CONFERENCE PROCEEDING

# Fragile brains, 'The Brain of the Elderly'

*Sergio Bergese*

The last decades were marked by efforts to define the cognitive decline experienced by elderly patients undergoing major surgeries. Delirium and dementia are distinct clinical entities defined by DSM V criteria. Post-operative cognitive decline (POCD) has a controversial history, being recognised more as a research entity evaluated by comprehensive psychometric tests. No consensus was reached for an operational definition, the lack of standardised questionnaires being detrimental for POCD identification and follow-up. Older patients undergoing surgeries have multiple co-morbidities; these confounding variables increasing the difficulty of selecting study population.[1]

POCD is identified as an important predictor of outcome in both cardiac and non-cardiac surgical patients. The elderly population exhibits an increased vulnerability to neurocognitive impairment triggered by surgical procedures, perioperative anaesthetic management and age-related organ function decline and comorbidities.

The first and second International Study of The Brain of the Elderly POCD enrolled more than 2500 patients from 12 countries and concluded that cognitive dysfunction after non-cardiac surgeries is associated with increased mortality, pre-mature withdrawal from the labour market and nursing home placement. A POCD prospective study protocol was approved by 13 hospitals in eight European countries and the United States, and a number of 1218 patients, 60 years of age and older, completed the study. POCD was diagnosed in 266 patients 1 week after surgery (25.8% [95% confidence interval 23.1–28.5]) and in 94 patients –3 months after surgery (9.9% [8.1–12.0]) when compared with 176 UK controls. The study considered as risk factors for POCD: An older age, the length of anaesthesia, multiple surgeries, post-operative complication and fewer years of education.[2]

The authors invited future studies to confirm the possible link of POCD to irreversible brain damage and neuronal loss and to analyse the effects of anaesthetic agents on central neurotransmission. They reported no major contribution of hypotension and hypoxemia to POCD, without underestimating individual variation. The frailest patients were excluded based on mini mental status examination (MMSE) score. The study emphasised the importance of pre-operative cognitive testing to differentiate a POCD from a pre-existing cognitive impairment.[2,3]

A prospective study conducted by Vanderbilt University focused on long-term cognitive impairment experienced by adults with respiratory failure or shock admitted in the medical and surgical Intensive Care Unit (ICU). The study enrolled 821 patients and 6% were diagnosed with cognitive impairment at baseline –74% of this group developing delirium during the hospital stay. At 3 months, 26% of patients had scores similar to patients diagnosed with Alzheimer's disease (AD) and 40% similar to scores for traumatic brain injury patients. Patients experiencing delirium for a longer duration were consistently associated with worse cognitive impairment at 3 and 12 months follow-up.[4]

Delirium, defined as an acute brain dysfunction associated with inflammation and brain apoptosis, is linked to a persistent cognitive deficit by a not well-understood mechanism.[5]

Some authors refers to the term of delirium when describing ICU patients with fluctuating mental status, disorganised thinking or perceptual changes, when alcohol or drug abuse is excluded as a possible

Director of Neuroanaesthesia, Director of Neuroanaesthesia Fellowship and Director of Clinical and Neurological Research, The Ohio State University, USA


| Access this article online | |
|---|---|
| Quick Response Code: | Website: www.jnaccjournal.org |
| | DOI: 10.4103/2348-0548.174734 |




**How to cite this article:** Bergese S. Fragile brains, 'The Brain of the Elderly'. J Neuroanaesthesiol Crit Care 2016;3:41-3.

aetiology. Cross-talk among clinicians and researcher calls to replace terms such as acute brain failure, ICU syndrome or metabolic encephalopathy with delirium or 'sepsis-associated delirium.'[5]

Monk *et al*. discussed the three categories of predictors of perioperative morbidity and mortality – patient comorbidities, surgical intervention and anaesthesia management. The authors concluded that a cumulative deep hypnotic time – an unexpected new finding, intraoperative hypotension, surgical trauma and pre-existing conditions (comorbidities) could influence the morbidity and mortality in the 1st year after surgery.[6]

Bispectral index (BIS) was used since 1994 to measure the depth of anaesthesia and help anaesthetics titration based on electroencephalogram-derived multivariate scale. Chan *et al*. studied the effect of BIS monitoring in 921 patients undergoing non-cardiac surgeries, and concluded that for every 1000 elderly patients undergoing major surgery, a BIS guide anaesthesia to a range of 40–60 would be able to prevent 23 patients from POCD and 83 from delirium.[7]

