JOURNAL of ANESTHESIA and PERIOPERATIVE MEDICINE

Review Article

General Anesthetics and Perioperative Management of the Geriatric Patients: What We Know and Do Not Know

Jing Xu, and Qiang Wang

ABSTRACT

Aim of review: The main purpose of this review is to gather the historical evolution on why people pay more and more concerns about postoperative cognitive dysfunction (POCD) and the postoperative management of the old people, and provide a synopsis of the available clinical and preclinical data and summarizes current research that is relevant to the occurrence of POCD due to anesthetics we are now commonly using. As the whole world is becoming an aging society, POCD and the physiological and pathological changes caused by aging have a great impact on and the further postoperative outcomes.

Methods: To have a complete understanding of anesthetics and their effects on POCD in elderly, certain keywords have been used to identify the relevance to anesthesia. The terms, Isoflurane, Sevoflurane, Desflurane, Ketamine, Propofol, and Dexmedetomidine, were searched to identify correlations between POCD as postoperative cognitive dysfunction, cognitive disabilities and elderly. The search consisted of all possible combinations of one anesthesia term and one cognitive term. This review mainly focused on the results published in the past 5 years and summarized the entire story in a structured way.

Recent findings: Aging is one of the top risk factors of POCD, and it is mainly connected to the postoperative brain damage and cognitive deficiency. POCD is associated with numerous of postoperative complications, and anesthetic drugs may play a very important role in these changes. Though many opinions came out as both volatile and intravenous anesthetics might affect and increase the brain damage, the results vary as the different criteria they use. Anesthetics are not the only cause of the onset of POCD, surgery itself may cause the cognitive dysfunction as well. Dexmedetomidine can contribute to prevent and reduce the occurrence of POCD, and additional measures were taken during the whole perioperative period and early postoperative recovery would also help keep the patients from suffering from POCD.

Conclusion: POCD occurs frequently in patients older than 65 years, and it is clearly related to some postoperative complications. The core mechanism is the aging immune system and inflammation. There is plenty to do both in clinically preventing its occurrence in old patients, and determining its original mechanism in basic science. (Funded by the National Natural Science Foundation of China, the Overseas, Hong Kong & Macao Scholars Collaborated Researching Fund, and the Natural Science Foundation of Shaanxi Province)

From the Department of Anesthesiology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China.

Correspondence to Dr. Qiang Wang at dr.wangqiang@139.com.

Citation: Jing Xu, Qiang Wang. General Anesthetics and Perioperative Management of the Geriatric Patients: What We Know and Do Not Know. *J Anesth Perioper Med* 2017;4:266-73. doi: 10.24015/JAPM.2017.0092

Around the world, especially some in some developing countries, populations are undergoing rapid and dramatic aging, which affects socio-economic challenges, as well as opportunities, for individuals, families, governments, and societies. It has been estimated that in 2051, the proportion of elderly individuals receiving anesthetics and surgeries would be over 50% in total (1). POCD, which is short for postoperative cognitive dysfunction, is now becoming a more and more important topic for elderly not only during the hospitalization period but also throughout the preoperative period. On PubMed and Medline, keywords, such as "POCD", "postoperative cognitive dysfunction" and "cognitive disabilities", were searched to obtain over 500 articles written in the past 5 years to come to the general conclusion that POCD is likely to be multifactorial. The occurrence of POCD could be a result of the effects of surgery, general anesthesia, or other factors that remain unclear. Aging, as the most important risk factors of POCD, is now catching the world's attention in regards to perioperative recovery for elderly patients. In this review, we summarized the history of how does aging change the function in our brain, the mechanism of aging and the occurrence of POCD, what is the role of aesthetics in relation to POCD, and the direction we might be heading towards in the coming future.

Concept of POCD, POCI and Their Influence on Elderly

The history of POCD dates back 60 years ago. The first article on POCD was published in 1955, in which the symptoms of postoperative behavior disability were found in 10% of elderly patients, 2% of which showed significant dementia (2). In 1961, an article discussing no changes in memory and learning abilities was published, and this started the argument about the whether there is a relationship between surgery, anesthesia, and postoperative cognitive functions of elderly (3).The prevailing biomedical strategy for reducing the healthcare impact of population aging has been "compression of morbidity". With increasing age, speed in spatial orientation, perceptual speed, numeric ability, verbal ability, and verbal memory decreases (4). Last year in 2016, a concept about "Optimal Longevity" was proposed, and people started to seek a way to maintain the balance between releasing the bother of disease affecting the elderly and improving their quality of life (5). Although doctors now understand the hazards of POCD and have identified it as a medical problem, the mechanism still remains unclear.

