Postoperative Cognitive Dysfunction

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The term postoperative cognitive dysfunction (POCD) describes a deterioration of cognition that is temporally associated with surgery. As opposed to delirium, in which behavior is paramount, detecting, assessing the severity of, and characterizing POCD depends upon valid assessments of pre- and postoperative cognitive function. The neuropsychological examination measures the information processing abilities of the brain through a battery of tests (assessing attention, perception, verbal abilities, learning and memory, and abstract thinking) that are sensitive to the effects of brain injury and disease[1]

The wide variability in normal human cognitive capacities associated with aging make baseline (i.e. pre-operative) measures vital. In the absence of baseline data, it is impossible to associate low postoperative test scores to surgical, anesthetic, or illness variables with certainty. Subjective self-reported cognitive symptoms do not substitute for objective cognitive testing, since the poor relationship between the two types of data has been demonstrated repeatedly.[2]

Methodological Issues in the Study of POCD

There are a number of methodological inconsistencies among studies that makes the limited literature on POCD difficult to interpret. These include the selection of test instruments, timing of postoperative testing, inclusion and exclusion criteria, the inherent variability of cognitive testing, and most fundamentally, the operational definition of POCD.

Test Selection: Mental status screening instruments such as the Mini-Mental State Exam (MMSE) are useful for detecting frank dementia, but lack the sensitivity and specificity required to detect milder or more selective forms of cognitive impairment.[1] High functioning patients who have experienced a mild decline in cognitive function, and patients with “focal”, as opposed to “diffuse” cognitive dysfunction, may achieve high MMSE scores. Cognition is not a unitary process, but rather is the result of activity in multiple complex, distributed, and interacting neuronal circuits that underlie specific information processing functions. There is no single measure of cognitive status, thus comprehensive neuropsychological assessment requires that a battery of tests assessing a variety of cognitive domains must be employed. There are, however,

a wide variety of tests available, which differ in their test-retest reliability, sensitivity, specificity, and the degree to which they are subject to practice effects.

Timing of Postoperative Testing: Another methodological inconsistency among the studies is the timing of postoperative cognitive testing. In general, studies measuring cognitive function shortly after surgery find a much higher incidence of POCD than studies measuring cognitive function weeks to months after surgery. Longitudinal studies have the problem of attrition, which does not occur randomly but is influenced by the postoperative health status, functional status, and possibly the cognitive status of the patient. Patients who develop POCD may be more likely to drop out of the study, thus underestimating the true incidence of POCD.

Inclusion and Exclusion Criteria: It is also important to consider the subject inclusion and exclusion criteria when interpreting study findings. Recently, the term Mild Cognitive Impairment (MCI) has come to represent a transitional zone in the spectrum of cognitive function from normal aging to progressive dementing conditions, such as Alzheimer's and cerebrovascular diseases. Unfortunately, patients with preoperative MCI have not been differentiated in studies of POCD. Thus, there is no information available concerning the impact of surgery and anesthesia on this subset of patients that may be at greatest risk for POCD. There is no evidence that anesthesia and surgery increase the incidence of Alzheimer's disease.

Operational Definition of POCD: One of the greatest problems facing the investigation of postoperative cognitive function is the absence of a consensus regarding the operational definition of POCD. Variations in the means that different groups have used to define deteriorations in cognitive function in part underlie the difficulty in comparing studies. Furthermore, few studies use control groups and take practice effects into account.[3]

The percent change method involves converting the pre- to postoperative difference score into a percent of baseline score [i.e., (postoperative score – preoperative score)/preoperative score]. This method generates continuous data, which can then be averaged across patients for group comparisons. The use of group mean analyses, however, is discouraged, as a subset of subjects experiencing significant deterioration may be masked when other subjects exhibit improved performance over time. The standard deviation method involves identifying patients who experience a postoperative decline of some criterion number of standard deviation units (Z-scores). The International Study of Postoperative Cognitive Dysfunction (ISPOCD studies, see below) required a two standard deviation decline to qualify as POCD. Limitations of standard deviation method include: (1) in patients with low baseline scores it may not be possible to decline by more than one standard deviation (i.e. floor effect); and (2) the absolute magnitude of change in raw test scores required to meet the criterion differs between studies, since they are derived from the preoperative tests scores of the baseline sample. A third strategy involves identifying patients who experience a specific percentage (e.g., 20%) decline from baseline of at least a specific percentage (e.g., 20%) of the tests administered. A limitation of this technique is that patients with lower preoperative test scores require a smaller decline in raw score to meet the 20% criterion.

