self-perceived cognition, delirium, pain, activities of daily life and sleep. Evaluation of confounding factors was not uniform across studies, with considerable heterogeneity.

POCD incidence

Five studies used group analysis for comparing scores on neurocognitive testing. This method does not allow recognizing changes at individual level of cognition and is not suitable for estimating incidence.

Nineteen studies used individual analysis of neurocognitive testing thus allowing for incidence calculation. 756 of 6477 patients were diagnosed with POCD at 3 months according to the definition used in each of these studies. This allowed us to calculate an overall incidence of POCD of 11.7% [95% CI 10.9 - 12.5].

Discussion

Our search after data extraction yielded us an overall incidence of 11.7% of POCD at 3 months in adult patients after non cardiac surgery. This is consistent with the finding of the largest prospective cohort study (ISPOCD1). Increasing age was the most important risk factor for POCD identified in seven studies.

Since many of the studies on POCD are observational, definitive conclusions cannot be drawn about the relationship between use of anesthesia and POCD risk. It is difficult to establish with certainty based on current evidence whether POCD is the result of different noxious stimuli in an already deteriorated brain or the response of a normal brain to drug toxicity, as has been addressed previously²⁶.

This review differs from the one published by Newman et al.¹⁴ nearly ten years ago in which they included papers with different timing of neuropsychological testing. Evaluating cognition during the first postoperative week may be too early to reflect a real incidence of POCD due to the effect of other factors that may confound evaluation like opioid use for pain, postoperative infectious complications, and benzodiazepine use among others.

Only five studies of the nineteen that used a control group reported the incidence of cognitive dysfunction. This is mainly a reporting bias that precludes from performing a meta-analysis to obtain a pooled effect measurement. It is important to have a control group to account for practice effects and ceiling effects of neuropsychological testing⁷. It is not clear if an historical control group is appropriate for comparing results of neuropsychological testing in different populations and it would be preferable to sample a non-surgical group from the local area of the studies similar in age and chronic conditions as these factors may be confounding.

Another methodological difference across studies is the neurocognitive battery applied to patients. In one study that evaluated a computerized neurocognitive battery for evaluating POCD²⁷ there was only a moderate agreement between pencil and paper testing and the one administered through a computer. Thus it is not possible to compare studies that used these two different approaches.

There is no consensus to which test should be included in the evaluation of cognition in surgical patients. In the pilot study of neuroanatomical markers conducted by Price et al.²⁸ a secondary objective was to evaluate the sensitivity for each test. They conclude that the Stroop Color-Word Test is a key element in evaluating executive function. However, a standardized battery of tests has not been defined up to this date and other tests are often used in other trials, such as Mini-Mental State Examination which has been shown to be not reliable in diagnosing POCD because it is a dementia screening tool and learning effect has been demonstrated²⁹. Number of tests used also varied greatly between the studies found.

Timing of evaluation is another element that varies through studies. We sought to eliminate this variation by restricting inclusion criteria to studies that evaluate cognition at 3 months after surgery. Despite this, the majority of published literature that was excluded did not do a 3-month follow up. It is not clear which timing is best for evaluating cognition before and after surgery. If testing is done too early before surgery, there is a risk of subsequent cognitive decline associated with age before the surgery commences. If testing after surgery is done before 7 days there is a possibility of assessing the patient under influence of drugs that could affect cognitive functioning.

Study Limitations

A possible limitation in this review is that studies might have been missed. There is no MeSH term in PubMed associated with this condition so indexing of studies is made under different terms, such as “cognition” and “anesthesia”. These terms make the search too broad and there is the possibility of missing papers. To overcome this we checked references of the papers included and found no evidence of missing important studies, so we are confident our search was exhaustive.

The majority of studies were excluded because they did not meet inclusion criteria or met exclusion criteria. Many clinical studies use only MMSE for evaluating POCD and this is a major flaw in their methodology as was mentioned earlier in this review. Due to

language restrictions, some studies may have been missed. We decided to include only prospective studies because they are less prone to bias than retrospective studies, which may suffer from missing data or memory recall bias³⁰. Studies made on animals were also excluded because findings of incidence may be not extrapolated to human subjects, but we recognize that basic science studies are very important in making progress to determine the physiopathology and probable causes of POCD.

