

Neuroinflammation and Postoperative Cognitive Dysfunction: What Do We Know?

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Following the initial publication by Bedford in 1955 (1) that the older people exhibit cognitive decline after surgery, postoperative cognitive dysfunction or decline (POCD) has become a recent focus in perioperative medicine. POCD is a common and well-known complication after anesthesia and surgery, especially for the elderly (≥ 60 years) (2). It occurs not only after cardiac surgery but also non-cardiac surgery (e.g., abdominal and orthopedic surgery) or even noninvasive procedures with sedation (2-5). In fact, anesthesia and surgery-induced long-lasting cognitive deficits has gained significant public concerns over the last decade because it is associated with poor patient outcomes, including increased hospital stay, reduced quality of life, loss of social dependence, and increased mortality (2-6).

POCD affects a wide variety of cognitive domains, such as attention, memory, executive function, and speed of information processing (3-6). Detection of POCD requires a sensitive battery of neuropsychological tests performed before and after surgery. Cognitive dysfunction can occur in all age groups at hospital discharge after major non-cardiac surgery, but only the elderly are at significant risk for long-term cognitive problems (2). The incidence of POCD varies widely from 41-75% at 7 days to 18-45% at 3 months postoperatively (2, 3, 6, 7). The wide range of prevalence is due to the inconsistencies in defining and quantifying what actually constitutes significant cognitive dysfunction as well as the diversity in the time and method of neuropsychological tests (7). There are many risk factors for the development of POCD. Among them are preoperative elements, including advanced age, lower education level, diabetes, a history of cerebral vascular accident with no re-

sidual impairment, and severe atherosclerotic disease (3). Intraoperative hypotension, hypoxia, medications, postoperative infections, and reoperation have also been reported to increase the likelihood of developing POCD (3, 7). However, the most significant risk factors for POCD are the increasing age and extent of surgical trauma (3, 7). Despite the great progress in POCD, the underlying mechanisms leading to POCD remain largely to be determined.

Accumulating evidences have demonstrated that neuroinflammation plays a substantial role in the pathogenesis of POCD (8-15). Systemic pro-inflammatory cytokines in response to aseptic surgical trauma disrupt the blood-brain barrier integrity, facilitate the migration of macrophages into the brain parenchyma and induce subsequent neuroinflammation (16). Importantly, the peripheral immune system has several modes of communication to the brain, and a peripheral stress (such as surgery) is able to result in de novo production of pro-inflammatory cytokines within the brain (17). In addition to surgical trauma, anesthetics, such as isoflurane, can also up-regulate pro-inflammatory cytokines, including tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1), and IL-6, in mouse neurons (18). Interestingly, another study has demonstrated that surgery under general anesthesia induces neuroinflammation and cognitive impairments, independent of the anesthetic choices (19), suggesting that surgery is the major stimulus for postoperative neuroinflammation and cognitive impairments. Although postoperative neuroinflammation in response to peripheral trauma may resolve properly with no consequence, it is capable of interfering with processes required for learning and memory via interruption of long-term potentiation in the hippo-

campus (20). Animal studies have shown that the development of POCD is associated with significantly enhanced expression of pro-inflammatory cytokines, including TNF- α , IL-1, IL-6, and high-mobility group box 1 protein (HMGB1) (8-15). Several lines of evidence have demonstrated that primed microglia are the main cellular source for this amplified neuroinflammatory response in the development of POCD (5, 21). Pro-inflammatory cytokines, in particular IL-1 β , is considered to be a viable target to interrupt the POCD pathogenesis, as IL-1 β -mediated inflammation is triggered by peripheral surgery-induced innate immune response (10). Importantly, specific blocking of the IL-1 β production or IL-1 transmission prevents neuroinflammation and the development of POCD (10, 13, 22). In addition, in mice model, treatment with prophylactic administration of either a monoclonal antibody to TNF- α or disabling HMGB1 with a blocking monoclonal antibody can also improve this postsurgical cognitive decline (11, 12). Notably, resolving postoperative neuroinflammation by aspirin-triggered resolvin D1 ameliorates memory decline and abolishes signs of synaptic dysfunction after peripheral orthopedic surgery (20). Also, inhibition of inflammation reduces learning and memory impairment after surgery (4, 23). Finally, IL-1 β and IL-6 can impair the trafficking of glutamate receptors to the plasma membrane (8), a basic biochemical process for learning and memory. These lines of evidence suggest that neuroinflammation is a significant pathological process for POCD.

