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Postoperative Cognitive Dysfunction: Current Developments in Mechanism and Prevention

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Postoperative cognitive dysfunction (POCD) is a subtle disorder of thought processes, which may influence isolated domains of cognition and has a significant impact on patient health. The reported incidence of POCD varies enormously due to lack of formal criteria for the assessment and diagnosis of POCD. The significant risk factors of developing POCD mainly include larger and more invasive operations, duration of anesthesia, advanced age, history of alcohol abuse, use of anticholinergic medications, and other factors. The release of cytokines due to the systemic stress response caused by anesthesia and surgical procedures might induce the changes of brain function and be involved in the development of postoperative cognitive dysfunction. The strategies for management of POCD should be a multimodal approach involving close cooperation between the anesthesiologist, surgeon, geriatricians, and family members to promote early rehabilitation and avoid loss of independence in these patients.

MeSH Keywords: **Anesthesia • Behavior and Behavior Mechanisms • Cognition • Postoperative Complications**

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Background

Postoperative cognitive dysfunction (POCD) is a subtle disorder of thought processes, which may influence isolated domains of cognition such as verbal memory, visual memory, language comprehension, visuospatial abstraction, attention, or concentration [1,2]. It is to be distinguished from postoperative delirium, which tends to be a transient and fluctuating disturbance of consciousness that tends to occur shortly after surgery, whereas POCD is a more persistent problem of a change in cognitive performance as assessed by neuropsychological tests [3,4]. The extent of cognitive deterioration following surgery and anesthesia has a significant impact on patient health and is substantially associated with prolonged hospital recovery, greater morbidity, and delays in functional recovery [5]. Most studies suggest that elderly patients are at higher risk of developing POCD than young patients [6–9]. With the advances in surgical and anesthetic techniques, and in combination with the increased life expectancy, POCD is becoming an area of focus in hospitals.

Incidence and Diagnosis

POCD affects a wide variety of cognitive domains, such as memory, information processing, and executive function [10–12]. In the beginning, patients usually complain about deterioration of memory, and some patients even find it hard to work effectively [13]. It is usually not apparent right after surgery, and in many cases is not detected until the patient, family members, or colleagues note that the patient is having difficulties with normal activities at home or work [10–12].

The reported incidence of POCD varies enormously depending on the definition, composition of the test battery, and time of postoperative assessment. The incidence after cardiac surgery is reported to be 30–80% a few weeks after surgery and 10–60% after 3–6 months [14–19]. In a well-designed observational study in 1218 patients more than 65 years of age with non-cardiac surgery, Moller et al. explored the risk factors of POCD in these older patients in comparison with 321 controls who did not undergo an operation but were also repeatedly tested with neuropsychological tests. This study found that 1 week after surgery, the prevalence of POCD was 26%, decreased to 10% at 3 months postoperatively, and a similar prevalence was found 12 months after the operation. In the nonsurgical controls, a 3% incidence of POCD was found at every time interval [20].

Cognitive performance tests are the main approach to diagnose POCD in patients after surgery. However, to date there are no formal criteria to use in assessing and diagnosing this mental disorder associated with surgery, and there is no ideal test internationally accepted to diagnose POCD [12,21]. The problems of the current cognitive tests include the limitations of specificity and sensitivity. Some of the tests are not able to specifically detect the minor changes of brain functions and cognitive performance in patients with POCD [22]. To compensate for these limitations, it is highly recommended that various tests should be performed to determine the cognitive disorders after surgery. These tests should cover various domains of cognitive function, such as memory, concentration, orientation, mathematical functions, and executive functions. Moreover, considering the differences in basic cognitive functions between individuals, it would be useful to perform cognitive tests pre- and post-operatively to determine changes of cognitive functions in the same patient after surgery [23].

The methods that have been used to detect postoperative cognitive impairment include interviews, questionnaires, mental status exams, and neuropsychological tests [8,24]. Tests of mental status are the most frequently used methods of assessing cognition in postoperative recovery studies [25–27]. The most common of these is the Mini-mental status exam (MMSE) [28]. However, neuropsychological testing provides the most reliable and sensitive indicator of postoperative cognitive impairment [29].