POCD describes a decline in cognitive function after surgery with a predominance in the elderly patient. Not the same as delirium, POCD could not be diagnosed until the patient has done the formal neuropsychological testing before and after surgery, which is not commonly happening outside a research setting. Partly as a result of this, there is no International Classification of Diseases (10th Revision) code for POCD, and it is not listed as a diagnosis in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) (6). Some neuropsychological testing and psychiatric scales are used to try to define the cognitive changes among the patients, for example, the Mini-Mental State Examination (MMSE), the Digit Span Forward subtest from the WAIS-III, the Stroop Color Word Test and Hopkins Verbal Learning Test, Revised (HVLT-R) are the most commonly accepted and used scales to measure the occurrence and severity of POCD (7-9). What's more, human cerebrospinal fluid (CSF) biomarkers as S-100β, IL- 6 may make a difference in neuroinflammatory response, which is involved in the mechanism of POCD, are used as detective markers for POCD diagnosis these days (10). Another concept comes up as we describe and study POCD, which is POCI, short for Postoperative Cognitive Improvement, also plays an important role in the function of aging brains. Using the same neuropsychological tests, some patients would show cognitive performance improvement after the surgery. For example, after carotid endarterectomy, the postoperative restoration of cerebral perfusion would be very helpful for POCI (11). Some anesthetics used would also make various of effects on the geriatric patients, based on the combination and their doses. Because there are so many factors involved, it becomes very hard to find a balance between the dysfunction and improvement in the postop-

erative management for elderly.

Aging is The Top Risk Factor for Postoperative Complications

In the 6th national census of population in China, it has been reported that over 13% of the population is over 60 years (12). During the perioperative period, the main challenge is to decrease the rate of mortality and increase mobility. Ten years ago, patients over 80 who had developed one or more complications had a 30-day mortality rate of 26% compared to a 30-day mortality rate of only 4% for the patients who suffered no complications and recovered smoothly through the perioperative period. In 2015, the incidence of major adverse cardiac events (MACE) in elderly Chinese patients with CAD who underwent non-cardiac surgery was 9.1% (13).

Among all the postoperative complications, postoperative brain damage and cognitive deficiency begin to attract our attention the most. As an increasing amount of surgeries are performed on more patients over 60 years old, the complaints from the patients themselves and their family members increased. The elderly suffered from memory loss, difficulties in learning, disorientation, and inability to concentrate (14,15). Although people are not sure about whether the anesthetic drugs or the surgery itself causing the postoperative brain damage, scientists identified the issue from finding out the mechanism of aging and the changes in brain structure and function.

Potential clues about the relationship between epigenetic changes and aging come from studies in Saccharomyces cerevisiae, where epigenetic changes are a primary cause of the aged phenotype. Genomic instability and alterations in gene expression are hallmarks of eukaryotic aging. DNA damage-induced redistribution of SIRT1 and other chromatin-modifying proteins may be a conserved mechanism of aging in eukaryotes. Oxidative stress, DNA repair factor, growth factors, and oxidative DNA damage are all linked to both transcriptional and epigenetic changes (16). In another issue, altered expression of different inflammatory factors can either promote or counteract neurodegenerative processes. Since many inflammatory responses are beneficial, directing and instructing the inflammatory machinery may be a better therapeutic objective than suppressing it (17). Neutrophil gelatinase-associated lipocalin (NGAL) has recently gained interest as a marker for neuroinflammation and associated behavioral dysfunction; scientists also found that NGAL may serve as a sensitive marker in connecting the peripheral inflammatory state to cognitive changes (18). What's more, researchers also focused on the function of the telomere, accumulating evidence that implicated telomere damage as a driver of age-associated organ decline and disease risk. The marked reversal of systemic degenerative phenotypes observed in adult mice supported the development of regenerative strategies designed to restore telomere integrity (5,19,20). New theories regarding the relationship between aging and brain changes never stopped, and continuing development of effective behavioral approaches for enhancing adherence to healthy aging practices in diverse populations, and ongoing analysis of the socio-economic costs and benefits of health span extension will be important supporting goals.

