

Post-Operative Cognitive Dysfunction: Pre-Operative Risk Assessment and Peri-Operative Risk Minimization: A Pragmatic Review of the Literature

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Post-operative cognitive dysfunction (POCD) is one of the most well recognised neuropsychological consequences of anaesthesia. One of the difficulties in studying POCD however is that although it is recognised as a mild cognitive disorder separate to delirium and dementia, and characterised by subtle impairments in memory, concentration and information processing, it is not yet described formally as a psychiatric diagnosis with exact diagnostic criteria [1].

Recent studies have shown that many elderly surgical patients develop Postoperative Cognitive Dysfunction (POCD). While some of this dysfunction can be attributed to ageing, Clinical scientists posit a number of reasons why this syndrome occurs. Many clinical scientists believe that the duration of surgery and the type of anaesthesia are major contributing factors in the development of POCD. Other clinical scientists speculate that the health status of an elderly patient is a precursor in the development of POCD, particularly those individuals with non-cardiac problems.

For more than fifty years, health care providers have acknowledged that some patients emerge from surgery and anaesthesia with noted deficits in cognitive function that were not present preoperatively [2]. This impairment is referred to in the literature as Postoperative Cognitive Dysfunction (POCD) [3] and has been also defined as a “state of cerebral cognitive alterations”. Patients undergoing cardiac surgery are reported to have a higher incidence of cognitive dysfunction than any other major surgical procedures [4, 5]. The incidence of POCD in the immediate postoperative period has been reported to be as high as 80% [6]. Although reported as being transient, a review by [3] suggests that some patients may experience long-term dysfunction and this dysfunction may even become permanent. Newman and colleagues [7] reevaluated patients 5 years after surgery and found that 42% showed decline in cognitive function from preoperative baseline assessment and decline in cognitive function in the immediate postoperative period was predictive of long-term decline. The incidence of POCD is particularly prevalent in patients over 60 years of age [8]. Moreover, studies suggest [9] that patients who develop POCD may be at higher risk for cognitive decline/dementia later in life. Longitudinal studies of normal ageing without surgery suggest that any sudden decline in cognitive function leads to a loss of independence

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and withdrawal from society, and is an important predictor of mortality [10, 11]. Monk and colleagues [12] evaluated patients one-year after surgery and reported that patients exhibiting POCD in the immediate postoperative period and 3-months after surgery had a significantly higher mortality ($p = 0.02$) than patients who did not experience POCD.

The literature suggests that age is the number one factor to be predictive of postoperative cognitive decline [6, 13, 14]. The patient population is ageing and based on favorable perioperative outcomes, more high-risk patients are undergoing surgical procedures including cardiac surgery. Even if the surgical procedure is uneventful, it may be followed by a decline in cognitive functional status.

Cognitive function is of critical importance in relation to independent living, need for care, personal and economic cost, and quality of life. When optimising patients for surgery, Hence perioperative assessment and planning strategies for prevention of potential for development of POCD need to be part of the pre-assessment package. In doing so, perioperative management should include a long-term perspective with consideration to cognitive assessment as well as patient education regarding the potential impact of POCD.

Cognitive processing is a unique and vital human experience. From

a physiologic perspective, the process of cognition is dependent in part upon the neuron, which is the functional unit of the central nervous system. Neurologic function is vital to information processing and adaptation. A classical synapse is responsible for transmitting information from a presynaptic neuron to its target cell. In contrast, the function of a neuromodulatory synapse is to transmit information that will have long-term effects on the postsynaptic neuron's activity, most importantly its response to succeeding input. Synaptic plasticity is an activity-dependent process, which involves continuous use of synaptic pathways. This process is widely believed to be elemental to learning and memory, as well as providing an important role in the development of new neural pathways [15]. To better understand the significance of neural plasticity, it is important to research the potential of modifying neuromodulatory synapses through cognitive training. Through these modifications it may be possible to promote neurogenesis, change sequences of neuronal firing, promote learning and memory, and alter behavior [16-19].

