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Is postoperative cognitive dysfunction a risk factor for dementia? A cohort follow-up study

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Editor's key points

- Postoperative cognitive dysfunction (POCD) has been proposed as a risk factor for the development of dementia.
- This study followed 686 Danish patients previously enrolled in the ISPOCD 1 and 2 studies for several years after surgery.
- There was no association between POCD at 1 week or 3 months and a later diagnosis of dementia or depression.
- POCD seems to be largely reversible, but further studies of its long-term effects are needed.

Background. Postoperative cognitive dysfunction (POCD) is a common complication in elderly patients after major surgery. An association between POCD and the development of dementia has been suspected. In this study, we assessed if POCD was a risk factor for the occurrence of dementia.

Methods. Danish patients enrolled between November 1994 and October 2000 in the two International Studies of Postoperative Cognitive Dysfunction (ISPOCD 1 and 2) were followed until July 1, 2011. Cognitive performance was assessed at three time points: before operation, at 1 week, and 3 months after surgery, using a neuropsychological test battery. The time of (first) occurrence of dementia after surgery was assessed using the National Patient Register and the Psychiatric Central Research Register. Recorded dementia diagnoses (ICD-8 and ICD-10) were: Alzheimer's disease, vascular dementia, frontotemporal dementia, or dementia without specification. The risk of dementia according to POCD was assessed in the Cox regression models.

Results. A total of 686 patients with a median age of 67 [inter-quartile range (IQR) 61–74] yr were followed for a median of 11.1 (IQR 5.2–12.6) yr. Only 32 patients developed dementia during follow-up. The hazard ratio (95% CI) for any dementia diagnoses in patients with POCD at 1 week (n=118) and POCD at 3 months (n=57) after surgery compared with those without POCD was 1.16 (0.48–2.78), P=0.74, and 1.50 (0.51–4.44); P=0.47, respectively.

Conclusions. POCD was not significantly associated with registered dementia over a median follow-up of 11 yr.

Keywords: dementia; postoperative cognitive dysfunction; postoperative complications

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Postoperative cognitive dysfunction (POCD) is a common complication among the elderly after major surgery. Age is an important risk factor for both the development of POCD and the appearance of dementia, and because of the population ageing, the number of elderly patients undergoing surgery is likely to grow in the future.[1] At the same time, dementia represents a large burden to the healthcare system.[2] It has been shown that POCD has long-term consequences in terms of increased all-cause mortality, risk of leaving the labour market prematurely, and dependency on social subsidy.[3] Furthermore, it has been proposed that there is an association between POCD and the development of dementia due to a common pathological mechanism through the anaesthetic effect on amyloid β peptide oligomerization and deposition.[4] However, some clinicians have questioned whether surgery or major illness can cause cognitive decline at all, and if at all POCD exists as a clinical entity.[5] Hence, it remains uncertain whether POCD can be a precursor of dementia.

We aimed to assess a possible association between POCD and the occurrence of dementia. Furthermore, we wanted to explore if POCD was related to the development of depression, organic amnesic syndrome, or mild cognitive disorder.

Methods

Ethics

The ISPOCD studies were approved by the research ethics committees for all of the Danish centres, and patients were enrolled after giving written informed consent.[6–10] The processing of personal follow-up data was approved by The Danish Data Protection Agency (Datatilsynet, Copenhagen, Denmark; journal number 2010-41-5167).

The cohort and databases

Patients were enrolled in both International Studies of Postoperative Cognitive Dysfunction (ISPOCD 1 and 2) in the USA and in Europe. Patients were aged 40 yr or above and presented for major or minor non-cardiac surgery in regional or general anaesthesia.[6–10] We excluded patients already diagnosed in the databases with dementia at any time point before enrolment, scored ≤23 on the Mini-Mental State Examination (MMSE) test, had disease in the central nervous system, were abusing drugs, alcohol or taking antidepressants, had previously been admitted for cardiac or neurological surgery or already performed a neuropsychological test, were unable to comprehend the test language, had visual disorder, or hearing impairment. In Denmark, we recruited from four centres between November 1994 and May 1996 in the ISPOCD1 study and between October 1998 and October 2000 in the ISPOCD2 study.[3] For the present study, we conducted a long-term follow-up of the Danish patients from surgery (years 1994–6 and 1998–2000) until July 1, 2011, using the unique national personal identification (CPR) number assigned by the Danish Civil registration system to all 5.6 million residents of Denmark at birth or immigration.[11] The Danish Civil registration system contains data on date of birth, sex, home address, immigration, emigration, and date of death.

