Surgical procedures and postoperative cognitive dysfunction

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Postoperative cognitive dysfunction is a serious side effect of surgery with the potential to affect the long-term wellbeing of patients. Here the authors discuss the risk factors and possible aetiology of the disorder.

Postoperative cognitive dysfunction (POCD) refers to the decline in cognitive ability after anaesthesia and surgery. There is no consensus either on what constitutes POCD or the validity of the actual condition. It is generally accepted that POCD is common in the first few weeks of surgery. The dispute is about the long-term existence of the disorder. Some studies have found no connection between cognitive impairment and surgery and anaesthesia, others have found a link between the two in certain population cohorts only. The abilities that have been observed to be affected include learning and memory, verbal abilities, perception, attention, executive functions, and abstract thinking.

The incidence of POCD can range from 26% at one week and 10% at three months in patients older than 60 years. As far back as 1955, Bedford identified 120 cases of dementia after a retrospective study of over 4000 elderly surgical patients. Awareness of the cognitive effect of anaesthesia and surgery is still limited among the medical profession.

Historically the effects of anaesthesia have been viewed as short-lived, with no major long-term effects. Increasingly evidence suggests that this may not be the case. POCD may be detected days to weeks after surgery and may remain as a permanent disorder. POCD is encountered after cardiac surgery, non-cardiac surgery and even with procedures under sedation, such as coronary angiography. POCD has been observed to show a bimodal pattern – initial decline followed by improvement up to a year later, the second phase of decline has been observed up to three to five years later in case of cardiac surgery.

POCD after non-cardiac surgery has been associated with increased mortality, decreased quality of life, early retirement from work and increased dependency. After cardiac surgery 42.4% of patients experienced a decline of at least one standard deviation in at least one domain of cognitive function at five years, resulting in a poor quality of life.

Risk factors and possible aetiology
Several risk factors have been proposed for POCD, eg age greater than 50 years, low education, diabetes, atherosclerotic disease, genetic disposition, high alcohol intake, pre-existing mild cognitive impairment, history of cerebral vascular accident, major operations, repeat operations, cardiac surgery, longer duration of surgery and anaesthesia, intraoperative cerebral desaturation, postoperative delirium, and postoperative infection. Most authors now view a combination of surgery, anaesthesia and patient-related factors as important considerations in the aetiology of POCD.

Major surgical procedures appear to accelerate cognitive decline following a delay of several years after the operation, with an increased incidence of dementia, although Steinmetz and colleagues did not find POCD to be significantly associated with dementia over a median follow-up of 11 years. Similarly at the end of five years none of the patients were diagnosed with dementia in a study by Selnes et al.

Anaesthetic agents interfering with brain neurotransmitters have been proposed as a cause of POCD. Animal and cell culture studies have shown that inhalational anaesthetics induce apoptosis and increase Aβ formation. Several anaesthetic agents can also promote hyperphosphorylation of the microtubule-associated protein tau when associated with hypothermia. Culley et al. showed that isoflurane exposure causes significant memory impairment in elderly rodents leading to long-term deficit in learning and memory in rats in a pre-learned spatial memory task. POCD has been shown to be independent of the type of anaesthesia (ie general or regional anaesthesia).

Cognitive deficits after cardiac surgery were thought to be caused by physiological disturbances associated with the cardiopulmonary bypass technique. Recent large, prospective, randomised studies comparing the rate of adverse neurological outcomes after on-pump and off-pump surgery have not shown a significant risk reduction associated with the use of off-pump surgery. Most cases of brain infarction are assumed to be due to micro emboli, hypoperfusion and systemic inflammation are also receiving attention as a cause of neurological damage.
Pre-existing cognitive impairment might constitute an important risk factor for POCD, as pre-existing cognitive impairment is found in 20% of elderly patients presenting for total hip joint replacement,1 this figure is as high as 35% for female CABG patients.16

Data from the Alzheimer’s disease Neuroimaging Initiative found that surgical patients, in the first five to nine months, had increased rates of atrophy for cortical grey matter and hippocampus, and lateral ventricle enlargement, as compared to non-surgical controls.8 This risk was greater in subjects who had pre-surgical mild cognitive impairment.

