The neuropsychiatry of dementia: psychometrics, clinical implications and outcome
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CHAPTER 7

Mortality associated with delirium after hip-surgery. A 2-year prospective cohort study

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Submitted
ABSTRACT

OBJECTIVES: To study the hazard risk associated with delirium in elderly hip-surgery patients at 2-year follow-up; and to explore risk factor stratification of poor outcome from delirium.

DESIGN: Prospective cohort study.

SETTING: Large medical school-affiliated general hospital in Alkmaar, The Netherlands.

METHODS: Participating patients (n=603) in a controlled clinical trial of haloperidol prophylaxis for delirium were followed-up for two years. Predefined risk factors and other potential risk factors for delirium were assessed prior to surgery. Primary outcome was time of death during the follow-up period. Cox proportional hazards were estimated and compared across patients who had postoperative delirium during hospitalization and those who did not.

RESULTS: A total of 90/603 patients (14.9%) died during the study period and 74/603 (12.3%) had postoperative delirium. Incidence of delirium was higher in patients who died (32.2%) compared with those who survived (8.8%). The effect of delirium on mortality was significant after adjusting for predefined delirium risk factors and other potential covariates including study intervention (adjusted Hazard risk=1.98, 95% CI 1.24-3.17). Ten percent of delirious patients at low risk of poor outcome (0-1 risk factors) died, 40.7% at intermediate risk (2-3 risk factors), and 59.3% at high risk (4-5 risk factors), compared to 6.1%, 13.5% and 43.1% of non-delirious patients.

CONCLUSIONS: Delirium independently predicts mortality at two-years follow-up in elderly hip-surgery patients. Outcome from delirium is particularly poor when other risk factors are present.

Keywords: delirium, long-term outcome, follow-up, risk factors, cognitive impairment, epidemiological, mortality, clinical prediction rule
INTRODUCTION

Delirium is highly prevalent in elderly hospital patients and it is associated with high morbidity and mortality, increased length of hospital stay and a high rate of institutionalization following discharge. Incidence rates for delirium after orthopedic hip-surgery vary from 5 to 40.5%. Of the investigations conducted to date, few have examined the mortality risk associated with delirium in elderly hip-surgery patients after one year or more.

The causal relationship between delirium and death at follow-up is largely still unclear and controversy exists whether delirium is independently associated with mortality at follow-up. Delirium and its symptoms often persist for months after onset. It has been suggested that the protracted course of delirium may contribute to its long term adverse outcomes. Some studies found that delirium in hip-surgery patients is associated with an increased risk of death at follow-up, while other studies did not. However, none of the positive studies examined the hazard risk associated with postoperative delirium after controlling for important delirium risk factors assessed preoperatively.

Prognosis of delirium is particularly poor when predisposing and precipitating risk factors for delirium are present. Several risk factors for delirium are independently associated with follow-up mortality. Some of these factors are modifiable, such as comorbid disorders. Accurate risk stratification would be useful for identifying low-risk hip-surgery patients with delirium for whom hospitalization period may be relatively short; and intermediate or high risk delirium patients, who might require prolonged hospital stay, intensified treatment and special care programs, also during post acute care. To our knowledge no risk stratification for poor outcome from delirium studies have been published.

The primary aim of this study was to examine the effect of postoperative delirium in elderly hip-surgery patients on mortality at follow-up two years later, controlling for baseline risk factors present at admission before onset of delirium. The secondary objective was to explore risk stratification of poor outcome from delirium.
CHAPTER 7

METHODS

Ethical Considerations
The study was undertaken in accordance with the Declaration of Helsinki and the guidelines on Good Clinical Practice. Approval of the regional research ethics committee was obtained. All patients or their relatives gave fully informed written consent.

