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Review Article

Difficulties in Understanding Postoperative Cognitive Dysfunction

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ABSTRACT

Aim of review: Firstly brought up by Bedford in 1955, postoperative cognitive dysfunction (POCD) has been given increasing attention due to the increase of the elderly population. Although many researches have been conducted on POCD, the understanding of this clinical syndrome is still limited. There are currently many disputes regarding almost every aspects of POCD, even the term itself has not been included in the MeSH Database. This review aims to discuss the major disputes about POCD that hinder research consistency and provide possible perspectives for future research.

Method: Recent articles and literatures about POCD were searched and reviewed. First, basic knowledge of POCD, including characteristics and incidence, risk factors, mechanisms, prevention and intervention are introduced. Second, the major obstacles of investigating POCD are discussed. Then two major problems are proposed: 1) Does the POCD in patients really start postoperatively? 2) Is POCD only related to old age? Finally, the never-ending argument regarding the role of anesthesia on POCD is discussed.

Recent findings: Recent researches regarding POCD focused on the surgery-related neuroinflammation mechanism, and efforts have been made to find some biomarkers of POCD. In terms of POCD, there are many fundamental concepts and in urgent need of consensus. First, unifying the terms used among studies will benefit the communication of knowledge. Second, questions like whether POCD should be defined as a general cognitive decline that include other forms such as postoperative delirium, or they should be considered as separate unique illnesses, and whether or not young patients should be included when POCD is discussed, need to be answered. Only after answering these questions, will the study of POCD be less disputable. Third but not the least, efforts should be made trying to make "golden-standard" in regard of the testing methods of POCD both clinically and pre-clinically.

Summary: Although lots of researches have been conducted on POCD, the understanding of this clinical syndrome is still very limited. There are currently many disputes regarding almost every aspect of POCD. It's time for clinicians and scholars to strike some fundamental consensus for the better investigation of POCD. How to find a way to increase the rigor of experimental design is an important question that still seeks answers.

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Firstly brought up by Bedford in 1955, postoperative cognitive dysfunction (POCD) has been given increasing attention due to the increase of the elderly population. Although many researches have been conducted on POCD, the understanding of this clinical syndrome is still limited. There are currently many disputes regarding almost every aspects of POCD, even the term itself has not been included in the MeSH Database. This review aims to discuss the major disputes about POCD that hinder research consistency and provide possible perspectives for future research.

Basic Knowledge of POCD

Characteristics and Incidence

POCD is a multifactor syndrome seen mostly in elderly patients who underwent major surgeries and is characterized as declines in memory, concentration and information processing after surgery (1). It has a bimodal incidence including a reversible decline during the early postoperative period and a delayed cognitive decline 3 to 5 years later which may be relevant to dementia (2). Although 60 years have passed since POCD was firstly brought up, there is currently no International Classification of Diseases, 10th Revision code (ICD-10) for POCD, and there are also no specific diagnostic criteria for POCD in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V).

The types of surgery are usually divided into cardiac surgery and non-cardiac surgery when POCD was studied. It's now been widely accepted that the incidence of POCD is higher in patients after cardiac surgery when compared with that of non-cardiac surgery. According to the International Study of Post-operative Cognitive Dysfunction (ISPOCD1), the incidences of POCD in elderly patients who underwent major non-cardiac surgery were 25.8% at one week after surgery and 9.9% at three months after surgery, respectively (1). In case of cardiac surgery, the incidence of POCD was as high as 40% (3). Besides, the duration of POCD was mostly transient, however, it can be persistent especially among elderly patients aged over 65 (4).

Risk Factors

Typically, the risk factors of POCD can be divided into three groups: patient-relevant, surgery-relevant and anesthesia-relevant factors (Table 1). The patient-relevant risk factors reported in previous studies included little education (1), preoperative silent brain ischemia (5), preoperative subclinical dementia (6), pre-existed metabolic syndrome (7), hereditary vulnerabilities such as apolipoprotein E4 (8, 9) which is a gene polymorphism of apolipoprotein E, and obesity (10), etc. The possible anesthesia-relevant risk factors included premedication, specific inhaled or intravenous anesthetic agents, the duration and depth of anesthesia, and the imbalances of internal environments such as intraoperative hyperglycemia in non-diabetic patients (11), etc. The surgery-relevant risk factors included second operation, postoperative complications (1) and surgery-induced neuroinflammation (12), etc, and the last one has gained lots of attention in recent years.

