Cognitive Trajectories after Postoperative Delirium

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Cognitive Trajectories after Postoperative Delirium


BACKGROUND

Delirium is common after cardiac surgery and may be associated with long-term changes in cognitive function. We examined postoperative delirium and the cognitive trajectory during the first year after cardiac surgery.

METHODS

We enrolled 225 patients 60 years of age or older who were planning to undergo coronary-artery bypass grafting or valve replacement. Patients were assessed preoperatively, daily during hospitalization beginning on postoperative day 2, and at 1, 6, and 12 months after surgery. Cognitive function was assessed with the use of the Mini–Mental State Examination (MMSE; score range, 0 to 30, with lower scores indicating poorer performance). Delirium was diagnosed with the use of the Confusion Assessment Method. We examined performance on the MMSE in the first year after surgery, controlling for demographic characteristics, coexisting conditions, hospital, and surgery type.

RESULTS

The 103 participants (46%) in whom delirium developed postoperatively had lower preoperative mean MMSE scores than those in whom delirium did not develop (25.8 vs. 26.9, P<0.001). In adjusted models, those with delirium had a larger drop in cognitive function (as measured by the MMSE score) 2 days after surgery than did those without delirium (7.7 points vs. 2.1, P<0.001) and had significantly lower postoperative cognitive function than those without delirium, both at 1 month (mean MMSE score, 24.1 vs. 27.4; P<0.001) and at 1 year (25.2 vs. 27.2, P<0.001) after surgery. With adjustment for baseline differences, the between-group difference in mean MMSE scores was significant 30 days after surgery (P<0.001) but not at 6 or 12 months (P=0.056 for both). A higher percentage of patients with delirium than those without delirium had not returned to their preoperative baseline level at 6 months (40% vs. 24%, P=0.01), but the difference was not significant at 12 months (31% vs. 20%, P=0.055).

CONCLUSIONS

Delirium is associated with a significant decline in cognitive ability during the first year after cardiac surgery, with a trajectory characterized by an initial decline and prolonged impairment. (Funded by the Harvard Older Americans Independence Center and others.)
Cognitive Impairment is Common after Cardiac Surgery...
with the use of the CAM for the Intensive Care Unit, a validated nonverbal version of the CAM. Our combined assessment for delirium was highly reliable (kappa = 0.95).

As we expected, there were times when we were unable to perform the daily delirium assessments. Overall, 24.4% of the daily delirium assessments were missing because of patient or staff unavailability (e.g., weekend staffing). The percentage of missing assessments did not differ significantly between the patients with and those without delirium (24.7% and 24.1%, respectively). All patients underwent at least one delirium assessment on postoperative day 2 or 3.

Daily interviews (including the MMSE, digit-span test, and other assessment tools) to assess the patients for delirium were supplemented by reviewing the medical records for evidence of clinical features of delirium. The Charlson comorbidity index, a weighted sum of 17 medical conditions (with higher scores indicating a greater burden of illness), was also calculated.

The duration of delirium was calculated as the number of days between the initial positive delirium assessment and the final positive delirium assessment. After discharge, patients were interviewed in person in their homes or at other locations (e.g., a rehabilitation facility) at 1, 6, and 12 months to assess cognitive function.

**STATISTICAL ANALYSIS**

Baseline characteristics of the patients with and those without postoperative delirium were compared with the use of the chi-square test for categorical variables and analysis of variance for continuous variables. A hierarchical linear regression model was used to characterize the trajectory of MMSE scores over time. This framework was chosen because of its flexibility with the timing of patient interviews and the repeated observations in each patient over time. We examined the rate of postoperative cognitive change over five intervals from baseline (preoperative cognitive function): postoperative day 2, days 3 to 5, days 6 to 30, days 31 to 183, and days 184 to 365 or more. Postoperative delirium was included as a time-invariant indicator variable. We constructed two models: the first examined MMSE scores over time in the overall population without regard to delirium status, and the second added delirium and a delirium-by-time interaction term to see how MMSE scores differed between the group of patients with delirium and the group without delirium, both at baseline and over time. Analyses were conducted with the use of SAS software, version 9.2 (SAS Institute), and Stata software, version 12.0 (StataCorp).

In estimating MMSE scores, we adjusted for age, educational level, sex, race or ethnic group, score on the Charlson comorbidity index, and presence or absence of a history of stroke or transient ischemic attack (TIA), since these factors were likely to be associated with the long-term cognitive trajectory and have also been shown to be associated with the risk of delirium. We also adjusted for surgery type and hospital. We did not adjust for status with respect to alcohol use because in previous work in this cohort, consumption of alcohol was not associated with delirium and only two patients reported problematic drinking (defined as five or more drinks per day for men and four or more for women). There were no cases of delirium tremens in hospitalized patients. We evaluated model fit by graphically dis-
We summarized the model results by computing, tabulating, and plotting the expected MMSE scores, given the model parameters, and we obtained interval estimates with bootstrap methods. In a secondary analysis, we used logistic regression to examine the probability that a follow-up MMSE score was lower than the preoperative (baseline) score as a function of time after surgery and delirium status.

