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GUEST EDITORIAL

Anesthesia and Alzheimer's disease: time to wake up!

It has long been observed that some patients suffer a significant cognitive impact following anesthesia and surgery. This should not be surprising when considering that not only is the target organ for general anesthetic agents the brain itself but also that the process of anesthesia is a form of deep, pharmacologically induced coma rather than "sleep." The expectation that such a process should be fully reversible with transient neurophysiological effects contradicts our experience with repeated abuse of other central nervous system depressants such as glue, petrol, and alcohol. Of great concern is that, while approximately 10% of populations in developed countries undergo anesthesia and surgery of some form each year, the proportion of the elderly making up this group is much greater. In addition, it is the elderly who are potentially at a greater risk of cognitive impairment following such procedures because many have decreased cognitive reserve, either due to pre-existing mild cognitive impairment (MCI) or frank dementia, which may be diagnosed or unknown. The impact of anesthesia on these individuals is poorly understood, as are the implications of the emerging laboratory data that suggest an effect of anesthetic agents on the pathological processes of Alzheimer's Disease (AD) itself.

It has long been suspected that the process of anesthesia and surgery "unmasks" underlying dementia. In 1887, Savage observed that "I have met with a series of cases . . .in which the use of anesthesia, in predisposed cases, has been followed by insanity." He then refers to perioperative delirium, followed in some cases by "progressive dementia which cannot be distinguished from general paresis of the insane" (Savage, 1887). The link between anesthesia and cognition remained dormant until rekindled in 1955 by Bedford in an article describing a connection between anesthesia and dementia (Bedford, 1955), followed in 1961 with a well-conducted study investigating dementia following anesthesia and surgery (Simpson *et al.*, 1961). It was another 25 years before this issue re-emerged after more subtle cognitive changes following anesthesia and surgery were identified by Shaw in 1987 in cardiac surgical patients (Shaw *et al.*, 1987). This construct became known as Postoperative Cognitive Dysfunction (POCD). Approximately 87% of patients were identified with POCD at discharge using neuropsychological testing, and the cause was attributed to the use of the Cardio-Pulmonary Bypass (CPB) pump needed for cardiac surgery. Research into POCD was beset by many challenges, including the variability in diagnosis, with some investigators using complex neuropsychological test batteries, others using changes on the Mini-Mental State Examination (MMSE), and yet others including acute confusional states such as delirium. Recommendations from a consensus guideline developed in 1995 (Murkin *et al.*, 1995) helped to some extent in formalizing testing protocols; however, because the "diagnosis" relied purely on a change in test performance, the attribution of POCD remained problematic. The use of time and age-matched control groups has enabled more objective evaluation, and it is now apparent that POCD affects patients following all types of surgery and anesthesia, even regional or local anesthetic procedures. The incidence of POCD has been shown to be similar at three months following cardiac surgery with or without CPB (Van Dijk *et al.*, 2002), non-cardiac surgery with regional or general anesthesia (Rasmussen *et al.*, 2003), and even with sedation for coronary angiography (Evered *et al.*, 2011). The incidence of POCD reportedly ranges from 10% to 21% and is consistently associated with increasing age and lower estimated IQ. A matter of concern, however, is that most studies have ignored the patient's pre-existing cognitive state, other than to exclude patients with diagnosed dementia or low MMSE. Over a dozen large population studies have shown a prevalence of MCI of 14%–18% in individuals over 70 years of age (Petersen *et al.*, 2009). The failure to identify such patients with less overt forms of cognitive impairment compromises the analysis and conclusions of many investigations into POCD. Another major shortcoming is that dementia outcomes following anesthesia and surgery have not been prospectively studied.

