Delirium in the elderly: biomarkers and outcomes
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Citation for published version (APA):

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Chapter 4

Preoperative Cerebrospinal Fluid Cortisol is Not Associated With the Incidence of Postoperative Delirium

Submitted
CHAPTER 4

ABSTRACT

**Background:** Ageing, depression, and neurodegenerative diseases are common risk factors for delirium. They are associated with an increased sensitivity of the brain to stress resulting in higher levels of cortisol under normal and stressed conditions and a slower return to baseline cortisol levels after acute stress. We investigated whether hip fracture patients with postoperative delirium already show altered cortisol levels in the cerebrospinal fluid (CSF) before the operation.

**Methods:** Patients were 75 years or older and admitted for surgical repair of hip fracture. CSF samples were collected pre-operatively. We compared pre-operative CSF cortisol levels between patients with and without postoperative delirium and examined the association between cortisol levels and delirium severity. Mann-Whitney-U tests or Student t-tests were used for between group comparisons and the Spearman correlation coefficient was used for correlation analyses.

**Results:** Twenty-three out of 66 (35%) patients developed postoperative delirium. We found no significant differences in preoperative CSF cortisol levels between patients who did or did not develop postoperative delirium. Also, no association was found between preoperative CSF cortisol levels and the severity of the delirious episode.

**Conclusions:** Preoperative cortisol levels were not associated with the incidence or the severity of postoperative delirium in elderly patients who underwent surgical repair of hip fracture. These findings suggest that CSF cortisol does not mediate the increased risk for delirium that is associated with aging, depression and dementia.
BACKGROUND

Delirium is a severe neuropsychiatric syndrome characterized by inattention and acute cognitive dysfunction. Delirium is very common, especially following orthopaedic surgery for hip fracture, with up to half of all patients developing delirium. Moreover, delirium is independently associated with an increased risk of death, institutionalization and dementia. Despite these severe consequences the pathophysiology of delirium remains poorly understood.

One hypothesis regarding the underlying mechanisms of delirium states that high levels of cortisol may play a role in its pathogenesis. The brain controls the response to stress, yet, the central nervous system (CNS) is also a target of stress hormones. Sustained high levels of cortisol can have harmful effects on the brain causing inattention and other cognitive deficits. Moreover, frequent precipitating factors of delirium, such as trauma and surgery, increase cortisol levels and several studies have found associations between cortisol and the presence of delirium.

Old age, depression, and neurodegenerative diseases are important predisposing risk factors for delirium and associated with an increased sensitivity of the brain to stress due to structural and functional changes in the limbic-hypothalamic-pituitary-adrenal (LHPA) axis. These changes result in impaired feedback regulation of cortisol which leads to higher levels of cortisol, particularly under conditions with stress, and a slower return to baseline cortisol levels following acute stress. Thus, this suggests that elevated levels of cortisol can signal an increased risk for delirium.

Elderly hip fracture patients constitute a very frail population with a high occurrence of depression, cognitive impairment and postoperative delirium. Hip fracture patients undergo two events that elicit a stress response, that is the fracture, then the surgery. Given the increased vulnerability of the brain to stress with ageing, depression, and neurodegenerative disease it can be hypothesized that hip fracture patients who develop delirium after the operation already show altered CNS cortisol levels before the operation, that are stimulated by the fracture.

Previous studies that examined the relationship between preoperative cortisol levels and postoperative delirium did not find any significant associations. However, these studies have measured cortisol levels in plasma and plasma levels of cortisol are only variably related to cerebrospinal fluid (CSF) cortisol levels which more closely reflect CNS exposure to cortisol. Only one small preliminary study examined the association between CSF cortisol levels and delirium and found that elevated preoperative CSF cortisol levels were associated with preoperative delirium. However, there are no previous studies that examined whether high levels of CSF cortisol before the operation are related to the occurrence of delirium after the operation.
Therefore, the aim of the present study was to investigate whether preoperative cortisol levels measured in CSF are associated with the development of postoperative delirium in elderly patients with hip fracture. Given the exaggerated vulnerability of the brain to stress with ageing, depression, and neurodegeneration we hypothesized that CSF cortisol levels before surgery were elevated in hip fracture patients who were prone to develop postoperative delirium.

