



## COMMENTARY

## Postoperative Cognitive Dysfunction: What Anesthesiologists Know That Would Benefit Geriatric Specialists

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Post-operative cognitive decline (POCD) in the elderly is well known to the anesthesiologists, but others are not as knowledgeable about this complex phenomenon and its causes. POCD is characterized by a slowing of brain processing speed, deficits in memory and executive function, in addition to other neuropsychological domains [1]. POCD is also associated with permanent brain damage, especially in those populations with more vulnerable central nervous systems due to age, children under two years of age and, increasingly, the elderly [1-10]. Although the problem of POCD has been reported in the literature for over a century and remains an ongoing interest in anesthesia research today [9], it is largely unknown among many clinicians such as family practitioners, internal medicine specialists and geriatricians that have daily contact with the elderly. It has been estimated that approximately 41 percent of elderly patients demonstrate some cognitive impairment following surgery with anesthesia [6,7]. With the increasing number of elderly undergoing surgery with general anesthesia worldwide, problems with POCD following surgery is an important topic in clinical medicine [11,12]. Given the scientific evidence in anesthesia literature and the growing anecdotal evidence of POCD, primarily among clinicians treating the elderly, there appears to be the need for a more interdisciplinary discussion regarding the risks and the long term effects of POCD that are costly for both health care systems and for the quality of life of the affected individuals [13,14].

Some of the more common surgeries associated with POCD are cardiovascular and orthopedic interventions such as hip and spinal interventions. In some cases of consecutive surgeries in the elderly, there is an incremental cognitive decline with each successive surgery, replicating the step-wise decrement seen in vascular dementia [15] and in persons with multiple traumatic brain injuries [16]. The case dependent risk factors for COPD in the elderly such as advanced age, genetic disposition, pre-existing cognitive impairment, pre-existing inflammatory conditions, pattern of diurnal variation in cortisol level [12], complexity and duration of surgery and anesthesia, postoperative delirium and infection. Several modifiable risk factors include pre- and post-surgery pain, use of potentially neurotoxic drugs and low intraoperative cerebral oxygenation.

As clinicians, we see many of our geriatric patients emerge from major surgery with both transitory and permanent cognitive changes which may cause fear and threaten their independence. The pervasive symptoms of POCD usually are reported to the family practitioners, internists and geriatricians as static or progressing mental status changes along the continuum of cognitive decline following surgery. Such situations provoke anxiety if the patient has not had presurgical education from their internist or geriatric clinician about the risks of POCD. This is often due to a lack of medical team knowledge about POCD sequelae.



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Frequently the elderly that experience POCD do not discuss their memory problems with their medical team as they fear being diagnosed as having “psychiatric problems” [17]. When patients present in clinic with reports of POCD, if the treatment team does not have an explanation or neglects to offer a plan to treat the symptoms, the afflicted individuals remain anxious, fearful and often attempt to ignore their memory loss as they may be under the impression that there is no medical explanation or treatment. Unfortunately the stress associated with the fears of losing one’s memory and/or having psychiatric problems often accelerates cognitive degradation with reduced volumes of the hippocampus, amygdala, thalamus, hypothalamus, bed nucleus of stria terminalis, nucleus accumbens, and the descending projections which synapse at the thoracic spinal cord. In addition, shorter telomeres in white blood cells may be an unwelcomed consequence [18-23]. Clinicians also see worried patients and family members that come to clinic with questions about post-operative cognitive changes, with frequent complaints of, “I’m worried, I can’t remember things that I could before the operation”; or “my memory is not getting better (following surgery)”.

What do we know about POCD and why is it important, especially for clinicians treating the elderly? This commentary is not a tutorial, rather a brief introduction to POCD for those readers unfamiliar with the diagnosis, with suggestions for treatment of the memory deficits postsurgically. The reader is referred to POCD reviews for additional in-depth information [24-27].

## Anesthesia

The risk of developing POCD is related to many variables including, but not limited to, immune response to surgery, advanced age, pre-existing cerebral, cardiac, and vascular disease, alcohol abuse, low educational level, and intra- and postoperative complications [7,13,14,28]. Many randomized controlled studies suggest the method of anesthesia is also a major variable associated with prolonged cognitive impairment. Therefore, one of the first POCD factors investigated was the use of volatile gases, such as isoflurane, sevoflurane, desflurane, nitrous oxide, pentobarbital, midazolam and ketamine during surgical procedures [29-32]. In vitro and animal studies have demonstrated that inhalational and intravenous anesthetics are principal components of POCD neuropathology. These anesthetic agents may cause neuroapoptosis, caspase activation, neurodegeneration,  $\beta$ -amyloid protein (A $\beta$ ) accumulation, oligomerization and neurocognition impairment [9]. Studies demonstrate that certain volatile anesthetics, such as desflurane, may have a less harmful neurotoxic profile compared to others in the surgical and clinical settings [9,12,33,34].

Propofol and other more modern volatile anesthetics are among the recommended choices for general

anesthesia in the inpatient and outpatient settings. The choice of anesthesia may reduce cognitive complications such as delirium and POCD [12]. Some hospitals are routinely utilizing 2,6-diisopropylphenol (propofol) with a benzodiazepine, ketamine or fentanyl during conscious sedation during both ambulatory surgery and inpatient surgery for appropriate elderly patients [35-39]. Propofol when used in conjunction with fentanyl appears to be a safe, quick, and effective method of providing conscious sedation which is advantageous for the elderly, especially during spinal and neurological blocks in the effort to avoid general anesthesia [35]. Propofol has an attractive pharmacokinetic profile of rapid onset and offset, but must be employed with caution for patients with cardiac and respiratory complications and when egg and soy allergies are present [40]. Propofol in combination with benzodiazepines such as flurazepam facilitates GABA receptor activity and increases the apparent GABA<sub>A</sub> receptor complex affinity for propofol, resulting in a synergistic potentiation by the combination [41]. A case control study demonstrated that both propofol-ketamine (Group I) and propofol-fentanyl (Group II) combinations produced rapid, pleasant and safe anesthesia. Group I had stable hemodynamics during maintenance phase while Group II recorded a slight increase in both pulse rate and blood pressure. During recovery, ventilation score was better in Group I, while movement and wakefulness scores were better in Group II. The authors concluded that both groups’ anesthesia combinations produce rapid and safe anesthesia with few minor side effects [36].

