Long-term postoperative cognitive dysfunction in the elderly

Long-term postoperative cognitive dysfunction in the elderly: ISPOCD1 study

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Summary

Background Long-term postoperative cognitive dysfunction may occur in the elderly. Age may be a risk factor and hypoxaemia and arterial hypotension causative factors. We investigated these hypotheses in an international multicentre study.

Methods 1218 patients aged at least 60 years completed neuropsychological tests before and 1 week and 3 months after major non-cardiac surgery. We measured oxygen saturation by continuous pulse oximetry before surgery and throughout the day of and the first 3 nights after surgery. We recorded blood pressure every 3 min by oscillometry during the operation and every 15–30 min for the rest of that day and night. We identified postoperative cognitive dysfunction with neuropsychological tests compared with controls recruited from the UK (n=176) and the same countries as study centres (n=145).

Findings Postoperative cognitive dysfunction was present in 266 (25·8% [95% CI 23·1–28·5]) of patients 1 week after surgery and in 94 (9·9% [8·1–12·0]) 3 months after surgery, compared with 3·4% and 2·8%, respectively, of UK controls ($p<0·0001$ and $p=0·0037$, respectively). Increasing age and duration of anaesthesia, little education, a second operation, postoperative infections, and respiratory complications were risk factors for early postoperative cognitive dysfunction, but only age was a risk factor for late postoperative cognitive dysfunction. Hypoxaemia and hypotension were not significant risk factors at any time.

Interpretation Our findings have implications for studies of the causes of cognitive decline and, in clinical practice, for the information given to patients before surgery.

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Introduction

Early postoperative cognitive dysfunction, confusion, and delirium are common after major surgery in the elderly.[1,2] Previous studies and anecdotal reports suggest that symptoms may persist in some patients for months or years.[3] Events such as anaesthesia may contribute to age-related cognitive decline, even when they occurred many years previously.[4] Long-term postoperative cognitive dysfunction can occur after cardiac surgery, but the cause was thought to be the cardiopulmonary bypass.[5,6] The prevalence, causes, risk factors, and consequences of long-term postoperative cognitive dysfunction after non-cardiac surgery are unknown.

The monitoring of oxygen saturation has shown that hypoxaemia is most severe during nights 2 and 3 after surgery.[7] Studies to characterise risk factors, to identify the deleterious effects of hypoxaemia on the heart, brain, and other organs, and to clarify the influence of hypoxaemia on outcome after surgery have been called for.[8]

In a multicentre study (the International Study of Post-Operative Cognitive Dysfunction [ISPOCD 1]), we investigated the occurrence of long-term postoperative cognitive dysfunction in elderly patients after major abdominal and orthopaedic surgery. We assessed the role of age as a major risk factor, and the causative roles of hypoxaemia and hypotension.

Methods

The protocol was approved by the research ethics committees in the centres and all patients gave written informed consent.

13 hospitals in eight European countries and the USA recruited patients to the study by the same protocol. Eligible patients were aged at least 60 years, had presented for major abdominal, non-cardiac thoracic, or orthopaedic surgery under general anaesthesia between Nov 1, 1994, and May 31, 1996, and expected a hospital stay of at least 4 days. We gave priority to patients presenting for major abdominal and thoracic surgery. Centres were asked to recruit no more than 25% of their patients from those admitted for major orthopaedic surgery (hip and knee arthroplasty). Patients could not be included twice, even if they had an unrelated second procedure. We excluded patients if they had: a score on the mini-mental state examination (MMSE)[9] at screening of 23 or less; a disease of the central nervous system; were taking tranquillisers or antidepressants; had been admitted for neurological or cardiac surgery; previously undergone neuro-psychological testing; were unwilling to comply with the protocol or procedures or were unable to understand the language used; had any severe visual or auditory disorders; were illiterate; had Parkinson's disease; alcoholism, or drug dependence; and if they were not expected to be alive for discharge from hospital or to be able to complete tests at 3 months after surgery.

Characteristic*	Patients (n=947)	UK controls (n=176)
Age (years)	68 (60–79)	67 (61–81)
Sex (M/F)	485 (51%)/464 (49%)	101 (57%)/75 (43%)
Cattell culture-fair IQ test	5 (2–10)	8 (3–11)
Zung depression scale	35 (24–49)	34 (24–47)
Cognitive failures questionnaire	33 (13–76)	36 (16–57)

*Data are median (5th–95th percentile) except for sex.