**METHODS**

**Ethical considerations**
This study was conducted 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 gave written informed consent.

**Study design and objectives**
Patients were participants in a clinical trial that compared the effectiveness of taurine versus placebo in reducing morbidity and one-year mortality in elderly hip fracture patients (the results of this trial will be described elsewhere). Evaluating the relationship between risk factors and delirium was a pre-specified secondary aim of this trial. All risk factors for delirium were assessed preoperatively. Presence and severity of delirium were assessed daily before and after the operation. All patients were undergoing surgical repair of hip fracture. CSF samples were collected after cannulation for the introduction of spinal anaesthesia but prior to the administration of any anesthetic. We compared preoperative CSF cortisol levels and baseline risk factors between patients who did or did not develop postoperative delirium and investigated the association between preoperative CSF cortisol levels and delirium severity. Even though patients with a low delirium severity score would generally not be regarded as categorically delirious the analysis of delirium severity included all patients. We also performed additional analyses to examine the association between levels of CSF cortisol on the one hand and pre-existent cognitive impairment and depressive symptoms on the other hand. Since all participants were at high risk for delirium (i.e. age 75 years or older, and acute hospital admission) patients received routine care with prophylactic treatment of 0.5 mg haloperidol, three times daily, from time of admission until postoperative day three, unless contraindications regarding its use were present.20

**Participants**
The study was conducted in a series of consecutively admitted elderly hip fracture
patients to a teaching hospital in Alkmaar, the Netherlands. Eligibility was checked for all patients 75 years and older admitted for primary surgical repair of hip fracture. Patients were not eligible if they had no acute trauma, received total hip prosthesis for surgical repair of their hip fracture, had a pathological fracture, were not capable (e.g. dementia in the medical case notes, aphasia, coma) or not willing to provide informed consent, or had contraindications regarding the administration of taurine (i.e. renal failure defined as a creatine clearing less than 30 ml/min). Written informed consent was obtained after eligibility was checked and the trial had been explained. From March 2008 to March 2009 122 hip fracture patients fulfilled criteria for participation and provided consent.

Figure 1. Flow-chart. CSF= cerebrospinal fluid
Baseline assessment
Baseline assessment was completed within 12 hours after admission and before surgery. This comprised delirium assessment, patient and proxy interviews and questionnaires, and inspection of the medical record to assess risk factors for delirium. Preoperative cognitive functioning was assessed with the Mini Mental State Examination (MMSE) on a scale of 0 (poor) to 30 (good) with scores lower than 24 indicating cognitive impairment. Prefracture cognitive decline was estimated with the short version of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE-N) which is scored by a close relative or caregiver and measures pre-existent cognitive decline over the past 10 years on a scale of 16 (improvement) to 70 (decline). A score higher than 57 (i.e. a mean score higher than 3.6) indicates cognitive decline. Visual impairment was assessed with the standardized Snellen test for visual impairment and was defined as binocular near vision, after correction, worse than 20/70. The medical record was reviewed to determine the preoperative Acute Physiology Age and Chronic Health Examination (APACHE II) score. The APACHE II score measures severity of acute illness on a scale of 0 (no acute health problems) to 70 (severe acute health problems). The Geriatric Depression Scale (GDS) was administered as a 15 item self-rating scale for depression. A cut-off score of 4 or more points was chosen to indicate depression. The Barthel Index was used to determine prefracture functioning in activities of daily living and is scored by a close relative or caregiver on a scale from 0 (dependence) to 20 (independence). Prefracture Instrumental Activities of Daily Living were assessed with the Lawton IADL scale, range 8 (no disability) to 31 (severe disability). Biomedical factors included the number and type of medical co-morbidities and medications before admission to hospital and the American Society of Anesthesiologists (ASA) physical status classification system, range 1 (normal health patient) to 5 (moribund patient). Demographic factors included age, gender, living arrangement, and low or high educational level. For the IQCODE-N, BI and Lawton IADL proxies were asked to describe the patient’s condition a week before the fracture as to determine function unbiased by the event of hip fracture itself or any acute or sub-acute event leading to hip fracture.