## Blood Brain Barrier

Aging is often accompanied by changes in blood-brain barrier permeability due to chronic inflammatory processes, a component of POCD pathology. Increasing blood-brain barrier permeability augments the burden of inflammation, infection and toxins passing into the brain that in turn accelerate degenerative processes [42,43], reduce brain reserve [44] and render the brain more susceptible to POCD [45]. Moreover, reduced drug elimination rates contribute to increased episodes of toxic medication effects peripherally [46]. When the toxic medications cross the blood-brain barrier, they escalate the risk of neurodegenerative disorders [34].

## Perioperative considerations

Literature regarding the treatment of POCD is presently limited, in part related to the suspected multifactorial pathophysiology. Jildenstål, et al. in 2014 noted that anesthesiologists in general have not systematically addressed the reversible and irreversible symptoms of POCD in the elderly as they primarily focus on minimizing cardiovascular and pulmonary risks and on diminishing nausea, vomiting and pain postoperatively [10]. A Swedish study sent questionnaires to greater than 2500 anesthesiologists and nurse anesthetists.

The survey revealed that postoperative neurocognitive deficits were not primary outcome indices of anesthesia protocols of the anesthesiologists contacted [10]. However, anesthesia research regarding perioperative anesthesia sequelae and pain management problems is ongoing and contributing to an understanding of POCD pathology [26,36,39,47-51]. Addressing perioperative pain management is an important treatment for reducing the risk of delirium and POCD [49,51].

Both pain and the resulting administration of opioids are notable contributors to delirium and POCD [49,52-55]. Moreover, the elderly have many comorbid medical conditions, including chronic pain conditions such as low back pain, chronic tension-type headaches and fibromyalgia which complicate post-surgery recovery and return to presurgical cognitive and functional levels [53,56]. Chronic pain has been associated with changes in global and regional brain morphology and brain volume loss including structural brain changes in the middle corpus callosum, middle cingulate white matter and the grey matter of the posterior parietal cortex as well as impaired attention and mental flexibility as measured by neuropsychological tests [53,54]. Brain atrophy and white matter lesions have been shown to be associated with increased risk of delirium which in some cases is the prodrome to POCD [26,48,54,57]. Studies also suggest that presurgery dementia and post-surgery intensive care unit admission are more important predictors of postoperative delirium than are opioid medications [55].

Anesthesia research is making advances in postsurgical pain management [49,51,52,54]. Minimal incision surgery for total hip and total knee arthroplasties with closely supervised pain management and physical therapy protocols markedly improved outcome variables compared to the same interventions with standard incisions [52]. Midwest Orthopedists in Rush surgical teams have been advancing protocols to reduce postsurgery pain with reduced inpatient hospital narcotic consumption, resulting in reduced inpatient nausea, vomiting and hospital length of stay [57].

## Treatment of POCD

When the patient comes to the outpatient clinic with POCD symptoms, what can be done? The literature gives clinicians few hints as no protocol or consensus guidelines could be found in a literature search. Many clinics go through a differential diagnosis including ongoing postsurgical delirium from comorbid infection, inflammation, metabolic (e.g., Vitamin B12, folate, thyroid function), medical, psychiatric, pharmacy and substance abuse problems. This replicates the clinical approach often employed for persons presenting with memory disorders from subjective cognitive impairment (SCI), mild cognitive impairment (MCI) and the dementias (Alzheimer's disease, vascular dementia, Lewy Body dementia, Parkinson's Dementia, Frontotemporal dementia, etc.).

Some clinicians are addressing the complexity of POCD treatment by utilizing the 36 point ReCODE (reversing cognitive decline) protocol which has been proven to reverse Alzheimer's disease even for persons with two copies of ApoE4 allele. This treatment protocol has been supported by over 200 peer reviewed publications [43]. The ReCODE protocol of Dr. Dale Bredesen and colleagues at the Buck Institute for Research on Aging at UCSF address most of the complex issues involved in precipitating the memory deficits of POCD: Insulin resistance; inflammation and infections; hormone, nutrient and trophic factor optimization; toxins (biological, chemical, physical); and restoration and protection of damaged synapses [43]. The protocol includes changes in lifestyle, diet, sleep patterns, and exercise to reverse cognitive decline. Outcomes are measured by cognitive scales, homocysteine levels, hippocampal volume changes and other biomedical markers. It is speculated that the ReCODE protocol will provide the treatment advances for POCD in the future.

## Conclusions

POCD is a debilitating surgical sequelae. Understanding its complex physiology and treatment are ongoing endeavors. Clinicians treating the elderly and infant populations need to have a working understanding of the syndrome in order to treat patients, to educate both the patients and families and to proactively address the symptoms of POCD. In addition to continuing interdisciplinary research of POCD, more education about this clinical entity should be included in the teaching of medical student, residents and fellows in most specialties. Moreover, there needs to be more information about POCD in those journals read by pediatricians, family practitioners, internists and geriatricians to better prepare them when they encounter POCD clinically.

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