However, it's frustrating to say that after all these years of research, maybe the only risk factor of POCD we have known for sure is the increasing age (13). Tim Johnson et al. (14) reported that the incidences of POCD among middle-aged (40-60 years old) patients at 7 days and three months after surgery were 19.5% and 6.2%, respectively, a little lower than those of the elderly patients. Other risk factors mentioned above are all controversial to some extent. For example, intraoperative hypotension and hypoxemia were not considered as risk factors of POCD in the studies done by Moller et al. (1), whereas reported to be related to POCD in later studies (15, 16).

Mechanisms

The possible mechanisms of POCD investigated included platelet activation (17), oxidative stress (18), cholinergic function impairment (19,20), impairment of synaptic integrity (2, 21), similar mechanisms of Alzheimer's disease (AD) such as beta-amyloid accumulation (22, 23) and tau phosphorylation (24), and immune response and inflammation related mechanisms such as the bone marrow-derived macrophages recruitment in hippocampal area (25) and the recent popular surgery-induced neuroinflammation (12, 26, 27) (Table 2).

Platelet activation was investigated among pa-

tients underwent cardiopulmonary bypass (CPB) surgery (28). Transcerebral platelet activation gradients were examined by using three markers of platelet activation. Statistics showed a relationship between the increased transcerebral gradient of P-selectin (CD62P) and the incidence of post-CBP cognitive decline. As the immediate marker of platelet activation, P-selectin mediates leucocyte-platelet cell adhesion (29). Gene variants of P-selectin, SELP 1087G/A SNP, were associated with the susceptibility to cognitive deficits after cardiac surgery (29). Compared with non-cardiac surgery, cardiac surgery has a high risk of embolic events. Due to the current lack of researches investigating the relation of platelet activation and the cognitive decline after non-cardiac surgery, whether platelet activation plays its role as a part of coagulation process or as a component of inflammatory and immune process is still uncertain.

Jiang et al. (30) found that oxidative stress can lead to neural injuries and was widely studied in various neurodegenerative diseases. Compared with non-POCD rats, the malondialdehyde (MDA) level was significantly higher and the activity of superoxide dismutase (SOD) was significantly lower in rats developing POCD (13), which were both the markers of oxidative status. Using proteomic analysis, Li et al. (31) reported that the expression levels of four oxidative stress related proteins including SOD1, glutathione S-transferase P (GSTP1), peroxiredoxin 2 (PRDX2) and aldose reductase (ADR), were significantly changed in POCD rats. Wang et al. (32) proved that Edaravone, a free radical scavenger, had protective effects on cognitive impairment, and its protective effects may act through anti-oxidant mechanism.

Cholinergic neurotransmitter, acetylcholine, is widely distributed within the brain. Cholinergic pathway participates in various cognitive processes including short-term memory, learning and attention (33). The deterioration and impairment of central cholinergic system is not only related to normal aging (33), but also to neurodegenerative diseases such as AD (20). Cholinesterase inhibitors have been shown to improve cognitive function (20). Several clinical studies showed that drugs with anti-cholinergic effects had negative effects on the cognitive function of patients (33-35). Thus, it's possible that cholinergic function impairment may participate in the development of POCD.

Synapsin (SYN) and postsynaptic density protein (PSD)-95 are markers of synaptic function. Several studies have shown that the decrease of SYN (2) and PSD-95 (21) were both related to cognitive impairment, suggesting that there exits synaptic integrity impairment during POCD. However, whether synaptic impairment is caused directly by surgery and anesthesia, or induced by neuroinflammation, is still unknown.

Researches regarding POCD often focus on the relationship and similarity of POCD and AD. Many studies investigating the mechanisms and biomarkers of POCD have resorted to the same ones of AD. Review articles of POCD tended to discuss them together when introducing the mechanisms and intervention of the mentioned diseases (20, 36). Recently, studies have focused on trying to find biomarkers that can predict POCD before surgery (23, 37, 38). These studies resorted to amyloid β (Aβ), a biomarker for AD, and tried to find a relationship between the change of Aβ and the risk of developing POCD. However, although the two diseases all caused cognitive dysfunction, there are still huge differences between them. After all, most of POCD are much more subtle and transient than AD, although it may have some influences 5 years later (39). Thus, efforts should be made to find specific biomarkers of POCD.

