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Prehabilitation for Prevention of Postoperative Cognitive Dysfunction?

Deborah J. Culley, M.D.¹ and Gregory Crosby, M.D.¹

¹Associate Professor, Harvard Medical School; Department of Anesthesiology, Perioperative and Pain Medicine, Brigham & Women's Hospital, Boston, MA.

Surgery sets the old brain on fire and prehabilitation is a fire retardant. That's conclusion of an interesting study by Kawano et. al.¹ in this issue of the Journal. Specifically, they hypothesized that the old brain is more vulnerable than a young one to surgery-induced neuroinflammation because its innate immune cells, principally microglia, develop an exaggerated inflammatory response to a peripheral surgical procedure. Furthermore, in a novel twist, Kawano et. al. theorized that preoperative environmental enrichment (PEE) consisting of both physical and cognitive activity would attenuate the neuroinflammation and prevent postoperative cognitive impairment. They tested these hypotheses by exposing young adult and old rats to brief abdominal surgery under isoflurane anesthesia with or without a 2-week period of PEE, while age-matched controls were housed under standard lab conditions. They discovered that reference memory was impaired and hippocampal concentrations of the cytokines TNF α and IL1 β were increased 7 days after surgery in old sedentary but not young adult rats and that PEE negated both the neuroinflammation and memory impairment in the old animals. Moreover, they found that microglia from the hippocampus of PEE exposed rats had markedly lower lipopolysaccharide-stimulated cytokine release in vitro compared to those from sedentary cage-controls. Hence, Kawano et. al. provide evidence that prehabilitation might prevent surgery-induced cognitive impairment in old subjects and identify a cellular mechanism by which it could occur.

Neuroinflammation is a credible candidate mechanism for postoperative cognitive dysfunction (POCD). Surgery causes tissue injury, release into the circulation of damage-associated and proinflammatory molecules which, by stimulating vagal cholinergic afferents or directly entering the central nervous system (CNS), activate astrocytes and microglia to release a host of proinflammatory mediators.^{2–6} Many of these mediators disturb neuronal function and, if concentrations become high enough and last long enough, can kill neurons. It is no surprise then that an inflamed, smoldering brain does not work well. In fact, neuroinflammation is implicated in the pathogenesis of a wide array of acute (e.g. delirium) and chronic cognitive impairments (e.g. dementia).^{7,8} Thus, it is an attractive theory for POCD—the brain fog of which patients complain after surgery.

This cascade of surgery, neuroinflammation, and cognitive impairment has been studied previously but often using young animals and short-term outcomes.^{3,4} What makes the study

of Kawano et. al. relevant is that they used an aged animal model, looked at cognitive and biochemical outcomes a week postoperatively, and investigated a natural non-pharmacologic potential remedy. These are not trivial considerations because long-lasting postoperative cognitive debility is mainly an affliction of the old. Furthermore, the immune system becomes dysregulated with age; CNS responses are either hypoactive or hyperactive (i.e. 'primed') and resolution of inflammation is impaired.^{9,10} Inasmuch as a coordinated neuroimmune response is thought to be beneficial and promote recovery whereas an exaggerated, uncoordinated response is deleterious, it is easy to see how older age might predispose to greater vulnerability to and slower recovery from surgery-induced cognitive impairment. Like others,^{5,11} Kawano et. al. found this to be the case. In fact, they identified no change in hippocampal cytokines or behavioral performance in the young adult rats after surgery. This could be explained by the relatively minor nature of the surgical procedure (i.e. 10 min bowel manipulation) but is at odds with previous animal studies^{3,4} and undermines the premise that neuroinflammation is a unifying mechanism of POCD because young and middle aged patients also develop it but recover quickly.¹² Still, Kawano et. al. provide important support for age as a vulnerability factor for surgery-induced neuroinflammation and cognitive impairment.

