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High Risk of Cognitive and Functional Decline after Postoperative Delirium

A Three-Year Prospective Study

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Key Words
Delirium, prognosis · Confusional state · Cognitive decline, prediction · Disability

Abstract
Background/Aims: The aim of the study was to investigate the association of postoperative delirium with the outcomes of cognitive impairment, functional disability and death. ***Methods:*** Hip surgery patients aged 60 years or over (n = 200) underwent preoperative and daily postoperative assessment of their cognitive status during hospital stay. Outcome variables were determined at an average of 8 and 38 months after discharge from hospital. ***Results:*** Fourty-one patients developed postoperative delirium. Delirium was a strong independent predictor of cognitive impairment and the occurrence of severe dependency in activities of daily living. The associations were more marked for the long- than for the short-term outcome. Thirty-eight months after discharge from hospital, 53.8% of the surviving patients with postoperative delirium suffered from cognitive impairment, as compared to only 4.4% of the nondelirious participants. Logistic regression analysis adjusted for age, sex, medical comorbidity and preoperative cognitive performance revealed highly significant associations between delirium and cognitive impairment (OR = 41.2; 95% CI = 4.3–396.2), subjective memory decline (OR = 6.2; 95% CI = 1.5–25.8) and incident need for long-term care (OR = 5.6; 95% CI = 1.6–19.7). ***Conclusion:*** The present study confirms a poor prognosis after delirium in elderly patients. The findings suggest that delirium does not simply persist for a certain time but also predicts a future cognitive decline with an increased risk of dementia.

Introduction

A high proportion of elderly hospital patients develop delirium, which is related to several adverse outcomes, including a greater length of hospital stay, deterioration of activities of daily living, transition to nursing homes and death [1–5]. Several follow-up studies have challenged the view that the cognitive deficits which arise in the context of a delirium episode in old age are transitory and fully reversible. Rather, cognitive dysfunction has been reported to persist for 3–24 months in 20–72% of the patients after delirium [6–9]. Francis and Kapoor [10] noted that patients who recover from delirium have an increased risk of developing long-term cognitive decline over the following 2 years. A few studies even found a greatly elevated risk of dementia, with incidence rates of 55–69% within 2–5 years after the occurrence of delirium [11–14].

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The aim of our study was to investigate the association between postoperative delirium and long-term outcome with regard to objective and subjective cognitive decline, severe functional disability and death.

Methods

The sample consisted of 200 consecutive patients aged 60 years or over, who underwent hip surgery at the Klinikum rechts der Isar of the Munich Technical University [15]. Out of a total of 250 patients, 25 were excluded due to a lower age, known dementia, terminal illness or inadequate linguistic competence; a further 25 subjects refused to participate.

The patients were examined preoperatively and postoperatively on a daily basis. All examinations were performed by trained physicians from our research group. Preoperatively, the patients were screened for cognitive impairment and delirium using the Mini-Mental State Examination (MMSE) and the Confusion Assessment Method [16, 17]. The interview procedure included sections dealing with personal data, medication and physical disability. Medical comorbidity was quantified using the Charlson Comorbidity Index [18]. Alcohol abuse was measured with the CAGE screening method [19] and depression with the Zung Self-Rating Depression Scale [20]. A German version of the Zung scale has been validated extensively and its clinical usefulness has been approved. The feasibility and validity of a verbal administration have been demonstrated [21]. Postoperatively, the patients were assessed daily by means of the Confusion Assessment Method. Diagnosis of delirium was based on its criteria.

The first follow-up examination was carried out at an average of 8 months (SD = 2.9) after discharge from the hospital and the second after 38 months (SD = 5.7). Both patients and informants were mainly interviewed by telephone. The interviews were again carried out by doctors or psychologists trained for this purpose. We collected information on the vital status and incident need for long-term care (defined as receiving benefits from the German long-term care insurance plan). We administered a telephone version of the MMSE, consisting of the first 21 items which are suitable for this purpose. The telephone version of the MMSE that we used, and which will be designated in the following as T-MMSE, has been extensively tested and has proved to be quite valid and reliable [22]. Furthermore, we asked the patients whether or not they had experienced a worsening of memory after their hip surgery. If it was possible to conduct only informant interviews, then the grade of severity of cognitive impairment was rated according to the criteria of the Clinical Dementia Rating (CDR) [23].

The outcome of 'cognitive impairment/dementia' was defined as a score of 16 points or less on the 21-item T-MMSE. This is approximately equivalent to the usual 23-point cutoff on the original scale. If it was not possible to test the patients, we used the CDR instead of the T-MMSE score and regarded those with an overall severity rating of mild, moderate or severe dementia as cognitively impaired.

The study protocol was approved by the institutional review board of the faculty of medicine at the Technical University of Munich, and written informed consent was obtained from the participants.

