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Review Article

Peri-operative cognitive dysfunction and protection

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Summary

Cognition may decline after surgery. Postoperative delirium, especially when hyperactive, may be easily recognised, whereas cognitive dysfunction is subtle and can only be detected using neuropsychological tests. The causes for these two conditions are largely unknown, although they share risk factors, the predominant one being age. Ignorance of the causes for postoperative cognitive dysfunction contributes to the difficulty of conducting interventional studies. Postoperative cognitive disorders are associated with increased mortality and permanent disability. Peri-operative interventions can reduce the rate of delirium in the elderly, but in spite of promising findings in animal experiments, no intervention reduces postoperative cognitive dysfunction in humans.

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The clinical problem

'Grandfather was never the same after his operation'. Brain function usually recovers after surgery, but recovery may be prolonged or incomplete. Significant cognitive decline will be noticed by the patient, relatives, friends and hospital staff but subtle changes may remain unnoticed until the patient has returned home. Memory disruption is common and difficulties with processing information can be annoying at work and home. The problem is becoming more common: cognitive dysfunction is more likely in the elderly, there are more elderly patients and more are undergoing surgery [1]. The risk of cognitive deterioration after surgery is a serious health and social issue, particularly as the age for retirement is increased and because grandparents often contribute to the care of grandchildren [2].

Postoperative delirium

Postoperative delirium is a non-specific cerebral syndrome characterised by inattention and a disturbance of various other aspects of brain function, such as perception, thinking, memory, psychomotor behaviour and the sleep–wake schedule. It has an acute onset and is most common in the first few days after surgery. The clinical features for three in four cases of postoperative delirium consist of fatigue and a poverty of activity, which may simply be mistaken for sleepiness by the unthreatened and undisturbed staff. On the contrary, the hyperactive (agitated) form of delirium is rarely missed, as these patients disturb the flow of care, and they can be demanding for the healthcare personnel on the ward due to the patient's inability to cooperate and the high risk of falls [3].

The confusion assessment method (CAM) is the most commonly used test to detect delirium, modified as the CAM-ICU for critically ill patients [4, 5]. The rate of postoperative delirium ranges from 1 in 20 to more than 1 in 2, with the type of surgery being a major risk factor [3]. Delirium should be considered a

continuum of severity and duration, rather than an event.

Postoperative cognitive dysfunction

Postoperative cognitive dysfunction does not affect the level of consciousness. Unlike delirium there is no generally accepted definition for cognitive dysfunction in ICD-10 or DSM-IV. Cognitive dysfunction is subtle and can only be detected with several neuropsychological tests, applied before and after surgery, that are more time consuming than delirium screening tools. Prospective studies should include a non-operative control group to obtain normative data: only a significant deterioration in cognition in the surgical population compared with the control group should be classified as postoperative cognitive dysfunction. What constitutes 'significant' is the topic of much discussion and varies with the type of test, when the tests are conducted and how the results are analysed. Cognition deteriorates after cardiac surgery in 3 in 10 to 8 in 10 patients, with deficits lasting several postoperative months in up to 6 in 10 patients [6, 7]. Approximately one in four elderly patients exhibits cognitive deterioration one week after non-cardiac procedures and 1 in 10 exhibits dysfunction three months after major surgery with general anaesthesia (Fig. 1) [8]. Rates are lower in younger patients and after minor surgery [9, 10].

Risk factors and aetiology

Age is the predominant risk factor for both postoperative delirium and cognitive dysfunction. Elective outpatient surgery is associated with lower rates of postoperative cognitive complications than major surgery. Patients with fractured hips are most likely to be delirious, but delirium is also common after cardiac surgery, peripheral vascular surgery and repair of abdominal aortic aneurysm.

Postoperative cognitive dysfunction is more frequent after cardiac surgery than non-cardiac surgery and is associated with the duration of cardiopulmonary bypass, valve surgery and poor cardiac function. It has been very difficult to verify whether cerebral embolisation is the cause – the rates of cognitive dysfunction are equivalent after coronary artery bypass surgery without cardiopulmonary bypass [11].

