Mortality associated with delirium after hip-surgery: a 2-year follow-up study

MARTIN G. Kat1, JOS F. DE JONGHE1, RALPH VREESWJK2, TJEERD VAN DER PLOEG3, WILLEM A. VAN GOOL4, PIET EIKELENBOOM135, Kees J. Kalisvaart2

1Department of Geriatric Medicine, Medical Center Alkmaar, Alkmaar, The Netherlands
2Department of Geriatric Medicine, Kennemer Gasthuis, Haarlem, The Netherlands
3Pieter van Foreest Institute for Education and Research, Medical Center Alkmaar, Alkmaar, The Netherlands
4Department of Neurology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
5Department of Psychiatry, Vrije Universiteit Medical Center, Free University of Amsterdam and University of Amsterdam, Amsterdam, The Netherlands

Address correspondence to: J. F. M. de Jonghe. Tel: (+31) 725482380; Fax: (+31) 725482197. Email: j.de.jonghe@mca.nl; M. G. Kat. Tel: (+31) 725482380; Fax: (+31) 725482197. Email: psykat@hetnet.nl

Abstract

Background: delirium after hip-surgery is associated with poor outcome. Few studies examined the mortality risk associated with delirium in elderly hip-surgery patients after 1 year or more. Aim of this study was to examine the hazard risk associated with delirium in elderly hip-surgery patients at 2-year follow-up, controlling for baseline risk factors and interaction effects.

Methods: this is a secondary analysis based on data from a controlled clinical trial evaluating efficacy of haloperidol prophylaxis for delirium conducted in a large medical school-affiliated general hospital in Alkmaar, The Netherlands. Randomised and non-randomised patients (n = 603) were followed-up for 2 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 hospitalisation 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 interaction effect of delirium by illness severity on mortality was significant after adjusting for predefined delirium risk factors and other potential covariates including study intervention (adjusted Hazard risk = 1.05, 95% CI 1.02–1.08). A total of 14/27 delirium patients who were severely ill on admission died during follow-up versus 15/47 delirium patients who were not (RR 1.63 CI 0.93–2.83).
Conclusions: Delirium does not independently predict mortality at 2-year follow-up in elderly hip-surgery patients. However, outcome from delirium is particularly poor when other risk factors are present.

Keywords: Delirium, long-term outcome, cognitive impairment, mortality, hip-surgery, elderly

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 institutionalisation following discharge [1]. Incidence rates for delirium after orthopaedic hip-surgery vary from 5 to 40.5\% [2–4], and incidence is particularly high in at risk patients [5]. Few studies have examined the mortality risk associated with delirium in elderly hip-surgery patients after 1 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. While some studies found that delirium in hip-surgery patients is associated with an increased risk of death at follow-up [4, 6–8], others did not, probably due to small sample sizes [9–17]. However, none of the positive studies examined the hazard risk associated with postoperative delirium after controlling for important delirium risk factors assessed preoperatively.

Risk stratification for delirium in medical and surgical patients has been a major objective and several studies tried to develop predictive models based on the presence of known risk factors [18]. Several risk factors for delirium are independently associated with follow-up mortality [19–22]. Delirium prognosis might be correlated with identifiably risk factors in a particular patient. And if so, accurate risk stratification for poor outcome from delirium should be based on delirium and delirium risk factors interactions. Such risk stratifications could be useful for identifying low-risk hip-surgery patients with delirium for whom hospitalisation period may be relatively short; and intermediate or high-risk delirium patients, who might require prolonged hospital stay, intensified treatment and special care programmes, also during postacute care. To our knowledge, no outcome studies on delirium and risk factor interactions have been published.

The aim of this study was to examine the effect of postoperative delirium in elderly hip-surgery patients on mortality at follow-up 2 years later, controlling for baseline risk factors present at admission before onset of delirium. We hypothesised that long-term outcome from delirium is particularly poor in at risk patients.

Methods

Ethics

The study was approved by the local research ethics committee. All patients or their relatives gave fully informed written consent.

Study design and objectives

Study data on case mix variables were collected as part of a randomised, 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 study sample represents a prospective cohort study with longitudinal follow-up, which has been described previously [5, 23]. The aim of the RCT was to assess the effectiveness of 1.5 mg of haloperidol daily versus placebo on the primary and secondary prevention of postoperative delirium in at risk-hip-surgery patients. The primary outcome was the incidence of postoperative delirium as defined by DSM-IV criteria. Secondary outcomes were the severity of delirium (Delirium Rating Scale revised version-98), the duration of delirium, and the length of hospital stay [23]. Outcomes were assessed during daily patient visits. Risk classification was based on the presence of four predictive and validated baseline risk factors; Mini-Mental State Examination (MMSE), Visual Impairment (Snellen test), Acute Physiology Age and Chronic Health Examination (APACHE II) and Dehydration (BUN/creatinine) [5, 23, 24]. Demographic data, type of admission (acute versus elective, all acute patients were fractured hip patients), and depressive symptoms as measured with the Geriatric Depression Scale 15 items version (GDS-15) (3.2\% missing values) were recorded prior to surgery. A total of 603 patients consented to participate and 430/603 had one or more risk factor for delirium and were randomised to haloperidol or placebo [23]. Briefly stated, no effect was found on incident delirium, but there was an effect on severity and duration of delirium.