For statistical analyses, SPSS 15.0 for Windows was used. Differences in categorical variables between patients with and without postoperative delirium were assessed using χ^2 tests, and variation in continuous variables with t tests for independent samples. Logistic regression analysis was performed to assess the association between postoperative delirium and dichotomous outcome variables. In multiple logistic regression models, we adjusted for the effects of age (in years), sex, comorbidity (Charlson Comorbidity Index), preoperative cognitive performance (MMSE) and individual length of the observation interval (in months). Since the preoperative MMSE scores were lacking for a total of 11 patients, a categorical variable was formed in order to adjust for the initial cognitive performance and to take the missing values into account. This variable had 3 categories and was based on the 21 items of the preoperative MMSE which form the T-MMSE. The participants who achieved a preoperative score of 17–21 points were grouped together in the first category, those with fewer than 17 points in the second category, and the participants with missing values in the third category. A separate analysis for the association between delirium and cognitive impairment/dementia was carried out for the subsample of patients with a preoperative MMSE of 24 or more; from this analysis patients with a lower score or missing values had been excluded. Other variables, including hip fracture, general anesthesia, depression, alcohol abuse, sensory impairment and use of psychotropic drugs, did not appreciably alter the risk estimates and were not adjusted for in our final analyses. The results are reported as unadjusted and adjusted odds ratios (OR) together with the 95% confidence intervals (95% CI).

Results

The 200 patients were between 60 and 97 years old, with the mean age being 73.8 years (SD = 9.0). Of these, 69.5% were women. The reasons for hip surgery were either hip fracture (28%) or elective hip replacement (72%). In none of the patients had delirium been diagnosed on the day before surgery; none of them had a diagnosis of dementia. The mean preoperative MMSE score for the total sample was 27.1 points (SD = 3.3).

Of the 200 patients studied, 41 developed delirium after surgery. The average duration of the delirium, including symptom-free intervals, amounted to 4.5 days. The patients with a postoperative delirium differed significantly from those without delirium in several variables (table 1). In the multivariate analysis, advanced age, a low preoperative MMSE score and medical comorbidity proved to be independent risk factors for the occurrence of delirium, whereas impairment of vision and hearing, depressive symptoms, the preoperative use of psychotropic medications, a hip fracture versus elective surgery, and general versus epidural anesthesia no longer showed any significant correlation with postoperative delirium [15].

Table 1. Sample characteristics at baseline

Characteristic	Patients without postoperative delirium (n = 159)	Patients with postoperative delirium (n = 41)	Significance (p value)
Age, years	72.1 (8.5)	80.5 (7.6)	<0.001
Sex, % female	69.2	68.3	>0.05
Elementary education only, %	47.2	60.5	>0.05
Preoperative MMSE score	27.9 (2.0)	23.4 (5.4)	<0.001
Comorbidity (Charlson Index)	0.75 (1.3)	1.34 (1.4)	<0.05
Impaired vision, %	15.7	35.9	<0.01
Impaired hearing, %	28.3	56.4	<0.01
Zung Self-Rating Depression Scale	30.3 (7.5)	34.2 (9.7)	<0.05
Alcohol abuse, %	8.8	10.3	>0.05
Hip fracture, %	20.8	56.1	<0.001
Use of psychotropic drugs, %	7.5	24.4	<0.01
General anesthesia, %	71.7	73.2	>0.05

Figures in parentheses represent SD. Significance: Fisher's exact test or t test for independent samples.

Table 2. Association of delirium during hospital stay with outcome after 8 and 38 months following discharge from hospital

Outcome	8 months after discharge			38 months after discharge		
	with outcome/ total observed	unadjusted OR	adjusted OR	with outcome/ total observed	unadjusted OR	adjusted OR
Cognitive impairment/dementia	15/174	11.2 (3.5–35.8)	4.6 (0.9–24.2)	20/163	25.5 (8.3–78.4)	41.2 (4.3–396.2)
Complaints about memory decline after surgery	33/163	3.1 (1.3–7.5)	4.7 (1.6–13.5)	17/146	8.3 (2.6–26.6)	6.2 (1.5–25.8)
Incident need for long-term care	20/186	3.9 (1.5–10.2)	1.7 (0.5–5.4)	28/167	9.2 (3.6–23.9)	5.6 (1.6–19.7)
Death	10/199	4.2 (1.2–15.5)	1.3 (0.2–8.5)	32/199	4.8 (2.1–10.8)	1.7 (0.6–5.0)

Figures in parentheses represent 95% CI. Adjusted OR: adjustments were made for age (years), sex, medical comorbidity (Charlson Comorbidity Index), preoperative cognitive performance (T-MMSE >16, <17, missing) and length of observation interval (months). Cognitive impairment/dementia was defined as a T-MMSE score of 16 or less or as a CDR rating of mild, moderate or severe dementia. Complaints about memory decline after surgery: no adjustment for preoperative memory complaints due to unavailability of information.