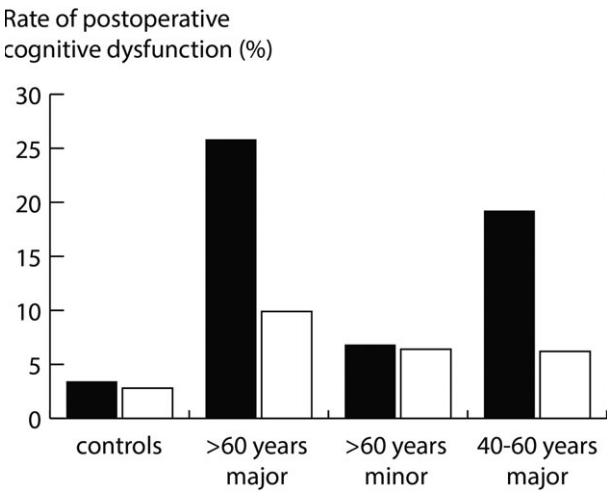

Figure 1 Rates of cognitive dysfunction in patients after non-cardiac surgery or controls not undergoing surgery, at 7 days (black) and 3 months (white) [8–10].

Cognitive dysfunction has been studied less after non-cardiac surgery. Early studies often failed to detect any cognitive dysfunction after non-cardiac surgery, particularly when applying methods used in cardiac surgery studies. Subsequent studies have identified factors associated with cognitive dysfunction, which in addition to age include a low level of education and postoperative complications, while the type of anaesthesia may be unimportant [8, 12]. Factors that predispose to cognitive dysfunction have been identified more easily than those that precipitate delirium [3].

Cardiopulmonary bypass and embolisation

Cardiopulmonary bypass is probably not the primary cause of cognitive dysfunction after cardiac surgery. Several studies have not shown a difference in the rates of cognitive dysfunction after cardiac surgery with or without cardiopulmonary bypass [11, 13]. However, cardiopulmonary bypass might be associated with an increased rate of delirium [14]. Structural alterations on magnetic resonance imaging seen after cardiopulmonary bypass were not apparent in patients who had cardiac surgery without bypass. The authors suggested cardiopulmonary bypass caused small emboli [15]. In contrast, no significant association was found between cognitive dysfunction and the number of micro-emboli detected by transcranial Doppler during knee surgery [16].

Hypoxaemia

Severe hypoxia damages the brain. Therefore, moderate postoperative hypoxia could contribute to cognitive dysfunction, but results have been inconsistent. One or more episodes of oxygen saturation below 80% for at least 2 min, within the first three postoperative days, was not associated with cognitive dysfunction in one study, whereas another study showed correlation between hypoxaemia five days after surgery and cognitive dysfunction [8, 17]. Postoperative hypoxaemia is associated with delirium [18].

Hypotension

Intra-operative hypotension, as a proxy for hypoperfusion, has often been blamed as a cause of postoperative cognitive deterioration. One or more 30-min episodes of mean arterial pressure less than 60% of the pre-operative baseline was not associated with postoperative cognitive dysfunction in two studies, totalling more than 1000 patients [8, 19]. Intra-operative hypotension is also not associated with delirium, whereas fluctuations in blood pressure may play a role [20]. However, a study of only 45 patients undergoing spine surgery showed an association between intra-operative hypotension and postoperative cognitive dysfunction in the subgroup of patients with pre-operative hypertension [21].

Inflammation and stress

Surgery is associated with activation of an inflammatory response syndrome and the release of cytokines that can impair brain function. Recurring episodes of peri-operative stress activates the hypothalamic–pituitary–adrenal axis for prolonged periods due to loss of inhibition [22, 23]. The general marker for inflammation, C-reactive protein, is also associated with delirium [24].

Neurotoxicity of anaesthetics

General anaesthesia changes animal brains, especially at a very young age [25, 26]. Several studies have shown an association between anaesthesia in childhood and subsequent cognitive disorders, learning problems and behavioural disability [27–31]. However, association does not prove causation. It is possible that developmental cognitive deficits arise from the disease that precipitated surgery, or factors that predispose to both the developmental abnormality and the operative disease. An epidemiological study concluded that lower academic performances in patients who have had surgery compared with people who have not had surgery are explained by factors present before surgery [32].