Study Design and Objectives
This is a prospective cohort study evaluating the long term outcome of post-operative delirium on mortality in elderly hip-surgery patients. Study data on case mix variables were collected as part of a randomized, placebo-controlled, double-blind, clinical trial of low-dose haloperidol prophylaxis for postoperative delirium in elderly hip-surgery patients who were at intermediate or high risk for this complication. The aim of the RCT was to assess the effectiveness of 1.5 mg of haloperidol daily versus placebo on the primary (incident delirium) and secondary (deterioration of delirium) prevention of postoperative delirium in hip-surgery patients.26 Men and women aged 70 and older admitted for acute or elective hip surgery were considered for inclusion in the haloperidol prophylaxis study. Risk classification was based on the presence of four predictive risk factors as described by Inouye et al.27: Visual impairment, defined as binocular near vision worse than 20/70 after correction, Severe illness, measured by the Apache II (Acute Physiology Age and Chronic Health Examination,28 scale of 0 to 70), with a cut-off score of > 16 indicating increased severity, Cognitive impairment Mini Mental Status Examination29 (MMSE score of <24 on a scale of 0 to 30) and Dehydration (ratio of blood urea nitrogen to creatinine of ≥18).27 Intermediate risk for postoperative delirium was defined as presence of one or two risk factors and high risk as presence of three or more risk factors. The low-risk patients were assessed daily according to the protocol for incident delirium but received no prophylactic medication.

Patients were ineligible if they had delirium at admission, or no risk factors for postoperative delirium present at baseline. Detailed ineligibility criteria, including medication use and comorbid conditions, are described elsewhere.26 Eligible patients were sequentially randomly assigned to study treatment (placebo or haloperidol 0.5 mg three times daily).

Trial medication was started on admission and continued until 3 days after surgery. All patients were assessed daily for efficacy and safety evaluations. Experienced geriatric nurses and geriatricians provided proactive geriatric consultation to all patients. If postoperative delirium occurred, patients were treated according to standard procedures (haloperidol three times per day, lorazepam three times per day, or both
in increasing doses, depending on symptoms of delirium) and assessed for delirium severity and duration. A total of 430/603 had one or more risk factor for delirium and were randomized to haloperidol or placebo.

Primary outcome of the clinical trial was delirium as defined by Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) and Confusion Assessment Method criterion. Secondary outcome variables were severity of delirium as measured with the Delirium Rating Scale Revised (DRS-R-98), delirium duration, and length of hospital stay. Daily patients assessments using the MMSE, DRS-R-98, and Digit Span test (assessment of attention) were used to make the DSM-IV and CAM diagnoses possible and to assess delirium severity. A total of 74/603 had postoperative delirium.

Briefly stated, no effect was found on incident delirium, but there was an effect on severity and duration of delirium. Incidence of delirium was higher in patients at intermediate or high risk of delirium as compared to those at low risk, supporting validity of the medical risk factor model in a hip-surgery patient sample. In addition to these predefined risk factors, other risk factors for delirium, particularly age and acute admission to hospital, were identified.

In this study 2-years follow-up data on mortality were searched for and compared to incident delirium during hospital stay, controlling for demographical variables; predefined baseline risk factors used in the randomized clinical trial; and admission type.

Participants
The original study sample has been described elsewhere. All 603 patients were eligible to participate in the follow-up part of the study.

Measurements and Procedures
Date of death data were retrieved from the Alkmaar hospital database and other sources. The hospital serves the region where all participating patients lived and any deaths to occur are reported back regularly. Great efforts were made to include data from all patients by writing to the patients’ general practitioners (GP) and requesting for any relevant information. If necessary, e.g. when patients had moved out of the area, the GP, patients or patient’s family members were contacted by telephone.

Outcomes
The primary outcome was time to death during 2-year follow-up.
Statistical analysis

Means or proportions were used to describe demographic and clinical characteristics of the study sample at baseline and during 2-year follow-up. Kaplan-Meier survival curves for delirium an no delirium cases were examined using the Log rank test. Inspection of the survival tables showed that more delirium patients died within the first 6 months than in next 18 months ($\text{Chi}^2 = 8.65, P=.03$), indicating that the Cox proportional hazards assumption was violated. Mortality risk associated with delirium was estimated using a time dependent Cox proportional hazards regression model; the outcome was time to death. Censoring event was 2-year follow-up survival. Presence of delirium and potential other independent predictors of time to death were entered in the regression models to calculate unadjusted and adjusted (backward elimination) hazard risks ($P < .10$). Age and predefined risk factors APACHE, MMSE, Vision and Dehydration were entered in the analysis as continuous variables and incident postoperative delirium, Admission type and Gender as dichotomous variables. A time by delirium interaction factor was added to the model.