Cerebrospinal fluid
CSF samples were collected by the anaesthesiologist when patients underwent spinal anaesthesia for surgical repair of hip fracture. Lumbar punctures were performed with a 25-gauge needle between the L3-L4 or L4-L5 intervertebral space. Of each patient 13 ml of CSF was collected in polypropylene tubes and transported to the laboratory within two hours. The CSF samples were centrifuged at 1800 g for 10 minutes at 4°C and aliquoted into polypropylene tubes that were stored at -80°C.
After all CSF samples had been collected they were sent in one batch on dry ice with express delivery to the laboratory of pulmonary diseases of the University Medical Centre Utrecht. Upon arrival the status of the CSF samples was checked and they were stored for a few weeks at -80 C until further analysis. CSF cortisol levels were determined with a cortisol ELISA kit (Salimetrics, USA). The lower limit of detection for this kit was 0.003 μg/dL. All CSF samples were measured in duplo and the investigators that performed the cortisol measurements were blinded to the clinical status of the patients.

Outcome
The main outcome was postoperative delirium. Delirium was defined according to the Confusion Assessment Method (CAM), which consists of acute onset and fluctuating course of cognitive function, inattention, and either disorganized thinking, and/or altered level of consciousness. Delirium severity was measured using the Delirium Rating Scale Revised-98 (DRS-R-98), a 16-item rating scale with thirteen severity items (and 3 diagnostic items) and a range of 0 (no severity) to 39 (maximum severity). Presence and severity of delirium were assessed within 12 hours after admission and before surgery and continued daily until the fifth post-operative day or discharge. In case of a positive CAM score assessments were continued at least until the CAM was negative for three consecutive days or discharge. Severity of postoperative delirium was defined as the highest DRS-R-98 score. The CAM and DRS-R-98 rating were based on brief formal cognitive testing with the MMSE, patient and hospital staff interviews, and scrutiny of the medical and nursing records.

Statistical analysis
Statistical analyses were preformed using SPSS for Windows, version 17.0. Quantitative variables are presented as mean (standard deviation (SD)) or median (interquartile range (IQR)). Categorical variables were analysed using Chi-Square or Fisher Exact tests. Continues variables were tested with Mann-Whitney-U tests or Student t-tests depending on the sample size, distribution, and skewness of the data. The assumption of normality was tested with the Kolmogrov-Smirnov test and exploration of histograms. Because the cortisol variable was significantly skewed, Mann-Whitney-U tests were employed for pair-wise comparisons of this variable. The Spearman correlation coefficient was used for correlation analyses. Statistical significance was set at $P<.05$. 
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RESULTS

A total of 122 out of 257 consecutive hip fracture patients were included in this study. Twenty-six patients received general anaesthesia and in 18 instances there were logistical limitations that did not allow collection of CSF (e.g. polypropylene

Table 1. Baseline Characteristics of Patients With and Without Postoperative Delirium

