Global Journal of Health Science; Vol. 9, No. 1; 2017
ISSN 1916-9736 E-ISSN 1916-9744
Published by Canadian Center of Science and Education

Risk Factors for the Development of Post-Operative Cognitive Dysfunction

Maria D. Pappa[1], Nikolaos V. Theodosiadis[2], Andreas Tsounis[3] & Pavlos Sarafis[4]

[1] 414 Military Hospital of Special Diseases, Athens, Greece

[2] 401 Military Hospital of Athens, Athens, Greece

[3] Centers for the Prevention of Addictions and Promoting Psychosocial Health of Municipality of Thessaloniki, Thessaloniki, Greece

[4] Cyprus University of Technology, Nursing Department, Limassol, Cyprus

Correspondence: Dr Pavlos Sarafis, Assistant Professor, Department of Nursing, School of Health Sciences, Cyprus University of Technology, 15, Vragadinou Str, 3041 Limassol, Cyprus. E-mail: pavlos.sarafis@cut.ac.cy

Received: March 30, 2016 Accepted: May 19, 2016 Online Published: June 21, 2016

doi:10.5539/gjhs.v9n1p303 URL: http://dx.doi.org/10.5539/gjhs.v9n1p303

Abstract

Background: Many studies have shown that a large number of patients undergoing surgery show a measurable cognitive deterioration after surgery, while many of them still show cognitive deficits even three months later an operation. These specific cognitive deficits in which there is a temporal association between surgery and mental disorders are defined as postoperative impairment of cognitive function. Among cognitive disorders occurring during the postoperative period, the post-operative cognitive dysfunction (POCD) is less studied.

Aim: Risk factors concerning POCD will be overviewed in order to be considered as a measure of prevention of POCD.

Method: A literature search using combined keywords was undertaken on bibliographic databases including PubMed, Google Scholar and Scopus and through systematic selection 72 scientific articles were identified. Concerning the selection criteria, the material of this study consists of sources published mainly over the last fifteen years, while some articles that published before 2000 were selected because they were considered to be important.

Results: These disorders frequently occur in patients of advanced age. It is obvious that as the population of humanity ages, many older people are likely to develop health problems that require surgery and therefore a large number of people are likely to develop post-operative cognitive disorders. For the appearance of POCD, as for other mental disorders (e.g. delirium), several factors are implicated. According to the findings, except the advanced age, genetic polymorphism, idiosyncratic condition, the presence of metabolic syndrome and neurological diseases, the type of anaesthesia and surgical operation and sleep disturbance are among the most important risk factors.

Keywords: memory deterioration, post-operative cognitive dysfunction, post-operative mental disorder, risk factors

1. Introduction

The decline in mental level is a phenomenon which is often observed in patients after chronic illness or trauma. A factor which has been associated with the decline of the mental level is surgical operations (Rasmussen, 2006; Newman et al., 2007). A post-operative drop of the mental level concerns a wide range of cognitive functions in human including the short and long-term memory, data process, focus of attention and cognitive adaptation (Hovens et al., 2012). Studies have shown that about 26% of patients undergoing surgery show a measurable cognitive deterioration one week after surgery, and 10% of these patients still show cognitive deficits three months later (Moller et al, 1998) while more recent ones have shown that at least 30% of patients undergoing noncardiac surgery show a cognitive deterioration at hospital discharge (Monk et al., 2008). These particular cognitive deficits in which there is a temporal relationship between the surgery and mental disorders are defined as post-operative cognitive dysfunction (POCD). Specifically, surgical patients are likely during the post-operative hospitalization, to experience postoperative delirium or even more serious disorders of cognitive capacity. These disorders frequently occur in patients of advanced age. In the general population, many people remain healthy into old age. This process is referred as "normal aging" (Prough, 2005a). However, a fairly large number of elderly people have chronic diseases, which makes them more prone during surgical interventions (Prough, 2005a). Clinicians and researchers have observed that a considerable number of elderly patients have "changes in personality" after surgery (Prough, 2005b), which led them to the description of the syndrome of POCD and in search for the predisposing factors for the occurrence of this phenomenon. It is understood that as the population of humanity is aging, many older people are likely to develop health problems requiring surgery and hence a large number of people are expected to develop POCD (Monk et al., 2008).