Incidence of POCD

In 1998, Möller and colleagues presented the first of a series of multicenter studies from the International Study of Postoperative Cognitive Dysfunction (ISPOCD) that primarily

included European centers.[4] Information from the ISPOCD studies is available at www.sps.ele.tue.nl/ispocd/. The ISPOCD1 study tested the hypothesis that insufficient oxygen delivery to the brain, as assessed by the presence of hypotension and/or hypoxemia, is a causative factor for POCD. The study included 1218 patients, 60 years of age or older, who underwent major abdominal, non-cardiac thoracic, or orthopedic surgery under general anesthesia. Patients were tested preoperatively, and at one week and three months postoperatively. Test results were compared to a total of 321 controls recruited from the United Kingdom, 11 centers in Europe, and two centers in North America. Patients were classified as experiencing cognitive dysfunction when two Z-scores in individual tests declined by 1.96, or the combined average Z-score declined >1.96. At one week postoperatively, 25.8% of 1011 patients experienced a decline in cognitive function, compared with 3.4% of 176 control subjects. At three months postoperatively, 9.9% of 910 patients experienced a decline relative to preoperative level of function, as compared to 2.8% of controls.

A number of subsequent studies have described cognitive impairment within the first 10 days following surgery and anesthesia.[5] Williams-Russo found a rate of POCD of 5% at six months following surgery, although, in the absence of a control population, the significance is hard to determine. A follow-up study which evaluated patients at 1 and 2 years found that the rate of POCD dropped to approximately 1%, which was not statistically significant.[6] Taken together, it appears that elderly patients manifest measurable deterioration shortly after surgery and anesthesia (25% at 2-10 days), with gradual resolution such that the incidence declines (10% at 3 months, 5% at 6 months, 1% at 1 year) to levels nearly indistinguishable from control subjects by approximately one year. Two important limitations are: (1) given the tendency of impaired patients to drop out of such studies, the long-term follow-up may underestimate the true incidence of deterioration; and (2) the clinical course of an individual patient cannot be clearly inferred from this understanding, in that there is inconsistency between the testing sessions. In the ISPOCD studies, less than half of the participants who were classified at having POCD at 3 months had detectable decline at 1 week (i.e., POCD at 1 week did not predict POCD at 3 months).[7]

In a follow-up evaluation of the data collected from the ISPOCD studies, Rasmussen et. al. sought to determine the impact of variability on the determination of POCD.[7] They hypothesized that if variability in cognitive testing results could explain POCD, then improvement following surgery would be as frequent as deterioration. This secondary analysis confirmed that cognitive decline occurred at 1 week but found that there was no significant change at 3 months. Further study will be required to determine if long-term impairment is an important clinical finding. Variability in cognitive testing is an important factor that contributes to the low consistency between testing sessions that should be addressed in future studies of POCD.

Predictors and Risk Factors

Essentially all of the studies to date have concluded that advancing age is a risk factor for POCD. An evaluation of patients 40-60 years of age undergoing major surgery (n=463) showed a minor, but statistically significant decline in cognitive function at one week that was no longer apparent at three months (using the original ISPOCD definition), suggesting that persistent POCD is primarily a problem of elderly patients.[8]

Major surgery appears to be the principal trigger for POCD. A study comparing 164 patients undergoing general anesthesia and surgery with at least a single night hospital stay with 159

patients who underwent general anesthesia for ambulatory surgery, indicated that minor surgery was not associated with significant POCD.[9] For major surgery, postoperative cognitive dysfunction at one week was significantly associated with increased age, increased duration of anesthesia, fewer years of education, second operations, postoperative infections, and respiratory complications. Only age was a significant risk factor for POCD at three months.[4]

Acute postoperative pain has also been associated with poorer postoperative cognitive function. In a study of 24 patients aged 61-86 who underwent elective lumbar spine surgery, greater pain on postoperative day one was associated with poorer performance on some neuropsychological tests.[10] The degree of chronic preoperative pain was not related to preoperative cognitive test performance.