Inflammatory processes play a key role in the pathogenesis of POCD. Interleukin-6 (IL-6) and S-100β are POCD-related pro-inflammatory markers.17 The S100β is a calcium-binding peptide and is a marker of glial activation and/or death in disorders of the central nervous system such as brain damage from circulatory arrest, stroke and traumatic brain injury. POCD animal models show postoperative hippocampal neuroinflammation marked by blood-brain barrier (BBB) disruption, glial response, and activation of inflammation/NF-κB signalling. Li et al.18 investigated modulation of the brain renin-angiotensin system in an aged rat model of POCD and the influence of angiotensin-1 inhibition (AT1 inhibition) on neurobehavioral outcome, BBB permeability, and brain inflammation after surgery. They observed significant inhibition of hippocampal neuroinflammation, evidenced by decreased glial reactivity and phosphorylation of the NF-κB p65 subunit, as well as marked reductions in interleukin-1β, tumour necrosis factor-alpha, and cyclooxygenase-2. AT1 inhibition improved learning and memory outcome after surgery.

Chen et al.20 observed a neuroprotective effect of intravenous lidocaine on early POCD in elderly patients following spine surgery as evidenced by significantly higher mini mental status examination scores. They suggest that the benefits may be due to inhibition of release of IL-6, malondialdehyde, S100β, and neuron-specific enolase.

Kong et al.20 found pretreatment with minocycline mitigated isoflurane-induced cognitive deficits and suppressed the isoflurane-induced excessive release of IL-1β and caspase-3 in the hippocampus.

However, Dokkedal et al. in a study of 8503 twins exposed to surgery, found no clinically significant association of major surgery and anaesthesia with long-term cognitive dysfunction.21 Neither did Fischer et al.20 in the Vienna Transdanube Ageing ‘VITA’ study. Potter et al. found a positive cognitive outcome following coronary artery bypass graft (CABG) surgery in elderly male twins.22

The Oxford Project to Investigate Memory and Ageing (OPTIMA) study found that elderly patients with pre-existing cognitive impairment were at risk of more rapid cognitive decline after an episode of moderate or major surgery with general or regional anaesthesia.23

Ballard and colleagues25 report increased frequency of cognitive impairment in people over the age of 60 years undergoing major non-cardiac surgery after 52 weeks in comparison with age-matched controls. Optimising anaesthetic depth and maintenance of cerebral oxygenation with bispectral index and cerebral oximeter monitoring conferred a significant reduction in mild and moderate POCD, global cognitive impairment and attentional impairments at one week post-surgery as well as in reducing mild POCD and improving attention, executive performance and global cognition up to 52 weeks following surgery.25

A large Taiwanese study24 found a doubling of the risk of developing dementia within three to seven years of anaesthesia and surgery with a shorter time to diagnosis of dementia in the anaesthesia group than the control group. All modes of anaesthesia, i.e., intravenous or intramuscular anaesthesia, regional anaesthesia and general anaesthesia, were associated with an increased risk of dementia.

**Conclusion**

POCD is a serious side effect of surgery having a potential to affect the long-term wellbeing of patients. In most cases it is self-limiting, but in a significant minority it can become permanent and even progress to dementia. Age is the most consistent risk factor for developing POCD. Patients with pre-existing mild cognitive impairment are predisposed to developing POCD. There have been inconsistent findings to blame anaesthesia, although preclinical studies implicate inhalational anaesthetics in causing cognitive impairment in aged animal lasting several weeks. The surgical process itself produces an inflammatory response and is considered important in the development of POCD. Recent studies have evaluated the inflammatory response and small-scale trials have found benefits from anti-inflammatory treatment.

A careful and thorough preoperative discussion of the risk of cognitive change, with appropriate informed consent is essential.

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**Declaration of interests**

No conflicts of interest were declared.

**References**

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