Sessler *et al*. linked the increased hospital stay and 30-day mortality to the concept of 'triple low': Low blood pressure, low BIS and low minimum alveolar concentration.[8] The concept was rejected by Kertai *et al*. based on a multivariable logistic and Cox regression analyses of data collected from 16,263 patients undergoing non-cardiac surgeries at Duke University Medical Center between January 2006 and December 2009. The authors reported a statistically significant association between 30-day mortality and age, American Society of Anesthesiologists status or emergency surgery. However, no association was found between cumulative duration of triple low and perioperative or intermediate mortality.[9]

Laboratory studies suggest that some general anaesthetics have toxic effect on central nervous system. Long-term follow-up of cognitive status in patients undergoing general versus local anaesthesia found no significant difference. Mason *et al*. published a systematic review with meta-analysis focused on the influence of general anaesthesia, regional anaesthesia or combined (general and regional) on POCD and post-operative delirium (POD). They found a non-significant association of general anaesthesia with POCD and no correlation with POD. Based on their results, the authors suggest the use of regional anaesthesia, especially in patients vulnerable to develop POCD or POD.[10]

Animal studies proved that general anaesthetics act as modulators for γ-amino-butyric acid receptors and antagonists for *N*-methyl-D-aspartic acid glutamate receptors and are responsible for apoptotic neurodegeneration, especially during brain development. The altered synaptogenesis was linked with signs of cognitive impairment into adulthood. Aged rats undergoing general anaesthesia showed signs of cognitive impairment, isoflurane and halothane being responsible for an increased amyloid β production and toxicity.[11]

Increased inflammatory biomarkers activity was linked to an early cognitive decline after surgery. A pre-existing cognitive impairment in older patients, perioperative use of narcotics and benzodiazepines, alcohol abuse, depression and a previous history of POD have been associated with the development of delirium in surgical patients. Perioperative blood loss, urinary bladder catheter and electrolytes imbalance associated with certain types of injuries (orthopaedic trauma) have been described in patients diagnosed with long-term cognitive impairment.

A baseline geriatric consult should be focused on assessing risk factors such as visual and hearing impairment, and identifying cognitive decline, sleep deprivation, immobility and dehydration. Hospital Elder Life Program include three essential rehabilitation protocols based on three risk factors: early mobilisation (functional), oral and nutritional assistance (nutritional) and communication/orientation (cognitive status).[12]

Leung *et al*. examined 557 non-demented patients enrolled in successful ageing after elective surgery study and identified at least one copy of apolipoprotein e4 allele in 24.2% patients of whom 35.3% experienced delirium in both day 1 and day 2 after surgery. They concluded that apolipoprotein E genotype is not linked with POD incidence.[13]

Laboratory animal and clinical studies are suggesting common perioperative risk factors such us hypoxia, different types of anaesthetics and hypocapnia being involved in AD and POCD.[14]

Zhang *et al*. showed that a defective calcium homeostasis triggers isoflurane-induced caspase activation and apoptosis. They found that memantin, a drug used to treat Alzheimer's patients, can prevent isoflurane-induced caspase-3 activation and apoptosis *in vivo* and *in vitro*.[15]

A prospective observational study published in 2009 reported that POD rates were 11.5% when statins were used pre-operatively in cardiopulmonary bypass patients. The authors suggested that the anti-inflammatory, immunomodulatory and antithrombotic effect of statins protect older brain by reducing the permeability of blood-brain barrier, limiting the migration of leucocytes, improving endothelial function and stimulating neovascularisation.[16]

A retrospective analysis of 50 patients with mild cognitive impairment, 25 of whom received melatonin daily for 9–18 months, reported an improvement in MMSE scores in melatonin group. The results reflected as well an improvement in sleep-wake cycle and depression based on Beck inventory and.[17]

Previous studies reported sleep improvement and sun downing alleviation in AD patients receiving daily melatonin treatment.[18]

In 2009, a group of researchers from Cambridge University published a preliminary prospective data sustaining a reduction in delayed ischaemic deficits (DIDs) following systemic erythropoietin (EPO) administration in patients diagnosed with aneurysmal subarachnoid haemorrhage. The study was not able to correlate the EPO therapy with a reduction in the overall incidence or duration of cerebral vasospasm. However, the decreased manifestation of DIDs following EPO treatment suggested its neuroprotective and cerebrovascular effects.[19]

The multifaceted interplay between comorbidities, inflammatory cascade initiated by surgery and anaesthesia, and genetic inheritance is responsible for the cognitive outcome of a surgical patient. Effective therapies and pre-conditioning techniques associated with an early detection of cognitive impairment are future directions.