Anesthesia and POCD in Geriatric Patients

In order to have a complete understanding of anesthetics and their effects on POCD in aging, we have conducted a literature search. The following terms were used to identify relevance to anesthesia: Isoflurane, Sevoflurane, Desflurane, Ketamine, Propofol, and Dexmedetomidine. The following terms were searched in order to identify relevance to POCD as postoperative cognitive dysfunction and cognitive disabilities. The search consisted of all possible combinations of one anesthesia term and one cognitive term, and we mainly focused on the results recently.

Effects of Potent Volatile Anesthetics on POCD

While there are various pieces of evidence that many different anesthetic agents may affect cognitive function during aging, the potent volatile anesthetics are among the most frequently implicated in studies of POCD. Numerous investigations of isoflurane and several of sevoflurane have been conducted to explore their potentially deleterious effects on neurogenesis, with mixed

Table. The Relationship Between Different Anesthetic Drugs, Methods and Cognitive Dysfunction.

Item	Functional impairment	Mechanism involved
Anesthetics		
Volatile Anesthetics		
Isoflurane	Impair retention memory Spatial learning deficits Increase neuroinflammatory Hippocampus-dependent cognitive impairment Hippocampal neuroinflammation	 NMDA receptor mediated signaling pathways Anti-inflammatory agents Induce hippocampus BBB disruption TNF-alpha receptor antagonist
Sevoflurane	Spatial memory deficits Did not impair their acquisition learning and retention memory	Reversible hippocampal tau phosphorylation mTOR signaling pathway inhibition
Intravenous Anesthetics		
Propofol	Cognitive dysfunction	Increases tau phosphorylation
Ketamine	Attenuates the POCD occurrence	Decreases C-reactive protein concentration
Lidocaine	Attenuates the incidence rate of POCD	Decreases serum s-100β, NSE and IL-6 levels
Dexmedetomidine	Ameliorating postoperative cognitive impairment	Reduce these proinflammatory cytokines
Anesthetic technique		
Regional vs. General anesthesia	Regional anesthesia is less affected to cognitive function than general anesthesia	
Surgery		Increase HMGB1, IL-1β, TNF-α and Iba1 Inhibit GluR1 trafficking

NMDA denotes N-methyl-D-aspartate, BBB Blood-Brain Barrier, TNF Tumor Necrosis Factor, POCD Postoperative Cognitive Dysfunction, NSE Neuron-Specific Enolase, HMGB1 High Mobility Group Box 1, IL Interleukin, iba1 ionized calcium-binding adapter molecule 1, GluR1 Glutamate Receptor Subunit 1.

results (Table).

Of the 580 articles we searched, almost 60% percent were focused on the influence of volatile anesthetics and aging brains. On one hand, articles are being published to explain the neuroprotection role of volatile anesthetics, while other specialists are coming up with various mechanisms regarding the neurotoxicity of isoflurane and sevoflurane. It has been reported that isoflurane exposure impaired retention of memory in platform location, 1 week after exposure in young adult rats and resulted in a delayed, although weak, impairment at 4 weeks in middle-aged rats (21). NMDA receptor-mediated signaling pathways in the hippocampus and cortex of rats treated with isoflurane/N2O anesthesia at 18-months-old, result in spatial learning deficits in these animals (22). There is also an article that discusses how cognitive disorder was mitigated by anti-inflammatory agents even 14 days after isoflurane exposure in aged mice; in addition, isoflurane-induced upregulation of neuroinflammatory cytokinesis was only limited to 48 hours (23). For the function of the blood-brain barrier (BBB), it has been reported that isoflurane would induce hippocampus BBB disruption, and may contribute to hippocampus-dependent cognitive impairment in twenty-month-old rats that randomly received 1.5% isoflurane (24). TNF-alpha receptor antagonist may serve as a potential agent for the prevention of anesthesia-induced cognitive decline for the 20-month-old rats that were exposed to 1.3% isoflurane for 4 h (25). Another issue regarding isoflurane and cognitive impairment in aged rats focuses on the induction of hippocampal neuroinflammation, as calcineurin (CaN) serves an important role in the initiation of mitochondrial retrograde signaling, and nuclear factor-kappaB (NFkappaB) is involved in CaN signaling (26). Acute sevoflurane anesthesia in normothermic conditions led to a significant dose-dependent and reversible hippocampal tau phosphorylation, which suggested that sevoflurane exposure is associated with increased tau phosphorylation through specific kinases activation and spatial