<table>
<thead>
<tr>
<th></th>
<th>Delirium</th>
<th>No delirium</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=23</td>
<td>n=43</td>
<td></td>
</tr>
<tr>
<td>Age years</td>
<td>83.2 (80.4-88.8)</td>
<td>82.4 (79.3-86.2)</td>
<td>.22</td>
</tr>
<tr>
<td>Gender n/N (% female)</td>
<td>16/23 (70)</td>
<td>31/43 (72)</td>
<td>.83</td>
</tr>
<tr>
<td>Living independently, n/N (%)</td>
<td>19/23 (83)</td>
<td>37/43 (86)</td>
<td>.71</td>
</tr>
<tr>
<td>Low educational level, n/N (%)</td>
<td>7/21 (33)</td>
<td>14/39 (36)</td>
<td>.84</td>
</tr>
<tr>
<td>Visual impairment*, n/N (%)</td>
<td>1/21 (5)</td>
<td>2/43 (5)</td>
<td>.98</td>
</tr>
<tr>
<td>APACHE II† score</td>
<td>13.0 (12.0-14.0)</td>
<td>13.0 (11.0-14.0)</td>
<td>.41</td>
</tr>
<tr>
<td>ASA‡ group, n/N (%)</td>
<td>4/23 (17)</td>
<td>20/43 (47)</td>
<td>≤0.05</td>
</tr>
<tr>
<td>Group I;</td>
<td>12/23 (52)</td>
<td>17/43 (40)</td>
<td></td>
</tr>
<tr>
<td>II;</td>
<td>7/23 (30)</td>
<td>6/43 (14)</td>
<td></td>
</tr>
<tr>
<td>III;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of co-morbid diseases</td>
<td>2.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>0.43</td>
</tr>
<tr>
<td>Number of medications at home</td>
<td>4.0 (3.0-5.0)</td>
<td>3.0 (1.0-5.0)</td>
<td>0.06</td>
</tr>
<tr>
<td>median (IR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IQCODE-N§ score</td>
<td>3.8 (3.3-4.1)</td>
<td>3.2 (3.0-3.4)</td>
<td>≤0.001</td>
</tr>
<tr>
<td>IQCODE-N§ score &gt;3.6, n/N(%)</td>
<td>13/21 (62)</td>
<td>6/42 (14)</td>
<td>≤0.001</td>
</tr>
<tr>
<td>MMSE</td>
<td></td>
<td>score</td>
<td>23.5 (22.4-25.8)</td>
</tr>
<tr>
<td>MMSE</td>
<td></td>
<td>score &lt;24, n/N(%)</td>
<td>11/22 (50)</td>
</tr>
<tr>
<td>GDS¶ score</td>
<td>2.0 (1.0-3.0)</td>
<td>2.0 (1.0-3.0)</td>
<td>0.67</td>
</tr>
<tr>
<td>BI# score</td>
<td>18.0 (14.8-20.0)</td>
<td>19.5 (17.6-20.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>Lawton IADL** score</td>
<td>14.5 (11.3-17.8)</td>
<td>10.0 (8.0-15.5)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SD or median (IQR), n/N is number with characteristic/total number, (%) is percentage

* Visual impairment measured with the standardized Snellen test for visual impairment and defined as binocular near vision worse than 20/70 after correction.

† APACHE II is Acute Physiological and Chronic Health Evaluation II, range 0 (no acute health problems) to 70 (severe acute health problems).

‡ ASA is American Society of Anesthesiologists physical status classification system, range 1 (normal health patient) to 5 (moribund patient).

§ IQCODE-N is Informant Questionnaire on Cognitive Decline in the Elderly - Short Form, range 16 (cognitive improvement) to 80 (severe cognitive decline), mean score >3.6 indicates cognitive decline.

|| MMSE is Mini Mental State Examination, range 0 (severe cognitive impairment) to 30 (no cognitive impairment), score <24 indicates cognitive impairment.

¶ GDS is Geriatric Depression Scale, range 0 (depression not likely) to 15 (depression very likely).

# BI is Barthel Index, range 0 (severe disability) to 20 (no disability).

** Lawton IADL is Lawton Instrumental Activities of Daily Living scale, range 8 (no disability) to 31 (severe disability).
tubes were unavailable or emergency situation in operating room). In two cases CSF cortisol levels could not be reliable determined. Because we were specifically interested in the question whether preoperative CSF cortisol levels are associated with postoperative delirium another four patients were excluded from further analyses; one patient without postoperative delirium assessments available, and three patients with delirium before the operation. We excluded an additional 6 patients because they were on corticosteroid therapy (figure 1).