Table 1: **Characteristics of patients and UK controls**

We calculated that a sample size of 900 patients would be sufficient to show an association between postoperative oxygen saturation and a decrease in cognitive function with a power of 95%, and a 5% risk of a type I error. We assumed an overall risk of long-term postoperative cognitive dysfunction of 10%, and the association was quantified as an odds ratio of 1·5 for patients with hypoxaemia 1 SD below the mean. A sample size of 900 also allowed for other risk factors to enter the model, with a multiple correlation coefficient to hypoxaemia of up to 0·3.

We recorded details of medical and drug histories and baseline physiological variables at recruitment with purposely designed software. We placed no restrictions on the anaesthetic or surgical techniques, which conformed to local practice. During surgery, however, capnography was required to ensure normocapnia. We recorded all drugs administered before surgery, and the operative procedure and all complications were recorded with the date of discharge from hospital. At follow-up, we recorded all complications that occurred and all drugs that were administered after discharge. Explanations for all deviations from the protocol and the circumstances of any patient withdrawing from the study were recorded.

Patients completed neuropsychological tests at entry to the study—generally the day before surgery—and at discharge from hospital or 1 week, whichever was earlier, and 3 months after surgery.

We measured oxygen saturation by continuous pulse oximetry throughout the night before and during surgery, for the first 24 h and during nights 2 and 3 after surgery. We used 6 s as the averaging time for oximetry, and a value was stored in the data-collection system every 10 s. If recording during the night before surgery was not possible, we made recordings during a short period before induction of anaesthesia. Arterial blood pressure was measured by oscillometry every 3 min during surgery, every 15 min in the recovery room, and every 30 min for the first 24 h on the ward after the operation. Oximetry and blood-pressure values were not available to the ward staff caring for the patient, and additional monitors were used if these measurements were required for clinical purposes. Oxygen therapy was prescribed at the discretion of the surgeon or anaesthetist and administration was noted on the database.

All data for neuropsychological tests and physiological recordings were collected on computer disk and transferred to a central database in Eindhoven. Completeness of data collection and data validity were checked by the program. We eliminated artefacts from the pulse oximetry data before they were entered on to the database (details available from the investigators). We checked that the system was reliable and neuropsychological tests were familiar to investigators during a pilot study in all centres.

We required that the neuropsychological tests were sensitive, not influenced by culture, suitable for use in this study population, and took no longer than 45 min to complete. We assessed 12 single tests on 50 volunteers of similar age to the study population, and we selected the most appropriate tests for our study. We used these tests, before the start of the study, in 176 volunteers from the UK, recruited as controls through advertisements with the same criteria as the study patients. To ensure that controls were representative of all nationalities, we also recruited 145 national controls, aged at least 60 years, who were partners of patients included in the study or were recruited through advertisement in the same countries as the study centres. All controls underwent neuropsychological testing in the same way as the patients, and none was admitted to hospital.

Complication	Patients (n=1218)
Major cerebral	7 (0·6%)
Minor cerebral	99 (8·1%)
Respiratory	147 (12·1%)
Cardiovascular	186 (15·3%)
Infection	168 (13·8%)
Long stay in intensive care (>24 h)	202 (16·6%)
Second operation	67 (5·5%)

Table 2: **Postoperative complications in whole group**

The neuropsychological tests were translated into the native languages of the participating countries (Danish, Dutch, French, German, Greek, and Spanish) and tests that might be culturally sensitive (eg, the visual verbal learning test) were validated in those languages.

The first test was the visual verbal learning test, based on Rey's auditive recall of words.[10] A list of 15 words had to be learned in three consecutive presentations at a fixed rate on a computer screen. The patients were asked to recall as many words as possible. We noted the number of correctly recalled words. The second test was the concept shifting test, based on the trail-making test from Halstead and Reitan's neuropsychological test battery.[11] We measured time taken and counted the number of errors. The fourth test was the Stroop colour word interference test.[12] We recorded the time and number of errors made for each part. The fourth was the paper and pencil memory scanning test,[4] for which we noted the time taken and number of errors made (omissions or wrong letters). The fifth test was the letter-digit coding, based on the symbol-digit substitution task from the Wechsler adult intelligence scale.[13] We recorded the number of correct answers. The sixth test was the four boxes test.[14] We measured the reaction time by computer, four choices for 52 responses and calculated an error score and a median value of all correct responses.

We measured all other times with a stopwatch, and participants were asked to work as fast and accurately as possible. Three parallel versions of the letter-digit coding, memory scanning task, concept shifting task, and visual verbal learning tests were given in random order.

The tests were carried out in quiet rooms in each study centre and only the patient and investigator were present. If the patient could not be tested in the test room, we tried to find a quiet setting on the ward or in the patient's home. Investigators were trained to administer the tests by the psychologists responsible for development of the test battery, and regular site visits were made to ensure uniform collection of data and administration of tests.

