The wave called delirium, from onset to consequences
Slor, C.J.

Citation for published version (APA):
Slor, C. J. (2013). The wave called delirium, from onset to consequences

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter

Anesthesia and postoperative delirium in elderly hip-surgery patients

Chantal J. Slor
Jos F.M. de Jonghe
Ralph Vreeswijk
Erwin Groot
Tjeerd v.d. Ploeg
Willem A van Gool
Piet Eikelenboom
Marc Snoeck
Ben Schmand
Kees J. Kalisvaart

ABSTRACT

Background: Anesthetic agents and several classes of medication may be risk factors for postoperative delirium. The aim of this study was to examine effects of general anesthesia on the risk of incident postoperative delirium in older hip-surgery patients.

Methods: Secondary analysis of haloperidol prophylaxis for delirium clinical trial data. Predefined risk factors for delirium were assessed prior to surgery. Primary outcome was postoperative delirium. Study outcome was compared across patient groups who received either general or regional anesthesia, and for individuals receiving various perioperative medications (benzodiazepines, anticholinergics, and opioids), using multivariable logistic regression after controlling for potential confounders. Subgroup analyses based on baseline cognitive impairment and delirium risk were also undertaken.

Results: A total of 60/526 patients (11.4%) had incident postoperative delirium, 337/526 (64.1%) received general anesthesia and 189/526 (35.9%) regional anesthesia. 18/189 (9.5%) general anesthesia patients developed postoperative delirium, vs. 42/337 (12.5%) regional anesthesia patients (OR=0.81, CI0.43 – 1.52 adjusted P=.51). Results were stratified for baseline cognitive impairment, age, acute admission, perioperative medication and other delirium risk factors. Delirium was not independently associated with specific drugs nor the medication classes opioids, benzodiazepines and anticholinergics.

Conclusion: This study found that general anesthesia has no distinct effect on incident postoperative delirium in geriatric hip-surgery patients. This also holds for patients suffering from cognitive impairment or who are otherwise at risk for postoperative delirium. Perioperative use of narcotics, benzodiazepines and anticholinergic agents was not associated with incident delirium in this cohort of elderly hip fracture patients.
INTRODUCTION

Delirium is a serious, common postoperative complication in elderly patients, with occurrence rates as high as half of the patients. Postoperative delirium is associated with high mortality, cognitive deterioration and a high rate of institutionalization. Pathogenesis of delirium remains for the most part unexplained, although different risk factors have been identified. Potential risk factors for delirium after hip surgery include general anesthesia and perioperative medications used.

Contrary to popular belief, there is little evidence that general anesthesia is associated with delirium after hip surgery. Most studies do not link general anesthesia with postoperative delirium. A recent structured clinical update by Bryson and Wyand included eight trials that evaluated the relationship between type of anesthesia and postoperative delirium. Seven trials found that general anesthesia did not increase the risk of postoperative delirium as compared to regional anesthesia. One trial (n=60) showed that patients who had received regional anesthesia had poorer immediate post-operative cognitive performance than patients who had received general anesthesia. However, these studies have not stratified patients according to low, intermediate or high risk for developing postoperative delirium. Moreover, the majority of trials did not use validated instruments for diagnosing delirium, included relatively small patient numbers, and used different diagnostic concepts.

Few studies have examined the association between perioperative use of medications and postoperative delirium in geriatric hip-surgery patients. Benzodiazepines such as lorazepam, and opioids may increase the risk of postoperative delirium in ICU patients. ICU patients are often on mechanical ventilation. Sedation and prolonged intubation during mechanical ventilation are associated with negative outcomes and are potential risk factors for delirium. Therefore, these results cannot readily be generalized to hip-surgery patients. Though medications administered during surgery are potential precipitating or preventive factors for postoperative delirium, their effects on outcome have not previously been studied in detail.