In this study, 2-year follow-up data on mortality were searched for and compared with incident delirium during hospital stay, controlling for demographical variables; predefined baseline risk factors; admission type and depressive symptoms.

Participants

The original study sample has been described elsewhere [5, 23]. All 603 patients were eligible to participate in the follow-up part of the study.

Measurements and procedures

Date of death data was 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 (GPs) 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 and 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 the next 18 months ($\chi^2 = 8.65$, $P = 0.03$), 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, potential other independent predictors of time to death, and interactions terms (delirium by risk factors) were entered in the regression models to calculate unadjusted and adjusted (backward elimination) hazard risks ($P < 0.10$). Age, predefined risk factors and GDS-15 scores 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 potential confounding effects of in-hospital deaths and the RCT intervention on study outcome, intermediate analyses were performed that excluded in-hospital deaths; and that included randomised patients only ($n = 430$).

Statistical calculations were performed using SPSS for Windows, version 14 (SPSS, Inc., Chicago, IL, USA).

Results
Descriptive findings and Cox proportional hazard analysis
A total of 90/603 patients (14.9%) died during the study period (Table 1). For only 4/90 patients the exact date of death could not be retrieved and these patients were not included in subsequent survival analyses. 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 ($\text{Log rank} = 46.35$, df = 1, $P < 0.001$).

Incidence of delirium in more severely ill patients, as measured with the interaction term delirium x APACHE II, was higher in patients who died compared with those who survived (Table 2). Patients who died during follow-up were more often at risk for delirium as indicated by male gender, old age, acute admission, depressive symptoms and visual impairment. In contrast, delirium per se, illness severity per se, cognitive impairment and dehydration were not associated with time to death in multivariate analysis, nor was there a significant effect of the interactions between time and delirium, and delirium and other risk factors.

<table>
<thead>
<tr>
<th>Table 1. Characteristics of hip-surgery patients in the sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died during study period ($n = 90$)</td>
</tr>
<tr>
<td>Agea ($\pm$)</td>
</tr>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>Acute admission</td>
</tr>
<tr>
<td>GDS$^{b,c}$</td>
</tr>
<tr>
<td>Predefined delirium risk factors</td>
</tr>
<tr>
<td>MMSEa ($\pm$)</td>
</tr>
<tr>
<td>APACHE scorea ($\pm$)</td>
</tr>
<tr>
<td>Dehydration index$^{b,c}$ ($\pm$)</td>
</tr>
<tr>
<td>Visual impairment$^a$ ($\pm$)</td>
</tr>
<tr>
<td>Study intervention</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Haloperidol</td>
</tr>
<tr>
<td>Not randomised</td>
</tr>
<tr>
<td>Length of stay$^{c}$ ($\pm$)</td>
</tr>
<tr>
<td>Postoperative delirium</td>
</tr>
</tbody>
</table>

aData are given as mean. 
$b$Missing data GDS 19/603; dehydration 1/603. 
$c$Data on length of in-hospital stay were available for randomised patients only. ±, standard deviation; (), percentages.

Figure 1. Kaplan–Meier survival curves patients with or without delirium.
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.

Discussion

This study examined mortality at follow-up associated with delirium in elderly hip-surgery patients. Patients who developed delirium after surgery had a 93% increased risk of mortality in the 2-year follow-up period. Delirium interacting with baseline acute illness severity independently predicted poor outcome. The strengths of this study are the near complete primary outcome data set (<0.6% missing values); inclusion of a large sample hip-surgery patients; inclusion of a case mix of low, intermediate and high risk for delirium patients; use of standardised 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 with 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 an almost 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 [25].

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 [4, 6–8]. Nightingale et al. assessed hip-fracture patients between 2 and 5 days after surgery; the adjusted 2-year HR associated with delirium was 2.4 (CI 1.7–3.5) [7]. 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) [4]. Landstrom et al. found that 21/29 femoral neck fracture patients with postoperative delirium died within 5 years, compared with 17/49 who did not have delirium (P = .001) [8]. The HR found in our sample if no interaction terms were added to the regression model is comparable with those found in the earlier studies of fractured hip patients [1]. However, we clinically assessed a large number of patients prior to surgery; included patients at low, intermediate and high risk of delirium; and we evaluated additive effects and interaction effects of delirium and other predictors of poor outcome. By doing so we were able to examine independent effects of delirium and baseline risk factors on mortality and our methods represent a rigorous approach to study the important problem of adverse long-term outcomes associated with delirium.