This phenomenon, which has been described in 1955 (Bedford, 1955) had various names such as acute confusion, acute stroke syndrome, mental impairment, etc. (Heyer et al., 2008). The post-operative mental disorders have been associated with a reduced capacity for the process of daily activities by the time of discharge from the hospital for up to three months post-operation, which affects patients' quality of life and possibly disturb the balance in their family (WillamsRusso et al., 1995). Another effect of these disorders is the significant economic costs of caring for these patients after their discharge from the hospital (Avidan et al., 2009). So, the investigation of the risk factors for this phenomenon is currently more intensive than ever as there are many unanswered questions.

In the present study, a literature review on bibliographic databases including PubMed, Google Scholar and Ssopus was undertaken, using the following keywords "memory deterioration", "post-operative cognitive dysfunction", "post-operative mental disorder", and "risk factors". Through systematic selection 72 scientific articles were identified. Concerning the selection criteria, the material of this study consists of sources published mainly over the last fifteen years, while some articles that published before 2000 were selected because they were considered to be important.

2. Risk factors

Several studies have attempted to identify the factors which can contribute to the emergence of POCD, some of which include the type of surgery, the type of anaesthesia and factors associated with the patient. Table 1 summarizes the main findings of the literature.

2.1 Non-Modifiable Patient Factors

Risk factors associated with patients that cannot be modified are: the advanced age (Shaw et al., 1987; Diijkstra et al., 1996; Roach et al., 1996; Moller et al., 1998; Abildstrom et al, 2000; Stockton et al., 2000; Ancelin et al., 2001; Newman et al., 2001; Canet et al., 2003; Monk et al., 2008), the educational status (Moller et al., 1998; Abildstrom et al, 2000; Ancelin et al., 2001; Newman et al., 2001; Monk et al, 2008) and the genetic polymorphism (considering apolipoprotein E4) (Abildstrom et al., 2004; Heyer et al., 2005; Lelis et al., 2006). The advanced age is associated with a large number of health problems, many of which can be successfully treated by surgical operations. Unfortunately, persistent cognitive impairments can be developed as a side effect of such operations (Krenk et al., 2010). An increase in the aging population and the clear progress in anaesthesiology and surgery, led to an increase in the number of elderly patients undergoing surgery. Thus, it is likely that POCDs will become more and more frequent.

2.2 Metabolic Syndrome

About 25% of the 45 million surgical patients in the United States (US) suffer from metabolic syndrome (Hall et al., 2010) although the exact definition of the term and the diagnostic criteria continue to evolve (Eckel et al., 2010). The metabolic syndrome comprises an increased resistance to insulin, visceral obesity, hypertension, and dyslipidaemia, which increase the risk of post-operative complications that contribute to a significant increased post-operative mortality (Kajimoto et al., 2009; Hudetz et al., 2011a; Hudetz et al., 2011b). While each of the sub-phenotypes defining the metabolic syndrome has a strong genetic component, various lifestyle factors contribute to these conditions including sedentary behaviour and a diet high in calories from saturated fat and / or simple hydrocarbons (Cornier et al., 2008). About one-quarter of the adult US population has metabolic syndrome. Furthermore, 50% of patients undergoing cardiac surgery suffer from metabolic syndrome (Tung, 2010). Finally, recent data suggest that patients suffering from metabolic syndrome can be particularly susceptible to the development of POCD (Hudetz et al., 2011a; Hudetz et al., 2011b).