Different factors may underlie relationships between general anesthesia, anesthetics and delirium. Older patients are likely to be more sensitive to adverse side effects of certain anesthetics and analgesics compared to younger patient groups. Specific characteristics of anesthetic and analgesic drugs represent potential precipitating factors for postoperative delirium in geriatric patients. The increased sensitivity is thought to be causally related to the relative decrease in cholinergic activity that accompanies the physiologic changes of the body in normal aging. An imbalance in acetylcholine mediated neural systems has been associated with delirium. Though some progress has been made, the precise mechanisms of delirium are yet to be identified.

This study examined the effect of general anesthesia on postoperative delirium in a large homogenous patient group. Study outcomes were also stratified for patients with
delirium risk factors, examining risk of delirium associated with general anesthesia in hip-surgery patients with or without cognitive impairment. Effects of classes of medications on postoperative delirium were explored. Understanding the role of anesthetic technique and perioperative medications as risk factors for POD may further increase our knowledge of potential methods to prevent POD.

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
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 study sample represents a prospective cohort study, which has been described previously. Hip-surgery patients (n=603) aged 70 and older were screened for risk factors for postoperative delirium in a randomized, double-blind, placebo-controlled clinical trial (RCT). A total of 430 patients at intermediate or high risk for delirium were randomized to pre-surgery prophylactic treatment with either haloperidol or placebo. Patients in the haloperidol group received a dose of 0.5 mg three times a day. Daily screening for postoperative delirium was carried out according to DSM IV and Confusion Assessment Method (CAM) criteria. The intervention showed no difference in the incidence of postoperative delirium between the haloperidol and placebo group. In addition to the predefined predictive risk factors cognitive impairment, visual impairment and severity of illness, other risk factors for delirium, particularly age and acute admission to hospital, were identified. In this study postoperative delirium was compared across patient groups with general versus regional anesthesia and across patients groups with or without specific perioperatively administered drugs grouped according to class. Data was collected prospectively, without knowledge of primary outcome for participants. We controlled for potential confounders of effects by examining baseline patient characteristics between patients with and without delirium as well as patients with general and regional anesthesia; baseline characteristics included demographics, admission type, well-known risk factors for delirium and perioperative medication. Data of haloperidol and placebo treated patients were pooled, and group assignment was analyzed as a potential confounder of results.
Participants
Participants were recruited among patients admitted for hip surgery to a 915 bed teaching hospital in Alkmaar, The Netherlands. The study period was from August 2000 to August 2002. 603 patients aged 70 or over, admitted for either acute or elective hip surgery, were screened for inclusion in the study. Participants were classified at baseline as low, intermediate or high risk for delirium. This was done according to the presence of four predictive risk factors as described by Inouye et al.: cognitive impairment, visual impairment, index of dehydration and severity of illness. These factors were measured using the Mini Mental State Examination, the standardized Snellen test, ratio blood urea nitrogen to creatinine and by the APACHE II score which was determined by chart review. A risk factor was present in each of the following situations: an MMSE score of <24 on a scale of 0 to 30, APACHE II score of >16 on a scale of 0 to 70, binocular near vision worse than 20/70 after correction (Snellen Test), and a ratio of blood urea nitrogen to creatinine ≥18. The presence of one or two risk factors was defined as ‘intermediate risk’ for delirium, while three or more was defined as ‘high risk’ for delirium.

Exclusion criteria were: delirium at admission, inability to participate in interviews (profound dementia, language barrier, intubation, respiratory isolation, aphasia, coma or terminal illness), a delay of surgery of more than 72 hours after admission, use of cholinesterase inhibitors, parkinsonism, levodopa treatment, epilepsy or a prolonged QTc interval of 460 ms or higher for men and 470 ms or higher for women on their electrocardiogram. Figure 1 shows the flow chart of the patients participating in this study.

A total of 526/603 (87.2%) patients had complete data on anesthesia type and anesthetics used. Patients with incomplete data more often had lower MMSE scores \( (P=.04) \), lower visual acuity scores \( (P=.048) \), were older \( (P=.004) \) and were more often acutely admitted \( (P=.004) \) compared to those with complete data. Incidence of delirium was not significantly different in patients with complete or incomplete data.