Unlike previous studies, our findings suggest that delirium per se is not independently associated with excess mortality. Primary outcome in this study was predicted by delirium interacting with illness severity as measured with

### Table 2. Univariate and multivariate analysis of time to death for hip-surgery patients (n = 579) 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>1.13 (1.09–1.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.55 (0.95–2.53)</td>
<td>0.08</td>
</tr>
<tr>
<td>Acute admission</td>
<td>4.55 (2.89–7.16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GDSa</td>
<td>1.27 (1.15–1.39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Predetermined factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>1.16 (1.10–1.21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>APACHE</td>
<td>1.22 (1.15–1.29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dehydration</td>
<td>1.03 (0.96–1.09)</td>
<td>0.38</td>
</tr>
<tr>
<td>Visual</td>
<td>1.36 (1.23–1.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Impairment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative prophylaxisb</td>
<td>4.46 (2.75–7.25)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

interaction terms: delirium

| By time               | 0.99 (0.996–0.999) | <0.001 |
| By age                | 1.02 (1.01–1.03)  | <0.001 |
| By sex                | 3.66 (1.68–7.97)  | 0.001  |
| By admission type     | 7.74 (4.54–13.20) | <0.001 |
| By GDS                | 1.41 (1.25–1.58)  | <0.001 |
| By MMSE               | 1.06 (1.04–1.08)  | <0.001 |
| By APACHE             | 1.12 (1.08–1.15)  | <0.001 |
| By Dehydration        | 1.09 (1.06–1.13)  | <0.001 |
| By vision             | 1.17 (1.06–1.28)  | 0.001  |
| Haloperidol prophylaxisb | 1.48 (0.90–2.42)  | 0.12   |

GDS 3.2% missing data.

Data available for randomised patients (n = 430) only.

Results from the Cox model show that the hazard risk is increased 1.05 with a unit change in the delirium by illness severity indicator, holding other factors constant. Comparisons based on dichotomous variables may be useful in clinical practice. Patients with postoperative delirium who were severely ill on admission (n = 14/27), were at an increased risk for death after 2 years (51.9 versus 13.2%; RR 3.9 CI 2.6–6.0). Delirium patients without severe illness (n = 15/47) were at an increased risk for death after 2 years (31.9 versus 13.5%; RR 2.4 CI 1.5–3.8).

Intermediate Cox proportional hazard analyses

If no delirium by risk factors interaction terms were entered in the analyses, incidence of delirium was higher in patients who died compared with those who survived (adjusted hazard ratio (HR) 1.93, CI 1.15–3.20).

A total of 14/90 were in-hospital deaths and 7/14 had delirium. Incidence of delirium interacting with acute admission was higher in patients who died in the post-hospitalisation period compared with those who survived (adjusted HR 3.40, CI 1.77–6.55).

A total of 79/430 randomised patients died during the study period and incidence of delirium interacting with illness severity was higher in patients who died compared with those who survived (adj. HR 1.05, CI 1.02–1.08).
the APACHE II. The APACHE II score incorporates different risk factors such as abnormal laboratory findings, high age and acute admission. The ways in which delirium affected illness severity and vice versa are unclear. Delirium severity and duration were not significantly different for those with or without baseline illness severity. However, there was a trend showing longer of hospital stay was 6 days longer in more severely ill patients when compared with those who were less severely ill at baseline ($P = 0.09$). It might be that morbidity associated with delirium in at risk, vulnerable patients could in part explain our results. Others have found that risk factors for delirium are associated with poor outcome [19–22]. Although in this study no data were available on the pathological pathways involved by which risk factors lead to delirium and mortality, our findings show that delirium prognosis is correlated with baseline risk for delirium. Future outcome studies could explore the exact nature in which delirium interacts with predisposing factors.

Our study results may have practical consequences. Risk stratification for poor outcome could mean that specifically those patients with delirium who are at high risk for poor outcome 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 programmes should target the intermediate and high-risk patients; post-acute facilities should prepare treatment and care for those who need it most and patients and their families may want to be informed about delirium prognosis. Notably, risk stratification validity was not tested in this study and associations found between risk factors for poor outcome need to be verified in future studies. In turn, this could result in a clinical prediction rule.

Unlike many US-based studies that include patients still delirious at discharge [10, 26, 27], this study included participants in a Dutch RCT with delirium duration as a secondary outcome; none of the patients had delirium at discharge. Also, many elective patients were included as opposed to fractured hip patients. Although we were able to control for some, differences exist between our study sample and other delirium outcome study samples.