Another limitation of this review is that global incidence may be influenced by larger studies. Conversely, incidences reported by smaller studies may be biased by attrition rates or small sample size. We acknowledge that by grouping the large and small studies, the resulting incidence may be closer to those reported by the largest studies. Moreover, selected studies in this review focus on different types of patients (minor surgery, under 60 years, preexisting cognitive impairment) in contrast to the larger studies that focus mainly on one type of patient. Some of the studies were done on the same cohort of patients from a previous study and we tried to minimize this bias by excluding two trials from analysis. Apart from these two studies, which were excluded, we are not aware that patients were used in more than one study.

Another caveat of this SR is that we chose to include studies that diagnose POCD at 3 months after surgery. Many patients with POCD may have not returned for evaluation due to illness or cognition dysfunction. However, many studies selected this time frame for performing a late evaluation to allow patients to return to a state as close as it can be previous to surgery. Incidence of POCD is highest during the first 7 postoperative days and then declines²², so patients that persist with cognitive dysfunction at 3 months maybe represent a more fragile group of patients that certainly would benefit from therapy that reduces POCD at 3 months.

An important limitation in this SR is that studies included used different cutoffs for defining POCD. Most studies included used a 2 SD decline compared to the control population to diagnose POCD. Other studies used a 1 SD criteria and this yielded a higher incidence (46%) of POCD at one year after surgery. There is no consensus on what should be the ideal cutoff for defining POCD so global incidence calculated in this SR may be different from the real incidence, as evidence from this study that used this criteria shows that

patients that were diagnosed with POCD had a higher mortality than those that were not diagnosed with POCD (3.16% vs 1.25%). It remains as an important question for future studies to define an optimum cutoff that remains sensitive as well as specific enough for defining clinically meaningful POCD.

We conclude that causality between POCD and anesthesia cannot be established from current evidence. Further studies are needed before making any conclusions and surgery should not be delayed if deemed necessary. On the other hand, health care professionals should be aware of the possibility that patients may exhibit some form of neuropsychological impairment after a surgical intervention and that this is the result of different interactions (drugs, inflammation, poor functional, etc.).

We estimated an overall incidence of POCD was 11.7% at 3 months after surgery. Evidence concerning incidence of POCD is derived from heterogeneous studies in regard of methods used for diagnosis. Common criteria for a definition of POCD, a standard neuropsychological testing, the timing of evaluation and the diagnostic criteria has to be established before any definitive conclusions can be drawn from available evidence.

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Figure 1. Search strings used in PubMed.

1. ("postoperative period"[MeSH Terms] OR ("postoperative"[All Fields] AND "period"[All Fields]) OR "postoperative period"[All Fields] OR "postoperative"[All Fields]) AND ("Cogn Int Conf Adv Cogn Technol Appl"[Journal] OR "cognitive"[All Fields]) AND ("physiopathology"[Subheading] OR "physiopathology"[All Fields] OR "dysfunction"[All Fields])
2. ("postoperative period"[MeSH Terms] OR ("postoperative"[All Fields] AND "period"[All Fields]) OR "postoperative period"[All Fields] OR "postoperative"[All Fields]) AND ("Cogn Int Conf Adv Cogn Technol Appl"[Journal] OR "cognitive"[All Fields]) AND decline[All Fields]

Table 1. Characteristics of prospective cohort studies on POCD included.

Study, year	Type of study	Population	Controls	Nr. tests used	Follow up	Other assessments
1 Moller (ISPOCD1), 1998 ²²	MC	> 60 years; major abdominal, non-cardiac thoracic, orthopaedic surgery with GA	Yes	6	7 days, 3 months	Orientation, mood, IQ, self-perceived cognition, ADL

2	Dijkstra, 1999 ³¹	SC	> 60 years; major abdominal, non-cardiac thoracic, orthopaedic surgery with GA	Yes	4	7 days, 3 months	Mood, self-perceived cognition
3	Johnson, 2002 ³²	MC	Age 40-59 years; major abdominal, orthopedic surgery with GA	Yes	4	7 days, 3 months	Mood, self-perceived cognition, ADL
4	Canet, 2003 ³³	MC	> 60 years; minor surgery with GA, outpatient or inpatient with two nights of stay (one preoperative and one postoperative)	Yes (from ISPOCD1)	4	7 days, 3 months	Mood, subjective perceived cognition, ADL
5	Rasmussen, 2005 ³⁴	MC	> 60 years; major surgery under GA or RA	Yes (from ISPOCD1)	4	7 days, 3 months	Salivary cortisol
6	Benoit, 2005 ¹⁹	SC	Ages between 41 - 88 years; undergoing elective management of AAA with combined anesthesia	No	9	Discharge, 3 months	Mood, delirium, pain
7	Rodriguez, 2005 ³⁵	SC	Patients undergoing total knee arthroplasty with GA, RA or mixed; ages between 45-82	No	13	7 days, 3 months	Intellectual functioning, mood, emboli in MCA (TCD)
8	Monk, 2008 ³⁶	SC	Patients > 18 years; surgery under GA; stratified in 3 age groups	Yes	5	7 days, 3 months	Mood, anxiety, pain, ADL, delirium
9	McDonagh, 2010 ³⁷	SC	> 55 years; GA and/or RA for elective vascular, thoracic or major orthopedic surgery	No	5	6 weeks, 1 year	APOE4 allele
10	Ancelin, 2010 ³⁸	MC	> 65 years; elective orthopedic major surgery (hip or knee replacement); GA or RA	Yes	7*	8 days, 4 months, 13 months	Mood, ADL, subjective perceived cognition

