Cognitive changes in the perioperative setting

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Abstract
With an aging population and a surgical demand expected to grow over the coming decades, it remains imperative to address perioperative factors that may impair cognition. Both postoperative cognitive dysfunction (POCD) and postoperative delirium (POD) carry significant social, clinical, and economic burdens on both caregivers and clinicians alike. Further understanding of the mechanisms by which various physiologic insults lead to cognitive dysfunction may bring about more effective measures for prevention and treatment. In this commentary, factors that may affect cognition in the perioperative setting will be reviewed. Notably, patient comorbidities, anesthesia, surgery and inflammation, pain, and sleep disturbance will be evaluated for their respective effects on cognition. Some of these risk factors may be more readily modifiable than others, and potential strategies for minimizing perioperative cognitive dysfunction will be reviewed by a systematic approach. Recent and ongoing clinical studies offer hope for future pharmacologic and non-pharmacologic means by which to reduce harm to cognitive reserve in the perioperative setting. Ultimately, employing a multi-modal methodology for minimizing POCD and POD may prove most efficacious.

Keywords: Post-operative cognitive dysfunction, Post-operative delirium, Alzheimer’s disease, Anesthesia, Surgery, Pain, Sleep disturbance

Introduction
There are an estimated 234 millions surgeries performed each year worldwide [1]. In the United States, annual inpatient surgical volume has increased from approximately 23.8 million surgeries in 1998 to over 30 million in 2010 [2,3]. Ambulatory surgical center visits have also increased by an estimated 300 percent between the years 1996 and 2006 [4]. Concomitant with this increased surgical volume is the increasingly aging population in the United States. While those age 65 and older represented about 13% of the population in 2010, this number is expected to climb to 19% (an additional 31.9 million people) by 2030 [5]. Given both the growth in surgical volume as well as the aging population in the United States, significant perioperative surgical risks should continue to be studied, managed, and prevented when possible. In particular, focus on perioperative cognition may become even more relevant with both an aging population and an increase in patients with cognitive disorders. For example, the incidence of patients with Alzheimer’s disease (AD) is expected to grow over the coming decades. At present, 11% of those age 65 and older (5.3 million people) are estimated to have AD, though by 2050, those with AD age 65 and older is projected to reach 13.8 million—an almost tripled incidence since 2010 [6]. Ultimately, many patients within this demographic will require surgical services.

Based on the above estimates, it is imperative that elements affecting cognition in the perioperative setting be analyzed. Further, those elements which may be deleterious to cognition should be addressed and either temporized or avoided. In this review, we will (1) examine components of the perioperative setting (i.e. patient comorbidities, anesthesia, surgery and inflammation, pain, and sleep disturbance) which may contribute to post-operative delirium (POD) and post-operative cognitive dysfunction (POCD) and (2) review strategies to avoid damaging cognitive reserve.
Review

As mentioned above, we will review five elements of the perioperative setting – patient comorbidities, anesthesia, surgery and inflammation, perioperative pain, and sleep disturbance, which may modify the risk of POCD and POD. As portrayed in Figure 1, these factors likely work in combination to develop a patient's risk of developing cognitive dysfunction in the perioperative setting and beyond. Data examining the effect of these factors on cognitive function and potential strategies for minimizing cognitive dysfunction in the perioperative setting will be reviewed.

![Diagram showing Baseline Comorbidities leading to Anesthesia, Pain, Surgery/Inflammation, Sleep Deprivation, and Cognitive Dysfunction]

Fig.1 Proposed Perioperative Factors Affecting Cognition: Chronological depiction of perioperative factors which may affect perioperative cognitive function