To further support our findings, we conducted a series of sensitivity analyses. First, to address baseline differences in MMSE scores according to delirium status, we repeated the analysis, with patients in whom delirium developed individually matched according to baseline score to patients drawn (with replacement) from the group without postoperative delirium. Second, we examined the duration of delirium (1 to 2 days vs. ≥3 days) in relation to the trajectory of cognitive function. Third, we excluded seven patients who had a stroke postoperatively. Finally, we used a rank-based transformation of MMSE scores as the outcome variable to address nonnormal distribution of scores.

### RESULTS

#### CHARACTERISTICS OF THE PATIENTS

The mean (±SD) age of the patients was 73±6.7 years (range, 60 to 90). Approximately one quarter were women, and most were white and non-Hispanic (Table 1). The median follow-up time was 363 days (range, 2 to 482). There was no significant difference in the mean follow-up time between the group of patients with delirium and the group without delirium (358 days [range,
Cognitive Function Scores

Using multilevel modeling, we examined the change in cognitive function from before surgery to 1 year after surgery in the overall study population. Our final model fit well ($r^2=0.76$). With adjustment for age, sex, educational level, race or ethnic group, presence or absence of a history of stroke or TIA, score on the Charlson comorbidity index, surgery type, and hospital, the model-estimated MMSE score for all patients before surgery was 26.9. There was a significant decline in cognitive function of 4.6 points on the MMSE from baseline to postoperative day 2 ($P<0.001$) (Table 2). This initial drop was followed by significant increases in cognitive function of 1 point on the MMSE each day on days 3 to 5 ($P<0.001$). The rate of improvement slowed considerably from day 6 to day 365 after surgery. After day 183, cognitive performance stabilized, with no significant change from day 184 to day 365 after surgery (Table 2).

**Cognitive Trajectories According to Delirium Status**

The trajectory of cognitive function varied significantly according to delirium status over the entire follow-up period (Table 3 and Fig. 2A). Patients with postoperative delirium had significantly lower estimated MMSE scores preoperatively than those without delirium (25.8 vs. 26.9, $P<0.001$). These estimates differ from the values in Table 1 because they reflect adjustment for covariates. The patients in whom delirium developed had a greater decline in cognitive function immediately after surgery than did those without delirium (7.7 points vs. 2.1, $P<0.001$). Although the initial decline in the MMSE score was larger among patients with delirium than for those without delirium. Over this period, the patients without delirium had relatively stable scores, whereas those with delirium had an average gain of 1.2 points. With adjustment for baseline differences in MMSE scores between patients with and those without delirium, the mean scores at 6 and 12 months after surgery did not differ significantly between the groups ($P=0.06$) (Table 3). Although both groups had increases in adjusted MMSE scores in the year after surgery, relative to their scores immediately after surgery, patients without delirium returned to their preoperative level of cognitive function by approximately 1 month after surgery, whereas patients with delirium had not returned to their preoperative level of function by 1 year postoperatively (Table 3 and Fig. 2A). In addition, the proportion of patients who did not return to their preoperative level of function was significantly higher in the group with delirium than in the group without delirium through 6 months postoperatively (40% vs. 24%, $P=0.01$), but this proportion was not significantly different at 12 months (31% and 20%, respectively; $P=0.06$) (Table 3).

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**Table 2. Adjusted Estimates of MMSE Scores over Time.**

<table>
<thead>
<tr>
<th>Time of Assessment</th>
<th>Estimated Score (95% CI)†</th>
<th>Estimated Daily Change during Interval (95% CI) points</th>
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<tr>
<td>Before surgery</td>
<td>26.9 (26.5 to 27.3)</td>
<td></td>
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<tr>
<td>Day 2</td>
<td>22.3 (19.8 to 24.9)</td>
<td>–4.6 (–5.2 to –4.0)</td>
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<tr>
<td>Days 3–5</td>
<td>25.4 (23.7 to 27.2)</td>
<td>1.04 (0.8 to 1.2)</td>
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<tr>
<td>Days 6–30</td>
<td>26.3 (24.9 to 27.7)</td>
<td>0.036 (0.01 to 0.06)</td>
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<tr>
<td>Days 31–183</td>
<td>26.9 (25.7 to 28.2)</td>
<td>0.004 (&lt;0.001 to 0.008)</td>
</tr>
<tr>
<td>Days 184–365</td>
<td>26.7 (25.4 to 28.1)</td>
<td>–0.001 (–0.004 to 0.002)</td>
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* The estimated score before surgery was the baseline score. Estimates were adjusted for age, educational level, sex, race or ethnic group, score on the Charlson comorbidity index, presence or absence of a history of stroke or transient ischemic attack, hospital, and surgery type. CI denotes confidence interval.
† The estimated score is for the last day of the interval.

2 to 427] and 368 days [range, 3 to 482], respectively; $P=0.16$.