11	Krenk, 2014 ³⁹	MC	Aged 60 years or more; total hip or knee arthroplasty in fast-track approach; GA or RA	Yes	4	7 days, 3 months	CRP, quality of sleep, educational level, pain
12	Price, 2014 ²⁸	SC	Aged 60 years or older; total knee arthroplasty under GA	Yes	11	3 weeks, 3 months, 1 year	Brain MRI, IQ, mood, anxiety, pain, emboli (TCD)
13	Shoair, 2015 ²³	SC	> 65 years; elective knee or hip joint replacement and simple posterior cervical or lumbar spine surgery; no mention of type of anesthesia	Yes	5*	3 months	Mood, sleep, APOE4 allele, CRP
14	Silbert, 2015 ⁴⁰	MC	Aged 60 years or older; total hip joint replacement surgery; GA or RA anesthesia	Yes	7	7 days, 3 months, 1 year	IQ, mood, anxiety

Abbreviations: SC - Single center, MC - Multicentric, TCD - Transcranial Doppler, CRP - C-reactive protein, ADL - Activities of daily life, MCA - Middle cerebral artery, IQ - Intelligence coefficient, RA - Regional anesthesia, GA - General anesthesia

*: used computerized testing

Table 2. Characteristics of controlled studies on POCD included.

Study, year	Type of	Population	Interventio	Comparison	Control	Follow up	Nr. Tests	Other assessments
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		study		n		group		used	
1	Nielson, 1990 ⁴¹	RCT	Aged 60 or more; elective hip or knee replacement	RA	GA	No	3 months	7	Sickness impact profile
2	Jones, 1990 ⁴²	RCT	Aged 60 or more; elective hip or knee replacement	RA	GA	Yes	3 months	4	IQ, subjective cognition, ADL
3	Williams- Russo, 1995 ⁴³	RCT	Aged 40 or older; elective unilateral knee replacement	RA	GA	No	1 week, 6 months	10	IQ, mood, comorbidity index (Charlson), delirium
4	Rasmussen, 2003 ⁴⁴	MC RCT	Aged 60 or older; major surgery with RA or GA	RA	GA	Yes (from ISPOCD1	7 days, 3 months	4	Mood, ADL, subjective cognition
5	Rasmussen, 2006 ⁴⁵	RCT	Aged 60 or older; knee replacement surgery under RA or GA	Xenon	Propofol	Yes (from ISPOCD1)	Discharge, 3 months	4	
6	Salazar, 2011 ⁴⁶	RCT	Aged 65 or older; knee replacement surgery under RA	Active warming	No active warming	Yes	4 days, 3 months	10	Mood, anxiety, subjective cognition
7	Ballard, 2012 ⁴⁷	PC with nested RCT, MC	Aged 60 years or older; major abdominal or orthopedic surgery	BIS + rSO2 unblinded	BIS + rSO2 blinded (usual care)	Yes	7 days, 12 weeks, 1 year	3 plus MMSE	S100 β (brain damage biomarker)

under GA									
8	Chan, 2013 ²¹	RCT	Aged 60 years or older; major surgery under GA	BIS unblinded	BIS blinded	Yes	7 days, 3 months	3	Delirium, subjective cognition, functionality
9	Radtke, 2013 ²⁴	RCT	Aged 60 years or older; surgery under GA	BIS unblinded	BIS blinded	Yes	7 days, 3 months	6	Delirium
10	Silbert, 2014 ²⁵	RCT	Aged 55 or older; ESWL under GA or RA	GA	RA	Yes	7 days, 3 months	8	Fatigue, anxiety, mood, IQ

Abbreviations: MC - Multicentric, RCT - Randomized Clinical Trial, PC - Prospective cohort, GA - General anesthesia, RA - Regional anesthesia, ESWL - Extra-corporeal shockwave lithotripsy

Table 3. Summary: Findings in prospective cohort studies of POCD.