memory deficits. Almost the same as isoflurane, repeated sevoflurane anesthesia would lead to persistent tau hyperphosphorylation and significant memory impairments, as seen in the retention phase of the Morris water maze in sevoflurane-anesthetized animals(27). A different article focused on young mice that received 3.3% sevoflurane or 7.8% desflurane and found that it did not impair their acquisition learning and memory retention(28). Using rapamycin and p70 ribosomal S6 protein kinase (p70S6k), people found that with sevoflurane exposure, the postoperative cognitive dysfunction following surgery may be due to mTOR signaling pathway inhibition in aged rats (29).

While more than half of the articles are talking about the influence of inhaled anesthetics and POCD in aged animals, there are still some opposing views. An article showed that repeated exposures of isoflurane on 15-month old mice had no observable effects on performance of any operant tasks like fixed consecutive number (FCN), incremental repeated acquisition (IRA), and progressive ratio (PR) tasks (30).It has been found that exposure of sevoflurane for 4 hours on 20-24-week old rats would not affect their swimming and action speed compared to the 12weeks group (31). Another article that discusses sevoflurane and cognitive effects are suggesting that sevoflurane anesthesia can impair short-term cognitive function, which may be via down-regulating p-CREB1 and Bcl-2 expression and up-regulating Caspase-8 expression to reduce hippocampus neuronal apoptosis, but it will be back to normal a few days later (32). 1 MAC sevoflurane anesthesia for 2 hours may affect some part of the memory, but it induces neither contextual fear memory impairment nor alterations in local population connectivity of medial prefrontal cortex local field potentials networks in aged rats (33). Another study about sevoflurane exposure in mice found that hippocampal IL-1beta and IL-6 increased at 6 hours after surgery, but no impairment of the spatial reference memory was found (34). These various opinions regarding the final results of animal tests may depend on the dose of the anesthetics they use, the exposure time, and also the end point of the final test. What's more, the marker of how they define POCD and the level of neuroinflammation was different as well. There are no criteria for the definition of POCD in animal model yet, and the species and sex of these animals may also play some roles in the results.

Effects of Intravenous Anesthetics on POCD

Propofol is one of the most commonly used intravenous anesthetic and sedative drug in geriatric medicine. The data suggest that developmental exposure to propofol may have some effects on cognitive dysfunction. With the use of 8-week old rats for 2 hours sedation, propofol increased tau phosphorylation under both normothermic and hypothermic conditions, and temperature control could partially attenuate the hyperphosphorylation of tau (35). However, there are opposing results that discuss how sub-anesthetic doses of isoflurane and propofol have no significant effect on postoperative cognition in rats with mild cognitive impairment, and its mechanism is to maintain KCC2 expression in the hippocampus (36).

Ketamine, which has been widely used in the past, is not a commonly recommended drug for normal anesthesia nowadays according to its side effects known as double vision, nausea, vomiting and most important, neurotoxicity. Recently, there are several studies show that ketamine could attenuate POCD after surgery, which bring this anesthetic back to the clinic. It has been reported that a small bonus of ketamine before the cardiac surgery would decrease the incidence rate of POCD after a week, with the lower Serum C-reactive protein (CRP) level while there is another groups reported the same results in the orthopedic surgery (37). Another study using the small-dose lidocaine combined with ketamine would also attenuate the incidence rate of POCD by decreased serum S-100β, NSE and IL-6 levels (38).