Postoperative delirium developed in 46% of patients (103 of 225 patients), with delirium lasting 1 to 2 days in 65% of these patients and 3 or more days in 35%. As compared with patients without postoperative delirium, those with delirium were significantly older, less educated, more likely to be women, and less likely to be white (Table 1). In addition, patients with delirium were more likely to have a history of stroke or TIA and had a higher average score on the Charlson comorbidity index and a lower level of preoperative cognitive function.

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Sensitivity Analyses

A sensitivity analysis with exact matching on the baseline MMSE score yielded similar results (Fig. 2B). A longer duration of delirium (≥3 days vs. <3 days) was associated with a significantly greater drop in the score immediately after surgery and a slower recovery during the 1-year postoperative period (Fig. 2C). Results were also similar when we excluded patients who had a stroke postoperatively and when we used a rank-based transformation of MMSE scores to address nonnormal distribution (data not shown).

Discussion

We found that delirium after cardiac surgery was associated with a postoperative cognitive trajectory characterized by an initial decline in performance on the MMSE and a prolonged period of impairment. After adjustment for baseline differences, the mean MMSE score did not differ significantly between the patients with and those without delirium 6 months and 1 year after surgery. However, patients with postoperative delirium were significantly less likely to have returned to their preoperative level of performance at 6 months than were patients without delirium. These findings suggest that delirium, which was once thought of as a short-term, transient cognitive disorder, may have longer-term observed effects on cognitive function in patients who have undergone cardiac surgery. This study establishes an association between delirium after cardiac surgery and cognitive dysfunction by means of preoperative and serial objective assessments of cognitive function and state-of-the-art assessments of delirium, both of which were not, to our knowledge, used in previous studies.33-38

With the aging of the patient population undergoing cardiac surgery and increases in survival after surgery, clinicians and patients are increasingly concerned with factors associated with quality of life, including cognitive status, as major outcomes of surgery.11,15 Although a high proportion of patients undergoing cardiac surgery have cognitive impairment immediately after the surgery, impairment diminishes in the weeks and months after discharge.6,39,40 Whether postoperative delirium is associated with prolonged cognitive dysfunction has been unclear.

The few studies that have addressed the effect of delirium on the course of cognitive function...
after cardiac surgery differed with respect to the timing and frequency of follow-up assessments. One study assessed cognitive function in 112 patients (delirium developed in 21%) 1 to 1.5 years after cardiac surgery and showed that memory and concentration problems were more prevalent among patients with postoperative delirium than among those without delirium; however, preoperative cognitive function was not assessed. Hudetz et al. assessed cognitive function in 28 patients (delirium developed in 32%) 1 week after surgery and found that patients with delirium were more than 10 times as likely as patients without delirium to have impaired memory and executive function. We assessed cognitive function preoperatively and an average of five times during the year after surgery, allowing us to accurately model the course of cognitive function and to compare the rate of recovery among patients with and those without postoperative delirium.

In our cohort, postoperative delirium was common, affecting 46% of patients. The rate of delirium is dependent on the methods used for its ascertainment, and our study used a rigorous assessment with diagnosis by means of the CAM, the most widely adopted, validated approach in the literature. Most of the extensive literature examining neurocognitive function after cardiac surgery has not integrated these methods of assessing delirium and therefore has not been able to address our specific study question.

Our findings are of clinical significance, since the risk of delirium among patients undergoing cardiac surgery can be predicted preoperatively, and delirium is potentially preventable. Multifactorial proactive interventions such as the Hos-
COGNITIVE TRAJECTORIES AFTER DELIRIUM

In a sensitivity analysis, we controlled for baseline differences in cognitive function by matching patients with and those without postoperative delirium on preoperative MMSE scores, and the results did not change. We used sophisticated analytic methods that allowed the use of all available data and descriptions of nonlinear trajectories of cognitive function after surgery. However, several limitations should be noted. Our sample consisted of patients who were predominantly white and well educated and who were enrolled in a single geographic region, potentially limiting the generalizability of the findings. However, this study was conducted at multiple sites that included urban, rural, and socioeconomically diverse populations. In addition, the MMSE may lack the sensitivity to identify mild cognitive impairment; thus, it is possible that more sensitive measures would have shown a slower return to the preoperative level of function in the group of patients without postoperative delirium. We do not have data on cognitive function beyond 1 year after surgery and were unable to control for apolipoprotein E status, although on the basis of the current literature, its association with delirium remains unclear. Finally, as noted above, our study lacked a nonsurgical comparison group.

In conclusion, this prospective study of patients undergoing cardiac surgery showed that postoperative development of delirium was a risk factor for a decline in cognitive function and a prolonged period of impairment after surgery. Identifying patients at high risk for delirium and promoting the development of interventions to prevent delirium in patients undergoing cardiac surgery may reduce the rate of long-term cognitive impairment in this population. Patients in whom delirium develops after cardiac surgery may require further interventions and customized rehabilitation programs to optimize recovery.

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