Risk factor	1 week		3 months	
	Number of patients	Patients with POCD	Number of patients	Patients with POCD
Age (years)				
60–69	586	135 (23%)	532	37 (7%)
⩾70	425	123 (29%)	378	4 (14%)
Complication				
Hypoxaemia*	115	30 (26%)	98	11 (11%)
Hypotension†	229	60 (26%)	214	51 (9%)
Respiratory complication	99	40 (40%)	88	12 (14%)
Infectious complication	91	30 (33%)	138	12 (9%)
Second operation	24	13 (54%)	50	7 (14%)
Duration of anaesthesia (min)				
⩽120	196	35 (18%)	179	2 (11%)
121–240	503	121 (24%)	448	40 (9%)
⩾241	312	103 (33%)	283	4 (11%)
Education				
Less than high school	576	156 (27%)	518	47 (9%)
High school	290	75 (26%)	260	26 (10%)
More than high school	145	31 (21%)	132	16 (12%)
Benzodiazepines before surgery	116	33 (28%)	105	5 (5%)

POCD=postoperative cognitive dysfunction.
*One or more episodes of oxygen saturation ⩽80% for >2 min.
†One or more episodes of mean arterial pressure ⩽60% for ⩾30 min.

Table 3: **Proportion of patients with postoperative cognitive dysfunction at 1 week and 3 months by risk factor**

Risk factor	First postoperative test (n=1011)	
	p	Odds ratio (95% CI)
Age (difference of 10 years)	0·03	1·3 (1·0–1·7)
Hypoxaemia*	0·34	0·8 (0·5–1·3)
Hypotension†	0·74	1·0 (0·7–1·6)
Duration of anaesthesia (difference of 1 h)	0·01	1·1 (1·0–1·3)
Second operation	0·03	2·7 (1·1–6·5)
Respiratory complication	0·05	1·6 (1·0–2·6)
Infectious complication	0·04	1·7 (1·0–2·8)
Education at high school *vs* less than high school	0·002	0·6 (0·4–0·9)
Education at more than high school *vs* less than high school	. .	0·5 (0·3–0·8)
Centre	0·0001	. .

Table 4: **Analysis of major risk factors in relation to first postoperative test**

Before the operation, we estimated each participant's intelligence by part III of the Cattell culture-fair IQ test.[15] Mood was determined with the Zung depression scale,[16] and patients self-assessed cognitive decline from the short cognitive-failures questionnaire.[17]

After the operation, we used the orientation section of the MMSE each day to screen for confusion and delirium, and patients completed our neuropsychological tests and Zung scale at discharge or on day 7, whichever was earlier. Patients who were too ill to take the first postoperative test were tested as soon as possible after week 1. Patients also completed our neuropsychological tests, the Zung scale, and the cognitive-failures questionnaire 3 months after surgery.

Finally, at the same time as the postoperative tests, we estimated the activity of daily living score by five questions related to shopping, domestic work, preparation of meals, bodily care, and dressing. For each of the questions, a score of −1 showed decline, 0 showed no change, and 1 showed improved activity.

In the final assessment, we used four tests (visual verbal learning, concept shifting, Stroop, and letter-digit coding) that had correlated strongly with age and IQ in the UK controls. From the visual verbal learning test, we used the cumulative number of words recalled in three trials and the number of words at delayed recall; from the concept shifting test, we used time and number of errors in part C; in the Stroop colour word interference test, part three, we used time and error scores; and from the letter-digit coding test the number of correct answers.

We identified patients with long-term postoperative cognitive dysfunction by comparison of changes in individual patients with changes in test scores of UK controls, which allowed us to correct for learning effect. We used a cut-off test score to show deterioration that was expected to occur in less than 3·5% of UK controls.

We compared changes in performance among UK controls for each test from baseline (first session) to 1 week and 3 months after surgery. We calculated the mean (SD) of these differences. The mean changes may be taken as estimated learning effects.

For patients, we compared baseline scores with 1 week and 3 month test results, subtracted the average learning effect from these changes, and divided the result by the control-group SD to obtain a Z score for each test. Large positive Z scores showed a deterioration in cognitive function from baseline in patients compared with controls. We defined a composite Z score from the total of the Z scores for the UK controls, the SD of which we used to normalise the patients' composite Z scores at 1 week and 3 months. Patients had cognitive dysfunction when two Z scores in individual tests or the combined Z score were 1·96 or more. This definition took into account general deterioration (in all tests) or substantial deterioration in only some tests. We analysed the results for the national controls in the same way to ensure that the definition of cognitive dysfunction could be applied to patients of all nationalities.