## Financial support and sponsorship

Nil.


## Conflicts of interest

There are no conflicts of interest.

## REFERENCES


1. Avidan MS, Evers AS. Review of clinical evidence for persistent cognitive decline or incident dementia attributable to surgery or general anesthesia. J Alzheimers Dis 2011;24:201-16.
2. Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, *et al.* Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International study of post-operative cognitive dysfunction. Lancet 1998;351:857-61.
3. Rasmussen LS, Johnson T, Kuipers HM, Kristensen D, Siersma VD, Vila P, *et al.* Does anaesthesia cause postoperative cognitive dysfunction? A randomised study of regional versus general anaesthesia in 438 elderly patients. Acta Anaesthesiol Scand 2003;47:260-6.
4. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, *et al.* Long-term cognitive impairment after critical illness. N Engl J Med 2013;369:1306-16.
5. Morandi A, Pandharipande P, Trabucchi M, Rozzini R, Mistraletti G, Trompeo AC, *et al.* Understanding international differences in terminology for delirium and other types of acute brain dysfunction in critically ill patients. Intensive Care Med 2008;34:1907-15.
6. Monk TG, Saini V, Weldon BC, Sigl JC. Anesthetic management and one-year mortality after noncardiac surgery. Anesth Analg 2005;100:4-10.
7. Chan MT, Cheng BC, Lee TM, Gin T; CODA Trial Group. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. J Neurosurg Anesthesiol 2013;25:33-42.
8. Sessler DI, Sigl JC, Kelley SD, Chamoun NG, Manberg PJ, Saager L, *et al.* Hospital stay and mortality are increased in patients having a "triple low" of low blood pressure, low bispectral index, and low minimum alveolar concentration of volatile anesthesia. Surv Anesthesiol 2013;57:71-2.
9. Kertai MD, White WD, Gan TJ. Cumulative duration of "triple low" state of low blood pressure, low bispectral index, and low minimum alveolar concentration of volatile anesthesia is not associated with increased mortality. Surv Anesthesiol 2015;59:44-5.
10. Mason SE, Noel-Storr A, Ritchie CW. The impact of general and regional anesthesia on the incidence of post-operative cognitive dysfunction and post-operative delirium: A systematic review with meta-analysis. J Alzheimers Dis 2010;22 Suppl 3:67-79.
11. Chen CC, Saczynski J, Inouye SK. The modified Hospital Elder Life Program: Adapting a complex intervention for feasibility and scalability in a surgical setting. J Gerontol Nurs 2014;40:16-22.
12. Johnson SA, Young C, Olney JW. Isoflurane-induced neuroapoptosis in the developing brain of nonhypoglycemic mice. J Neurosurg Anesthesiol 2008;20:21-8.
13. Vasunilashorn SM, Ngo L, Kosar CM, Fong TG, Jones RN, Inouye SK, *et al.* Does apolipoprotein E genotype increase risk of postoperative delirium? Am J Geriatr Psychiatry 2015;23:1029-37.
14. Xie Z, Tanzi RE. Alzheimer's disease and post-operative cognitive dysfunction. Exp Gerontol 2006;41:346-59.
15. Zhang G, Dong Y, Zhang B, Ichinose F, Wu X, Culley DJ, *et al.* Isoflurane-induced caspase-3 activation is dependent on cytosolic calcium and can be attenuated by memantine. J Neurosci 2008;28:4551-60.
16. Katznelson R, Djaiani GN, Borger MA, Friedman Z, Abbey SE, Fedorko L, *et al.* Preoperative use of statins is associated with reduced early delirium rates after cardiac surgery. Anesthesiology 2009;110:67-73.
17. Furio AM, Brusco LI, Cardinali DP. Possible therapeutic value of melatonin in mild cognitive impairment: A retrospective study. J Pineal Res 2007;43:404-9.
18. Mishima K, Okawa M, Hozumi S, Hishikawa Y. Supplementary administration of artificial bright light and melatonin as potent treatment for disorganized circadian rest-activity and dysfunctional autonomic and neuroendocrine systems in institutionalized demented elderly persons. Chronobiol Int 2000;17:419-32.
19. Tseng MY, Hutchinson PJ, Richards HK, Czosnyka M, Pickard JD, Erber WN, *et al.* Acute systemic erythropoietin therapy to reduce delayed ischemic deficits following aneurysmal subarachnoid hemorrhage: A phase II randomized, double-blind, placebo-controlled trial. Clinical article. J Neurosurg 2009;111:171-80.