MEASUREMENTS AND PROCEDURES
Members of the research team not involved in the clinical care of the patients carried out all assessments. The research team consisted of research nurses and experienced geriatricians, who were trained extensively and followed standard procedures. Data were collected on standardized patient record forms and thoroughly checked on errors and validity.

Data on type of anesthesia and perioperatively used medication were independently retrieved from anesthetic records. All drugs administered as premedication, during surgery, and in the post anesthesia care unit (PACU) were recorded. Only usage or non-usage of medication was registered; administered dosages were not recorded.
Registration of perioperative medication was carried out blinded to the outcome of the original study of Kalisvaart et al.\textsuperscript{20}

The standard procedure following hip fracture was spinal anesthesia. Patients preferring otherwise received general anesthesia, unless there were contraindications.

**Figure 1. Flow Diagram of the Study.**

Original study
Patients admitted
(n=681)

Patients not meeting inclusion criteria (n=78)
Refused to be screened/part (n=36)
Discharged without surgery (n=36)
Parkinsonism (n=6)
On antipsychotic drugs (n=4)
Not testable (n=8)
Surgery before testing (n=6)
Extreme liver failure (n=1)
Delirium at admission (n=1)
Missed by emergency department (n=3)

Eligible Patients
(n=603)

n=430 randomized
n=173 not randomized

Files could not be retrieved (n=77)

Low-risk patients (n=121)
Refused to participate in taking medication (n=52)

Present study (n=526)

n=182 haldol
n=191 placebo
n=153 not randomized

Regional Anesthesia
(n=337)

n=111 haldol
n=134 placebo
n=92 not randomized

General Anesthesia
(n=189)

n=71 haldol
n=57 placebo
n=61 not randomized

Outcome

The primary outcome was postoperative delirium occurring within a period of 5 days postoperatively. Criteria for the diagnosis of the syndrome were based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)\textsuperscript{21} and the Confusion Assessment Method (CAM).\textsuperscript{22} To achieve the DSM-IV and CAM diagnoses, patients were assessed daily by means of the Mini Mental State Examination (MMSE), Digit Span test (assessment of attention, range 0 (no attention) to 42 (good attention) and the Delirium Rating Scale, revised version (DRS-R-98).\textsuperscript{23} A CAM score indicative of delirium was followed by a DSM-IV diagnosis made by the geriatrician.
Statistical Analysis
Statistical evaluations were performed with SPSS for Windows, version 14.0.

Means or proportions were used to describe demographic and clinical characteristics of the study sample. Baseline characteristics were compared across patients with or without delirium using Chi-square, Fisher exact test or t-test. Baseline characteristics were also compared between patients with general and regional anesthesia, in order to explore differences in characteristics between both groups. Associations between delirium and anesthetic technique, and delirium and three medication classes, were examined using chi-square or Fisher exact test and by calculating odds ratios and confidence intervals. The three selected medication classes were benzodiazepines (diazepam, lorazepam, midazolam, oxazepam and temazepam), anticholinergic agents (atropine and ipratropium) and opioids (alfentanil, morphine, nalbuphine, piritramide and sufentanil). Subsequently, potential independent predictors of delirium were entered in logistic regression models (backward elimination, $P<.10$) to calculate adjusted odds ratios (ratio is the chance of developing postoperative delirium). Age and predefined risk factors APACHE II, MMSE and Snellen test were entered in the analysis as continuous variables, and type of admission, anesthetic technique and the three medication classes were entered as dichotomous variables.

As a further stratification procedure associations between delirium and anesthetic technique were examined within each risk factor group (MMSE<24, APACHE>16, acute admission, visual acuity $>$20/70, dehydration, female and total number of risk factors present) separately. In an intermediate multivariate analysis we controlled for potential interaction effects of the intervention by including patients receiving treatment or placebo, and excluding haloperidol treated patients.