To investigate the outcomes of interest, we used the National Patient Register[12] and the Psychiatric Central Research Register.[13] These national databases contain data on a daily basis on all inpatient or outpatient hospital contacts to somatic hospital departments since 1977 and psychiatric hospital departments since 1969, respectively. ICD-8 codes were used until 1993, and since January 1994 ICD-10 codes have been used in both databases, and in 1995, data on outpatients were included in both registers. ISPOCD data were linked to the Danish Civil Registration System, the National Patient Register, and the Psychiatric Central Research Register by the CPR number. Hence, it is possible with great certainty to establish whether a Danish ISPOCD patient has been admitted to a Danish hospital (as inpatient or outpatient), irrespective of changes in the patient's name, or address.

Neuropsychological assessment and criteria for POCD

There is no consensus definition of POCD in the medical community. As previously described, the cognitive performances were assessed at three time points:[6] before surgery (usually 1 day before operation), at 1 week (or at hospital discharge if earlier), and at 3 months after surgery using a battery of neuropsychological tests. We used data from the four following tests: the Visual Verbal Learning test, the Concept Shifting test, the Stroop Colour Word Interference test, and the Letter Digit Coding test. We used seven variables in the calculation of the endpoint of POCD: (i) cumulative number of words recalled in three trials and at (ii) delayed recall from the Visual Verbal Learning test; (iii) time and (iv) number of errors in part C from the Concept Shifting test; (v) time and (vi) error scores from the Stroop Colour Word Interference test, part three; and (vii) number of correct answers from the Letter Digit Coding test. We adjusted for learning effects by the use of normative data obtained from 352 healthy age-matched controls (not undergoing hospitalization or surgery) who performed the same tests at the same time interval as the patients. We defined the learning effect as the mean change (in controls) from baseline in each test. A patient was considered to have POCD if the *Z*-score (at least two *Z*-scores in individual tests, or the composite *Z*-score of all seven variables) of the difference with the preoperative cognitive assessment, using the mean and standard deviation from the control group, was larger than 1.96.[6]

Primary outcome measure

The primary outcome was time to (first) diagnosis of dementia given at an inpatient or outpatient hospital contact; hence, only physicians (of all specialties) at a hospital could diagnose the patients. Risk estimates for any (of the several possible) dementia diagnoses in patients with POCD were compared with those without POCD at both 1 week and 3 months after surgery. Registered International Classification of Diseases (ICD) dementia diagnoses are: Alzheimer's disease (ICD-10: F00.0, F00.1, F00.2, F00.9, G30.0, G30.1, G30.8, G30.9), vascular dementia (ICD-10: F01.0, F01.1, F01.2, F01.3, F01.8, F01.9), frontotemporal dementia (ICD-10: F02.0), and dementia without specification (ICD-10: F03.9).

The diagnosis of the different subtypes of dementia was made at the discretion of the physician treating the patient. We assessed dementia as a single non-specific term using the ICD-8 codes 290-290.10 and 290.18-290.19 and ICD-10 codes F 00.0-01.9, F03.9, and G30-30.9.[14] We used ICD-8 codes (before January 1994) to exclude patients diagnosed with dementia before the operation.

Secondary outcome measures

Furthermore, we wanted to explore secondary outcome measures that were either co-existent or predictors of dementia. Hence, we sought for a possible association between POCD at both time points and the development of depression (ICD-10: F32–F33.31),[15] 'Organic amnesic syndrome, not induced by alcohol and other psychoactive substances' (ICD-10: F 04), or 'Mild cognitive disorder' (ICD-10: F06.7).

Covariates

The analyses were adjusted for sex, age, education, and a history of co-morbidity. We defined co-morbidity as being present if one or several of the following conditions were recorded before operation: heart disease, pulmonary disease, diabetes, or cancer.