Anesthesia and surgery may induce or exacerbate cognitive dysfunction, potentially affecting long-term outcomes, by a variety of mechanisms. Events such as hospitalization itself, postoperative pain, and the perioperative neuroinflammatory response may all lead to cognitive dysfunction. Direct pharmacological effects of anesthetic drugs

may persist well after the surgery, and finally anesthetic drugs themselves may directly affect the pathophysiological processes underlying AD. The evidence for the latter was presented at "Anesthesia and Alzheimer's Disease" Featured Research Session as part of the AAIC 2012 conference in July by a number of researchers (Evered *et al.*, 2012).

General anesthesia is frequently maintained by inhaled volatile agents such as isoflurane, desflurane, or sevoflurane. In some circumstances, intravenous agents such as propofol are used in addition or as the sole anesthetic agent. These drugs all depress cerebral electrical activity as can be shown by electroencephalography (EEG) or processed EEG such as the BIS® monitor (Coviden, Mansfield, MA, USA). Rat behavioral models show that volatile anesthetic agents (at doses equivalent to those used in humans) lead to decrements in memory and learning (Culley *et al.*, 2004; 2007). Laboratory findings indicate that anesthetic agents promote amyloid beta (Aβ) cytotoxicity (Eckenhoff *et al.*, 2004; Xie *et al.*, 2006; Zhen *et al.*, 2009). Carnini *et al.* have hypothesized that anesthesia-facilitated disinhibition of protein binding helps Aβ monomers oligomerize to protofibrils that are neurotoxic (Carnini *et al.*, 2006). Lowering of the threshold for oligomerization by anesthetic agents may initiate cytotoxicity and synaptic degeneration. Anesthesia has also been shown to lead to tau hyperphosphorylation, a marker of AD pathology (Wan *et al.*, 2007; Planel *et al.*, 2008). In old rats, surgery provokes astrogliosis, β-amyloid accumulation, and tau phosphorylation, which is associated with cognitive dysfunction (Wan *et al.*, 2010). Finally, there may be differential effects between volatile anesthetic agents (Zhang *et al.*, 2012).

Neuroinflammatory responses are possibly a central component of the effects of anesthesia and surgery on cognitive outcomes (Xie *et al.*, 2009; Eckenhoff and Laudansky, 2012), and have been proposed as a link between AD and anesthesia (Hu *et al.*, 2010). The effect of anesthesia on inflammatory responses is supported by laboratory data (Murkin, 2010; Wan *et al.*, 2010), as well as limited human data (Tang *et al.*, 2011). Cerebrospinal fluid (CSF) collected during surgical repair of CSF leaks from 11 patients showed evidence of AD and inflammatory biomarkers, which differed according to the anesthetic agent used. It is also important to consider not only the factors which initiate inflammation or cell injury, but also the factors regulating, limiting, and reversing these responses. Recovery after an inflammatory insult may be impaired by volatile agents, which have been shown to affect neural stem cells (Culley *et al.*, 2011).

From a clinical perspective, no prospective studies have yet been reported; consequently, data are limited to retrospective studies with all the inherent limitations. The evidence of an association between dementia and surgery/anesthesia from these studies is conflicting. Lee *et al.* found an increased incidence of AD after cardiac surgery compared to percutaneous interventions (95% CI = 1.02–2.87; $p = 0.04$) (Lee *et al.*, 2005), while other retrospective studies have failed to show any association with surgery (Bohnen *et al.*, 1994; Gasparini *et al.*, 2002).

A retrospective review of memory clinic patients found no association between anesthesia and incident dementia (Avidan *et al.*, 2009). This report had a number of other limitations, including group analysis, definitions used, and variable time points between baseline testing and event (Silbert *et al.*, 2010). A large European study identified prior anesthesia as a risk factor for AD, although the authors considered this to be an unexplained association (Ritchie *et al.*, 2010). It is unfortunate that most prospective longitudinal community studies of progression of AD have failed to document and/or detail the anesthetic or surgical interventions in individuals. It is critical to our understanding of all the factors involved that collaboration between AD researchers and clinicians in the areas of anesthesiology and psychogeriatrics improves. An important development is the recent establishment of the *Anesthesia, Surgery, and Cognition* Professional Interest Area in the International Society to Advance Alzheimer's Research and Treatment (ISTAART) group of the Alzheimer's Association. We advocate joining the call from Xie and Tanzie that "more studies to assess the potential relationship between anesthesia/surgery and AD dementia are urgently needed" (Xie and Tanzi, 2006).