Treatment condition was not independently associated with study outcome. Furthermore, in-hospital deaths were 2.4% in the intervention group and 4.1% in the placebo group. Admittedly, attempts to control for haloperidol prophylaxis and other variables by carrying out subgroup analyses lead to smaller sample sizes and increased imprecision. Possible detrimental effect of prophylactic treatment on survival warrants careful monitoring in future studies.

Some study limitations that need to be discussed. At first, there is the issue of selection bias as clinical trial populations may not be truly representative of the deriving population due to the variable consent rates. In relation to delirium research, under-recruitment of patients with dementia is usual. In this study profound dementia was an exclusion criterion, but dementia per se was not. Second, chronic co-morbid conditions were not assessed. Risk factor selection was based on a validated medical model that included cognitive impairment [5, 24]. No independent effect of study medication on mortality was found. We conclude that the original randomised clinical trial design does not invalidate results and conclusions of this study.

This study shows that delirium interacting with illness severity 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 co-morbid conditions, delirium might be an exceptionally good marker for co-morbid conditions. Efforts should be made to investigate the causal mechanism(s) that explain for mortality associated with delirium and to develop prevention programmes targeted at decreasing the risk of death after delirium. These programmes would probably include the use of a risk factor stratification; extra care for frail elderly that extends the hospitalisation 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.

Key points
- Delirium is associated with poor long term outcome.
- Delirium is a marker of co-morbid disease.
- Outcome from delirium is particularly poor in at risk patients.

Acknowledgements
We thank Tjerk Schoemaker and Milko van Langen for their assistance.

Conflicts of interest
None declared.

Funding
This study was funded by Medical Center Alkmaar.

Author contributions
The first and second author contributed equally in writing the manuscript.
M.G.K.: responsibility of the whole content, conception and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for intellectual content, administrative, technical, material support, supervision, statistical analysis.

J.F.M.J.: responsibility of the whole content, conception and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for intellectual content, supervision, statistical analysis.

R.V.: responsibility of the whole content, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for intellectual content, supervision, statistical analysis.

T.P.: statistician, responsibility of the whole content, conception and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for intellectual content, statistical analysis.

W.A.G.: responsibility of the whole content, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for intellectual content, supervision, statistical analysis.

K.J.K.: responsibility of the whole content, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for intellectual content, administrative, technical, material support, supervision, statistical analysis.

References


The association between habitual sleep duration and sleep quality in older adults according to health status

ARTHUR EUMANN MESAS, ESTHER LÓPEZ-GARCÍA, LUZ Mª LEÓN-MUÑOZ, AUXILIADORA GRACIANI, PILAR GUALLAR-CASTILLÓN, FERNANDO RODRÍGUEZ-ARTALEJO

Departamento de Medicina Preventiva y Salud Pública, Facultad de Medicina, Universidad Autónoma de Madrid, Calle Arzobispo Morcillo, 2, 28029 Madrid, Spain

Address correspondence to: F. Rodríguez-Artalejo. Tel: (+34) 91 497 5444; Fax: (+34) 91 497 5353.
Email: fernando.artalejo@uam.es

Abstract

Background: research on the association between habitual sleep duration and quality in older adults is scarce and has shown conflicting results. Moreover, no previous study has assessed the influence of health status on this association.

Objectives: to examine the association between habitual duration and quality of sleep in older adults, and to test if this association varies with health status, as approximated by self-rated health, quality-of-life and functional limitation.

Design: cross-sectional study with data collected by telephone interview.

Setting: community-based study.

Subjects: a total of 1,567 community-dwelling individuals aged ≥68 years in Spain.

Methods: poor sleep quality was ascertained through nighttime complaints (sleeping-pill consumption, difficulty falling asleep, awakening during the night and early awakening), and daytime complaints (feeling unrested in the morning and daytime sleepiness). The analyses were adjusted for the main confounders, and were stratified by health status (self-rated health, health-related quality-of-life and functional limitation).

Results: when compared with those sleeping 7–8 h, those who slept ≤6 h were more likely to report difficulty falling asleep [odds ratio (OR) 3.51; 95% confidence interval (CI) 2.37–5.20], frequent awakening during the night (OR 1.97; 95% CI 1.42–2.75), early awakening in the morning (OR 2.78; 95% CI 2.02–3.82) and feeling unrested in the morning (OR 1.73; 95% CI 1.18–2.54). Moreover, those who slept ≥9 h were more likely to report daytime sleepiness (OR 1.68; 95% CI 1.17–2.42). In stratified analyses, these associations generally did not vary with health status.

Conclusions: in older adults, short sleep is associated with nighttime sleep complaints and feeling unrested in the morning, while long sleep is associated with daytime sleepiness.

Keywords: sleep duration, sleep quality, sleep disorders, older adults, elderly