Baseline comorbidities

Advancing age, pre-existing cognitive dysfunction, functional impairment, sensory impairment, substance abuse, and psychotropic drug use are among many preoperative risk factors identified with the development of POD [7-9]. Clinical prediction models have been developed which have corroborated these findings [8,9]. More recently, an association between obstructive sleep apnea (OSA) and POD has also been demonstrated [10]. Though the mechanistic link for this association is unclear, disrupted sleep patterns and vulnerability to hypoxia are postulated contributors [11]. Predictors of POCD are similar for those of POD, which include age, level of education, higher ASA physical status, and previous cerebrovascular accident (CVA) [12,13]. Of concern in the former study is that mortality rates were higher in patients with POCD both at hospital discharge and 3 months after surgery. Although this link was not necessarily causal, this finding generates concern as to whether or not cognitive dysfunction during and after the perioperative setting may render patients vulnerable to higher mortality. Recently, POD after cardiac surgery was also marked with decline in cognitive ability during the first year after cardiac surgery [14]. More prospective investigation will ultimately be needed to answer these questions.

Though patient comorbidities may not represent risk factors as modifiable as the elements that we will discuss below, some effort has gone into proactive prevention of delirium based on patient population targeting. For example, in one prospective, blinded trial, perioperative geriatric consultation was prospectively obtained for patients age 65 and older, and this included patients with pre-existing cognitive dysfunction, functional impairment, and high medical comorbidity index [15]. Geriatric consultation in these patients resulted in lower delirium incidence and severity. These findings were similar to reported reductions in delirium in medicine patients [16]. Unfortunately, however, there is a paucity of high quality studies demonstrating efficacious techniques for preventing delirium in surgical patients based on baseline comorbidities.

Anesthetics

More recently, concern has been growing as to the effects of routinely used anesthetic agents on cognitive function [17,18]. Moreover, anesthetics may modify the pathophysiologic substrates of neurodegenerative syndromes such as AD [19-22]. As surgical volume is expected to increase over the coming decades, it will be paramount to discern any potentially neurotoxic side effects of anesthetics, including those that may affect cognition.

Over the years, many retrospective and prospective studies have investigated the possibility of anesthesia-induced perioperative cognitive dysfunction. Newman et. al conducted a systematic review in 2007 comparing regional and general anesthesia and their respective associated incidences of POCD [13]. There were 17 studies total in the
review, and all but 2 were randomized. Unfortunately, many of the studies were underpowered statistically. Surgical procedure varied greatly – ophthalmologic, orthopedic, gynecologic, and plastic surgeries were among those included. Follow-up time ranged from 7 days to 6 months. Ultimately, there was no clear evidence that using anesthetic techniques other than general anesthesia resulted in a lower incidence of POCD. Though one prospective, randomized study demonstrated a reduced risk of POCD with regional anesthesia as compared to general anesthesia shortly after surgery on a per-protocol basis, this difference resolved by 3 months [23]. However, it is still possible that the severity of POCD could be affected by using general anesthesia. Unfortunately, such studies have not been performed.

Comparing different, specific anesthetic agents represents another dimension by which anesthetics may contribute to POD/POCD pathophysiology. Small, underpowered studies comparing various inhalational anesthetic agents have failed to show a difference in perioperative cognitive dysfunction among these agents [24-26]. A recent pilot study, however, did demonstrate decreased POCD incidence in orthopedic surgery patients exposed to spinal anesthesia and desflurane anesthesia when compared to isoflurane anesthesia [27]. Of course this was a pilot study, with a small sample size (15 patients per arm), and limited follow-up time (1 week). These studies do generate interesting hypothesis, however, with regards to different anesthetic medications and their potentially varied effects on perioperative cognitive function. As there are of yet no clear, consistent data demonstrating different rates of POCD or POD with different anesthetic techniques, larger prospective trials with a longer follow-up time are warranted.