Risk Factors and Pathogenesis

The pathogenesis of delirium, cognitive dysfunction and other neuropsychological sequela following anaesthesia, surgery and critical illness are not fully understood, but are likely to be multifactorial. Some of the risk factors for POCD such as advancing age, increasing duration of anaesthesia, lower education level, second operation, post-operative infections, and respiratory complications have been described previously [20]. Various other risk factors appear to be associated with cognitive dysfunction following critical illness including hypoxaemia [21], dysglycaemia [22], sepsis [23] and delirium [24, 25]. Delirium has many similar risk factors, including age, medical comorbidities, cognitive, functional, visual and hearing impairment, anticholinergic drugs, alcohol or drug withdrawal, infections, iatrogenic complications, metabolic derangements and pain [26] (**Table 1**). The leading hypotheses for the pathogenesis of delirium and cognitive dysfunction following anaesthesia and critical illness are that of a) neurotoxicity, b) neuromodulatory and c) neuroinflammatory mechanisms, which are co-exist rather than compete [27]. Some researchers present the argument that disturbed sleep associated with the effects of acute illness, sedative medications and environmental factors can influence these pathways and also lead to psycho-emotional symptoms as well as delirium and cognitive dysfunction [28-30] (**Table 1**).

The key pathogenic mechanisms of postoperative cognitive dysfunction are

- a) Neurotoxicity
 - b) Defect in neurotransmission
 - c) Neuroinflammation
- a) Neurotoxicity

There is mounting evidence revealing anaesthetics to be powerful modulators of neuronal development and function [31]. Experimental work in young rodent and primate brains demonstrate the effect of anaesthesia on developmental neuroapoptosis, neuronal network assembly, and neurogenesis; due to their effect on GABA receptors, brain derived neurotropic

Table 1 This table summarizes the main risk factors associated with cognitive dysfunction and delirium in the perioperative period.

Patient Related Risk Factors	Hospital Related Risk Factors
Advancing age (> 60 years of age)	Increasing duration of anaesthesia (> 90 min)
Baseline cognitive function	Depth of anaesthesia
Lower education level	Type of surgery
Visual & Hearing Impairment	Second Operation
Alcohol or drug withdrawal	Postoperative infections
Lack of Sleep	Respiratory complications
Neurodegenerative diseases	Hypoxia
Parkinson	Dysglycaemia
Diabetes	Pain
	Use of vasoactive drugs
	Use of benzodiazepines

factor (BDNF), oxidative stress, ROS production, glial cell modulation, and activation of complement and inflammatory cascades [32]. In older adults, anaesthesia appears to promote tau hyperphosphorylation; and it has been noted that the $\alpha 5$ GABAA receptor may play an important role in modulating post-operative decline following anaesthesia [31]. Both inhalation and intravenous anaesthetics have been implicated although there may be variations between agents [31, 33].

b) Neurotransmitters

As indicated in the risk factors for delirium, cognitive dysfunction and other neuropsychological symptoms, there are many factors that may affect neurotransmitter synthesis, function and/or availability that could result in these neuropsychological manifestations. In general, the most commonly described neurotransmitter alterations, particularly seen in association with delirium, include deficiencies in acetylcholine and/or melatonin availability; excess in dopamine, norepinephrine, and/or glutamate release; and variable alterations in serotonin, histamine, and/or γ -aminobutyric acid [27, 34].

c) Defects in Neuroinflammation

It is increasingly understood that the immune system and inflammatory mediators have a key role in the formation of memory and learning, and that their dysregulation has a role in the pathogenesis of cognitive dysfunction [35, 36]. Current evidence demonstrates that most neurodegenerative disorders have an inflammatory component; including both acute pathological conditions, such as traumatic brain injury and stroke, and chronic conditions, such as epilepsy, Alzheimer's disease, Parkinson's disease, and ageing [37, 38].

There have been several animal studies that have implicated systemic and neuroinflammation in the pathogenesis of POCD [39-41], and shown that by reducing neuroinflammation the cognitive deficits can be prevented [35, 42, 43].

The pathophysiological mechanisms relating systemic inflammation and neuroinflammation have been eloquently described in recent reviews [36, 44, 45], but in summary, anaesthesia, surgery and critical illness exert a systemic inflammatory insult, which leads to neuroinflammation via

direct passage of cytokines and macrophages over the blood brain barrier (BBB), receptor interactions across the BBB leading to cytokine production and neural communication via vagal afferents. Neuroinflammation consists of increased production of cytokines and reactive oxygen species that activate microglial and lead to synaptic and neuronal disruption [46-48]. It is possible that the ageing brain, or the brain exposed to a chronic low level of inflammation due to disease such as diabetes, is further 'primed' to produce noxious substances on exposure to additional inflammatory insults such as surgery – the so called microglial 'priming' hypothesis [49].