RESULTS
Primary outcome
A total of 18/60 (30%) delirium patients had general anesthesia, compared to 171/466 (36.7%) non-delirious patients, indicating no effect of type of anesthesia on primary outcome (OR=0.74, CI 0.41 – 1.33 $P=.31$). Based on an average 1.5 years age difference between the two groups, patients with regional anesthesia were at a slightly higher risk of delirium compared to those with general anesthesia as evidenced (Table 1). However, no effect of anesthesia type was found on study outcome after controlling for age differences, as well as after controlling for differences in perioperative medication. Both groups were similar on the distribution of other baseline delirium risk factors.
Table 1. Delirium Risk Factors between Anesthesia Groups.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>General Anesthesia n=189</th>
<th>Regional Anesthesia n=337</th>
<th>OR (95% CI) for developing delirium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*</td>
<td>76.7 ± 5.5</td>
<td>78.2 ± 6.0</td>
<td>0.96 (0.93 – 0.99)</td>
</tr>
<tr>
<td>Female°</td>
<td>148 (78.3)</td>
<td>262 (77.7)</td>
<td>1.03 (0.67 – 1.59)</td>
</tr>
<tr>
<td>Mini-Mental State Examination score*</td>
<td>25.4 ± 4.1</td>
<td>25.4 ± 3.9</td>
<td>1.01 (0.97 – 1.05)</td>
</tr>
<tr>
<td>APACHE II score*</td>
<td>13.0 ± 3.0</td>
<td>13.0 ± 3.1</td>
<td>1.01 (0.95 – 1.07)</td>
</tr>
<tr>
<td>Visual acuity**</td>
<td>0.43 ± 0.16</td>
<td>0.41 ± 0.16</td>
<td>2.70 (0.86 – 8.43)</td>
</tr>
<tr>
<td>Blood urea nitrogen/creatinine ratio**</td>
<td>12.6 ± 4.0</td>
<td>12.8 ± 3.8</td>
<td>0.99 (0.94 – 1.03)</td>
</tr>
<tr>
<td>Geriatric Depression Scale-15 score**</td>
<td>1.2 ± 1.5</td>
<td>1.1 ± 1.5</td>
<td>1.06 (0.94 – 1.19)</td>
</tr>
<tr>
<td>Barthel Index Score°</td>
<td>18.6 ± 3.5</td>
<td>19.0 ± 2.8</td>
<td>0.96 (0.91 – 1.03)</td>
</tr>
<tr>
<td>Acute admission (fracture)°</td>
<td>36 (19)</td>
<td>72 (21.4)</td>
<td>1.16 (0.74 – 1.81)</td>
</tr>
<tr>
<td>Haloperidol prophylaxe°</td>
<td>71 (37.6)</td>
<td>111 (32.9)</td>
<td>1.23 (0.85 – 1.78)</td>
</tr>
<tr>
<td>Predefined risk factors° (dichotomous values):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mini-Mental State Examination score &lt;24</td>
<td>40 (21.2)</td>
<td>84 (24.9)</td>
<td>0.81 (0.53 – 1.24)</td>
</tr>
<tr>
<td>APACHE II score &gt;16</td>
<td>20 (10.6)</td>
<td>53 (15.7)</td>
<td>0.63 (0.37 – 1.10)</td>
</tr>
<tr>
<td>Vision score worse than 20/70</td>
<td>19 (10.1)</td>
<td>44 (13.1)</td>
<td>0.74 (0.42 – 1.32)</td>
</tr>
<tr>
<td>Age ≥80</td>
<td>55 (29.1)</td>
<td>121 (35.9)</td>
<td>0.73 (0.50 – 1.08)</td>
</tr>
<tr>
<td>Blood urea nitrogen/creatinine ratio ≥18</td>
<td>130 (68.8)</td>
<td>223 (66.2)</td>
<td>1.13 (0.77 – 1.65)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or n (%) unless otherwise indicated.
* = continuous variables, ° = dichotomous variables.
OR = odds Ratio, the chance of developing postoperative delirium, CI = confidence interval
APACHE II = Acute Physiological and Chronic Health Evaluation II
¶ Range 0 (severe cognitive impairment) to 30 (no cognitive impairment).
§ Range 0 (no acute health problems) to 70 (severe acute health problems).
# Range 20/20 (no visual impairment) to 20/800 (severe visual impairment).
¥ Ratio ≥18 indicating dehydration.
† Range 0 (depression not likely) to 15 (depression very likely).
¢ Range 0 (severe disability) to 20 (no disability).