2.3 Neurological Diseases

The two most common causes of dementia are vascular dementia and Alzheimer's disease, although most cases of dementia include pathological factors from both of these types. Preoperative mental disorders, e.g. mild cognitive impairment (which constitutes a potential precursor of Alzheimer's disease), may already exist in many elderly patients undergoing surgery. Although the POCD and Alzheimer's disease may have some common neuropathological features and biochemical mechanisms, however there is no direct evidence linking the pathogenic mechanisms of Alzheimer's disease to that of POCD. Also there are very few epidemiological data to connect the onset of Alzheimer's disease symptoms with a surgery (Bohnen et al., 1994). Epidemiological studies have shown that neurodegenerative disorders, including Alzheimer's disease, may be accelerated by the conduction of surgical interventions (Gasparini et al., 2002). However, large retrospective studies have so far not managed to connect surgical operations or anaesthesia with the onset of dementia or Alzheimer's de novo disease (Avidan et al., 2009). Of course it should be noted that symptomatic pre-operative neurological diseases, including dementia and any disorders of the central nervous system, are considered as exclusion criteria for studies concerning POCD (Monk et al., 2008). Data from experimental models pose the suggestion that exposure to inhaled anaesthetics increases cerebral pathological findings that are normally observed in Alzheimer's disease, including the increase of β-amyloid (Xie et al., 2006). Furthermore, hypothermia during anaesthesia induces hyperphosphorylation of proteins by reducing the phosphatase 2a activity (Planel et al., 2008). Finally, it is noteworthy that anaesthesia, only at higher concentrations and prolonged periods, has been reported to produce pathological lesions similar to those of Alzheimer's disease but this is also a fact which is being disputed (Xie et al., 2006; Xie et al., 2007;Donk et al., 2012).

2.4 Association with Anaesthesia

There are several risk factors that are directly related to anaesthesia and may be involved in the pathogenesis of POCD. Intra-operative hypotension, hypoxia, emboli, drugs and post-operative infections have been described as risk factors for developing POCD. Although drugs used for general anaesthesia are capable of producing long-term cognitive impairment under certain conditions (Culley et al., 2003; Culley et al., 2004), the incidence of POCD is similar after regional and general anaesthesia (Newman et al., 2007) and this is why the attention has been focussed on the role of the surgical procedure as a causative factor for POCD. Post-operative pain is a possible causative factor for the development of POCD (Lynch et al., 1998). Epidural analgesia with local anaesthetics and / or opioids can be more effective compared to parenteral analgesics for the control of post-operative pain and the prevention of POCD (Morrison et al., 2003). Furthermore, patients under post-operatively oral analgesics, have less chance for the development of POCD compared with those receiving parenteral treatment (Wang et al., 2007). Although several studies have shown that the intra-operative monitoring of the depth of anaesthesia and cerebral oxygenation would constitute a realistic intervention to reduce the incidence of POCD (Ballard et al., 2012) this factor still remains a controversial issue and a large number of studies have failed to correlate the depth of anaesthesia with the incidence of POCD (Farag et al., 2006). The same conclusion arises from certain studies showing that animals with short-term isoflurane exposure didn't develop memory deterioration (Cibelli et al., 2010).

2.5 Association with Sleep

Sleep is vital for the rehabilitation of many disease entities that mainly concern the central nervous system and the immune system. In addition, sleep has anabolic effects and properties to improve both the neuropsychological state and immunogenic functions. During sleep phase with non-rapid eye movement (NREM), slow waves activity performs a homeostatic function in order to reduce the intensity of synapses (Sanders and Maze, 2011). This synaptic homeostasis improves the subsequent cognitive function, allowing new changes in synaptic stability. For example, both NREM and REM phases of sleep are necessary for the consolidation of learning and memory while sleep deprivation leads to cognitive impairment (Aurell and Elmqvist, 1985). Polysomnography tests revealed extreme sleep disorders in intensive care unit (ICU) patients with a decrease in total sleep time, changes in the architecture of sleep (predominance of stage 1 and 2 of sleep, reduced or absent stage 3 NREM and REM stage of sleep) and the fragmentation of sleep (Hilton 1976; Aurell and Elmqvist, 1985). Also, patients in the ICU had up to 50% of total sleep time during the day. Lack of normal sleep leads to cognitive dysfunction (Misra & Malow, 2008; Walker, 2008), contributes to the emergence delirium (Yildizeli et al., 2005), affects the immune response negatively (Irwin et al., 1996; Oztürk et al., 1999) and increases morbidity and mortality (Gallicchio and Kalesan, 2009). Sleep disturbance during hospitalization negatively affects the health, the treatment result and also causes an increase in expense.