For secondary data analysis we used multiple logistic regression to investigate associations between risk factors, especially postoperative hypoxaemia, and impaired performance on the neuropsychological tests 1 week or 3 months after surgery. We included a term for study centres to correct for variations between countries and data collection centres. We assessed the relation between activity of daily living score and long-term postoperative cognitive dysfunction by test for trend in proportions and Spearman's rank-correlation analysis on the composite Z score.

Results

We enrolled 176 UK controls, 145 national controls and 1218 patients. 271 (22%) patients did not complete the assessment at 3 months because of refusal to participate (118) and death (57). Those who withdrew did not differ significantly in any characteristics from those who continued in the study. The age, sex distribution, and other characteristics of the patients and the UK controls were similar (table 1).

At 7 days (5th–95th percentile 4–19) after surgery, we found cognitive dysfunction in 266 (25·8% [95% CI 23·1–28·5]) of patients. The second postoperative test was done a median of 99 days (5th–95th percentile 72–146) after the operation, and we found cognitive dysfunction in 94 (9·9% [8·1–12·0]) of patients. In the UK control group, 3·4% (1·3–7·3) of participants had scores that showed cognitive dysfunction at 1 week, and 2·8% (0·9–6·5) at 3 months ($p<0·0001$ and $p=0·0037$, respectively). The national controls did not differ from the UK control group in any of the tests.

Seven patients had major cerebral complications after surgery (table 2). Of these, four could not complete the test at 1 week and were excluded from the study.

We found a significant relation between early postoperative cognitive dysfunction and increasing age, increasing duration of anaesthesia, little education, second operation, postoperative infections, and respiratory complications (tables 3 and 4). We found significant associations between long-term (3 months) postoperative cognitive dysfunction and age (odds ratio 2·1 [1·4–2·9] $p<0·0001$]) and benzodiazepines before surgery (0·4 [0·2–1·0], $p=0·03$, table 5).

Benzodiazepines before surgery seemed to have a protective effect against long-term postoperative cognitive dysfunction, but 53 of the 116 patients who received benzodiazepines had discontinued their use at 3 months, and none of these had cognitive dysfunction. The frequency of long-term postoperative cognitive dysfunction among patients who had continued taking benzodiazepines was similar to that of the remaining patient population. 31 patients had been started on benzodiazepines before the 3-month test and among these 19% had long-term postoperative cognitive dysfunction.

We found no relation between different degrees and durations of hypoxaemia or hypotension and early and late postoperative cognitive dysfunction. Hypoxaemia was common among patients in the perioperative period.

Risk factor	3-month test (n=910)	
	p	Odds ratio (95% CI)
Age (difference of 10 years)	0·0001	2·1 (1·4–2·9)
Hypoxaemia*	0·60	1·2 (0·6–2·4)
Hypotension†	0·54	0·9 (0·5–1·4)
Benzodiazepines before surgery	0·03	0·4 (0·2–1·0)
Centre	0·18	. .

*Oxygen saturation ⩽80% for >2 min.
†Mean arterial blood pressure ⩽60% for ⩾30 min.

Table 5: **Relation of major risk factors to results of 3-month test**

Oxygen saturation of 80% or less for more than 2 min occurred in 11% of patients and oxygen saturation of 75% or less for more than 5 min occurred in 4%. During the night before surgery, oxygen saturation of 80% or less for more than 2 min was recorded in 1% of patients and saturation of 75% or less for more than 5 min in only 0·1%. Hypotension was common after surgery. 23% of patients had mean arterial blood pressure of 60% or less of the reference value before surgery for 30 min or more during or in the first 24 h after surgery. In 7% of patients mean arterial blood pressure was 50% or less of the reference value for 30 min or more. In a sample of 88 patients in whom blood pressure was monitored during the night before surgery, 5·7% had mean arterial blood pressure of 60% or less of the reference value for 30 min or more; no patient had mean arterial blood pressure of 50% or less for 30 min or more.

Only seven patients had simultaneous mean arterial blood pressure of less than 60% of the reference value and oxygen saturation of 80% or less for more than 2 min, of whom none had cognitive dysfunction at 3 months.

No relation was found between: ASA physical status, history of lung disease, heart disease, peripheral ischaemia, hypertension, head injury, stroke, atrial fibrillation, delirium, cardiovascular complications, diagnosis of cancer, long-term stay in the intensive-care unit, major drug groups, anaesthetic technique, postoperative-pain treatment, smoking, alcohol consumption, blood loss, perioperative fluids given, type of operation, and sex.