Anesthesia was not a precipitating event in at risk patients, as evidenced by no increased risk of postoperative delirium after general anesthesia in cognitively impaired patients, nor across patients at low, intermediate and high risk of delirium (Table 2).

Outcome and agents used perioperatively
Pooled analysis according to medication class shows that patients without postoperative delirium more often received a benzodiazepine (394/466, 84.5%) compared to patients with delirium (36/60, 60%) (P<.001). However, controlling for predefined risk factors indicated that the use of benzodiazepine was not an independent predictor of primary outcome (OR=0.73, CI 0.35 – 1.51 P=.39). A total of 46/60 (76.7%) delirious patients received an opioid, versus 373/466 (80%) non-delirious patients (P=.54) and 8/60 (13.3%)
delirious patients received an anticholinergic agent, versus 38/466 (8.2%) non-delirious patients (P=.18).

A total of 344/526 (65.4%) patients received no treatment or placebo. In the intermediate analysis anesthesia technique was not independently associated with postoperative delirium (Adjusted OR = 0.53, CI 0.21 – 1.31, P=.0.16).

Table 2. Interaction between Risk Factors and Anesthetic Technique.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>GA and delirium/GA</th>
<th>RA and delirium/RA</th>
<th>OR (95% CI) for developing delirium</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE &lt;24</td>
<td>8/40 (20%)</td>
<td>29/84 (34.5%)</td>
<td>0.47 (0.19 – 1.16)</td>
</tr>
<tr>
<td>APACHE &gt;16</td>
<td>6/20 (30%)</td>
<td>14/53 (26.4%)</td>
<td>1.19 (0.38 – 3.71)</td>
</tr>
<tr>
<td>Visual acuity worse than 20/70</td>
<td>4/19 (21.1%)</td>
<td>8/44 (18.2%)</td>
<td>1.20 (0.31 – 4.60)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>13/130 (10%)</td>
<td>28/223 (12.6%)</td>
<td>0.77 (0.39 – 1.55)</td>
</tr>
<tr>
<td>Age ≥80</td>
<td>7/55 (12.7%)</td>
<td>26/121 (21.5%)</td>
<td>0.53 (0.22 – 1.32)</td>
</tr>
<tr>
<td>Acute Admission</td>
<td>11/36 (30.6%)</td>
<td>19/72 (26.4%)</td>
<td>1.23 (0.51 – 2.96)</td>
</tr>
<tr>
<td>Female</td>
<td>11/134 (8.2%)</td>
<td>16/216 (7.4%)</td>
<td>1.12 (0.50 – 2.49)</td>
</tr>
</tbody>
</table>

Number risk factors ¹

<table>
<thead>
<tr>
<th>Number</th>
<th>GA and delirium/GA</th>
<th>RA and delirium/RA</th>
<th>OR (95% CI) for developing delirium</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2/41 (4.9%)</td>
<td>3/74 (4.1%)</td>
<td>1.21 (0.19 – 7.58)</td>
</tr>
<tr>
<td>1</td>
<td>6/103 (5.8%)</td>
<td>14/164 (8.5%)</td>
<td>0.66 (0.25 – 1.78)</td>
</tr>
<tr>
<td>2</td>
<td>6/33 (18.2%)</td>
<td>13/65 (20%)</td>
<td>0.89 (0.30 – 2.60)</td>
</tr>
<tr>
<td>3</td>
<td>3/8 (37.5%)</td>
<td>9/26 (34.6%)</td>
<td>1.13 (0.22 – 5.86)</td>
</tr>
<tr>
<td>4</td>
<td>1/4 (25%)</td>
<td>3/8 (37.5%)</td>
<td>0.56 (0.04 – 8.09)</td>
</tr>
</tbody>
</table>

Data are presented as n (%) within each group unless otherwise indicated. n/n=people with delirium and risk factor within anesthesia technique group/total number of people with risk factor within anesthesia technique group