Pre-clinical studies in mice have demonstrated the destructive effect of lack of sleep in the neuropsychological status (Vacas et al., 2011). Moreover pre-operative sleep deprivation causes significant neuroinflammatory changes (Vacas et al., 2012; Zhu et al., 2012). The exact mechanism for the harmful consequences of a double major phenomenon (surgery and sleep deprivation) is still poorly understood, although and it has been shown to cause an increase in the expression of inflammatory cytokines in the brain (Vacas et al., 2012). However, tranquillizers has been proved to be a major causative factor for this sleep disorder (Pandharipande et al., 2007; Pandharipande et al., 2008).

2.6 Association with Surgical Operations

POCD is most common condition after major surgical interventions compared to minor surgery. In one multicentre study, the incidence of POCD after minor surgery was 6.8% a week after the operation (Canet et al., 2003), whereas the frequency of POCD after major surgery reached above 25% (Moller et al., 1998). At three months, however, difference was much smaller (6.6% vs. 9.9% in these studies) .The different rates of early POCD after these operations may be due to differences in the surgical process, type of anaesthesia and anaesthetic agents used (intravenous versus inhalational) as well as differences in the treatment of post-operative pain (Mann et al., 2000). Furthermore, several minor surgical operations are done in outpatients and not in an inpatient environment (Canet et al., 2003). Numerous studies suggest that both early and late POCDs are common after cardiac surgery. For example, the study done by Newman et al., of 261 patients who underwent coronary artery bypass graft (CABG), in 53% of these patients POCD was found at the time of exiting the hospital, 24% at 6 months after the surgery and 42% after 5 years (Newman et al., 2001). The possible etiological mechanisms include cerebral microemboli with concomitant ischemia, hypoxia, and inflammation. Numerous studies that were conducted in the 1980s and 1990s have shown that the above events were observed more frequently after cardiopulmonary bypass (CPB) (Pugsley et al., 1994; Smith et al., 2006). Impaired cognitive function in patients undergone selective CABG, as well as other cardiac interventions, had been described of both pre-operatively and post-operatively. The incidence of pre-existing cognitive impairment in patients undergoing cardiac surgery is 35-45% (Hogue et al., 2006; Silbert et al., 2007) and the incidence of deterioration of cognitive function after cardiac surgery varies at a rate of 25-80% (Rasmussen et al., 2001). These study results depend on the type of surgery, the cardiac patients being studied, the method to determine POCD, the surgical practice, the protocols implemented by individual medical centres and surgical teams and the post-operative time that cognitive assessment is made (Al Ruzzeh et al., 2006). The logical conclusion from these studies, as summarized in the review of Taggart et al. is the avoidance of these types of surgical operations whenever possible (Taggart & Westaby, 2001). More recent studies, however, challenge this recommendation. For example, Evered et al. found that the incidence of POCD in elderly patients on day 7 was higher after a CABG than a hip replacement, but at three months there was no difference between the two groups (Evered et al., 2011). Similarly, rates of POCD after cardiac surgery with or without CPB were not significantly different in elderly patients, one year (Jensen et al., 2006) or five years after surgery (Van Dijk et al., 2007). This was confirmed in a meta-analysis which included data of more than 900 patients (Marasco et al., 2008).