Etiology of POCD

To date, the etiology of POCD remains unclear. Cerebrovascular disease, cerebral hypoperfusion, genetic susceptibility, alteration in neurotransmitter function, neurohumoral stress and CNS inflammatory phenomenon have all been suggested, but the principal suspect has been general anesthesia. General anesthesia is a state achieved with multiple medications, many of which are purported to cause delirium. The preferred method of evaluating the potential of general anesthesia to produce POCD has been randomized trials of general versus regional anesthesia. Numerous studies suggest that choice of anesthesia is not an important factor in the development of POCD.[11] This issue is discussed in greater detail below. Even though such radically different anesthetic techniques as regional and general anesthesia have similar impact upon postoperative cognitive function in clinical studies, there are laboratory studies suggesting that general anesthetic agents have toxic effects on CNS structure and function.[12;13] The relevance of this work to the clinical syndromes described will require significant additional research.

Hypoxemia and ischemia are potential etiologies of POCD for which potential treatments exist (e.g., supplemental oxygen), that were initially evaluated in the 1940's.[14] The first ISPOCD study examined the role of hypotension and hypoxemia as potential etiologies. Oxygen saturation was measured by continuous digital pulse oximetry, and blood pressure by intermittent non-invasive oscillometry throughout the perioperative period. Despite high rates of profound hypoxemia and hypotension, neither condition was associated with POCD. A study utilizing a cerebral oximeter found that cerebral oxygen desaturation events were associated with a higher incidence of postoperative cognitive decline in patients undergoing major surgical procedures.[15] Further research is necessary to clarify the role of cerebral ischemia in the etiology of POCD.

The epsilon 4 allele of the ApOE gene is strongly associated with the development of Alzheimer's disease, but has not been found to be an important predictor of POCD in general surgery.[16] The search for either a genetic predisposition to POCD or a biomarker of POCD is intriguing, but all such efforts remain highly theoretical. In small studies of cardiac surgery patients, non-specific enolase, but not S100β, may be useful as a marker of early POCD.[17] Current research interests include small nucleotide polymorphisms (SNPs) that code for different aspects of inflammation (in cardiac surgery) and stable nitric oxide end products will require substantial additional research to establish clinical utility.

Regional versus General Anesthesia

It is intuitively appealing that general anesthesia which specifically affects the brain as compared to regional anesthesia which affects primarily the spinal cord or peripheral nerves

would be associated with different rates of POCD. Beginning in 1980, a series of relatively small studies suggested that patients undergoing general anesthesia, but not neuraxial anesthesia, were at greater risk for POCD.[11] In 1995, Williams-Russo presented an adequately powered, prospective, randomized studies of POCD that employed standard neuropsychological instruments.[18] This study compared the effect of epidural versus general anesthesia on the incidence of POCD in patients undergoing elective unilateral total knee replacement. Neurocognitive assessment was performed one to seven days preoperatively (n=262), and one week and six months (n=231) postoperatively. Group mean scores for each of the 10 measures were compared between the two anesthesia groups, but no statistically significant differences were observed postoperatively. Additionally, the proportions of patients exhibiting clinically important decrements for each test (defined by consensus) were compared. Overall, 5% of patients exhibited a decline in cognitive function six months following surgery, but no statistically significant differences were found between the anesthesia groups. As this was a comparative trial, there was no control group for reference. Recently, Wu et. al provided a comprehensive review of 24 studies that evaluated the choice of anesthesia and concluded that it does not influence the incidence of POCD.[11]

Relationship between Delirium and Cognitive Dysfunction

Despite the distinguishing characteristics of PD and POCD, it is important to consider that there may be an association between them. Postoperative delirium may be a harbinger of POCD or an emerging dementia. Patients that developed delirium in the ISPOCD1 study were not the same patients who developed POCD. In ICU patients, delirium does appear to be prodrome of POCD.[19] The majority of studies to date have focused on either PD or POCD. In the near future, studies that undertake sophisticated evaluations for both PD and POCD should shed further light on this issue.

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