POD=postoperative delirium, GA=general anesthesia, RA=regional anesthesia


DISCUSSION

This study examined the relationship between postoperative delirium, anesthesia and perioperative medication exposure. The risk of postoperative delirium was not increased in general anesthesia patients compared to patients receiving regional anesthesia. Moreover, the risk of delirium associated with general anesthesia was not increased in patients with baseline cognitive impairment, nor was it increased after stratification for other baseline delirium risk factors. The use of narcotics, benzodiazepines and anticholinergic agents was not independently associated with delirium. Strengths of this
study are the large sample size and the relatively homogeneous study population, which included patients who were or were not at risk of delirium; the use of standardized and valid methods for diagnosing delirium; and pre-surgery assessment of validated delirium risk factors.

The absence of a distinct association between general anesthesia and delirium is an important finding. In this study, 9.5% of patients with general anesthesia had delirium compared to the overall figure of 11.4%. In agreement with the overall trend, cognitively impaired patients were not at an increased risk of delirium after general anesthesia compared to regional anesthesia. In contrast with widespread popular belief, general anesthesia seems to be safe when it comes to the risk of delirium, even in elderly hip-surgery patients who are at risk of developing this serious complication.

Our findings with respect to outcome following general anesthesia are consistent with previous reports comparing delirium risk depending on anesthesia type. Papaioannou et al. found no association between postoperative delirium and general anesthesia in patients (n= 47) undergoing different classes of surgery. In a randomized trial by Williams-Russo et al., patients (n=262) older than 40 years undergoing knee-replacement surgery were assigned to receive epidural or general anesthesia, and patients in the latter group were not more likely to suffer from postoperative delirium. However, trials included relatively small patient groups or used different classes of surgery and none stratified study outcomes for patients with risk factors for delirium, particularly cognitive impairment.

Studies examining effects of peri-operative drugs on postoperative delirium in hip-surgery patients are lacking. Exposure to benzodiazepine and opioid medication has been associated with increased delirium risk but these findings must be interpreted with caution because of wide confidence intervals and different study populations. For the most part, there still is insufficient information on the pathophysiology of postoperative delirium. Impaired cholinergic function has been suggested as the common final pathway leading to delirium. We did find a higher percentage of patients receiving anticholinergics in the delirium group compared to non-delirium patients. However, this did not reach significance which might be explained by the small sample.

Although our results are consistent with other studies, we used a particularly rigorous approach to explore short-term outcomes of anesthesia. We clinically assessed patients on admission prior to surgery and included a large number of patients in one well-defined class of surgery, including many who were not at risk for delirium. Furthermore, in our study the diagnosis of postoperative delirium was based on clinical patient interviews and DSM IV criteria, and we used validated diagnostic instruments and delirium rating scales. By doing so, we were able to examine both the effects of anesthesia type, medication, and baseline risk factors on delirium in a single multivariate analysis.

This study has a number of noteworthy limitations including study power and the relevance of these results to the practice of anesthesia in patients prone to delirium. This
Anesthesia and postoperative delirium in elderly hip-surgery patients

was a single site study and involved a secondary analysis, as part of a randomized trial not specifically designed to examine the relationship between anesthesia and delirium risk. As such, anesthetic technique was not standardized, Moreover, patients receiving regional anesthesia were older than the patients receiving general anesthesia, but age effects were controlled for in multivariate analysis. Differences in prescribed perioperative drugs between anesthesia groups were also examined. Controlling for medication effects did not change the effect of anesthesia technique on primary outcome. Both anesthesia groups were comparable with regard to other delirium risk factors. An additional possibility is that patients with intact cognitive function may have been more likely to select regional rather than general anesthesia but MMSE scores did not differ between the regional and anesthesia group, moreover we controlled for the potential differences, also MMSE score, in our primary and secondary analysis. We therefore believe that these findings do not reflect a referral bias to either general or regional anesthesia.