Of the remaining 66 patients, 23 (35%) developed postoperative delirium. The characteristics of patients with and without postoperative delirium are shown in table 1. Patients with postoperative delirium showed more signs of pre-existent cognitive impairment and were more dependent in (I)ADL functioning at home. Also, patients with postoperative delirium were more severely ill before the operation as measured with the ASA classification system. Other baseline risk factors, including the number of depressive symptoms, were not significantly different between patients who did or did not develop delirium after the operation.

We found no significant difference in preoperative CSF cortisol levels between patients who did or did not developed postoperative delirium (1.56 μg/dL [IQR .98-1.91 μg/dL] vs. 1.30 μg/dL [IQR .92-2.13 μg/dL]; \( P=.49 \)) (figure 2). There was also no significant association between the severity of postoperative delirium and levels of CSF cortisol (Spearman’s \( r^2 .04; P=.73 \)).

Figure 2. Box plot of CSF cortisol by group based on 23 patients with delirium and 43 patients without delirium (\( P=.49 \)). Boxes represent the median, the 25th and the 75th percentiles, bars indicate the range of the data distribution.
We found no significant differences regarding the times of CSF sampling between patients with and without postoperative delirium (3:50 p.m. [IQR 11.40 a.m.- 7.43 p.m.] vs. 4:08 p.m. [IQR 12:35 p.m.-7:35 p.m.; \( P=0.80 \)). Also, the times of CSF collection were not related to levels of CSF cortisol (Spearman’s \( r^2 = 0.17; \ P=0.18 \)). The mean time from admission to surgery was 18.9 hrs (SD ± 10.1 hrs) and patients with and without delirium waited a comparable amount of time for surgery (21.9 hr [IQR 12.4-30.3] vs. 19.0 hr [8.1-23.8]; \( P=0.06 \)). However, the severity of postoperative delirium was associated with the time between admission and the operation (Spearman’s \( r^2 = 0.327; \ P=0.008 \)). CSF cortisol levels were not influenced by the time between hospital admission and surgery (Spearman’s \( r^2 = 0.17; \ P=0.18 \)). Additional analyses showed that patients with and without signs of pre-existent cognitive decline, as measured with the IQCODE-N, had similar CSF cortisol levels (1.45 μg/dL [IQR .93-1.85 μg/dL] vs. 1.34 μg/dL [IQR .93-2.08 μg/dL]; \( P=0.66 \)). Moreover, comparable CSF cortisol levels were also found for patients with few (<4 GDS items) or many (≥4 GDS items) depressive symptoms at baseline (1.55 μg/dL [IQR .76-1.97 μg/dL] vs. 1.30 μg/dL [IQR .93-2.10 μg/dL]; \( P=0.81 \)). Treatment allocation (i.e. placebo or taurine) did not affect CSF cortisol levels and had no influence on the incidence or the severity of postoperative delirium (data not shown).