	Study, year	N	Controls	Lost to follow up	Method to diagnose POCD	POCD at 3 months (%[95% CI])	POCD in controls at 3 months (%[95% CI])	Comments
1	Moller (ISPOCD1), 1998	1218	321	271 (22%)	Z-score	94/947 (9.9% [8.1 - 12.0])	2.8% [0.9 - 6.5]	Age and benzodiazepine use were identified as risk factors
2	Dijkstra, 1999	56	50	8 (14%)	Z-score	4/48 (8%)	1/50 (2%)	
3	Johnson, 2002 (ISPOCD2)	508	183	86 (16.9%)	Z-score	26/422 (6.2% [4.1 - 8.9])	7/169 (4.1% [1.7 - 8.4])	Self-perceived cognition problems were associated with depression
4	Canet, 2003 (ISPOCD2)	372	Same as ISPOCD 1	69 (18.5%)	Z-score	20/303 (6.6% [4.1 - 10.0])	Same as ISPOCD1	Age and inpatient as risk factors
5	Rasmussen, 2005	187	Same as ISPOCD 1	36 (19.2%)	Z-score	23/151 (15.2% [9.9 - 22.0])	Same as ISPOCD1	158 patients were in another study; loss of diurnal variation of cortisol levels associated with POCD at 7 days but not 3 months
6	Benoit, 2005	102	No	26/102 (25.5%)	MANCOVA	NI	----	Age and education as risk factors for cognitive decline
7	Rodriguez, 2005	37	No	9/37 (24.3%)	3 or more tests with decline in	5/28 (18%)	----	Postoperative complications as risk factor

) 0.5 SD								
8	Monk, 2008	1064	182 (loss of 28)	138/1064 (13%)	Z-score	74/926 (8.0%)	8/182 (4.4%)	Age as risk factor; 13% POCD at 3 months in elderly group; mortality increased in group with POCD at discharge and 3 months
9	McDonagh, 2010	394	No	103/394 (26.1%)	1 SD or more in one of the four domains evaluated	1 year: 135/291 (46.3%)	----	No association with APOE4; unusually high rate of POCD at 1 year
10	Ancelin, 2010	270	310	99/270 (36.7%)	Decline of one point between baseline and posterior visits	NI	NI	Decline in two domains at 13 months; improvement in other domains
11	Krenk, 2014	200	161	25/225 (11.2%)	Z-score	16/199 (8.0% [4.5 - 12.0])	NI	No association between CRP levels and POCD
12	Price, 2014	40	15	3/40 (7.5%)	Z-score	Memory 25% (9/37), executive function 22% (8/37)	NI	Leukoaraiosis/lacunae on MRI were associated with cognitive decline after surgery; number of patients with POCD not informed and were calculated

13	Shoair, 2015	75	54	6/75 (8%)	Z-score	11/69 (15.9% [7.3 - 24.6])	NI	Use of sevoflurane, anticholinergic medication and APOE4 carrier were risk factors for POCD
14	Silbert, 2015	300	51	16/300 (5.3%)	Z-score	27/284 (10% [6.0 - 13.0])	2/48 (4.2% [-2.0 - 10.0]	PreCI defined as a decline of 2 SD on two or more of seven tests compared to population, present in 32% of patients; patients with PreCI were more likely to develop POCD; age not a significant association

Abbreviations: MANCOVA - Multiple Analysis of Covariance, SD - Standard deviation, NI - Not informed, PreCI - Previous cognitive impairment, CI 95% - Confidence interval 95%

Table 4. Summary: Findings in controlled studies on POCD.