An association between delirium, dementia, and anesthesia/surgery is known but not well understood. Delirium is an extremely common postoperative complication, occurring in up to 65% of patients following proximal femoral fracture repair, and goes unrecognized in many more. As few as 25% of cases involve hyperactivity or agitation, with the majority of cases characterized by hypoactivity or lethargy, making them difficult to identify. Pre-existing dementia is the strongest predictor of an episode of delirium (Lundstrom *et al.*, 2003). Other predictors of postoperative delirium include increasing age, sensory deprivation, low albumin, and bladder catheterization. Lack of preoperative cognitive assessment makes

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identification of patients at higher risk difficult if not impossible, and eliminates any ability to recognize return-to-baseline cognition prior to discharge from hospital. Delirium is principally treated with anti-psychotics, although use of these for prevention has not proven effective (Kalisvaart *et al.*, 2005). Investigations of an association between delirium and POCD are limited and confounded by inconsistent definitions of POCD, as mentioned above. Saczynski demonstrated that patients who experienced an episode of delirium had lower cognitive scores using MMSE at 1 month and 12 months postoperatively (Saczynski *et al.*, 2012), while others have shown an association between delirium and POCD at day 7 (Rudolph *et al.*, 2008), and functional decline (Rudolph and Marcantonio, 2011) at one month postoperatively.

Currently, there is no treatment for AD that modifies the disease process. This does not mean that nothing can be done for these patients and indeed, we should be proactive in their perioperative management. Susceptible individuals need to be identified, and preoperative clinical assessment by anesthesiologists and other physicians needs to include evaluation of cognitive reserve (Crosby *et al.*, 2011). Unfortunately, current tools are either very crude (e.g. MMSE) or too complex to administer in the time available (e.g. CDR). Once at-risk patients are identified, decisions can be made wherever possible regarding the extent of the procedure considering risks versus benefit, or even whether a purely elective procedure should be undertaken at all. The amount of anesthetic agents required in patients with cognitive dysfunction may also be less (Xie and Xu, 2012). Future research will help inform us about selection of anesthetic type in susceptible individuals or the use of protective medications. Up-to-date guidelines should be developed to assist clinicians. Finally, stress can be reduced and well-being of patients at high risk can be improved by pragmatic but well-proven measures such as effective pain control, returning them promptly to familiar environments with same day or short stay surgery, and provision of familiar support people in the immediate postoperative environment.

In conclusion, anesthesia and surgery induce cognitive dysfunction in susceptible individuals. This may be subtle (POCD) with unknown long-term impact; it may be short-term (delirium), or possibly part of a longer-term change (dementia). These may be quite dissimilar phenomena or there may be overlap. There is an emerging body of laboratory data suggesting that anesthesia and/or surgery has direct effects on AD pathology. To identify patients at risk, preoperative assessment tools need to be provided for the brain in the same way that we pre-assess the heart and the lungs. Once identified, strategies can be used that may improve outcomes and in the future greater knowledge will inform our choices and therapies. The potential impact of anesthesia and surgery on patients with MCI or AD is unknown and cannot be ignored. Future collaborative research is essential.

Conflict of interest

None.

Description of authors' roles

DAVID A. SCOTT, BRENDAN S. SILBERT AND LISBETH A. EVERED were involved in manuscript preparation, editing and proofing.

Centre for Anaesthesia and Cognitive Function,
Department of Anaesthesia, St. Vincent's Hospital,
Melbourne, Australia
Email: david.scott@svhm.org.au

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