We found no correlation between the cognitive failures questionnaire scores and long-term postoperative cognitive dysfunction or between the Zung depression rating scale and early or long-term postoperative cognitive dysfunction. The correlation between a decline in the activity of daily living and long-term postoperative cognitive dysfunction was significant ($p<0·005$).

Discussion

We confirmed unequivocally that anaesthesia and surgery cause long-term postoperative cognitive decline in the elderly and that the risk increases with age. However, neither hypoxaemia nor hypotension was related to the risk. We were unable to find any specific risk factors to which therapeutic or preventive measures could be directed and we could not elucidate the pathophysiology of postoperative cognitive dysfunction any clearer.

Cerebral hypoxia can lead to severe brain damage, but the degree and duration of hypoxaemia in this study did not seem to affect the brain. This finding is in accord with a study in which 20 802 patients were randomly assigned monitoring with or without a pulse oximeter during and after surgery. Pulse oximetry monitoring did not decrease the number of postoperative complications,[18,19] although the rate of hypoxaemia in operating and recovery rooms was decreased by oximetry.[20] Neither pulse oximetry nor blood-pressure measurements are accurate when oxygen saturation or blood pressure is low, and we could not predict "safe" degrees of hypoxaemia and hypotension in this population.

The effect of centre in the risk-factor analysis for early postoperative dysfunction may reflect differences in procedures, anaesthetic agents, and population characteristics, but cannot be explained by this analysis.

Although Bedford[3] showed that postoperative cognitive dysfunction may occur in elderly patients, several investigations have found no evidence of long-term postoperative cognitive dysfunction after general surgery.[21–24] The methods of these studies had weaknesses, such as no appropriate control group or small sample size. The sensitivity of the tests used has not been investigated and the practice effect has been ignored. Many studies have used tests developed for diagnosis in neurological patients or to measure intelligence-related constructs in normal controls and patients, not to assess medical or other interventions. Moreover, most studies have been designed to find differences between two treatment groups rather than to investigate the existence of postoperative cognitive dysfunction. Despite our rigorous definition of postoperative cognitive dysfunction, we were able to identify cognitive deficits in a high proportion of patients. We believe this difference from previous studies could be explained by the inclusion of appropriate neuropsychological tests and correction for learning effects.

The high rate of postoperative cognitive dysfunction in our study, 25·8% at 1 week and 9·9% after 3 months, may not reflect the true rate in the general surgical population. We studied elderly patients undergoing major surgery as the group most likely to be at risk. However, these patients were not especially ill, physically or mentally, before surgery. Continuing ill health and frailty, which might be expected to be associated with a greater risk of postoperative cognitive dysfunction, commonly led to withdrawal. Wishes to conceal a degree of cognitive impairment may also have resulted in withdrawal.

We found no correlation between the patients' reports of cognitive impairment (cognitive failures questionnaire) and the neuropsychological test results. Such discrepancies are well known.[25,26] Additionally, the questions in the cognitive failures questionnaire may not have reflected the patients' current lifestyles. Future studies should use questions directed at patients and their carers. We showed that long-term postoperative cognitive dysfunction correlates significantly with decreasing activity of daily living, which suggests that patients with postoperative cognitive dysfunction need more assistance with everyday actions than before surgery. Postoperative cognitive dysfunction seems not to be related to depression. A similar conclusion has been reported in a study after coronary-artery bypass grafting.[27]

Whether postoperative cognitive dysfunction is a permanent disorder of irreversible brain damage associated with structural cerebral changes and neuron loss still needs to be confirmed. The possibility of postoperative cognitive dysfunction after minor surgery in elderly patients and major surgery in younger patients also warrants investigation. Causes other than those tested in our study may include effects of anaesthetic agents on central neurotransmission, such as cholinergic and glutamatergic function.

Hypoxaemia and hypotension did not seem to be major causes of postoperative cognitive dysfunction in our study, but these and drug-related factors may be important in some individuals. Environmental factors cannot be excluded, although we do not believe them to be important since we excluded the most frail patients with pre-existing cognitive impairment by the MMSE test.

The existence of postoperative cognitive dysfunction has implications for research into premature cognitive decline from other causes. In clinical practice, the findings may have implications for the information given to elderly patients before surgery.

Participants in the International Study of Postoperative Cognitive Dysfunction
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Contributors

J T Moller coordinated the study. J T Moller, L S Rasmussen, and C D Hanning wrote the draft of the manuscript. J Jolles, P Rabbitt and P Houx were responsible for the neuropsychological test battery and supervised the data-collection centres. P Cluitmans and K Larsen were handled and analysed the data. All authors contributed to the planning, reviewing of data, and editing the final version of the manuscript.

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