Incidence and risk factors for postoperative cognitive dysfunction in older adults undergoing major noncardiac surgery: A prospective study

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Abstract

Background & Aims: Postoperative cognitive dysfunction (POCD) is a decline in cognitive function that occurs after surgery. The purpose of this study was to estimate the incidence and identify potential risk factors of POCD in older adults undergoing major noncardiac surgery.

Materials and Methods: A total of 69 patients aged 65 years or older undergoing major noncardiac surgery were enrolled. Patients’ cognitive function was assessed before and 3 months after surgery using a computerized neurocognitive battery. A nonsurgical control group of 54 older adults was recruited to adjust for learning effects from repeated administration of neurocognitive tests. Data about potential risk factors for POCD were collected before, during, and after surgery, including patient, medication, and surgery factors. The incidence of POCD was calculated using the Z-score method. A multivariable logistic regression model was used to identify risk factors for POCD.

Results: POCD was present in eleven patients (15.9%, 95% confidence interval [CI] = 7.3-24.6) 3 months after major noncardiac surgery. Carrying the apolipoprotein E4 (APOE4) genotype (odds ratio [OR] = 4.74, 95% CI = 1.09-22.19), using one or more highly anticholinergic or sedative-hypnotic drugs at home prior to surgery (OR = 5.64, 95% CI = 1.35-30.22), and receiving sevoflurane for anesthesia (OR = 6.43, 95% CI = 1.49-34.66) were associated with the development of POCD.

Conclusions: POCD was observed in 15.9% of older adults after major noncardiac surgery. Risk factors for POCD in these patients were carrying the APOE4 genotype, using one or more highly anticholinergic or sedative-hypnotic drugs prior to surgery, and receiving sevoflurane for anesthesia.

Key words: Cognitive, dysfunction, noncardiac, older, postoperative, surgery

Introduction

Postoperative cognitive dysfunction (POCD) does not have a consensus definition in the literature or diagnostic codes. However, POCD is generally described as a decline in cognitive function that occurs in patients after surgery when compared to their preoperative cognitive status. This decline in cognitive function is usually subtle in nature and may be unrecognized by clinicians. Research about the incidence and risk factors of POCD after major noncardiac surgery is still in its infancy, and the results of current investigations are still conflicting and inconclusive.

The risk of POCD may be increased in older adults due to physiologic, pharmacokinetic, and pharmacodynamic changes that are associated with aging. These changes may result in increased sensitivity and susceptibility to the insult from the surgical experience, anesthetic agents, and other drugs that are administered before, during, and after surgery and are known to cause negative cognitive outcomes (e.g., highly anticholinergic and sedative-hypnotic drugs).¹⁴ POCD after noncardiac surgery has been associated with increased mortality, decreased quality of life, risk of early withdrawal from the workforce, and increased dependency.⁵
Patients’ preoperative cognitive function was assessed within 2 weeks before surgery. Follow-up cognitive testing was conducted 3 months after surgery allowing a 2-week flexibility period. The same neurocognitive battery was used to assess cognitive function in the control group at baseline and 3 months after major noncardiac surgery, respectively.[6]

**Assessment of depression and sleep quality**

Depression and poor sleep quality may adversely affect performance on neuropsychological tests.[8,9] For this reason,
we tested our study subjects for possible depression and poor sleep quality before each testing session using the Geriatric Depression Scale Short-Form (GDS-SF)\[10\] and Pittsburgh Sleep Quality Index (PSQI),\[11\] respectively. We compared the changes in depression and sleep quality test scores at baseline and follow-up between the patient and control groups to determine if there was a difference between the two groups that could have affected their performance differently on neurocognitive tests. We also compared the changes in depression and sleep quality test scores at baseline and follow-up within each of the two groups to determine if there was a change from baseline to follow-up that could have affected the performance of any of the two groups differently on neurocognitive tests.