Risk Factors of Developing POCD

In general, larger and more invasive operations such as abdominal, thoracic, and vascular surgery, present a greater risk than smaller, simpler procedures such as outpatient surgery [30]. Cardiac surgery and specific orthopedic procedures are interventions with a relatively high incidence of POCD [31–33]. The high incidence of POCD in cardiac patients has been attributed to microembolic events during the use of the cardiopulmonary bypass pump [34]. These microembolic events may cause focal cerebral infarcts leading to postoperative cognitive impairment [35–37]. Fat emboli have also been reported to be an important factor resulting in postoperative cognitive impairment in patients [38,39].

Irrespective of the type of surgery, advanced age is a major risk factor of POCD [31,32,40,41]. The ISPOCD1 study analyzed the risk factors for POCD in patients with non-cardiac surgery and found that the incidence of POCD at 3 months after surgery was 7% in patients aged 60–69 and 14% in those over 69 years old [20]. Advanced age is characterized by impairments in the function of the many regulatory processes, including increased physical and mental frailty and decreased ability to cope with stresses such as anesthesia and surgery. Advanced age is also accompanied with pharmacokinetic and pharmacodynamic changes, including reduction in renal and hepatic clearance, prolonged elimination half-life, and altered drug sensitivities [42]. Furthermore, older people more frequently have multiple conditions/impairments such as diabetes, renal insufficiency, and cardiovascular diseases, which increase the

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risk of a perioperative complication. The POCD incidence data in younger populations is limited. In a study of 508 patients between 40 and 60 years of age, a prevalence of 6% was reported 3 months after non-cardiac surgery, while the prevalence reported in nonsurgical controls was 4% [43].

The type of anesthesia might not contribute to the development of POCD. A study comparing regional versus general anesthesia in patients over 60 years old who have had major non-cardiac surgery has, surprisingly, found that there was no significant difference in the incidence of POCD at 3 months after surgery between general and regional anesthesia [44]. These results suggest POCD might be not related to the type of anesthesia.

A history of alcohol abuse is also a risk factor for POCD [45]. Use of anticholinergic medications (e.g., atropine and scopolamine) or medications with anticholinergic properties (e.g., tricyclic antidepressants and benzodiazepines) are commonly suggested to be involved in precipitating postoperative cognitive impairment [46,47]. Opiate medications (e.g., morphine, codeine, and meperidine), which also have anticholinergic properties, can contribute to short-term postoperative impairment [48].

Other risk factors for POCD might be: previous cerebral vascular accident, previous POCD, poor cognition, respiratory complications, infectious complications, and second operation. It was also found that well-educated patients experienced less POCD after surgery [20].

Potential Mechanisms of POCD

The majority of the research in this field has focused on cardiac surgery. Although the causes of POCD in cardiac surgery are multifactorial, the use of cardiopulmonary bypass has often been suggested as the major contributor to the problem. However, more and more studies have shown that off-pump cardiac surgery produces a similar effect on neuropsychological performance to that with the use of cardiopulmonary bypass [49–51]. Studies have shown that brain injury induced by cardiac surgery might be prevented by decreasing core body temperature. Cardiac surgeons have commonly used hypothermia during open heart surgery to reduce the metabolism and to minimize damage to vital organs during the surgery. Patients need to return to a normothermia after surgery, but neurons may be injured during the process of rewarming to normothermia due to inflammatory processes. It has also been shown that rapid rewarming may force anesthetic and other gases out of solution and thereby produce microemboli. All these procedures can result in the development of POCD. In a rat model of cardiopulmonary bypass, it has been reported that limited rewarming and prolonged postoperative hypothermia decreased the incidence of POCD [11].

In contrast to cardiac surgery, the study of POCD in non-cardiac surgery, especially the involved mechanisms, is in its infancy. One of the earliest explanations for postoperative cognitive impairment in non-cardiac surgery was hypoperfusion or hypoxia of the brain due to the systemic hypotension or blood loss during surgery [52]. However, in the ISPOCD1 study, no statistically significant correlation was found between hypoxemia or hypotensive episodes and POCD [20].