To counteract a potential confounding effect of in-hospital deaths on outcomes an intermediate analysis included patients who survived index hospitalization period only. In a second intermediate analysis including randomized patients only ($n=430$) study intervention (haloperidol vs. placebo) was also entered in the statistical model. In a third intermediate analysis those patients not receiving the haloperidol intervention were included only.

Risk factor stratification for poor outcome from delirium was explored using a logistic regression approach: the outcome was 2-year follow-up survival status. Similar to the Cox proportional hazard model, delirium and other independent predictors of survival were entered in the regression models to calculate the odds (backward elimination) ($P < .10$). Contrary to the Cox analysis, dichotomous variables were used in the logistic regression analysis based on predefined cut-off points for delirium risk factors MMSE, APACHE, Vision impairment and Dehydration. Age was conveniently dichotomized (70-79 years and 80 or over). It was decided to construct a simple algorithm useful for clinical practice by assigning 1 point for each significant outcome predictor variable. The relative risk for poor outcome was calculated based on the number of predictor variables, comparing delirium patients with few if any, intermediate or many risk factors with the referent group without delirium. Statistical calculations were performed using SPSS for Windows, version 14 (SPSS, Inc. Chicago, IL).
Table 1: Characteristics of Hip-surgery Patients in the Sample

<table>
<thead>
<tr>
<th></th>
<th>Died during study period (n= 90)</th>
<th>Survived the study period (n=513)</th>
<th>Total cohort (n=603)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*</td>
<td>82.7 +/- 7.4</td>
<td>77.1 +/- 5.3</td>
<td>77.9 (6.0)</td>
</tr>
<tr>
<td>Male sex</td>
<td>26 (28.9)</td>
<td>112 (21.8)</td>
<td>138 (22.9)</td>
</tr>
<tr>
<td>Acute admission</td>
<td>47 (52.2)</td>
<td>88 (17.2)</td>
<td>135 (22.4)</td>
</tr>
<tr>
<td>Predefined delirium risk factors:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE*</td>
<td>22.1 +/- 5.6</td>
<td>25.8 +/- 3.6</td>
<td>25.2 +/- 4.2</td>
</tr>
<tr>
<td>APACHE score*</td>
<td>14.7 +/- 4.1</td>
<td>12.7 +/- 2.7</td>
<td>13.0 +/- 3.0</td>
</tr>
<tr>
<td>Dehydration index*</td>
<td>12.2 +/- 4.8</td>
<td>12.8 +/- 3.6</td>
<td>12.7 +/- 3.8</td>
</tr>
<tr>
<td>Visual impairment*</td>
<td>0.31 +/- 0.15</td>
<td>0.44 +/- 0.15</td>
<td>0.42 +/- 0.16</td>
</tr>
<tr>
<td>Study intervention:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>33 (36.7)</td>
<td>185 (36.1)</td>
<td>218 (36.2)</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>46 (51.1)</td>
<td>166 (32.4)</td>
<td>212 (35.2)</td>
</tr>
<tr>
<td>not randomized</td>
<td>11 (12.2)</td>
<td>162 (31.6)</td>
<td>173 (28.7)</td>
</tr>
<tr>
<td>Length of stay**†</td>
<td>26.4 (28.7)</td>
<td>19.0 (21.0)</td>
<td>20.4 (22.8)</td>
</tr>
<tr>
<td>Post-operative Delirium</td>
<td>29 (32.2)</td>
<td>45 (8.8)</td>
<td>74 (12.3)</td>
</tr>
</tbody>
</table>

*: data are given as mean. †: data on length of in-hospital stay were available for randomized patients only.