In line with the results obtained from animal studies, anesthesia and surgery induced a robust neuroinflammatory response in humans, as evidenced by the enhanced expression of pro-inflammatory cytokines, such as TNF- α , IL-1 β , IL-6, IL-8, and HMGB1 (14, 15, 24-27). Furthermore, the development of POCD is also associated with neuronal injury markers, including S100 calcium-binding protein B (S-100 β), glial fibrillary acid protein, and neuron-specific enolase concentrations (25-27). For example, elevated levels of the pro-inflammatory cytokines, such as IL-6, and S-100 β protein, were detected in elderly patients who developed POCD after total hip replacement (24). However, another study indicated that the decline in

cognition at 1 month after shoulder surgery is associated with elevated plasma glial fibrillary acid protein concentration, but not S100 β or neuron-specific enolase concentrations (25). Lin et al. (26) observed that high levels of HMGB1 and IL-6 are associated with POCD after major gastrointestinal surgery. In our study of aged patients undergoing total hip replacement under spinal anesthesia, the POCD patients had higher postoperative plasma level of IL-1 β and lower level of amyloid β (A β) 1-42 in preoperative cerebrospinal fluid than did that in non-POCD patients (15).

The fact that aging has been associated with an exacerbated inflammatory response and more pro-inflammatory status (28) may provide an explanation of the higher incidence of POCD in the elderly (13, 23). It has been shown that aging primes microglial cells such that a subsequent immune challenge results in an exaggerated inflammatory response in the hippocampus, which in turn causes significant hippocampal-dependent memory deficits (29). On the other hand, it has been hypothesized that POCD shares similar pathological mechanisms with Alzheimer's disease (AD), and POCD may represent a preclinical stage of dementia (14, 30). Consistently, old mice that developed short-term POCD following abdominal surgery displayed AD-like brain changes, including gliosis in the brain, enhanced transcriptional and translational activity of the β -amyloid precursor protein, enhanced production of A β peptide, and hyper-phosphorylation of tau in the hippocampus (31). In parallel, human data showed that anesthesia and surgery induced an increase in the total-tau/A β (1-42) ratio in a pattern similar to AD, largely because of an increase in the total-tau rather than a decline in A β (1-42) (14). Moreover, POCD patients receiving liver transplantation had significantly elevated level of serum A β peptide, suggesting that anesthesia and surgery may specifically target AD pathways (32). These results support the notion that aged subjects are more vulnerable to anesthesia and surgery, which are often accompanied by an exaggerated and long-lasting increase of pro-inflammatory cytokines in the hippocampus, resulting in impaired synaptic plasticity and hippocampal-dependent memory deficits (13).

There is an ongoing public concern regarding the cognitive decline as a result of anesthesia and surgery, especially for the elderly, although some clinicians have challenged the importance of POCD because the cognitive decline seems to be elusive. Foremost, there is currently no standardized internationally accepted definition of POCD, which makes the evaluation and comparison between studies difficult (7). On the other hand, the conditions defining whether microglial activation and neuroinflammation are detrimental or beneficial to neuronal survival are poorly understood. However, it has become more widely accepted that although microglial activation is necessary and crucial for host defense and neuron survival, the over-activation of microglia results in deleterious and neurotoxic consequences (21). Therefore, understanding the causes and defining the characteristics of deleterious microglia activation in POCD have become a recent focus of researches (5). Although direct blocking of pro-inflammatory cytokines signaling in the brain of aged animals is reported to improve surgery-induced neuroinflammation and behavioral impairments, it should be noted that cytokines have dual roles in sustaining the innate immune response and key physiological processes, including synaptic plasticity and tissue healing (33). Importantly, we do not know exactly the time-window of these pro-in-

flammatory cytokine effects in the development of POCD and, thus, immune modulatory therapies by directly blocking pro-inflammatory cytokines may result in side effects, such as immune suppression. Therefore, immune modulatory therapy should be considered carefully and is currently still in its infancy in clinical practice. Lidocaine has been commonly used in clinical practice during general anesthesia with anti-inflammatory properties and may be an alternative for the immune modulatory therapies to reduce POCD (34). Furthermore, proper modulation of endogenous anti-inflammatory and pro-resolving pathways may have the therapeutic potential for preventing/reducing POCD and possibly other perioperative and neurodegenerative conditions (18, 35, 36). However, the effectiveness of these therapeutic options should be established in future studies.

Above all, we need to learn more about who is likely to develop POCD. At present, surgeons, anesthesiologists, and other perioperative clinicians should implement plans to limit the surgical trauma, reduce pain effectively, prevent postoperative complications, promote early mobilization and rehabilitation, and provide enriched environment for patients, as enriched environment may reduce POCD (37). When surgical trauma is minimized and general health is improved, it is likely that cognition will simultaneously be enhanced.

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