The relationship between neuroinflammation and POCD has gained lots of attention in recent years. Surgery can lead to blood-brain barrier dysfunction and induce systemic inflammatory response (12, 26). There is a detailed review of this mechanism described by Vacas et al. (27). Although various possible mechanisms of POCD have been brought up, the exact role of each mechanism and how they interact with each other are still not known.

Prevention and Intervention

Preoperative environmental enrichment has been reported to play a protective role in the neuroinflammation and memory impairment of elderly animals (40). Proper exercise also has anti-inflammation effects (41). Since the exact mechanisms and pathological reasons of POCD

are still unclear, there are currently no specific prevention and intervention routines of POCD. What's more, old age, the definite risk factor of POCD, seems by no means preventable.

However, it does not mean that nothing can be done about it. Generally, efforts should be made trying to maintain stable internal environment during the perioperative period, such as water and electrolytes balance, normal blood pressure, proper blood glucose and sufficient oxygen supply. Although the effects of monitoring anesthesia depth with bispectral index (BIS) are still disputable, adding this monitor index to patients at high risks can at least help to maintain stable and proper anesthesia. Also, minimal invasive surgery and some anti-inflammation drugs may have protective effects.

Besides, it was reported that specific intravenous anesthetic drugs had neuroprotective roles (42). Thus, when dealing with patients at high risks of POCD, cautious selection of drugs can have some benefits. More detailed information regarding the prevention and treatment of POCD can be found in previous reviews (43, 44).

Major Obstacles of Investigating POCD

Definition

As mentioned above, the term "POCD" has not been included in the MeSH Database yet, which increases the difficulty of document retrieval, thereby hindering researchers' knowledge acquirement. Many different names were used referring to this same clinical issue, such as postoperative cognitive decline (2), postoperative cognitive disorders (45), surgery-induced cognitive dysfunction, age-exacerbated cognitive dysfunction (46), and mild transient cognitive decline (7), etc.

A consensus agreement on assessing the neurobehavioral outcomes of patients after cardiac surgery was published in 1995 (47). The major principles approved in this statement still guided present studies of POCD, such as, there should be pre- and post-operative neuropsychological tests, avoiding ceiling and floor effects, etc. However, the specific diagnostic criteria of POCD are still lacking. Besides, cognition itself includes many brain functioning processes, and the vague description of the characteristics and the lack of specific diagnostic criteria may consequently lead to the inconsistent results between studies. For example, in the research of Price et al. (37), it was specifically pointed out that POCD was a different clinical syndrome compared with delirium. However, in the research of Feng et al. (7), postoperative delirium was defined as the temporary form of cognitive decline and POCD as the persistent form.

Likely, although delirium is clearly defined in DSM-V and ICD-10, the term "postoperative delirium" has not been included in the MeSH Database, either. It is characterized as an acute mental status with reduced attention and disorientation (48), which can also be presented during POCD. From the author's point of view, delirium is also a form of cognitive change, unless it can be distinguished from POCD with specific symptoms or neuropsychological tests, and it can be considered as a subtype within the definition of cognitive dysfunction.

Difficulties of Clinical and Animal Research

Clinical research of POCD has one major shortcoming, that is, the effect of surgery and the influence of anesthesia cannot be fully distinguished under most circumstances, since they often accompany each other (49). And there are also difficulties in setting up non-surgery or non-anesthesia control group (7). Conducting surgeries without anesthesia is impossible, while conducting anesthesia without surgeries is unethical. Usually, POCD is detected through neuropsychological test batteries which typically include five to eight individual tests (6, 49). There are many disadvantages of these tests, such as practice effects, ceiling and floor effects, the characteristics of subjectivity and the problems of interpreting different results (50). Besides, there are many inconsistencies between studies, for example, Mini Mental State Examination (MMSE), the clinical test most commonly used to screen subjects who meet the exclusion criteria, were used differently among studies (49, 51). The exclusion criteria were MMSE score$\leqslant$23 (51) and MMSE score$\leqslant$25 (49), respectively. This seemingly minor difference can add to the difficulty in interpreting different results and comparing different studies.