**Data collection**

Patients’ demographics, medical and medication history, level of education, and computer use familiarity were documented before surgery by questioning patients and reviewing their medical charts. During the surgery, information about the type and duration of anesthesia used was collected. We also documented the incidence of intraoperative hypothermic, hypotensive, and hypoxic events for the duration of surgery. A hypotensive event was defined as mean systolic blood pressure 20% lower than baseline. A hypothermic event was defined as body temperature equal to or less than 36°C. A hypoxic event was defined as oxygen saturation less than 90%. These events were operationally defined by a consensus of the surgeons and anesthesiologists involved in the study. Following surgery, we documented all postoperative medications taken by patients and any complications experienced until hospital discharge. Study data were recorded and stored in the VCU Research Electronic Data Capture (REDCap).\[12\]

**Genetic and inflammatory biomarker analysis**

To test the hypotheses if patients with the apolipoprotein E4 (APOE4) genotype or preoperative heightened inflammatory response, expressed by high level of C-reactive protein (CRP), are at higher risk for POCD, two 5 ml blood samples were collected on the day of surgery just before the induction of anesthesia from study patients who agreed to participate in this part of the study. The patient was identified as a carrier of the E4 genotype if he had at least one copy of the E4 alleles. A CRP level above 0.5 mg/dL was considered high.

**Statistical analysis**

Because of the exploratory nature and limited duration and funding of this study, we did not do power calculation. We have rather included all eligible patients who consented to be part of the study. Descriptive analysis of demographics and baseline characteristics for patients and controls was conducted. Continuous data were reported as mean and standard deviation and/or range, and were compared using t-test or analysis of variance (ANOVA). Proportions were reported as numbers and percentages and were compared using Chi-square or Fischer’s exact test, when applicable. Depression and sleep quality scores were compared within each of the study groups at baseline and follow-up using paired t-test, and the scores were compared between the two study groups at baseline and follow-up using ANOVA.

We identified patients with POCD using the Z-Score method that was originally used in the first and second international studies of POCD.\[6,13\] An individual Z-score was calculated for each patient for each test in the battery by subtracting the mean score change in each test in the control group from the score change between baseline and follow-up of that test in each patient in the surgical group. The result was then divided by the standard deviation for the mean score change in the control group to provide the individual Z-score for that specific test for each patient. A composite Z-score was then calculated for each patient by adding all individual Z-scores for that specific patient and dividing them by the standard deviation of the mean sum of Z-scores in the control group. The patient was classified as having POCD if he had an individual Z-score of less than 1.96 in two or more cognitive tests or a composite Z-score of less than 1.96.

A series of univariable logistic regression analyses were initially conducted using Chi-square tests at a significance level of 0.25 to screen for potential predictors of POCD. The tested patient variables were age (years), gender (male, female), race (White, African-American, other), education level (high school or less, more than high school), MMSE-2 score, computer familiarity (not familiar at all, little familiar or familiar, very familiar or expert), diagnosis of vascular or endocrine comorbidities (diabetes, hypertension, hypothyroidism, hypercholesterolemia), and APOE4 genotype (APOE4, non-APOE4).

The surgical variables included type of surgery (orthopedic surgery, neurosurgery), duration of surgery (<2 h, 2-4 h, >4 h), type of anesthesia (general anesthesia, regional anesthesia, combined general and regional anesthesia) and the use of individual general or regional anesthetic agents, duration of anesthesia (<2 h, 2-4 h, >4 h), preoperative level of CRP (normal, high), blood loss volume (ml), hypotensive events (yes, no), hypoxic events (yes, no), hypothermic events (yes, no), and length of hospitalization (days).

The medication variables included the use of highly anticholinergic or sedative-hypnotic medications at home, preoperatively, intraoperatively, or postoperatively (no use, use of one or more medications). We only included highly anticholinergic and sedative-hypnotic medications from the
American Geriatrics Society 2012 updated Beers criteria for potentially inappropriate medication use in older adults.\(^{[14]}\) This list is comprehensive and includes drugs that are supported with strong evidence to be associated with negative cognitive outcomes in older adults.\(^{[14]}\) We also evaluated the use of morphine, hydromorphone, and oxycodone as postoperative analgesics (use, no use) to determine if it was associated with POCD.

Significant variables in the preliminary univariable analyses, at the predetermined alpha level of 0.25, were included in a multivariable logistic regression model. Model building was done using stepwise backward logistic regression due to the exploratory nature of our study (\(P\) was set at 0.25 and 0.10 for entering and leaving the model, respectively), and Firth’s method was used to accommodate for a small sample size and a large number of tested potential risk factors. Results of the multivariable logistic regression model were reported as adjusted odds ratio (OR) and 95% confidence interval (CI). We considered \(P < 0.05\) to be statistically significant, and \(P\) values were two-sided for all statistical tests, when applicable. Data analysis was performed using JMP® Pro 11 (SAS® Institute Inc., Cary, NC, USA).