Table 1. Risk factors for the development of POCD (Literature Review of the Studies)

Factors		**Authors**
Non-modifiable patient factors		
	Age	(Shaw et al., 1987; Diijkstra et al., 1996; Roach et al., 1996; Moller et al., 1998; Abildstrom et al, 2000; Stockton et al., 2000; Ancelin et al., 2001; Newman et al., 2001; Canet et al., 2003; Monk et al., 2008; Krenk et al., 2010)
	Educational status	status (Moller et al., 1998; Abildstrom et al, 2000; Ancelin et al., 2001; Newman et al., 2001; Monk et al, 2008)
	Genetic predisposition	(Abildstrom et al., 2004; Heyer et al., 2005; Lelis et al., 2006).
Metabolic syndrome		
	Metabolic syndrome and development of POCD	(Hudetz et al., 2011a; Hudetz et al., 2011b)
Neurological diseases		
	Neurological diseases and cognitive dysfunction	(Bohnen et al., 1994; Gasparini et al., 2002; Monk et al., 2008;

Anaesthesia		
	Incidence of POCD after regional and general anaesthesia	(Newman et al., 2007)
	Post-operative pain and POCD	(Lynch et al., 1998; Morrison et al., 2003)
	Post-operatively oral analgesics vs parenteral treatment	(Wang et al., 2007)
	Depth of anaesthesia and incidence of POCD	(Ballard et al., 2012; Farag et al., 2006)
Quality of sleep		
	Cognitive dysfunction due to lack of normal sleep	(Misra &Malow, 2008; Walker, 2008)
Type of surgery		
	POCD after minor surgery	(Canet et al., 2003)
	POCD after major surgery	(Moller et al., 1998)
	POCD after cardiac surgery	(Pugsley et al., 1994; Newman et al., 2001; Rasmussen et al., 2001; Taggart & Westaby, 2001; Hogue et al., 2006; Jensen et al., 2006; Smith et al., 2006; Silbert et al., 2007; Van Dijk et al., 2007; Marasco et al., 2008; Evered et al., 2011)

3. Conclusion

POCD is a disorder that occurs more frequently in elderly patients after surgery. There is a wide range of cognitive functions and areas of mental state that are affected by this syndrome, like attention, concentration, executive function, memory, visuospatial ability and psychomotor speed (Rasmussen et al. 2001). Several studies indicate certain factors which contribute to the emergence of POCD. Except non-modifiable patient factors like age, educational status and genetic predisposition, the presence of metabolic syndrome and neurological diseases, the type of anaesthesia and surgical operation and sleep disturbance are among the most important of these risk factors.

Pre-, intra, and post-operative vigilance is required by the surgical team for its prevention and treatment. The exclusion of other diseases that can faulty appear as POCD, like latent infections, is of great importance when treating patients with POCD signs. Electrolyte disorders, dehydration, endocrine, kidney, liver or neurological diseases need to be investigated with diagnostic tests. In addition, supportive therapy during treatment, like sufficient ventilation and oxygenation, haemodynamic support, control of post-operative pain, which is correlated with POCD development (Lynch et al., 1998), and insuring of a suitable clinical environment must be secured to achieve an optimal environment for recovery. Furthermore, it is necessary for the phenomenon to be studied at the level of pathogenicity in order to be treated effectively.