RESULTS

Descriptive findings and Cox proportional hazard analysis
A total of 90/603 patients (14.9%) died during the study period (table 1). For 4/90 patients the exact date of death could not be retrieved. The Kaplan-Meier survival curves for patients with or without delirium are plotted in Figure 1. The survival curve for patients with delirium decreases faster than the curve for patients without delirium (Log rank=46.35, df=1, P=<.001).
Fig. 1: Kaplan-Meier Survival Functions Patients with or without Delirium

*excluding cases with exact date of death
Incidence of delirium was higher in patients who died compared with those who survived. Patients who died were also more often men, and were relatively old. They were more often at risk for delirium as indicated by higher rates of cognitive impairment and visual impairment. By contrast, illness severity and dehydration were not associated with time to death in multivariate analysis (table 2), nor was there a significant effect of the interaction between time and delirium.

Table 2: Univariate and Multivariate Analysis of Time to Death for Hip-surgery Patients (n=599)
During 2-Year Follow-up

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Unadjusted data</th>
<th>Adjusted data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P-Value</td>
</tr>
<tr>
<td>Age</td>
<td>1.14 (1.10-1.17)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.49 (0.95-2.37)</td>
<td>.09</td>
</tr>
<tr>
<td>Acute admission</td>
<td>4.63 (3.03-7.08)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Predefined risk factors:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>.88 (.85-.90)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>APACHE</td>
<td>1.21 (1.14-1.28)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Dehydration</td>
<td>.96 (0.90-1.02)</td>
<td>.16</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>.007 (.002-.027)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Postoperative Delirium</td>
<td>.24 (.15-.37)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Haloperidol Prophylaxis*</td>
<td>1.46 (0.93-2.30)</td>
<td>.10</td>
</tr>
</tbody>
</table>

*: data available for randomized patients (n=430) only.

Intermediate Cox proportional hazard analyses
In three intermediate analyses hazard risks were examined for patients who died after the index hospitalization, those randomized to placebo or haloperidol, or those not receiving the intervention. A total of 14/90 were in-hospital deaths and 7/14 had delirium. When these 14 patients were excluded from the intermediate analysis, we found that incidence of delirium was higher in patients who died in the post hospitalization period compared with those who survived (adjusted Hazard Ratio 1.92, CI 1.13-2.70).

A total of 79/430 randomized patients died during the study period. A second intermediate analysis showed that incidence of delirium was higher in patients who died
compared with those who survived (adj. HR 1.80, CI 1.11-2.94). Notably, haloperidol prophylaxis was not associated with death at follow-up in multivariate analysis. In-hospital deaths were 2.4% in the haloperidol prophylaxis group and 4.1% in the placebo group.

A total of 391/603 were randomized to placebo or were not randomized. A third intermediate analysis including patients not having had the intervention showed that incidence of delirium was not higher in patients who died compared with those who survived (adj. HR 1.39, CI .64-3.03).

Risk Factor Stratification for Poor Outcome from Delirium

In logistic regression analysis, a significant statistical association with 2-year survival status was evident for Delirium (OR=2.4, 95% CI 1.3-4.6), Male gender (2.0, 95% CI 1.1-3.6), Age 80 years or over (OR=2.5, 95% CI 1.5-4.4), Acute admission type (OR=2.2 95% CI 1.2-4.0), Cognitive impairment (OR=1.7, 95% CI .9-3.0) and Visual impairment (OR=2.6, 95% CI 1.4-4.9).

Examining the risk factor stratification shows (table 3) that patients with incident delirium were at an increased risk for death after two years when intermediate levels of risk points were present, but no so when few if any risk factors were present, nor when many risk factors were present. However, many of the patients at high risk died (delirium 59.3% vs. No Delirium 43.1%), suggesting a potential significant group effect when larger patient samples are included.