Alternative hypotheses include that disruption of the endothelial function (particularly in the BBB) due to hypoxia, endotoxin and inflammatory cytokine release, direct injury from surgical trauma or haemodynamic shear stress, may lead to increased movement across endothelial membranes, vasoconstriction, coagulation, and may lead to end organ dysfunction including POCD [50]. This has been seen in critically unwell patients, whose systemic endothelial function has been assessed and the severity of dysfunction has been associated with duration of acute brain dysfunction or otherwise described as delirium [51, 52], whether this is an epiphenomenon or has a causal association with either acute brain dysfunction, or long term cognitive dysfunction is as yet unclear.

Preventative Strategies and Long-term Management of Surgical Patients

We continue to excel in addressing the diverse needs of our patients in the perioperative period, with multiple sub-specialties such as; dieticians, physiotherapy, physicians specialised in the elderly care, speech and language therapy, the pain team, and diabetic nurses, we can be confident that when required, a referral to the appropriate team will result in the delivery of expert care. Unfortunately, where we have become so focused on the individual parts, we have lost sight of the fact that the sum of these, i.e. the patient, is always greater.

Current strategies towards neuroprotection focus mainly on the detection, treatment and management of delirium, using conservative approaches to control the environment, 'treating the cause', and managing agitation. However, the prevention of cognitive dysfunction in the perioperative period should be integrative and throughout the patients' journey in hospital (Table 2).

Introducing preventative strategies enhance the delivery of good quality patient-centred care. It is essential that we integrate our multiple management strategies to enable a personalised care plan that truly is in the patient's best interest to prevent long-term neurocognitive dysfunction and

Cognitive Rehabilitation

Specific cognitive rehabilitative therapies as part of long-term follow up and rehabilitation are becoming increasingly relevant to the management of patients in the postoperative period and

following discharge from hospital. This is due to the growing evidence that patients are affected by significant long-term cognitive problems as described above. Cognitive rehabilitation has been defined as "the systematic, functionally orientated service of therapeutic activities that is based on assessment and understanding of the patient's brain-behaviour deficits". Cognitive rehabilitation does not focus just on improving memory, but is a functional process that enables an individual to cope within their own environment via compensation strategies [53, 54]. Cognitive rehabilitation is still a growing field, but encouragingly, in relation to cognitive dysfunction following traumatic brain injury (TBI) or stroke, there is sufficient robust evidence to make practice standards recommendations for therapy, such as direct attention training and metacognition training to promote development of compensatory strategies and improve executive functioning, and evidence that comprehensive neuropsychological rehabilitation can improve community integration, functional independence and productivity [55]. Of relevance to future strategies for cognitive rehabilitation following discharge from hospital after surgical interventions are specific research questions such as which patients will benefit, when should cognitive rehabilitation begin, and what interventions are effective for elderly patients requiring non-neurological surgical interventions.

Several randomized controlled trials into the combined use of physical and cognitive rehabilitation strategies have been initiated to evaluate their utility in improving cognitive, physical, and functional outcomes following discharge from intensive care but there is no experience as yet in perioperative care. This is based on the hypothesis that exercise has beneficial effects on cognition, and potentially the responsiveness to cognitive training, and that the strategic combination of functional training can help assimilate new skills into daily life [55], in addition we know that cognitive impairment predicts poor outcome from physical rehabilitation [56]. The RETURN study found a significant improvement in cognitive function following a 12 week programme of rehabilitation compared with the 'usual care' package of sporadic rehabilitation [55]. The ACT ICU trial demonstrated the feasibility of providing combined cognitive and physical rehabilitation for mechanically ventilated patients whilst on the ICU. This study was insufficiently powered to demonstrate a significant improvement in function following these treatments; however it provides a framework for on-going investigation in intensive care and perioperative medicine [56].

Table 2 This table illustrates some strategies to prevent the development of cognitive dysfunction in the perioperative period.

Preventable Medical Conditions
Closed monitoring of the depth of anaesthesia
Reduction in the length of surgical interventions
Rationalization of the use of benzodiazepines
Rationalization of the use vasoactive drugs
Avoid hypoxia
Avoid hypotension
Effective management of pain

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