Surgery and inflammation

Surgery-specific stimuli have been implicated as risk factors contributing to the development of POCD. A potentially modifiable risk factor related to surgery may be the inflammatory response to the surgery itself. Pro-inflammatory cytokines released during surgical stimulation lead to systemic inflammation and neuroinflammation, which have been postulated to mediate pathology associated with POCD and AD [28-31]. Specifically, IL-1, IL-6, TNF-α, and TGF-β have all been implicated in this process [28,29,32]. Additionally, release of IL-1β after surgery of the tibia in mice has been demonstrated to cause hippocampal-dependent memory impairment post-operatively [32]. This effect was attenuated by functional inhibition of IL-1β. This finding has been supported by findings of increased mRNA expression of IL-1β, IL-6, and TNF-α in hippocampal cell layers of mice during peripheral immune system stimulation [33]. A recent association was demonstrated between elevated postoperative IL-6 and C-reactive protein (CRP) levels and cognitive dysfunction after coronary artery surgery [34]. Variance in alleles of CRP as well as P-selectin (along with lower serum levels of the former) was also associated with a reduction in cognitive deficit in European Americans in a prospective cohort trial [35]. Alternatively, in one single-center prospective observational study, a plasma biomarker panel (BNP, CRP, D-dimer, MMP-9, NSE, and S-100) was analyzed in both patients without POCD and patients experiencing POCD after non-cardiac surgery both perioperatively and again after 6 weeks and 1 year postoperatively [36]. In this study, no significant differences in biomarker levels were found between these groups. Thus, it may be possible that a specific surgical inflammatory milieu (consisting of proinflammatory cytokines IL-1, IL-6, and TNF-α) contributes to the neuropathology behind POCD and AD. In fact, emerging evidence indicates that anti-inflammatory measures may have a neuroprotective effect with regards to cognitive preservation. Specifically, ibuprofen was shown to restore learning ability in rats with portocaval shunts [37]. In a single-center pilot study, rapid cognitive improvement was noted in patients with AD after perispinal etanercept (TNF-α antagonist) administration [38]. Ketamine use, in conjunction with a decrease in CRP levels, was associated with decreased POCD and POD in cardiac surgery patients [39, 40].

Pain

According to the Institute of Medicine, there are approximately 116 million people in the United States living with pain [41]. Pertinently, previous studies have demonstrated a link between pain and cognitive impairment [42-47]. Those with chronic pain have been shown to demonstrate cognitive impairment with objective testing even when controlling for opioid use and depressive symptoms [48]. Over the years, studies have examined the link
between pain and delirium in surgical patients. Two prospective observational studies in patients presenting for non-cardiac surgery have demonstrated a link between increased perioperative pain scores and development of delirium [49,50]. Interestingly, in the latter study, patients solely receiving oral opioids (as compared to IV patient-controlled analgesia) had a lower risk of developing delirium, even after adjusting for pain scores. This was not a randomized trial, however, but suggests that pain management strategies may be a significant factor with regards to the development of delirium in surgical patients. In another prospective study in surgical patients presenting for hip repair, severe pain was again associated with increased risk (nine-fold) of POD [51]. Studies in healthy, young adults as well as in patients with chronic pain suggest mechanisms by which pain may impact cognition. Essentially, the presence of pain has been shown to interfere with attention and reaction time; pain distracted subjects from completing tasks and minimized mental flexibility [52-55]

Unfortunately, opioid therapy – a current mainstay treatment for pain – may have the undesirable side effect of worsening cognition via disruption of sleep-awake architecture and interference with cortical cholinergic transmission [56,57]. In laboratory animals, morphine has been shown to decrease levels of adenosine in the pontine reticular formation (PRF) and basal forebrain (BF), important nuclei for sleep-wake regulation [58]. Further, opioids have also been shown to decrease acetylcholine release in the BF [57]. As cortical cholinergic transmission is imperative for normal cognition [59,60], this opioid-induced decrease in cortical acetylcholine may render patients more susceptible to POD. In fact, opioid use has been shown to be a predictor of POCD at hospital discharge after non-cardiac surgery [12]. It should be noted, however, that increased pain has been associated with delirium (as described above), and pain requiring opioid use in the clinical setting may also contribute to POD and POCD. Ultimately, clinical judgment should be used with regards to opioid dosing in the perioperative setting with the goals of alleviating pain and monitoring for signs of delirium. Expert pain medicine consultation may be beneficial in the perioperative setting, especially in complex cases involving patients with chronic pain. Further, non-opioid analgesics may be beneficial given the disruption of normal sleep-wake architecture and cortical cholinergic transmission for which opioids can be responsible, as outlined above. More randomized, prospective trials are needed to further investigate these possibilities.