**Results**

**Demographics and baseline characteristics of study subjects**

A total of 69 surgical patients and 54 nonsurgical controls have completed the study follow-up and were included in the final analysis. Figures 1 and 2 show the recruitment process for the patient and control groups, respectively. Table 1 summarizes the demographics and baseline characteristics of both patients and controls.

**Depression status and sleep quality at baseline and follow-up**

There was no difference between the two groups in depression status at baseline (\(F[1, 121] = 1.37, P = 0.245\)) or follow-up (\(F[1, 121] = 0.03, P = 0.874\)). There was also no difference between the two groups in sleep quality at baseline (\(F[1, 121] = 0.45, P = 0.506\)) or follow-up (\(F[1, 121] = 0.73, P = 0.395\)). There was no change in depression status from baseline to follow-up within the patient or control group (\(t = 0.67, P = 0.51; t = 0.99, P = 0.33, \) respectively). There was also no change in sleep quality from baseline to follow-up within the patient or control group (\(t = 0.57, P = 0.57; t = 0.21, P = 0.83, \) respectively).

**Incidence and risk factors of postoperative cognitive dysfunction**

A total of 11 (15.9%, 95% CI = 7.3-24.6) patients were classified as having POCD using the \(Z\)-score definition. Table 2 shows the results of initial screening for potential risk factors of POCD, and the distribution of patients across different categories of each variable. The variables that were included in the final model were carrying the APOE4 genotype (OR = 4.74, 95% CI = 1.09-22.19), using one or more highly anticholinergic or sedative-hypnotic medication at home prior to surgery (OR = 5.64, 95% CI = 1.35-30.22), and receiving sevoflurane for anesthesia.

| Variable (% | Surgical | Nonsurgical | \(P\) |
|-------------|-----------|-------------|------|
| Age ± SD (range) | 71±5.4 (65-88) | 73±6.3 (65-92) | 0.043* |
| Gender (females) | 46 (66.7) | 35 (64.8) | 0.83 |
| Race | | | |
| White | 56 (81.2) | 28 (51.9) | <0.001* |
| African-American | 10 (14.5) | 26 (48.1) | |
| Other | 3 (4.3) | 0 (0.0) | |
| Education level | | | |
| High school or less | 15 (21.7) | 19 (35.2) | 0.109 |
| More than high school | 54 (78.3) | 35 (64.8) | |
| Computer familiarity | | | |
| Not familiar at all | 9 (13) | 10 (18.5) | 0.682 |
| Little familiar or familiar | 37 (53.6) | 26 (48.1) | |
| Very familiar or expert | 23 (33.3) | 18 (33.3) | |
| MMSE-2\(^{†}\) score ± SD | 28±1.4 | 28±1.7 | 0.124 |

\(^*\)P value is significant, \(^{†}\)MMSE-2 = Mini-Mental State Examination, Second Edition, SD = Standard deviation
(OR = 6.43, 95% CI = 1.49-34.66). Table 3 shows the results of the multivariable logistic regression analysis.

Discussion

Incidence of postoperative cognitive dysfunction

Our study showed that 15.9% of older adult patients developed POCD 3 months after elective major noncardiac surgery. Newman et al. conducted a meta-analysis of POCD studies until December 2005, and they showed that the incidence of POCD after noncardiac surgery was 6.2-9.4% 22 days to 6 months following surgery, after excluding one of the studies reporting an unexpectedly high incidence.[15] Monk et al. conducted a subgroup analysis of 308 patients aged 60 years or older, and they found that the incidence of POCD in this subgroup was 12.7% 3 months after surgery.[16] Evered et al. conducted a subgroup analysis of 157 patients aged 55 years or older, who underwent total hip joint replacement, and they reported a POCD incidence of 16% in this subgroup 3 months after surgery,[17] which is in agreement with our study.

Several studies have overestimated the incidence of POCD by assessing patients’ cognitive function too soon after surgery when patients are still recovering from the effect of surgery and anesthesia, and receiving several drugs that are known to temporarily impair their cognitive function. In our study, we chose to evaluate the incidence of POCD 3 months after surgery to avoid this issue. Furthermore, one of the strengths of our study is the use of a robust computerized neurocognitive battery to assess changes in cognitive function. Computerized neurocognitive assessment has the advantages of minimizing floor and ceiling effects, standardizing test administration, and precisely recording accuracy and speed of response to various tests with a level of sensitivity not possible in standard administration with conventional paper-and-pencil testing.[18]

We have decided to combine some of the levels of computer familiarity (little familiar/familiar) and (very familiar/expert) as shown in Table 1. The reason is that as we were collecting this information from both patients and controls, they were not able to strictly distinguish between these combined categories, and they would sometimes leave the choice for the data collector between each of these two close levels, which is very subjective, and therefore we decided to combine them together so as not to be biased.