	Study, year	N	Interv.	Comp.	Controls	Lost to follow up	Method to diagnose POCD	POCD at 3 months (%[95% CI])	POCD in controls at 3 months (%[95% CI])	Comments
1	Nielson, 1990	98	25	39	NI	34/98 (35%)	ANCOVA	NI	NI	More patients from RA lost to follow up; no difference in cognition between groups
2	Jones, 1990	146	74	72	50	RA 9; GA 8; 17/146 (11.6%)	Comparison between before and after scores	NI	NI	9 patients received general anesthesia instead of regional; improvement in scores in GA group
3	Williams- Russo, 1995	262	134	128	NI	RA 19; GA 10; 29/260 (11%)	Delphi panel consensus; deterioration of 3 points in a converted score was defined as POCD	6 months: 7/114 (6%) in RA group; 5/117 (4%) in GA group; total 12/231 (5.2%)	NI	6 patients crossed treatment groups (3 in GA and 3 in RA); no statistical difference between groups
4	Rasmussen, 2003	428	211	217	From ISPOCD 1	RA 46; GA 42; 88/428 (20.6%)	Z-score	25/175 (14.3% [9.5 - 20.4]) in GA group vs. 23/165 (13.9%	Same as ISPOCD1	24 patients crossed from RA group to GA group and 35 patientes crossed form GA to RA; sample

								[9.0 - 20.2]) in RA group; total 48/340 (14.1%)		size not achieved due to technical problems; no statistical difference between groups
5	Rasmussen, 2006	39	21	18	From ISPOCD 1	4/39 (10.3%)	Z-score	3/18 (16.7% [4.0 - 44.1]) in xenon vs. 2/16 (12.5% [2.0 - 38.0]); total 5/34 (14.7%)	Same as ISPOCD1	Feasibility study; no statistical difference between groups
6	Salazar, 2011	150	75	75	55	Standard care 12/75 (16%); active warming 13/75 (17.3%); total 25/150 (16.7%)	Z-score	14/62 (22.6%) in active warming; 13/63 (20.6%) in standard care; total 27/125 (21.6%)	NI	More patients in the active warming group developed POCD, although not statistically significant at 3 months
7	Ballard, 2012	72	34	38	NI	6/34 (17.6%) intervention group; 4/38 (10.5%) control group; total 10/72 (13.9%)	Z-score, different levels of POCD according to number of SD	2/24 (8.3%) intervention group vs. 4/33 (12.1%) control group; total 6/57 (10.5%)	1 year: 3.8% for severe POCD; no data on 3 months	Data on loss presented for 3 months; data for POCD incidence at 3 months is for severe POCD (1.96 SD as defined by authors); global incidence of

										severe POCD at 52 weeks 11.2% (cohort part of study)
8	Chan, 2013	921	462	459	221	32/462 (6.9%) BIS guided; 25/459 (5.4%) routine care; total 57/921 (6.2%)	Z-score	42/412 (10.2%) BIS guided vs. 62/423 (14.7%) standard treatment; total 104/835 (12.5%)	NI	BIS guided group had higher values than BIS blinded group (median 53 vs. 36); adjusted OR 0.67 [0.32 - 0.98] for POCD at 3 months when using BIS; fewer episodes of delirium in BIS guided group
9	Radke, 2013	1277	638	639	93	63/638 (9.9%) in BIS guided; 59/639 (9.2%); total 122/1277 (9.6%)	Z-score	21/575 (8.0%) BIS guided vs. 28/580 (10.3%); total 49/1155 (4.2%)	NI	Trial stopped early due to insufficient funding; delirium during hospitalization found to be risk factor for POCD; no correlation between BIS use and POCD at 3 months; unblinding of BIS in 141 patients
10	Silbert, 2014	98	50	48	51	6/50 (12%) GA group; 2/48 (4.2%) RA group;	Z-score	3/44 (6.8% [1.4 - 18.7]) in GA group; 9/46 (19.6%	2/48 (4.2% [- 2.0 - 10.0]	6 year recruitment period due to low acceptance of patients; 6 patients in the RA group crossed to GA

total 8/98 (8.2%)	[9.4 - 33.9]) in RA group; total 12/90 (13.6%)	group (12.5%);
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Abbreviations: Interv. - Intervention group, Comp. - Comparison group, GA - General anesthesia, RA - Regional anesthesia, ANCOVA - Analysis of covariance, NI - Not informed, CI 95% - Confidence interval 95%

Table 5. Bias assessment for prospective cohort studies. Observations are presented for rater 1/rater 2 in each level.