Dexmedetomidine has been widely used and studied clinically, a plenty of scientists have started to look into its mechanism in our brain and all kinds of organ protections. A meta-analysis suggested that perioperative dexmedetomidine treatment is associated with significantly better neurocognitive function postoperatively in comparison to both saline controls and midazolam (39). In 2013, the scores on the MMSE for the Dexmedetomidine and control groups one week

after surgery were significantly different, which suggested dexmedetomidine administration may be an effective method for ameliorating postoperative cognitive impairment in elderly patients who have undergone laparoscopic cholecystectomy (40).Further research is required to confirm the findings of the present study. As a highly selective α2 adrenoreceptor agonist that provides anxiolysis, sedation, and modest analgesia with minimal respiratory depression, dexmedetomidine has recently come out of the clinical trial on patients aged over 65 years who were admitted to the intensive care unit after non- cardiac surgery. Prophylactic low- dose dexmedetomidine significantly decreased the occurrence of delirium during the first 7 days after surgery. Dexmedetomidine has shown its outstanding effects on elderly patients (41). Most of the studies on dexmedetomidine focused on clinical trials, but there are still plenty of in-vitro and in- vivo studies. Splenectomy increased the expression of IL-1β, TNF-α, Bax and caspase- 3 in the hippocampus, and dexmedetomidine could reduce these proinflammatory cytokines in 20−22-month old mice (42). Dexmedetomidine may have a lot more benefits for general anesthesia, and its mechanism and clinical usage remains unknown in some groups of specific patients. For geriatric patients and their perioperative care, we have plenty of research to do, even though the benefits of dexmedetomidine for reducing POCD has been widely accepted.

Anesthetic Technique on POCD

Regional anesthesia and general anesthesia may affect the outcome of POCD as we thought, but recent meta-analysis suggested that it is not taken for granted. Twenty-six RCTs including 2,365 patients does not support the concern that a single exposure to general anesthesia in an adult would significantly contribute to permanent POCD after non- cardiac surgery (43). It has also been supported by another meta-analysis that there was no effect of anesthesia type on the odds ratio of developing POD, and the data would advocate for the use of regional anesthesia wherever possible especially in people otherwise vulnerable to developing cognitive symptoms (44).

The anesthetic we concerned is not the only risk factor in regards to POCD in the elderly. According to a report in 2012, no matter what kind of anesthesia, the surgery itself upregulates high mobility group box- 1 and disrupts the blood- brain barrier causing cognitive dysfunction in aged rats (45). The same results came out last year with a group tested for fear conditioning 6 days after the surgery under propofol-buprenorphine or isoflurane- buprenorphine anesthesia. The level of IL-1β, tumor necrosis factor TNF- α, and ionized calcium binding adaptor molecule 1 (Iba-1) remained the same as the control group (46). It has been reported that surgery itself would increase proinflammatory cytokines that then inhibit GluR1 trafficking, leading to learning and memory impairment, and neuroinflammation may be the underlying pathophysiology of this dysfunction besides anesthetic drugs (47). The same result came out in 2014 that the peripheral surgery was able to induce cognitive impairment independent of general anesthesia, and that the combination of peripheral surgery with aging- or Alzheimer gene mutation-associated Aβ accumulation was needed for the POCD to occur (48)).

The Actions in The Future

The top concern nowadays in clinical practice is how to avoid the risks of catching POCD, and to try our best to reduce the rate of the complications and sequelae that may occur in the coming future. In the central mechanism of POCD, no matter whether it was caused by the surgery itself, or the dose and duration of anesthetic drugs, inflammation occurs the most. There is strong evidence that administration of supplemental oxygen and the avoidance of perioperative hypothermia, allogeneic blood transfusion, hyperglycemia or large swings in blood glucose levels reduces postoperative infection rates, which in case, may reduce the rate of POCD in elderly patients as well. There is also some evidence where the use of regional anesthesia techniques reduce chronic postsurgical pain and that avoidance of nitrous oxide reduces the long-term risk of myocardial infarction (49). It has also been reported that using the Bispectral Index to monitor and control the depth of anesthesia to remain at an anesthetic depth of 40 to 60 re-

duces the incidence of postoperative delirium (50). What's more, the impact of preoperative environmental enrichment to prevent the development of cognitive impairment following Surgery in the animal model, which is just one of the main ideas of enhanced recovery after surgery (ERAS) (51). To continue making further prospects that large-scale human trials with long-term follow-ups are required to clarify the association between anesthesia and an aging brain, and trying to figure out the original mechanism of long- term postoperative cognitive dysfunction in the elderly.