### Table 3: Risk Index Performance Predicting 2-Year Follow-up Survival Status

<table>
<thead>
<tr>
<th>Risk Factors*</th>
<th>Died during study period</th>
<th>Survived during study period</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Delirium</td>
<td>No Delirium</td>
<td>Delirium</td>
</tr>
<tr>
<td>0-1</td>
<td>2 (10.0)</td>
<td>21 (6.1)</td>
<td>18 (90.0)</td>
</tr>
<tr>
<td>2-3</td>
<td>11 (40.7)</td>
<td>18 (13.5)</td>
<td>16 (59.3)</td>
</tr>
<tr>
<td>4-5</td>
<td>16 (59.3)</td>
<td>22 (43.1)</td>
<td>11 (40.7)</td>
</tr>
</tbody>
</table>

* Mortality Risk Factors weighed equally (range 0-5).

( ): Percentages primary outcome within groups Delirium vs. No Delirium.
DISCUSSION

This study examined mortality at follow-up associated with delirium in elderly hip-surgery patients. Patients who developed delirium after surgery had an almost doubled increased risk of mortality in the 2 year follow-up period (table 2). In addition to baseline risk factors, delirium independently predicted the adverse long term outcome. The strengths of this study are the complete primary outcome data set; inclusion of a large sample hip-surgery patients; inclusion of patients who are at risk and who are not at risk for delirium; use of standardized and valid methods for diagnosing delirium; pre surgery and pre delirium measures of predefined baseline risk factors.

The association between delirium and risk of death is impressive. In this sample of 603 patients 29/74 with delirium died (39.2%) compared to the overall figure of 90/603 deaths (14.9%). Even when the 14 in-hospital deaths are left out from the equation, the odds still reflect a twofold risk of death. It goes without saying that such a high mortality rate raises concern, particularly when one considers that delirium is often under diagnosed and in many instances preventable.

One previous study found an increased mortality risk associated with delirium at 6 months of follow-up and three studies found increased risk at 12 months follow-up or more. In the Nightingale et al. study hip-fracture patients were interviewed by a psychiatrist or psychiatric nurse between 2 and 5 days after surgery and an adjusted 2 year hazard ratio associated with delirium of 2.4 (CI 1.7-3.5) was found. In the Edelstein et al. study 47/921 (5.1%) hip fracture patients had postoperative delirium and were more likely to have died at 1 year follow-up (unadjusted odds ratio 2.4, CI 1.1-4.9). Lundstrom et al. found that 21/29 femoral neck fracture patients with postoperative delirium died within 5 years, compared to 17/49 who did not have delirium (P=.001). The hazard ratio found in our sample is comparable to those found in the earlier studies. However, we clinically assessed patients on admission prior to surgery and included large numbers of patients many of whom were not at risk for delirium. By doing so we were able to examine both the effects of delirium and baseline risk factors on mortality. Thus, our method represents a rigorous approach to study the important problem of adverse long term outcomes associated with delirium.

Protracted delirium does not (fully) explain the relationship between delirium and long term mortality in this sample. Advanced age and pre-existing cognitive impairment, two of the risk factors for mortality found in this study, have been identified as two major risk factors for prolonged delirium. Delirium may lead to different complications such as insufficient nutritional intake, falls associated accidents and exhaustion, all of which may increase the risk of death. Some found that delirium independently predicts in-
Other studies show that unresolved delirium at discharge is highly prevalent in general medical patients, and that it is associated with mortality at long term follow-up.\textsuperscript{1,3,33} In this study 7 patients with delirium died during hospital stay, the other 22 delirium patients died during the post hospitalization period. Patients were participants in a RCT performed outside the U.S., Delirium severity and duration were measured in the RCT and none of the patients had delirium at discharge. Although some patients may have had (mild) delirium symptoms at discharge, we believe persistent delirium symptoms per se are not a likely explanation for excess mortality at follow-up. Alternatively, we hypothesize that vulnerability in delirium patients as expressed by presence of predisposing and precipitating factors explains, at least to some extend, excess mortality. Results from the risk factor stratification analysis seem to support this hypothesis.