Risk factors for postoperative cognitive dysfunction

Our study showed that patients who carry the APOE4 genotype were at increased risk for POCD 3 months after surgery. APOE4 genotype has been associated consistently with a threefold or greater increase in the risk of Alzheimer’s disease.[19] However, the mechanism by which APOE4 plays a role in the development of POCD is still unclear. Few studies have investigated the association between APOE4 and POCD after major noncardiac surgery, and their findings were inconsistent. McDonagh et al. studied patients older than 55 years undergoing major elective noncardiac surgery, and they could not find a significant association between cognitive decline and APOE4 at 6 weeks or 1 year after surgery.[20] Abildstrom et al. conducted a multicenter study in patients aged 40 years and older undergoing noncardiac surgery, and they were also unable to find an association between POCD and APOE4 at 1 week or 3 months after surgery.[21]

Table 2: Results of univariable analysis of potential risk factors for POCD (α = 0.25)

| Variable                                      | n   | POCD, n (%) | P      |
|-----------------------------------------------|-----|-------------|--------|
| Education level                               |     |             |        |
| High school or less                           | 15  | 4 (26.7)    | 0.237  |
| More than high school                         | 54  | 7 (13.0)    |        |
| APOE4 genotype                               |     |             |        |
| Non-APOE4                                     | 54  | 6 (11.1)    | 0.041  |
| APOE4                                         | 14  | 5 (35.7)    |        |
| Use of ≥1 highly anticholinergic or sedative-hypnotic drug at home prior to surgery |     |             |        |
| Nonusers                                      | 44  | 4 (9.1)     | 0.083  |
| Users                                         | 25  | 7 (28.0)    |        |
| Use of ≥1 highly anticholinergic or sedative-hypnotic drug after surgery |     |             |        |
| Nonusers                                      | 37  | 4 (10.8)    | 0.211  |
| Users                                         | 32  | 7 (21.9)    |        |
| Use of morphine for postoperative pain        |     |             |        |
| No                                            | 66  | 9 (13.6)    | 0.064  |
| Yes                                           | 3   | 2 (66.7)    |        |
| Type of surgery                               |     |             |        |
| Orthopedic surgery                            | 61  | 8 (13.1)    | 0.109  |
| Neurosurgery                                  | 8   | 3 (37.5)    |        |
| Type of anesthesia                            |     |             |        |
| Regional anesthesia                           | 49  | 5 (10.2)    | 0.059  |
| General anesthesia                            | 13  | 3 (23.08)   |        |
| Combined general and regional anesthesia      | 7   | 3 (42.9)    |        |
| Use of nitrous oxide for anesthesia           |     |             |        |
| No                                            | 62  | 8 (12.9)    | 0.075  |
| Yes                                           | 7   | 3 (42.9)    |        |
| Intraoperative hypothermia                    |     |             |        |
| Yes                                           | 59  | 8 (13.6)    | 0.192  |
| No                                            | 10  | 3 (30.0)    |        |
| Use of sevoflurane for anesthesia             |     |             |        |
| No                                            | 49  | 5 (10.2)    | 0.067  |
| Yes                                           | 20  | 6 (30.0)    |        |

*One patient chose not to have his blood withdrawn for genotyping. *Medication selection was based on the American Geriatrics Society 2012 updated Beers criteria for potentially inappropriate medication use in older adults.[14] APOE4 = Apolipoprotein E4, POCD = Postoperative cognitive dysfunction
Use of sevoflurane for anesthesia prior to surgery
deficits in mice 1 month after surgery.[24] On the other hand, with increased tau-phosphorylation and spatial memory.
interval, APOE4 = Apolipoprotein E4.
POCD = Postoperative cognitive dysfunction, OR = Odds ratio, CI = Confidence.
i inhalation anesthetics 10 days after noncardiac surgery.[22]
between APOE4 and POCD in older patients who received inhalation anesthetics, and they found that there was a strong association between APOE4 and POCD in older patients who received either inhalation or intravenous agents in the etiology of POCD. Our study showed that the use of highly anticholinergic or sedative-hypnotic drugs prior to major noncardiac surgery and the increasing risk of POCD. Finally, there is not enough evidence whether sevoflurane might be associated with higher risk of POCD compared to other anesthetics, and current studies that investigated this issue are mainly in animals. Our study sets the stage for future multi-center longitudinal studies to further investigate the association between these potential risk factors and POCD in the older adult population after major noncardiac surgery. Though our approach might not be the gold standard in reaching such conclusions, it is a first step toward addressing these contradictions and gaps in the current literature.