Summary

Even though much remains to be done and the fact that there is a great deal of uncertainty as to the outcome, the investigation into the hypothesis that anesthetics is one of the key reasons of POCD remains a promising one. There is solid evidence that under the right conditions anesthetics can interfere with brain function, and it is to be determined what the relevance of this has to any clinical manifestations of POCD. Thus, we conclude that further study in this area is warranted, but that it should be focused on the areas outlined above.

This study was supported by grants from the National Natural Science Foundation of China (81473488), the Overseas, Hong Kong & Macao Scholars Collaborated Researching Fund (81529004), and the Natural Science Foundation of Shaanxi Province (2017JZ029).

The authors have no other potential conflicts of interest for this work.

References

1. Parra VM, Sadurni M, Donate M, Rovira I, Roux C, Rios J, et al. Neuropsychological dysfunction after cardiac surgery: Cerebral saturation and bispectral index: A longitudinal study. *Rev Med Chil* 2011;12: 1553-61. (Article in Spanish)
2. Bedford PD. Adverse cerebral effects of anaesthesia on old people. *Lancet* 1955;6884: 259-63.
3. Simpson BR, Williams M, Scott JF, Smith AC. The effects of anesthesia and elective surgery on old people. *Lancet* 1961;7208: 887-93.
4. Manejias Parke SG, Yager J, Apfeldorf W. Severe eating disorder initially diagnosed in a 72- year- old man. *Int J Eat Disord* 2008;4: 376-9.
5. Seals DR, Justice JN, LaRocca TJ. Physiological geroscience: targeting function to increase healthspan and achieve optimal longevity. *J Physiol* 2016;8: 2001-24.
6. Berger M, Nadler JW, Browndyke J, Terrando N, Ponnusamy V, Cohen HJ, et al. Postoperative Cognitive Dysfunction: Minding the Gaps in Our Knowledge of a Common Postoperative Complication in the Elderly. *Anesthesiol Clin* 2015;3: 517-50.
7. Saczynski JS, Marcantonio ER, Quach L, Fong TG, Gross A, Inouye SK, et al. Cognitive trajectories after postoperative delirium. *N Engl J Med* 2012;1: 30-9.
8. Aleman A, van't Wout M. Repetitive transcranial magnetic stimulation over the right dorsolateral prefrontal cortex disrupts digit span task performance. *Neuropsychobiology* 2008;57(1-2):44-8.
9. Strangman GE, O'Neil- Pirozzi TM, Goldstein R, Kelkar K, Katz DI, Burke D, et al. Prediction of memory rehabilitation outcomes in traumatic brain injury by using functional magnetic resonance imaging. *Arch Phys Med Rehabil* 2008;5: 974-81.
10. Tang JX, Baranov D, Hammond M, Shaw LM, Eckenhoff MF, Eckenhoff RG. Human Alzheimer and inflammation biomarkers after anesthesia and surgery. *Anesthesiology* 2011;4:727-32.
11. Hemmingsen R, Mejsholm B, Vorstrup S, Lester J, Engell HC, Boysen G. Carotid surgery, cognitive function, and cerebral blood flow in patients with transient ischemic attacks. *Ann Neurol* 1986;1:13-9.
12. Silbert BS, Evered LA, Scott DA. Incidence of postoperative cognitive dysfunction after general or spinal anaesthesia for extracorporeal shock wave lithotripsy. *Br J Anaesth* 2014;5:784-91.
13. Xu L, Yu C, Jiang J, Zheng H, Yao S, Pei L, et al. Major adverse cardiac events in elderly patients with coronary artery disease undergoing noncardiac surgery: A multicenter prospective study in China. *Arch Gerontol Geriatr* 2015;3:503-9.
14. 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; 9106: 857-61.