Sleep disturbance

We have just described how opioid medications can disrupt normal sleep-wake architecture. Unfortunately, sleep disturbance is common in hospitalized patients, especially those in the ICU [61-63], and sleep disturbance may also be a risk factor for delirium [64]. Both sleep disturbance and delirium share many common clinical traits, such as inattention, cognitive dysfunction, decreased alertness, and deficits in working memory [65-68]. Mechanistically, interference with neural circuits involving the frontal lobe, parietal lobe, and thalamus seem to be common in both delirium and sleep deprivation states [69-72]. Specific deficits in these circuits include imbalance of cholinergic and dopaminergic tone [73,74], and imaging studies have demonstrated changes in perfusion and metabolism in these regions [75, 76]. Sleep disturbance has also recently been shown to induce neuroinflammation in the mouse hippocampus as well as hinder hippocampal-dependent learning and memory [77]. This may be due in part to an IL-6-mediated mechanism. Finally, although surgical patients may be exposed to general anesthesia for surgery during their hospital course, volatile anesthetics in laboratory animals have not been shown to satisfy the homeostatic need for rapid eye movement (REM) sleep [78,79]. Propofol, however, was used in laboratory rats for prolonged sedation, and no evidence of sleep deprivation was observed [80]. Thus, different anesthetic agents may differentially affect sleep homeostasis in surgical patients, though more clinical studies are warranted to support or refute this notion. Ultimately, the link between sleep disturbance and delirium warrants further study, and the differential effects of various anesthetics on sleep architecture and debt also need further investigation. At present, a supportive environment in the hospital setting with emphasis on good sleep hygiene may help to prevent sleep disturbance and delirium.

Conclusion

Prevention and effective management of cognitive dysfunction may be a vital part of good perioperative outcomes, especially with increasing surgical volume and an aging population. As
described above, some studies have alluded to the possibility of increased mortality rates with POCD and POD [7,12]. Successful interventions will likely involve a multi-modal approach. Though patients’ comorbidities, baseline cognitive functioning, and type of surgery for which they are presenting do not likely represent readily modifiable risk factors, optimal pain management (possibly with non-opioid approaches and adjuncts when feasible), restoration of a normal sleep-wake cycle, and a supportive environment may decrease the changes of developing POD and POCD. Further prospective studies are needed to determine if specific perioperative anti-inflammatory regimens and different anesthetic approaches may modulate the risk of developing cognitive dysfunction.

**Abbreviations**

POCD: postoperative cognitive dysfunction; POD: postoperative delirium; AD: Alzheimer’s disease; OSA: obstructive sleep apnea; CVA: cerebrovascular accident; IL-1: interleukin-1; IL-6: interleukin-6; TNF-α: tumor necrosis factor alpha; TGF-β: transforming growth factor beta; IL-1β: interleukin-1-beta; mRNA: messenger ribonucleic acid; CRP: C-reactive protein; BNP: B-type natriuretic peptide; MMP-9: matrix metalloproteinase-9; NSE: neuron-specific enolase; S-100B: PRF: pontine reticular formation; BF: basal forebrain; REM: rapid eye movement.

**Competing Interests**

PEV and ZX both deny any competing interests.

**Authors’ Contributions**

PEV performed much of the literature research and manuscript writing. ZX was the supervising author and provided final revisions and reference additions as appropriate. Both authors read and approved the final manuscript.

**Acknowledgements**

None

**References**


http://www.perioperative-science.com/content/01/07