Risk factor stratification for poor outcome was examined based on presence of delirium and other risk factors. Base rate mortality in the referent group at low risk was 6.1%. Prognosis of incident delirium was not significantly different when only few risk factors were present; all but two of the delirium patients with few risk factors survived. However, 40.7% of the delirium patients with two or three risk factors died; 59.3% died in case of four or five risk factors. So, prognosis of post hip-surgery delirium is reasonably good when you are relatively young and healthy. It is worse for cognitively impaired older men who are acutely admitted to hospital and who have poor vision. Unfortunately, many of the predictor variables that were identified are not amenable to treatment, but on the other hand risk factor stratification of low, intermediate and high risk is simple to use in everyday clinical practice. Practical consequences of the risk stratification may be that delirium patients who are at intermediate or high risk should not be transferred or discharged from hospital untimely; extra efforts should be made to identify and try to modify medical conditions associated with mortality; care programs should target the intermediate and high risk patients; post acute facilities should prepare treatment and care for those who need it most; patients and their families may want to be informed about delirium prognosis.

Validity of the risk stratification model was not tested in this study. Secondly, the small number of patients in the low and high risk groups may have reduced study power. Also, other risk factors for poor outcome from delirium after hip-surgery may exist, but they were not included in this study. We included risk factors that are robust predictors of delirium.\textsuperscript{31} However, although dehydration was associated with delirium in general medical patients,\textsuperscript{27} it was not in our hip surgery patient sample. Again, dehydration did not predict follow-up mortality in this study. So, risk factor selection may depend on the patient sample studied and different risk stratifications may be found in various patient samples.
samples based on risk factors that are not necessarily the same as the ones used in this study. The risk factors for poor outcome found in this study need to be verified in future studies. In turn, this could result in a validated clinical prediction rule.

Treatment condition was not associated with study outcome. The apparent trend for excess mortality in patients randomized to haloperidol was not significant after controlling for covariates. Furthermore, in-hospital deaths were 2.4% in the intervention group and 4.1% in the placebo group. So, low-dose haloperidol prophylaxis did not protect against increased risk of mortality. Vice versa, it did not have a negative effect on primary outcomes. It would seem to us that where short term effects may be expected, the duration and dosage of the prophylactic treatment were too short or too low to really make a difference two years later. Nevertheless, possible detrimental effect of prophylactic treatment on survival warrants careful monitoring in future studies.

Study limitations that need to be discussed relate to generalizability of results and risk factor selection. This was a single site study and it was part of randomized trial not set up to evaluate the natural history of delirium and its outcomes. Nevertheless, patients enrolled in the study were selected from a large sample representative of hip-surgery patients. Secondly, chronic comorbid conditions were not included as a covariate. Instead, acute comorbid conditions were measured by the APACHE. Risk factor selection was based on a validated medical model.27,31 We controlled for the intervention (haloperidol prophylaxis or placebo) and included non randomized patients. No independent effect of study medication on mortality was found. We conclude that the original randomized clinical trial design does not invalidate results and conclusions of this study.

This study shows that delirium among hip-surgery older patients is associated with mortality at follow-up. Our findings are consistent with the concept of delirium as a serious neuropsychiatric condition with adverse effects. Delirium outcome is most problematic in vulnerable patients. The symptoms that often persist for months may well be reflections of the unresolved underlying pathological conditions in these patients. Since we did not adjust for chronic comorbid conditions, delirium might be an exceptionally good marker for comorbid conditions. Our results suggest efforts should be made to investigate the causal mechanism(s) that explain for mortality associated with delirium and to develop prevention programs targeted at decreasing the risk of death after delirium. Such programs would probably include the use of a risk factor stratification; extra care for frail elderly that extends the hospitalization period; and monitoring of delirium symptoms for a prolonged period of time. The increased mortality risk associated with delirium warrants rigorous implementation of primary and secondary prevention strategies.
Reference List

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LONG-TERM OUTCOME OF MORTALITY