This study was underpowered to examine effects of specific medications. Analysis was restricted to three well known drug classes. Other classes of medication, particularly sedative-hypnotics and β-blockers may be associated with postoperative delirium. Postoperative medication use and many other in-hospital events can be associated with postoperative delirium. A recent study found evidence that limiting sedation depth during spinal anesthesia decreases the prevalence of delirium. This indicates that other in-surgery factors might be associated with postoperative delirium. This exploratory aspect of the study can be useful for generating hypotheses about delirium associated with perioperative agents. More precise documentation of drug dosage is required to estimate the precise anticholinergic activity of each drug, as this may have a mediating effect. We did not examine drug dosage for logistic reasons, but did include an examination of three classes of medication in this large patient sample. To summarize, because of limited study power, conclusions on the potential effects of perioperative agents on study outcome are preliminary, and the inclusion of RCT patients does not invalidate study results and conclusions.

This study suggests that the risk of developing delirium in patients receiving general anesthesia for hip-surgery may be overstated. The general understanding in the medical field s that regional anesthesia is preferred over general anesthesia because of perceived delirium risk, especially in patients already vulnerable to developing postoperative delirium. Contrary to this view, our study adds to the growing body of evidence that type of anesthesia does not increase delirium risk, even among a patient population at relatively high risk for postoperative delirium. It also highlights the relative importance of predisposing factors over precipitating events in delirium pathogenesis whereby a number of well recognised risk factors are most relevant to the risk of developing delirium and these may outweigh the impact of peri-operative events.
REFERENCES