Competing Interests Statement

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

Abildstrom, H., Christiansen, M., Siersma, V. & Rasmussen, L. (2004). Apolipoprotein E Genotype and Cognitive Dysfunction after Noncardiac Surgery. *Anesthesiology, 101*(4), 855-861. http://dx.doi.org/10.1097/00000542-200410000-00009

Abildstrom, H., Rasmussen, L., Rentowl, P., Hanning, C., Rasmussen, H., Kristensen, P. & Moller, J. (2000). Cognitive dysfunction 1-2 years after non-cardiac surgery in the elderly. *Acta Anaesthesiol Scand, 44*(10), 1246-1251. http://dx.doi.org/10.1034/j.1399-6576.2000.441010.x

Al Ruzzeh, S., George, S., Bustami, M., Wray, J., Ilsley, C., Athanasiou, T., et al. (2006). Effect of off-pump coronary artery bypass surgery on clinical, angiographic, neurocognitive, and quality of life outcomes: randomised controlled trial. *BMJ, 332*(7554), 1365-1370. http://dx.doi.org/10.1136/bmj.38852.479907.7C

Ancelin, M. L, de Roquefeuil, G., Ledésert, B., Bonnel, F., Cheminal, J. C., & Ritchie, K. (2001). Exposure to anaesthetic agents, cognitive functioning and depressive symptomatology in the elderly. *Br J Psychiatry, 178*(4), .360-366. http://dx.doi.org/10.1192/bjp.178.4.360

Aurell, J., & Elmqvist, D. (1985). Sleep in the surgical intensive care unit: continuous polygraphic recording of sleep in nine patients receiving postoperative care. *BMJ, 290*(6474), 1029-1032. http://dx.doi.org/10.1136/bmj.290.6474.1029

Avidan, M., Searleman, A., Storandt, M., Barnett, K., Vannucci, A., Saager, L., et al. (2009). Long-term Cognitive Decline in Older Subjects Was Not Attributable to Noncardiac Surgery or Major Illness. *Anesthesiology, 111*(5), 964-970. http://dx.doi.org/10.1097/ALN.0b013e3181bc9719

Ballard, C., Jones, E., Gauge, N., Aarsland, D., Nilsen, O., Saxby, B., et al. (2012). Optimised Anaesthesia to Reduce Post Operative Cognitive Decline (POCD) in Older Patients Undergoing Elective Surgery, a Randomised Controlled Trial. *PLoS ONE, 7*(6), p.e37410. http://dx.doi.org/10.1371/journal.pone.0037410

Bedford, P. (1955). Adverse cerebral effects of anaesthesia on old people. *The Lancet, 266*(6884), 259-264. http://dx.doi.org/10.1016/S0140-6736(55)92689-1

Bohnen, N., Warner, M., Kokmen, E., Beard, C. & Kurland, L. (1994). Alzheimer's Disease and Cumulative Exposure to Anesthesia: A Case-Control Study. *J Am Geriatr Soc, 42*(2), 198-201. http://dx.doi.org/10.1111/j.1532-5415.1994.tb04952.x

Canet, J., Raeder, J., Rasmussen, L., Enlund, M., Kuipers, H., Hanning, C., et al. (2003). Cognitive dysfunction after minor surgery in the elderly. *Acta Anaesthesiol Scand, 47*(10), 1204-1210. http://dx.doi.org/10.1046/j.1399-6576.2003.00238.x

Cibelli, M., Fidalgo, A., Terrando, N., Ma, D., Monaco, C., Feldmann, M., et al. (2010). Role of interleukin-1β in postoperative cognitive dysfunction. *Ann Neurol, 68*(3), 360-368. http://dx.doi.org/10.1002/ana.22082

Cornier, M. A., Dabelea, D., Hernandez, T. L., Lindstrom, R. C., Steig, A. J., Stob, N. R., et al. (2008). The metabolic syndrome. *Endocr Rev, 29*(7), 777-822. http://dx.doi.org/10.1210/er.2008-0024

Culley, D., Baxter, M., Yukhananov, R., & Crosby, G. (2003). The memory effects of general anaesthesia persist for weeks in young and aged rats. *Anesth Analg, 96*(4), 1004-1009. http://dx.doi.org/10.1213/01.ANE.0000052712.67573.12

Culley, D., Baxter, M., Yukhananov, R. & Crosby, G. (2004). Long-term impairment of acquisition of a spatial memory task following isoflurane–nitrous oxide anesthesia in rats. *Anesthesiology, 100*(2), 309-314. http://dx.doi.org/10.1097/00000542-200402000-00020