**DISCUSSION**

This study examined the association between preoperative CSF cortisol levels and the incidence and severity of postoperative delirium. Based on structural and functional changes in the LHPA axis in patients at risk of delirium we hypothesized that a more intense and sustained stress response following hip fracture would be associated with the development of postoperative delirium. In contrast to our hypothesis, preoperative CSF cortisol levels were not associated with the incidence or the severity of postoperative delirium in elderly hip fracture patients. Previous studies in acute and elective surgical populations have shown that postoperative delirium is associated with elevated levels of cortisol in blood.9-13 However, these investigations measured cortisol in the early postoperative period and although some of these studies described cortisol as a risk factor for delirium, in fact, many patients already suffered from delirium or were diagnosed with delirium very soon after collection of the blood samples. Only one previous study examined the association between delirium and cortisol in CSF.14 This preliminary study showed that preoperative CSF cortisol levels were highest in those patients with delirium before the operation. The association between preoperative cortisol levels and the incidence of postoperative delirium was not investigated.14 In contrast, studies that examined whether preoperative cortisol levels in blood predict postoperative
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Delirium did not find any significant associations.\textsuperscript{9,10,18} Taken together, these previous studies suggest that elevated levels of cortisol may mark an episode of delirium, may be involved in the pathogenesis of delirium, or may be an epiphenomenon of delirium. In contrast, pre-morbid high levels of cortisol did not seem to signal increased vulnerability for delirium. This conclusion is substantiated by our own study that failed to identify preoperative CSF cortisol levels as risk factor for postoperative delirium, even despite the presence of a noxious insult (i.e. the hip fracture) that can trigger a potent response of the LHPA axis. Interestingly, in spite of the well-described dysregulation of the LHPA axis in dementia and depression, pre-existent cognitive impairment and the number of depressive symptoms were not associated with elevated CSF cortisol levels in our population of elderly hip fracture patients. The exclusion of patients with dementia in the medical case notes and the relatively low scores on the depression scale at baseline may explain the lack of association between cortisol, cognitive impairment, and depressive symptomatology in our study. However, our study population does not represent a selection of “well” patients considering that the rate of pre-existent cognitive decline and postoperative delirium was substantial and comparable with other studies of elderly hip fracture patients.\textsuperscript{33} Moreover, if patients with more profound dementia were included and a relationship between cortisol and postoperative delirium was observed then the question had remained if cortisol is a risk marker for delirium by itself or whether both the activation of the LHPA axis and the increased risk for delirium can be explained by the presence of a severe neurodegenerative disease.

The collection of CSF occurred at different times of the day and this may have influenced our results given the diurnal rhythm of cortisol. However, operating times for patients with and without delirium were similar and the time of CSF collection was not related to levels of CSF cortisol. Thus, our findings are consistent with a flattening of the diurnal cortisol rhythm in the early phase after an acute injury.\textsuperscript{34} The time patients waited for surgery may also have confounded the association between delirium and CSF cortisol since cortisol levels may have returned to baseline while patients were waiting to be operated. However, levels of CSF cortisol in our population were considerably higher when compared with healthy elderly\textsuperscript{35} or patients with mild cognitive impairment or Alzheimer’s disease\textsuperscript{36} suggesting that our CSF cortisol levels were not at all normalized at the time of CSF sampling. More importantly, as the risk of a more severe episode of postoperative delirium increased as the time between admission and operation was prolonged, CSF cortisol levels did not. This dissociation suggests that other factors than an elevation of cortisol in the CNS confers the increased risk for a more severe episode of delirium.

In a condition resulting from impaired brain function, as in delirium, measurement
of cortisol in CSF has obvious advantages over measurement of plasma levels. Since several factors determine the level of cortisol in the CNS, including the degree of permeability of the blood brain barrier, the degree of active transport out of the brain, and the level of activity of cortisol metabolizing enzymes within the brain, peripheral cortisol levels may not necessarily reflect levels in the brain. Another strength of the present study is the systematic assessment of the presence and severity of pre-existent cognitive impairment, depressive symptoms, and delirium with standardized and validated instruments. Although this study would ideally have been performed in a larger and purely observational cohort the overlap in CSF cortisol levels between patients with and without postoperative delirium is apparent (figure 2). Furthermore, treatment allocation did neither influence CSF cortisol levels nor the incidence or severity of postoperative delirium. In conclusion, our results suggest that preoperative CSF cortisol levels are not associated with the occurrence of postoperative delirium. These findings are in agreement with previous studies on the association between cortisol and delirium and suggest that high cortisol levels do not predispose elderly hip fracture patients to delirium. Future studies should examine whether other factors than the level of cortisol itself, such as the sensitivity of the brain to cortisol confer an increased risk for delirium.
REFERENCES