15. Fodale V, Santamaria LB, Schifilliti D, Mandal PK. Anaesthetics and postoperative cognitive dysfunction: a pathological mechanism mimicking Alzheimer's disease. *Anaesthesia* 2010;4: 388-95.
16. Oberdoerffer P, Michan S, McVay M, Mostoslavsky R, Vann J, Park SK, et al. SIRT1 redistribution on chromatin promotes genomic stability but alters gene expression during aging. *Cell* 2008;5: 907-18.
17. Wyss-Coray T, Mucke L. Inflammation in neurodegenerative disease--a double-edged sword. *Neuron* 2002;3: 419-32.
18. Gouweleeuw L, Hovens IB, van Leeuwen BL, Schoemaker RG. Neutrophil gelatinase- associated lipocalin and microglial activity are associated with distinct postoperative behavioral changes in rats. *Behav Brain Res* 2017: 104-09.
19. Bernardes de Jesus B, Blasco MA. Aging by telomere loss can be reversed. *Cell Stem Cell* 2011;1: 3-4.
20. Jaskelioff M, Muller FL, Paik JH, Thomas E, Jiang S, Adams AC, et al. Telomerase reactivation reverses tissue degeneration in aged telomerase- deficient mice. *Nature* 2011;7328: 102-6.
21. Callaway JK, Jones NC, Royse CF. Isoflurane induces cognitive deficits in the Morris water maze task in rats. *Eur J Anaesthesiol* 2012;5: 239-45.
22. Mawhinney LJ, de Rivero Vaccari JP, Alonso OF, Jimenez CA, Furones C, Moreno WJ, et al. Isoflurane/nitrous oxide anesthesia induces increases in NMDA receptor subunit NR2B protein expression in the aged rat brain. *Brain Res* 2012: 23-34.
23. Luo X, Yang L, Chen X, Li S. Tau hyperphosphorylation: a downstream effector of isoflurane-induced neuroinflammation in aged rodents. *Med Hypotheses* 2014;1: 94-6.
24. Cao Y, Ni C, Li Z, Li L, Liu Y, Wang C, et al. Isoflurane anesthesia results in reversible ultrastructure and occludin tight junction protein expression changes in hippocampal blood- brain barrier in aged rats. *Neurosci Lett* 2015:51-6.
25. Yang N, Liang Y, Yang P, Wang W, Zhang X, Wang J. TNF- alpha receptor antagonist attenuates isoflurane-induced cognitive impairment in aged rats. *Exp Ther Med* 2016;1:463-68.
26. Li Z, Ni C, Xia C, Jaw J, Wang Y, Cao Y, et al. Calcineurin/nuclear factor-kappaB signaling mediates isoflurane- induced hippocampal neuroinflammation and subsequent cognitive impairment in aged rats. *Mol Med Rep* 2017;1: 201-9.
27. Le Freche H, Brouillette J, Fernandez-Gomez FJ, Patin P, Caillierez R, Zommer N, et al. Tau phosphorylation and sevoflurane anesthesia: an association to postoperative cognitive impairment. *Anesthesiology* 2012;4:779-87.
28. Kilicaslan A, Belviranli M, Okudan N, Nurullahoglu Atalik E. Single and repeated sevoflurane or desflurane exposure does not impair spatial memory performance of young adult mice. *Fundam Clin Pharmacol* 2013;6: 641-9.
29. Liu Y, Ma L, Jiao L, Gao M, Guo W, Chen L, et al. Mammalian target of rapamycin/p70 ribosomal S6 protein kinase signaling is altered by sevoflurane and/or surgery in aged rats. *Mol Med Rep* 2015;6: 8253-60.
30. Walters JL, Chelonis JJ, Fogle CM, Orser BA, Paule MG. Single and repeated exposures to the volatile anesthetic isoflurane do not impair operant performance in aged rats. *Neurotoxicology* 2016: 159-69.
31. Callaway JK, Jones NC, Royse AG, Royse CF. Sevoflurane anesthesia does not impair acquisition learning or memory in the Morris water maze in young adult and aged rats. *Anesthesiology* 2012;5: 1091-101.
32. Xie H, She GM, Wang C, Zhang LY, Liu CF. The gender difference in effect of sevoflurane exposure on cognitive function and hippocampus neuronal apoptosis in rats. *Eur Rev Med Pharmacol Sci* 2015; 4: 647-57.

