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Long-term Cognitive Decline

Is There a Link to Surgery and Anesthesia?

POSTOPERATIVE cognitive dysfunction or *decline* (POCD) refers to decline in a variety of neuropsychological domains, including memory, executive functioning, and speed of processing, and should be distinguished from *postoperative delirium*, which is an acute confusional state with alterations in attention and consciousness.[1] The term *POCD* has been described in the literature to include acute (1 week), intermediate (3 months), and long-term (1–2 yr) cognitive decline after surgery. The incidence of POCD after major noncardiac surgery has been estimated to be between 7% and 26%.[2–4] For those who experience POCD, the onset of cognitive decline likely occurs soon after surgery, but is this condition reversible, or does surgery and anesthesia accelerate further long-term decline in cognitive status? Evidence for the latter theory might be particularly important to the understanding of the cause of cognitive decline in Alzheimer disease, because the pathophysiology of this neurodegenerative condition is not completely understood. Specifically, if precipitating factors relating to surgery and/or anesthesia can be identified that lead to POCD, interventions can be designed to minimize the occurrence of POCD. This issue of ANESTHESIOLOGY contains a study by Avidan *et al.*[5] providing a challenge to the prevailing notion that long-term POCD is directly related to the surgical event.

Previous research addressing the role of surgery and anesthesia on long-term cognitive decline has yielded conflicting results. The study by Avidan *et al.*, "Long-term Cognitive Decline in Older Subjects Was Not Attributable to Noncardiac Surgery or Major Illness," suggests that the conclusions in previous studies may be due to methodologic issues that may have affected results. For example, there is a lack of standardized diagnostic criteria to detect POCD, lack of information about the trajectory of surgical patients' cognitive status before surgery, inadequate control for potential learning effects from repeated exposure to cognitive tests, and lack of relevant control groups. The authors attempt to overcome the above methodologic issues by conducting a retrospective study of subjects who were not recruited on the basis of their surgical status. They enrolled participants from an Alzheimer's Disease Research Center who had substantial pre-event data. The subjects were stratified into three groups based on whether they underwent surgery, were admitted to a hospital for a major illness not requiring surgery, or did not undergo surgery and had no major illness (control group). Subjects were assessed annually, and some were assessed for as many as 21 yr. The battery of neuropsychological tests administered at each occasion was comprehensive of those domains of cognitive function known to be affected by the presence of drugs and other precipitating events. The sophisticated statistical methods used in this study allowed assessments of subjects' trajectory of cognitive performance before and after the event of interest. The study findings suggest that neither nondemented nor mildly demented individuals had accelerated long-term decline in cognitive function attributable to surgery or major illness compared with matched controls.

The question of whether major surgery and anesthesia ultimately lead to long-term cognitive decline is controversial. In a population study, Dijkstra *et al.*[6] reported that the number of operations and the total duration of anesthesia were related to the number of subject health-related complaints but did not predict cognitive performance or memory complaints. Several other studies that included assessments more than 6 months after surgery similarly reported no decline in cognitive status from that measured before surgery.[7–11] However, two recent studies that included patients who had undergone noncardiac surgery reported that acute POCD was associated with increased mortality after surgery (for one study, at 1 yr, and for the second study, at 3 months).[12,13] Also, in cardiac surgical patients, Newman *et al.*[14] provided data showing that cognitive function at discharge was a significant predictor of long-term cognitive function. What possibly accounts for these differences in results?

The study by Avidan *et al.* effectively addressed a number of methodologic inconsistencies found in previous studies of POCD. However, as is true of any quasi-experimental study, it is not possible to experimentally or statistically control for all factors that may affect study results. For example, three groups of patients were defined according to whether or not they had experienced hospitalization for an acute illness, surgery, or neither. It is unclear how patients who had more than one event would be classified in this study. It is also unclear how multiple events related to group status were handled.

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For example, those in the hospital group may have experienced more than one acute admission. The cumulative burden of major illness or surgery may be more important than an individual event. An individual who was chronically ill or had repeated hospitalizations may be more vulnerable than one who had an isolated illness or operation. Finally, it is not clear how many subjects were lost to follow-up or not included because of missing data. In the study by Avidan *et al.*, participants were excluded if they had incomplete psychometric assessments, including those with fewer than two assessments after major illness or surgery. In cohort studies, nonresponders and dropouts are much more likely to occur in older than in younger participants as a result of illness, disability, cognitive impairment, institutionalization, and even death. For example, in one study evaluating hypertensive treatment and prevention of dementia in elders, participants who were alive and eligible for the annual cognitive evaluations during the follow-up but missed the assessments were significantly older, less educated, and nonwhite race compared with those who were assessed.[15] As a result, selective dropout and nonresponse may distort the result, biased toward the null.

The study by Avidan *et al.* included subjects who were assessed annually, so it is not possible to compare the results from their study with those from studies that assessed POCD at 1 week or 3 months after surgery, because it is entirely possible that early cognitive decline may occur with subsequent recovery. This retrospective study was not designed to address this because the timing of the cognitive tests was not synchronous with the specific medical illness or operation.

The work by Avidan *et al.* raises an important question relating to the long-term prognostic significance of POCD occurring soon after surgery. If, indeed, future research confirms their findings that early POCD is not a good indicator of accelerated long-term decline in cognitive function, should we abandon our current effort in the understanding and prevention of this phenomenon? The resounding answer is no, because acute POCD can impact postdischarge functioning such as taking medications, providing self-care, and so forth, that may ultimately result in other adverse health outcomes. The challenge in this field of research is to come up with a prospective study with sufficient sample size and to include both short-term and longitudinal follow-up to more fully understand how major illness and surgery may impact both short-term and long-term cognitive functioning and quality of life of elders, and to ultimately determine whether there are reversible precipitating factors that are modifiable. Continuing research on POCD may also shed light about the pathophysiology of other neurodegenerative disease, including Alzheimer disease. The study by Avidan *et al.* raises an important question regarding the prognostic importance of acute POCD on long-term cognitive function and hopefully will lead to more research in the understanding of the mechanisms and impact of POCD in elders.

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