It has been suggested that avoiding general anaesthesia by using regional techniques preserves cognition, particularly in the elderly [33]. One systematic review reported no difference in the rate of cognitive dysfunction after regional anaesthesia compared with general anaesthesia beyond the first week [34]. However, this research area is challenged by the diversity in methodology and definitions, making it difficult to compare one study with another [1]. Few trials have compared different general anaesthetics; a small study reported no difference in cognitive performance after inhalational vs intravenous anaesthesia [35]. A recent study proposed that the rate of postoperative cognitive dysfunction was similar irrespective of the type of surgery or anaesthetic [36]. Nevertheless, a few studies suggest that inhalational anaesthesia may be associated with less postoperative cognitive dysfunction than total intravenous anaesthesia [37, 38].

More anaesthetic drug, or 'deep' anaesthesia, has been associated with an increased rate of postoperative delirium [39–42]. The rate of early cognitive dysfunction appears unaffected by the amount of anaesthetic given [39, 41, 43], whereas evidence is inconsistent for the rate of cognitive dysfunction at three postoperative months [39, 41].

Other peri-operative factors

It is difficult to identify which elements within the package of care received by surgical patients are linked to cognitive dysfunction, such as fasting, analgesics, sleep disruption, excessive or inadequate fluid administration and blood transfusion. Factors associated with postoperative delirium may be categorised as unalterable 'predisposing' factors, such as age and permanent brain damage, and modifiable 'precipitating' factors, which might be affected by careful medical optimisation and rational utilisation of resources [3, 44–47].

It has been suggested that 'fast track' surgery or enhanced recovery can reduce the rates of postoperative delirium and cognitive dysfunction [48, 49]. For instance, bladder catheters increase the rates of delirium, so one should aim to avoid their use or

remove them quickly [47]. Visual and hearing impairments are associated with delirium so it is rational to keep spectacles and hearing aids on as much as possible [47]. Analgesia should be titrated to effect as both pain and an excess of analgesics are related to delirium; it can be advantageous to involve geriatricians in the care of the elderly surgical patient.

Cerebral protection

Numerous animal studies have reduced the amount of brain tissue damaged by hypoperfusion and hypoxaemia by interventions that modify apoptosis, the release of excitatory transmitters, inflammatory mediators and other mechanisms, including scavenging free oxygen radicals. The application of these interventions in human trials has not been successful [50]. The mechanisms may be slightly different in humans and the timing for the interventions is usually crucial to their success. Patients often have important comorbidity that can modify the effects of interventions, in some cases as a result of ongoing medical treatment.

The consequences of postoperative delirium and cognitive dysfunction

Postoperative cognitive decline can have serious long-term consequences. Delirium is associated with increased mortality and institutionalisation [51]. The relevance of cognitive dysfunction may not be as apparent because a neuropsychological test score is not a clinical outcome. However, postoperative cognitive dysfunction is associated with impaired performance of activities of daily living [8]. Cognitive dysfunction may also be associated with an increased long-term mortality, premature withdrawal from the labour market and social transfer payments [2, 12]. There is a significant correlation between quality of life and 5-year cognitive function after cardiac surgery [52, 53]. It is unclear whether postoperative cognitive dysfunction is associated with, or predisposes to, dementia. No significant association has been found in two studies of subjects who completed neuropsychological testing on several occasions [54, 55].

Research and future studies

Research should concentrate on cohorts of frail elderly patients as they have a high rate of postoperative cognitive decline, often in addition to pre-existing cognitive impairment, while few published studies have included many elderly patients. A fuller understanding of the pathophysiology should enable the adoption of neuroprotective strategies in connection with special types of surgical procedures, such as cardiac surgery or neurosurgery.

It is difficult to isolate one aspect of peri-operative care in human studies, for instance how much anaesthetic interventions contribute to cognitive impairment compared with surgical interventions: individual factors can be more easily assessed in animal studies. General anaesthesia alone seems to cause apoptosis in the developing rodent brain and enhanced amyloid beta oligomerisation has been observed in vitro [25, 56, 57]. It seems that surgery triggers cognitive dysfunction in rodents that is associated with an inflammatory response in the hippocampus, which is not present in anaesthetised animals not undergoing surgery [58, 59].

Peri-operative studies confront several methodological problems that probably result in the underestimation of the incidence of postoperative cognitive damage. The question remains, 'How should we interpret the animal studies showing brain changes after anaesthetic exposure, and how do we improve clinical care to prevent serious postoperative cognitive complications?'

Competing interests

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