### Study strengths
Though there are many studies in the literature that tried to estimate the incidence and identify risk factors of POCD, the results of these studies are still conflicting and inconclusive. Our study used a holistic approach in identifying potential predictors for POCD in older adults after major noncardiac surgery by including a large number of variables in our model; some of which are unique and were not included in previous studies, and others are still lacking strong and conclusive evidence for the association with POCD. The association of APOE4 with POCD is not well established yet, and the results of the current few studies that investigated this association are contradictory. In addition, our study is the first to investigate the association between using highly anticholinergic or sedative-hypnotic drugs prior to major noncardiac surgery and the increasing risk of POCD.

### Study limitations
Our study is limited by the small sample size and lack of generalizability. However, the objective of this pilot study was to generate hypotheses about potential risk factors in older adults after major noncardiac surgery. Our study will help in the development of larger longitudinal trials to further investigate our findings. Furthermore, due to the observational nature of this study, we can only draw inferences about the risk factors associated with POCD, and not necessarily causal effects.

### Conclusion
Postoperative cognitive dysfunction was present in about 16% of older patients in our study 3 months after major noncardiac surgery. Carrying the APOE4 genotype, using one or more highly anticholinergic or sedative-hypnotic drugs prior to surgery, and receiving sevoflurane for anesthesia were associated with POCD.

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**Table 3: Results of multivariable logistic regression showing risk factors of POCD (α = 0.05)**

| Variable                                | n  | POCD, n (%) | Adjusted OR (95% CI) | P   |
|-----------------------------------------|----|-------------|----------------------|-----|
| APOE4 genotype                          |    |             |                      |     |
| Non-APOE4                               | 54 | 6 (11.1)    | 1.00                 | 0.037|
| APOE4                                   | 14 | 5 (35.7)    | 4.74 (1.09-22.19)    |     |
| Use of ≥1 highly anticholinergic/       |    |             |                      |     |
| sedative-hypnotic drug at home          |    |             |                      |     |
| prior to surgery                        |    |             |                      |     |
| Nonusers                                | 44 | 4 (9.1)     | 1.00                 | 0.014|
| Users                                   | 25 | 7 (28.0)    | 5.64 (1.35-30.22)    |     |
| Use of sevoflurane for anesthesia       |    |             |                      |     |
| No                                      | 49 | 5 (10.2)    | 1.00                 | 0.010|
| Yes                                     | 20 | 6 (30.0)    | 6.43 (1.49-34.66)    |     |

*One patient chose not to have his blood withdrawn for genotyping, †Medication criteria for potentially inappropriate medication use in older adults.[14]

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To our knowledge, our study is the first to investigate the association between using highly anticholinergic or sedative-hypnotic drugs prior to major noncardiac surgery and increasing risk of POCD. We categorized the use of highly anticholinergic or sedative-hypnotic medications in this study into only two groups (no use or use of one or more medications). The reason for such categorization was that, with the exception of one patient who was using three and another who was using four medications in these groups, all other patients were either not using any or using only one medication of this group.

There is a growing interest in the role of individual anesthetic agents in the etiology of POCD. Our study showed that the use of sevoflurane was associated with an elevated risk of POCD 3 months after surgery. Other general anesthetics that were evaluated in our study were isoflurane, desflurane, and nitrous oxide. The relationship between sevoflurane and cognitive decline is debatable. Dong et al. showed that sevoflurane can induce apoptosis and increase β-amyloid protein levels in mice which suggests that sevoflurane may promote Alzheimer’s disease neuropathogenesis. [23] Le Freche et al. also demonstrated that sevoflurane was associated with increased tau-phosphorylation and spatial memory deficits in mice 1 month after surgery. [24]

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The inflammatory responses that occur during surgery.[25] It is unknown if these findings can be applied to humans, and whether the duration of anesthesia can play a role in modulating the effect of sevoflurane on cognitive function.

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