	Moller, 1998	Dijkstra, 1999	Johnson, 2002	Canet, 2003	Rasmussen, 2005	Benoit, 2005	Rodriguez, 2005	Monk, 2008	McDonagh, 2010	Ancelin, 2010	Krenk, 2014	Price, 2014	Shoair, 2015	Silbert, 2015
1. Question	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1
2. Population	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1
3. Participation	1/3	3/1	1/1	3/1	3/3	3/3	3/3	1/1	1/1	3/1	1/1	3/1	1/1	1/1
4. I/E criteria	1/1	1/1	1/1	3/1	2/1	1/1	3/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1
5. Sample size	1/1	2/2	1/1	1/1	1/1	2/2	2/2	1/1	1/1	2/2	1/1	1/1	2/2	1/1
6. Prior exp	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1
7. Timeframe	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1
8. Level exp	2/3	3/3	3/3	3/3	1/3	3/3	3/3	3/3	3/3	2/3	3/3	3/3	1/3	2/3
9. Exp measure	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1
10. Exp > 1*	3/2	3/2	3/2	3/2	1/2	3/2	3/2	3/1	3/2	3/2	3/2	3/2	3/2	3/2
11. Outcome	1/1	1/1	1/1	1/1	1/1	2/1	1/1	1/1	1/1	2/1	1/1	1/1	1/1	1/1
12. Blind	3/3	2/3	2/3	2/3	2/3	3/3	1/3	3/3	3/3	2/3	3/3	1/3	1/3	3/3
13. Loss	2/2	1/1	1/1	1/1	1/1	2/2	2/2	1/1	1/1	2/2	1/1	1/1	1/1	1/1
14. Confounding	1/1	1/1	1/1	1/1	2/1	2/1	1/2	1/1	1/1	1/1	1/1	1/1	1/1	1/1
Rating Obs. 1	Good	Good	Good	Good	Good	Fair	Fair	Good	Good	Fair	Good	Good	Good	Good
Rating Obs. 2	Good	Fair	Good	Good	Good	Fair	Fair	Good	Good	Fair	Good	Good	Good	Good

Abbreviations: I/E - Inclusion/exclusion, Exp - Exposure, Obs - Observer

* Exposure assessed more than once.

1 = Yes

2 = No

3 = N/A not applicable, CD cannot determine, NR not reported

Table 6. Bias assessment for controlled studies. Observations are presented for rater 1/rater 2 in each level.

	Nielson, 1990	Jones, 1990	Williams- Russo, 1995	Rasmussen, 2003	Rasmussen, 2006	Salazar, 2011	Ballard, 2012	Chan, 2013	Radke, 2013	Silbert, 2014
1. RCT	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1
2. Randomization	3/1	3/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1
3. Allocation	3/2	3/1	3/2	1/2	1/1	1/2	1/1	1/1	2/2	1/2
4. Blind P/P	2/2	2/2	2/2	2/2	2/2	3/2	1/1	1/1	3/2	2/2
5. Blind outcome	1/1	1/1	2/3	2/2	1/1	1/1	1/1	1/1	2/1	1/1
6. Baseline	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	2/1
7. Drop-out	2/2	1/2	1/1	2/1	1/2	1/1	1/1	1/1	1/1	1/1
8. Diff drop out	1/2	1/2	1/1	1/1	1/2	1/1	1/1	1/1	1/1	1/1

9. Adherence	2/1	2/2	1/1	2/2	1/2	1/1	1/1	1/1	2/2	2/1
10. Co-interventions	1/1	1/1	3/1	3/1	1/1	1/1	1/1	1/1	1/1	1/1
11. Outcome	1/1	2/1	2/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1
12. Sample size	2/2	1/1	1/2	2/1	1/1	1/2	1/1	1/1	2/1	2/2
13. Subgroup	2/1	1/3	1/1	1/1	1/3	1/3	1/3	1/1	2/3	1/3
14. Intention to treat	1/1	1/1	1/1	1/1	1/1	1/1	3/1	1/1	1/1	1/1
Rating Obs. 1	Poor	Fair	Fair	Fair	Good	Good	Good	Good	Poor	Fair
Rating Obs. 2	Fair	Fair	Fair	Fair	Fair	Fair	Fair	Good	Poor	Fair

Abbreviations: RCT - Randomized clinical trial, P/P - Participants/providers, Diff - Differential, Obs - Observer

1 = Yes

2 = No

3 = N/A not applicable, CD cannot determine, NR not reported

1. ("postoperative period"[MeSH Terms] OR ("postoperative"[All Fields] AND "period"[All Fields]) OR "postoperative period"[All Fields] OR "postoperative"[All Fields]) AND ("Cogn Int Conf Adv Cogn Technol Appl"[Journal] OR "cognitive"[All Fields]) AND ("physiopathology"[Subheading] OR "physiopathology"[All Fields] OR "dysfunction"[All Fields])
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Author/s:

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