Postoperative pain has been found to be associated with postoperative cognitive impairment [53,54]. A change from a familiar environment and sleep deprivation after surgery can be particularly distressing for elderly patients and is known to impair performance on cognitive tests. These are possible reasons that may contribute to POCD in the elderly [55,56].

Fundamental studies have identified several pathways that might be involved in the development of POCD. The systemic stress response caused by surgical procedures and anesthesia induces the release of neuroendocrine and changes related to neuroinflammation, which may influence neuronal functioning either directly or through modulation of intraneuronal pathways, such as the brain-derived neurotrophic factor-mediated pathway [57]. Animal studies using a rat model demonstrated the association between the inflammatory response in the hippocampus and POCD [58]. The orthopedic surgery and anesthesia-induced hippocampal-dependent memory impairment in a mouse model has also been found to be associated with increased plasma cytokines and the activated interleukin-1β pathways in the hippocampus [59]. Further study has shown that isoflurane alone activates the interleukin-1β pathway and causes cell injury in the hippocampus, which may contribute to isoflurane-induced cognitive impairment in animal models [60]. A review by Hua et al. found that leptin, a hormone made by adipose cells, plays an essential role in promoting structural and functional activities in the nervous system, and proposed that the leptin signaling pathway may have bearing on the pathogenesis of POCD [61].

Animal studies have also suggested that cell apoptosis in the brain might be involved in the development of POCD. Yon et al. reported that general anesthesia induces neuronal cell death in the developing rat brain via the intrinsic and extrinsic apoptotic pathways. Anesthesia-induced apoptotic neurodegeneration might also be a potential pathway mediating the development of POCD in the older brain [62].

Treatment and Prevention

The optimum treatment of POCD is still unclear, and the best treatment seems to be prevention. It is important to recognize and work on potential preoperative risk factors. It is also necessary to inform patients of the occurrence of POCD after

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surgery and reassure them about the recovery of these disorders in the following months. Moreover, a physiological day-night rhythm, social contacts, a short period of fasting before surgery, frequent visits by family and friends after surgery, and early discharge from hospital might be useful to reduce the incidence of postoperative cognitive impairment [63,64]. In parallel, nutritional status and hydration should be systematically evaluated preoperatively because these are factors associated with risk of emergence of POCD.

The strategy for the treatment of patients with POCD should involve close collaboration between surgeon and anesthetist to reduce the time between intake of these patients and their care in the operating room, choosing the anesthetic and surgical techniques most suited to the patients to allow them to have a functional rehabilitation as early as possible [65]. Studies suggest that surgical technique can affect the cognitive recovery of POCD patients, especially if the surgical technique chosen is short (decreased inflammatory response) with no use of cements [66,67]. In cardiac surgery, less invasive operations usually lead to lower incidence of POCD. Also, prolonged mild hypothermia and slow rewarming procedure might prevent the development of cognitive dysfunction after cardiac surgery [49].

The overall multidisciplinary care of these patients can improve the prognosis and reduce the incidence of POCD [68].

Adequate pain treatment after surgery might also be associated with lower incidence of POCD. Wang et al. reported in a clinical study that older patients who received oral postoperative analgesia were at significantly lower risk for the development of POCD in [69].

Conclusions

Anesthesia today is, in general, very safe; however, there are some risks for anyone undergoing surgery and anesthesia, especially for older patients. POCD is one of the most prominent complications and is also feared by elders undergoing anesthesia and surgery, as POCD might result in being long-term or even permanent dependence on social care systems in some patients [2,44]. Strategies for management of these patients should be a multimodal approach involving close cooperation between the anesthesiologist, surgeon, geriatricians, and family members to promote early rehabilitation and avoid loss of independence in these patients. Future clinical and basic research focusing on the mechanisms and pathways involved is critical for better understanding and management of this cognitive dysfunction after surgery.

Conflict of interests

None.

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