In the follow-up we were able to determine the vital status for 199 of the patients (99.5%). Of the 199 participants, 189 survived until the first follow-up and 167 until the second follow-up. The sample sizes of the surviving patients vary with respect to the outcomes, since it was not possible to obtain reliable information in all cases. We were able to assess cognitive impairment in the 2 follow-ups for 92.1 and 97.6% of the survivors respectively, to elicit subjective complaints about postoperative loss of memory in 86.2 and 87.4% respectively and to learn whether the need for care developed between discharge from the hospital and the follow-up for 98.4 and 100% respectively.

Table 2 summarizes the results of the first follow-up. Delirium during the hospital stay significantly increased the risk of all adverse outcomes after 8 months. After adjustment for age, sex, comorbidity, preoperative cognitive performance and length of the observation interval, however, a significant association with delirium persisted only for complaints about a memory decline after sur-

gery, whereas the associations of the delirium with cognitive impairment, with need for long-term care und with survival were no longer significant.

In the second follow-up, after 38 months, the associations between delirium and the various outcomes were closer than after 8 months and the adjusted OR were significant for 3 of the 4 outcomes. A delirium particularly strongly increased the risk of cognitive impairment in the follow-up. Of the 26 survivors with delirium who were observed for 38 months, 14 (53.8%) showed cognitive impairment/dementia as compared with only 6 (4.4%) among the 137 surviving patients without delirium. This corresponded to an unadjusted OR of 25.5 (95% CI = 8.3–78.4) and an OR of 41.2 (95% CI = 4.3–396.2) after adjustment for possible confounders. The exclusion of patients without valid preoperative MMSE scores did not alter the significance of the associations and reduced the adjusted OR only minimally. Just as little did an adjustment for further variables such as hip fracture versus elective surgery or general versus epidural anesthesia lead to changes in the results.

Crude OR as well as those adjusted for complaints about memory decline were significantly elevated for patients with postoperative delirium as compared with nondelirious ones. Whereas of the 17 patients with postoperative delirium questioned, 7 (41.2%) complained of memory disturbances as a result of the operation after 38 months, only 10 of the 129 (7.8%) participants without delirium did so.

Moreover, the incidence of need for care, which was rated independently of our study in the framework of the national care insurance program, was significantly higher. For 13 of the 25 patients with delirium (52.0%) and 15 of the 143 without delirium (10.5%), severe impairments developed, which led to the need for care.

It was only in regard to mortality that the risk differences were less clearly pronounced. Among the 41 patients with delirium a significantly higher proportion (36.6%) died than among the 158 without delirium (10.8%), but after adjustment for confounding variables there remained only a nonsignificant tendency toward an increased mortality risk.

We performed a separate analysis of the participants with postoperative delirium in order to find out whether the risk of cognitive impairment at the second follow-up was influenced by specific factors. The number of patients with postoperative delirium who survived to the second follow-up was very low for a statistical analysis (n = 26). Nevertheless, the participants with delirium who developed cognitive impairments (n = 14) differed significantly in several variables from those with delirium who remained cognitively unimpaired 38 months after discharge from the clinic (n = 12). The participants who suffered from cognitive impairments in the second follow-up were older than the patients without cognitive impairments [82.2 years (SD = 7.1) vs. 73.5 years (SD = 5.6); $p = 0.002$] and had a lower preoperative MMSE score [22.5 (SD = 4.7) vs. 26.8 (SD = 2.0); $p = 0.009$]. Acute patients with a hip fracture (n = 12) were more frequently cognitively impaired than participants with elective surgery (n = 14) (91.7 vs. 21.4%; $p < 0.001$). Patients with delirium who suffered from cognitive impairment in the follow-up tended to have had delirium of longer duration than subjects with delirium who were unimpaired in the follow-up (7.6 vs. 2.7 days; $p = 0.10$). In regard to sex, comorbidity, sensory impairment, depression, use of psychotropic drugs, alcohol abuse or type of anesthesia there were no differences between cognitively impaired and unimpaired patients with postoperative delirium.

Discussion

We investigated the association between incident delirium in older hip surgery patients and the outcomes of cognitive impairment, functional disability and death 8 and 38 months after discharge from hospital. The incidence of postoperative delirium (20.5%) corresponded to that in comparable studies [24, 25]. In agreement with the results from the literature the most important risk factors for the occurrence of delirium were advanced age, preoperative cognitive performance and somatic comorbidity [17, 26, 27].