Dijkstra, J., Houx, P. & Jolles, J. (1999). Cognition after major surgery in the elderly: test performance and complaints. *Br J Anaesth, 82*(6), 867-874. http://dx.doi.org/10.1093/bja/82.6.867

Dong, Y., Wu, X., Xu, Z., Zhang, Y., & Xie, Z. (2012). Anesthetic isoflurane increases phosphorylated tau levels mediated by caspase activation and Aβ generation. *PLoS ONE, 7*(6), p.e39386. http://dx.doi.org/10.1371/journal.pone.0039386

Eckel, R., Alberti, K., Grundy, S., & Zimmet, P. (2010). The metabolic syndrome. *The Lancet, 375*(9710), 181-183. http://dx.doi.org/10.1016/S0140-6736(09)61794-3

Evered, L., Scott, D., Silbert, B., & Maruff, P. (2011). Postoperative cognitive dysfunction is independent of type of surgery and anesthetic. *Anesth Analg, 112*(5), 1179-1185. http://dx.doi.org/10.1213/ANE.0b013e318215217e

Farag, E., Chelune, G., Schubert, A., & Mascha, E. (2006). Is depth of anaesthesia, as assessed by the bispectral index, related to postoperative cognitive dysfunction and recovery? *Anesth Analg, 103*(3), 633-640. http://dx.doi.org/10.1213/01.ane.0000228870.48028.b5

Gallicchio, L., & Kalesan, B. (2009). Sleep duration and mortality: A systematic review and meta-analysis. *J Sleep Res, 18*(2), 148-158. http://dx.doi.org/10.1111/j.1365-2869.2008.00732.x

Gasparini, M., Vanacore, N., Schiaffini, C., Brusa, L., Panella, M., Talarico, G., et al. (2002). A case-control study on Alzheimer's disease and exposure to anesthesia. *Neurol Sci, 23*(1), 11-14. http://dx.doi.org/10.1007/s100720200017

Hall, M. J, DeFrances, C. J, Williams, S. N, Golosinskiy, A., &Schwartzman, A. (2010). National Hospital Discharge Survey: 2007 summary. *Natl Health Stat Report, 26*(29), 1-20, 24.

Heyer, E., Gold, M., Kirby, E., Zurica, J., Mitchell, E., Halazun, H., et al (2008). A Study of Cognitive Dysfunction in Patients Having Carotid Endarterectomy Performed with Regional Anesthesia. *Anesth Analg, 107*(2), 636-642. http://dx.doi.org/10.1213/ane.0b013e3181770d84

Heyer, E., Wilson, D., Sahlein, D., Mocco, J., Williams, S., Sciacca, R., et al. (2005). APOE- 4 predisposes to cognitive dysfunction following uncomplicated carotid endarterectomy. *Neurology, 65*(11), 1759-1763. http://dx.doi.org/10.1212/01.wnl.0000184579.23624.6b

Hilton, B. (1976). Quantity and quality of patients' sleep and sleep -disturbing factors in a respiratory intensive care unit. *J Adv Nurs, 1*(6), 453-468. http://dx.doi.org/10.1111/j.1365-2648.1976.tb00932.x

Hogue, C., Hershey, T., Dixon, D., Fucetola, R., Nassief, A., Freedland, K., et al. (2006). Preexisting Cognitive Impairment in Women Before Cardiac Surgery and Its Relationship with C-Reactive Protein Concentrations. *Anesth Analg, 102*(6), 1602-1608. http://dx.doi.org/10.1213/01.ANE.0000219591.10826.17

Hovens, I., Schoemaker, R., van der Zee, E., Heineman, E., Izaks, G. & van Leeuwen, B. (2012). Thinking through postoperative cognitive dysfunction: How to bridge the gap between clinical and pre-clinical perspectives. *Brain Behav Immun, 26*(7), 1169-1179. http://dx.doi.org/10.1016/j.bbi.2012.06.004