When it comes to animal research, needless to say, the major flaw is that the memory and ex-

ecutive function of rodents reflected in Morris Water Maze (MWM) and Fear Conditioning Test, the most commonly used testing methods of POCD, cannot fully represent the exquisite cognitive function of mankind. What's more, behavioral tests are too lack of uniform standards, making it even harder to interpret the results. For example, Stratmann et al. (52) concluded that anesthesia with isoflurane did not impair the cognitive function of old rats, nor did it cause brain cell death. In the MWM test performed in their experiment, rats were allowed to stay on the platform for 20 seconds if they successfully found it, and the interval between the two daily sessions was 5 hours, and rats were trained for 6 days. However, conflicting results were concluded by Zhang et al. (22) that cognitive function of old rats was impaired by isoflurane anesthesia. The MWM test was performed differently in this experiment: rats were allowed to stay on the platform for 60 seconds if they successfully found it, and the interval between the two daily sessions was not mentioned, and rats were trained for 5 days.

Table 1. Risk factors of POCD

Categories	Possible risk factors
Patient-relevant	Little education;
	Preoperative silent brain ischemia;
	Preoperative subclinical dementia;
	Pre-existed metabolic syndrome;
	Hereditary vulnerabilities
Anesthesia-relevant	Premedication;
(Possible, not definite)	Specific anesthetic agents;
	Duration and depth of anesthesia;
	Imbalances of internal environments;
Surgery-relevant	Second operation;
	Postoperative complications;
	Surgery-induced neuroinflammation

Table 2. Possible mechanisms of POCD

platelet activation
Oxidative stress
Cholinergic function impairment
Impairment of synaptic integrity
Beta-amyloid accumulation and tau phosphorylation
Immune response and inflammation
Bone marrow-derived macrophages recruitment
Surgery-induced neuroinflammation

Does POCD in Patients Really Start Postoperatively?

Although there is a "post" in the definition of POCD, it's uncertain whether there was preoperative cognitive decline which was exacerbated postoperatively, or it may simply be a part of the ongoing preoperative pathology (53). Silbert et al. (54) found that there was a relationship between preoperative cognitive impairment and POCD. In some seemingly healthy people, preoperative silent brain lesions shown in magnetic resonance imaging (MRI) are related to a higher incidence of subsequent stroke and dementia (55, 56). Since neuropsychological tests and MRI are not routinely conducted before surgery, subtle change of cognitive function or minor brain lesions may be neglected, which further increased the research difficulty of POCD. As reviewed by Vacas et al. (27), some studies suggested that dementia and AD may be accelerated by surgery, and it's hard to distinguish whether the cognitive decline of one specific patient is POCD or the exacerbation of neglected preexisting diseases. To the author's point of view, it's meaningful to separate this two circumstances, for that most POCD is transient and reversible, whereas dementia and AD can lead to more severe and progressive cognitive decline.

Is POCD Only Related to Old Age?

Until now, most studies on POCD have been focused on adults, especially elderly patients (1, 8, 19). Morgan et al. (57) were the first to focus on the neuropsychological effects of general anesthesia on pediatric patients, namely, 5 years old children, and reported that children would present cognitive decline after anesthesia with halothane or nitric oxide. From then on, there were less than 10 studies published investigating POCD of children (58). Millar et al. (59) studied day-case surgery of 5 to 14 years old children and found that intravenous anesthesia with propofol or inhalation anesthesia with isoflurane both significantly affect children's cognitive function, but the influence was subsidized after 24 hours. This study didn't have control group and only investigated the influence on cognitive function shortly after surgery, what's more, they did not use premedication to exclude their potential

effects on POCD. Another study focused on children with similar ages tested their psychological function on Day 1 and 6 weeks after surgery (60) did not find a relationship between anesthesia and POCD, and they reported that only visual matching impairment was presented on Day 1 after surgery. This study included more individuals and used premedication which could ease the anxiety and fear of children before surgery and may therefore influence their postoperative performance. However, this study used multiple anesthetic drugs during anesthesia induction and maintenance, making it harder to just compare the effects of specific anesthetic drugs.

Although the influence on cognitive function seems only persisted for a short time, studies of adult POCD suggested that the transient cognitive decline after surgery was correlated with cognitive decline 5 years later (39), and that the acute memory deterioration happened postoperatively could result in persistent cognitive decline (61). It's hard to say cognitive function of children who present POCD after surgery will definitely not be affected several years later. Besides, the lately published article of Hu et al. (58) reported that the plasma β- amyloid (Aβ) levels were decreased after cardiac surgery of children less than 3 years old. Aβ levels are biomarkers of AD (22) and were reported to be associated with POCD both in clinical researches (23) and animal studies (62). Thus, the study performed by Hu et al. (58) implicated that POCD could also occurred in young patients.