The longitudinal findings confirmed previous results that the prognosis after a delirium episode is generally poor [3, 5, 28]. In univariate analyses the odds for cognitive impairment, for subjective memory loss, for the need for care and for death were significantly increased in comparison with patients without postoperative delirium, both after 8 and after 38 months.

After adjustment for potential confounders the associations between delirium and the outcome criteria of cognitive impairment, need for care and death failed to achieve the significance thresholds over the short prediction time period in spite of clearly elevated OR. In the second follow-up over a time period of 38 months after discharge from the hospital, closer relationships between delirium and outcome criteria were observed than after 8 months. Apart from mortality, which was significantly determined by age and comorbidity, but not by delirium

[29–32], a previous delirium increased the risk of need for long-term care and had significant effects on subjective and measured cognitive impairment.

The main result of our study is the close relationship between postoperative delirium and the greatly increased risk of cognitive impairment after more than 3 years. The far greater OR for the longer observation period suggests that delirium does not simply persist for a certain time but also predicts a future cognitive decline [28]. The fully adjusted OR for cognitive impairment among patients with delirium in comparison with the controls without delirium amounted to 4.6 (0.9–42.2) after 8 months and rose to 41.2 (4.3–396.2) after 38 months. An OR of 41.2 is unusually large, but it must be considered that the size of the OR is relatively instable in small samples such as the present one and must be interpreted cautiously. More important than the absolute magnitude of the OR is the fact that a highly significant association between delirium and later cognitive impairment persisted even after adjustment for important confounders.

Our results are in accordance with several other studies which reported a greater cognitive decline at follow-up among patients with a history of delirium in comparison with controls [6–10] or found higher rates of incident dementia [11–14]. After a period of 3 years, 53.8% of the surviving patients with delirium in our sample exhibited substantial cognitive impairment. Among the participants without delirium during hospital stay, on the other hand, only 4.4% suffered from cognitive impairment at the second follow-up. A close connection between delirium and cognitive impairment is supported by the significant associations between delirium and subjective memory impairments as well as newly arising need for care. The association between delirium and need for care is particularly noteworthy as the need for care is determined completely independently of our study by medical assessments in the context of the long-term care insurance system and thus represents an external validation criterion.

However, the results also show that the long-term course of delirium in old age is not necessarily adverse. Nearly half of the surviving patients with prior delirium were cognitively unimpaired 38 months after discharge from hospital. Cognitive impairment was observed primarily in the patients with delirium who were advanced in age and had pre-existing mild cognitive deficits and thus exhibited the strongest risk factors for the occurrence of dementia as demonstrated in earlier studies [33]. Moreover, a trend toward a more favorable long-term course was found when the patient recovered from the delirium after a short time [7, 32]. Further studies are needed to show whether different risk factors and clinical characteristics of delirium – e.g. visual hallucinations and Parkinsonism – are associated with a different outcome [34–36].

Our study has several limitations. Cognitive impairment was examined primarily by means of a telephone version of the MMSE [22]. Although telephone interviews for measuring cognitive status are now frequently being used in studies of the elderly and have proved reliable and valid in this context [22, 37, 38], the conditions of the telephone survey deviate from those at the baseline examination and thus may limit the comparability of the cognitive performance over time. In addition, cognitive impairment was represented in the follow-up by different criteria. If a personal examination of the participant with the T-MMSE was not possible, as in the case of 1.2% of the participants in the first follow-up and 15,3% in the second follow-up, the CDR on the basis of a proxy interview was used instead. It is possible that these 2 criteria do not lead to the same classification result in all cases.

Patients with pre-existing dementia had been excluded from the study in order to avoid confusion of these earlier deficits with cognitive decline developing during follow-up. However, 14 individuals scored below 24 on the preoperative MMSE so that we cannot rule out with certainty that several patients with early and previously undiagnosed dementia were included in the total sample. Therefore we undertook a second analysis excluding all individuals with incomplete data sets or low preoperative scores. Both analyses yielded similar results and supported an independent predictive effect of delirium on future cognitive deterioration.

The strengths of the study are above all that the occurrence and course of the postoperative delirium were closely monitored during the hospital stay, that all personal and telephone examinations were performed by highly qualified, experienced interviewers, that the preoperative cognitive performance of almost all patients was measured and adjusted for in the longitudinal analyses and that in addition to cognitive impairment as outcome, memory complaints and the need for care measured independently of our study were assessed.

Other investigations have also demonstrated an increased risk of cognitive impairment and dementia in elderly persons with delirium [30, 31, 39]. To our knowledge, however, the present study is the first to have found a closer association between delirium and cognitive impairment over a longer period of time than over a shorter

one, thereby suggesting that the association cannot simply be ascribed to the persistence of delirium and incomplete symptom recovery. Rather, delirium may be a harbinger of future cognitive decline and dementia.

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