33. Xu X, Zhang Q, Tian X, Wang G. Sevoflurane anesthesia induces neither contextual fear memory impairment nor alterations in local population connectivity of medial prefrontal cortex local field potentials networks in aged rats. *Fundam Clin Pharmacol* 2016;4: 338-46.
34. Zhao Y, Huang L, Xu H, Wu G, Zhu M, Tian J, et al. Neuroinflammation Induced by Surgery Does Not Impair the Reference Memory of Young Adult Mice. *Mediators Inflamm* 2016: 3271579.
35. Huang C, Ng OT, Ho YS, Irwin MG, Chang RC, Wong GT. Effect of Continuous Propofol Infusion in Rat on Tau Phosphorylation with or without Temperature Control. *J Alzheimers Dis* 2016;1: 213-26.
36. Liu SY, Wang HB, Wang HY, Wang GL. Effect of sub- anesthetic doses of isoflurane and propofol on postoperative cognition and underlying mechanism in rats with mild cognitive impairment. *Zhonghua Yi Xue Za Zhi* 2016;2: 142-6. (Article in Chinese)
37. Hudetz JA, Iqbal Z, Gandhi SD, Patterson KM, Byrne AJ, Hudetz AG, et al. Ketamine attenuates postoperative cognitive dysfunction after cardiac surgery. *Acta Anaesthesiol Scand* 2009;7: 864-72.
38. Zhu M, Li Y, Wan Z, Zhang D, Wang X. Effects of small- dose lidocaine combined with ketamine on early postoperative cognitive function in elderly patients undergoing gastrointestinal tumor surgery. *Nan Fang Yi Ke Da Xue Xue Bao* 2015;7:1076-8. (Article in Chinese)
39. Man Y, Guo Z, Cao J, Mi W. Efficacy of perioperative dexmedetomidine in postoperative neurocognitive function: a meta- analysis. *Clin Exp Pharmacol Physiol* 2015;8: 837-42.
40. Chen J, Yan J, Han X. Dexmedetomidine may benefit cognitive function after laparoscopic cholecystectomy in elderly patients. *Exp Ther Med* 2013;2: 489-94.
41. Su X, Meng ZT, Wu XH, Cui F, Li HL, Wang DX, et al. Dexmedetomidine for prevention of delirium in elderly patients after non- cardiac surgery: a randomised, double- blind, placebo- controlled trial. *Lancet* 2016;10054:1893-902.
42. Qian XL, Zhang W, Liu MZ, Zhou YB, Zhang JM, Han L, et al. Dexmedetomidine improves early postoperative cognitive dysfunction in aged mice. *Eur J Pharmacol* 2015: 206-12.
43. Guay J. General anaesthesia does not contribute to long- term post- operative cognitive dysfunction in adults: A meta-analysis. *Indian J Anaesth* 2011;4:358-63.
44. 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: 67-79.
45. He HJ, Wang Y, Le Y, Duan KM, Yan XB, Liao Q, et al. Surgery upregulates high mobility group box- 1 and disrupts the blood-brain barrier causing cognitive dysfunction in aged rats. *CNS Neurosci Ther* 2012;12: 994-1002.
46. Zhang J, Tan H, Jiang W, Zuo Z. The choice of general anesthetics may not affect neuroinflammation and impairment of learning and memory after surgery in elderly rats. *J Neuroimmune Pharmacol* 2015; 1:179-89.
47. Tan H, Cao J, Zhang J, Zuo Z. Critical role of inflammatory cytokines in impairing biochemical processes for learning and memory after surgery in rats. *J Neuroinflammation* 2014;11:93.
48. Xu Z, Dong Y, Wang H, Culley DJ, Marcantonio ER, Crosby G, et al. Age- dependent postoperative cognitive impairment and Alzheimer-related neuropathology in mice. *Sci Rep* 2014;4:3766.
49. Kavanagh T, Buggy DJ. Can anaesthetic technique effect postoperative outcome? *Curr Opin Anaesthesiol* 2012;2:185-98.
50. Siddiqi N, Harrison JK, Clegg A, Teale EA, Young J, Taylor J, et al. Interventions for preventing delirium in hospitalised non-ICU patients. *Cochrane Database Syst Rev* 2016;3:CD005563.
51. Kawano T, Eguchi S, Iwata H, Tamura T, Kumagai N, Yokoyama M. Impact of Preoperative Environmental Enrichment on Prevention of Development of Cognitive Impairment following Abdominal Surgery in a Rat Model. *Anesthesiology* 2015;1: 160-70.