It is nevertheless premature to conclude that neuroinflammation causes POCD or that microglia are responsible. POCD is typically defined by a battery of neuropsychological tests and is characterized by deficits in executive function and working memory.^{13,14} These cognitive domains were not tested by Kawano et. al. nor most other animal studies on the subject. The microglia story is similarly nuanced. There is controversy about how best to identify microglia, the resident phagocytes and immune competent cells of the brain. This is typically done by morphology or, as in Kawano et. al., by immunostaining for expression of certain purportedly microglia-specific surface protein markers. The problem, however, is that morphology is unreliable and mononuclear cells from the blood express many of the same markers as microglia, making it difficult—some would say impossible—to distinguish resident microglia from infiltrating blood bourn immune competent cells with these methods.^{15,16} The phenotype of cells in culture can also change with time, so cells harvested from old hippocampus may develop an older or younger phenotype in the dish. Therefore, although it does not detract from the primary observations of Kawano et. al., it is too early to say whether inflammatory microglial mechanisms underlie clinical POCD.

The most exciting and potentially translatable part of the study of Kawano et. al. is the observation that PEE can mitigate both the cognitive deficit and hippocampal cytokine response of surgery. Such prehabilitation has great appeal for improving cognitive outcomes of geriatric surgery. Older patients have a high rate of postoperative cognitive disability and often are deconditioned to start. Moreover, the pre-habilitation concept rests on a fairly strong and growing body of information that demonstrates enduring structural and cognitive benefits of even modest physical activity in seniors.¹⁷⁻¹⁹ Data for a benefit of cognitive training, such as with puzzles and games, are less consistent. Some studies find no advantage of generic brain training with commercial products but others report positive neuroplasticity and improvement in both trained and untrained aspects of cognition, especially with action video games.²⁰⁻²³ There are already some data that preoperative physical status forecasts surgical morbidity^{24,25} and that conditioning improves physical

outcomes²⁶ but the cognitive advantages, if any, of physical or cognitive prehabilitation are not well studied in the surgical setting. On this score, Kawano et. al. contribute important insight by showing that PEE modifies the surgically-induced neuroinflammatory response, an effect demonstrated for exercise in other models.²⁷ However, that is probably not the whole story; upregulation of neurotrophic factors, stimulation of neurogenesis, and enhanced synaptic plasticity are also strongly implicated in the cognitive benefits of exercise. In addition, exercise has potent systemic anti-inflammatory effects, so some of the CNS benefits of exercise may be an indirect result of improvement in the function of other organs or the circulating anti-inflammatory milieu.^{28, 29}

Whatever the mechanism, there are reasons to be cautious until more data are available. The sedentary cage controls might have biased the study in favor of finding an effect of PEE and probably do not mirror the activity state of most seniors. Clinical evidence that physical activity is cognitively beneficial is compelling but the duration of exposure is typically far longer (months or years) than the 2 week prehabilitation interval used by Kawano et. al. Prehabilitation is not feasible prior to urgent or emergency surgery, which are common in seniors and associated with a high risk of cognitive morbidity. Although the weekly amount of physical activity required for a cognitive benefit is modest, it may be impractical for surgical candidates with limited mobility due to cardiopulmonary, orthopedic, or neurologic disease. A prescription for preoperative exercise might also predispose older patients to falls, which are a major source of morbidity in seniors already. Finally, cognitive training might be unrealistic preoperatively because seniors are typically not facile with technology and it is difficult to imagine those who are taking to World of Warcraft (Blizzard Entertainment Inc., Irvine, California) anytime soon.

Nonetheless, the over-arching message of Kawano et. al. is clear: lifestyle based cognitive protection is possible and might have a positive impact on geriatric surgical outcomes. A pre-emptive, non-pharmacologic approach to POCD prevention—and better perioperative brain health—is an exciting prospect for geriatric surgical patients. Exercise is medicine that does not require a prescription.

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Pull Quote

“the pre-habilitation concept rests on a fairly strong and growing body of information that demonstrates enduring structural and cognitive benefits of even modest physical activity in seniors”

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