Anesthesia and postoperative delirium in elderly hip-surgery patients


## Appendix 1. Logistic Regression Analysis of Administered Perioperative Agents.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Unadjusted Data</th>
<th>Adjusted Data</th>
<th>Drug</th>
<th>Unadjusted Data</th>
<th>Adjusted Data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( N )</td>
<td>( \text{OR (95% CI)} )</td>
<td>( N )</td>
<td>( \text{OR (95% CI)} )</td>
<td>( N )</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>13</td>
<td>2.49 (0.79 – 7.90)</td>
<td>1.60 (0.42 – 6.18)</td>
<td>Lorazepam</td>
<td>3</td>
</tr>
<tr>
<td>Articaine</td>
<td>21</td>
<td>0.81 (0.18 – 3.57)</td>
<td>1.49 (0.32 – 6.84)</td>
<td>Magnesiumoxide</td>
<td>3</td>
</tr>
<tr>
<td>Atropine</td>
<td>34</td>
<td>2.15 (0.89 – 5.17)</td>
<td>2.15 (0.83 – 5.62)</td>
<td>Mepivacaine</td>
<td>11</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>290</td>
<td>1.07 (0.62 – 1.85)</td>
<td>0.98 (0.54 – 1.76)</td>
<td>Metoclopramide</td>
<td>33</td>
</tr>
<tr>
<td>Cefuroxim</td>
<td>433</td>
<td>1.07 (0.51 – 2.27)</td>
<td>0.72 (0.32 – 1.63)</td>
<td>Metoprolol</td>
<td>6</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>1</td>
<td>N.A.</td>
<td>N.A.</td>
<td>Midazolam</td>
<td>73</td>
</tr>
<tr>
<td>Clemastine</td>
<td>3</td>
<td>N.A.</td>
<td>N.A.</td>
<td>Morphine</td>
<td>246</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>23</td>
<td>1.68 (0.55 – 5.12)</td>
<td>2.73 (0.86 – 8.72)</td>
<td>Nabumetom</td>
<td>5</td>
</tr>
<tr>
<td>Clonidine</td>
<td>3</td>
<td>N.A.</td>
<td>N.A.</td>
<td>Nadroparine</td>
<td>5</td>
</tr>
<tr>
<td>Desmopressine</td>
<td>3</td>
<td>N.A.</td>
<td>N.A.</td>
<td>Nalbuphine</td>
<td>7</td>
</tr>
<tr>
<td>Dexamethason</td>
<td>14</td>
<td>1.31 (0.29 – 5.98)</td>
<td>1.29 (0.25 – 6.66)</td>
<td>Naloxon</td>
<td>1</td>
</tr>
<tr>
<td>Diazepam</td>
<td>1</td>
<td>N.A.</td>
<td>N.A.</td>
<td>Naproxen</td>
<td>70</td>
</tr>
<tr>
<td>Digoxin</td>
<td>2</td>
<td>N.A.</td>
<td>N.A.</td>
<td>Nitroglycerin</td>
<td>3</td>
</tr>
<tr>
<td>Dopamine</td>
<td>6</td>
<td>1.56 (0.18 – 13.61)</td>
<td>1.39 (0.15 – 12.87)</td>
<td>Neostigmine</td>
<td>26</td>
</tr>
<tr>
<td>Droperidol</td>
<td>4</td>
<td>N.A.</td>
<td>N.A.</td>
<td>Norepinephrine</td>
<td>2</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>202</td>
<td>0.45 (0.24 – 0.84)</td>
<td>0.61 (0.32 – 1.18)</td>
<td>Ondansetron</td>
<td>173</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>37</td>
<td>N.A.</td>
<td>N.A.</td>
<td>Oxazepam</td>
<td>4</td>
</tr>
<tr>
<td>Etomidate</td>
<td>105</td>
<td>2.91 (1.64 – 5.16)</td>
<td>1.22 (0.61 – 2.46)</td>
<td>Pantoprazol</td>
<td>2</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>3</td>
<td>N.A.</td>
<td>N.A.</td>
<td>Paracetamol</td>
<td>258</td>
</tr>
<tr>
<td>Flumazenil</td>
<td>1</td>
<td>N.A.</td>
<td>N.A.</td>
<td>Phenylephrine</td>
<td>182</td>
</tr>
<tr>
<td>Furosemide</td>
<td>10</td>
<td>1.97 (0.41 – 9.52)</td>
<td>1.35 (0.24 – 7.63)</td>
<td>Piritramide</td>
<td>116</td>
</tr>
<tr>
<td>Gentamycine</td>
<td>1</td>
<td>N.A.</td>
<td>N.A.</td>
<td>Prednisolone</td>
<td>10</td>
</tr>
<tr>
<td>Drug</td>
<td>N</td>
<td>Unadjusted Data OR (95% CI)</td>
<td>Adjusted Data OR (95% CI)</td>
<td>Drug</td>
<td>N</td>
</tr>
<tr>
<td>-----------------</td>
<td>-----</td>
<td>----------------------------</td>
<td>---------------------------</td>
<td>-----------------</td>
<td>-----</td>
</tr>
<tr>
<td>Glycopyronium</td>
<td>32</td>
<td>1.48 (0.55 – 4.00)</td>
<td>1.61 (0.53 – 4.92)</td>
<td>Promethazine</td>
<td>1</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>13</td>
<td>2.4 (0.64 – 8.98)</td>
<td>1.11 (0.22 – 5.50)</td>
<td>Propofol</td>
<td>146</td>
</tr>
<tr>
<td>Ipratropium</td>
<td>10</td>
<td>0.86 (0.11 – 6.92)</td>
<td>0.75 (0.08 – 6.85)</td>
<td>Ranitidine</td>
<td>3</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>2</td>
<td>7.88 (0.49 – 127.68)</td>
<td>14.44 (0.85 – 245.19)</td>
<td>Rocuronium</td>
<td>178</td>
</tr>
<tr>
<td>Ketamine</td>
<td>3</td>
<td>3.93 (0.35 – 44.03)</td>
<td>1.20 (0.09 – 15.56)</td>
<td>Salbutamol</td>
<td>9</td>
</tr>
<tr>
<td>Ketanserine</td>
<td>3</td>
<td>N.A.</td>
<td>N.A.</td>
<td>Sevoflurane</td>
<td>164</td>
</tr>
<tr>
<td>Lepobupivacain</td>
<td>57</td>
<td>0.90 (0.37-2.21)</td>
<td>1.00 (0.39-2.57)</td>
<td>Sufentanil</td>
<td>192</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>5</td>
<td>1.96 (0.22-17.81)</td>
<td>2.40 (0.20-28.26)</td>
<td>Temazepam</td>
<td>410</td>
</tr>
</tbody>
</table>

N.A. = no analysis possible  
N = number of patients who received the drug  
OR = Odds Ratio; CI = Confidence Interval