Also neurodevelopmental impairment occurred in almost one in three neonates who underwent surgery (63). DiMaggio et al. (64) reported that the increase of the risk for neurodevelopmental disorders was related to early exposure of anesthesia. The latest clinical article regarding this issue was reported by Davidson et al. (65). This randomized clinical trial compared the neurodevelopmental influence of sevoflurane anesthesia and awake- regional anesthesia on infants less than 60 weeks of age who underwent surgery. The secondary outcomes did not show a significant difference regarding the neurodevelopmental status between the two groups. However, this trial did not include a non- surgery control group, and the primary outcomes of this trial are still lacking, thus, a definite conclusion cannot be drawn from this trial yet. As mentioned above, POCD happened at early period can impact cognitive function even some years later, and lots of researches suggested a correlation between POCD and the risk of dementia (66). Meanwhile, we cannot exclude the possibility that POCD may also increase the risk of neurodevelopmental problems among children. After all, the US Food and Drug Administration (FDA), SmartTots and the American Academy of Pediatrics (AAP) reached an agreement and issued a consensus statement that avoidance should be made regarding the elective surgery with anesthesia of children under 3 years old (67). What's more, focusing on infants at this young age (65) means the authors cannot test the baseline status before surgery, making it harder to interpret its results.

The Never- Ending Argument Regarding the Role of Anesthesia on POCD

The specific effects of anesthesia on POCD seem full of arguments, due to the difficulty of investigating anesthesia alone without surgery. Culley et al. (68) pointed out that general anesthesia with isoflurane and nitrous oxide could impair the spatial memory of old rats, and this impairment could last until 2 weeks later, which could not be attributed to the drugs' pharmacokinetic. Amyloid-β oligomerization (69) was enhanced and phosphorylated tau levels (70) were increased by isoflurane anesthesia, suggesting a toxic effect of isoflurane. Similarly, sevoflurane anesthesia was found to increase tau phosphorylation and associated with spatial memory decline by Le Freche H et al (24), however, in another study by Callaway KJ et al (71), anesthesia with sevoflurane did not cause cognitive dysfunction in young adults or old rats. Both studies used Morris Water Maze to test the cognitive function of experimental animals, but there were differences between experimental procedures and animals in use.

In a clinical study, Silbert et al. (49) compared general anesthesia and spinal anesthesia, and they found no significant differences of POCD incidence and concluded that the effects of anesthetic drugs on POCD was limited. However, Radtke FM et al. (72) found that monitoring the

depth of anesthesia by BIS could decrease the rate of postoperative delirium, suggesting a role of anesthesia on cognitive function. Other studies suggested a protective effect of intravenous anesthetic drugs (42). In conclusion, many studies investigating the effects of different anesthetic drugs or techniques on cognitive function have yielded conflicting results. To solve this complicated puzzle, there still needs further studies with rigorous experimental design.

Anesthesia, an inseparable element of surgery, certainly has protective effect. By eliminating pain, sedating the body, and suppressing stress response, etc., anesthesia makes surgery possible. Investigating the potential detrimental effects of anesthesia on cognition does not mean that anesthesia is harmful and should be avoided. In contrast, understanding the specific effects of anesthetic drugs or techniques on cognitive function will lead to further improvement of anesthetic drugs and the best selection of anesthetic techniques, therefore to minimize the cons and maximize the pros.

Conclusion

In terms of POCD, there are many fundamental concepts, and in urgent need of consensus. First, unifying the terms used among studies will benefit the communication of knowledge. Second, questions like whether POCD should be defined as a general cognitive decline that include other forms such as postoperative delirium, or they should be considered as separate unique illnesses, and whether or not young patients should be included when POCD is discussed, need to be answered. Only after answering these questions, will the study of POCD be less disputable. Third but not the least, efforts should be made trying to make "golden-standard" in regard of the testing methods of POCD both clinically and preclinically, such as how many tests of battery and which ones should be used to define cognitive decline during clinical practices, and which is the best way to perform a Morris Water Maze, etc. Making consensus of these issues can reduce the inconsistency among studies and help with the comparison and interpretation of different results. Besides, the specific effects of different anesthetic drugs on cognitive function are still in urgent needs of further investigation. How to find a way to increase the rigor of experimental design is a question that still seeks answers.

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