Hudetz, J., Patterson, K., Amole, O., Riley, A. & Pagel, P. (2011a). Postoperative cognitive dysfunction after noncardiac surgery: effects of metabolic syndrome. *J Anesth, 25*(3), 337-344. http://dx.doi.org/10.1007/s00540-011-1137-0

Hudetz, J., Patterson, K., Iqbal, Z., Gandhi, S. & Pagel, P. (2011b). Metabolic syndrome exacerbates short-term postoperative cognitive dysfunction in patients undergoing cardiac surgery: results of a pilot study. *J Cardiothorac Vasc Anesth, 25*(2), 282-287. http://dx.doi.org/10.1053/j.jvca.2010.06.008

Irwin, M., McClintick, J., Costlow, C., Fortner, M., White, J., & Gillin, J. C. (1996). Partial night sleep deprivation reduces natural killer and cellular immune responses in humans. *FASEB J, 10*(5), 643-653.

Jensen, B. O, Hughes, P., Rasmussen, L. S, Pedersen, P. U, Steinbrüchel, D. A., (2006). Cognitive outcomes in elderly high-risk patients after off-pump versus conventional coronary artery bypass grafting: A randomized trial. *Circulation, 113*(24), 2790-2795. http://dx.doi.org/10.1161/CIRCULATIONAHA.105.587931

Kajimoto, K., Miyauchi, K., Kasai, T., Yanagisawa, N., Yamamoto, T., Kikuchi, K., et al. (2009). Metabolic syndrome is an independent risk factor for stroke and acute renal failure after coronary artery bypass grafting. *J Thorac Cardiovasc Surg, 137*(3), 658-663. http://dx.doi.org/10.1016/j.jtcvs.2008.11.043

Krenk, L., Rasmussen, L. S, & Kehlet, H. (2010). New insights into the pathophysiology of postoperative cognitive dysfunction. *Acta Anaesthesiol Scand, 54*(8), 951-956. http://dx.doi.org/10.1111/j.1399-6576.2010.02268.x

Lelis, R. G., Krieger, J. E., Pereira, A. C, Schmidt, A. P, Carmona, M. J., Oliveira, S. A, et al. (2006). Apolipoprotein E4 genotype increases the risk of postoperative cognitive dysfunction in patients undergoing coronary artery bypass graft surgery. *J Cardiovasc Surg (Torino), 47*(4), 451–456.

Lynch, E., Lazor, M., Gellis, J., Orav, J., Goldman, L., & Marcantonio, E. (1998). The Impact of Postoperative Pain on the Development of Postoperative Delirium. *Anesth Analg, 86*(4), 781-785. http://dx.doi.org/10.1213/00000539-199804000-00019

Mann, C., Pouzeratte, Y., Boccara, G., Peccoux, C., Vergne, C., Brunat, G., et al. (2000). Comparison of Intravenous or Epidural Patient-controlled Analgesia in the Elderly after Major Abdominal Surgery. *Anesthesiology, 92*(2), 433-441. http://dx.doi.org/10.1097/00000542-200002000-00025

Marasco, S., Sharwood, L. & Abramson, M. (2008). No improvement in neurocognitive outcomes after off-pump versus on-pump coronary revascularisation: a meta-analysis. *Eur J Cardiothorac Surg, 33*(6), 961-970. http://dx.doi.org/10.1016/j.ejcts.2008.03.022

Misra, S. & Malow, B. (2008). Evaluation of sleep disturbances in older adults. *Clin Geriatr Med, 24*(1), 15-26. http://dx.doi.org/10.1016/j.cger.2007.08.011

Moller, J., Cluitmans, P., Rasmussen, L., Houx, P., Rasmussen, H., Canet, J., et al. (1998). Long-term postoperative cognitive dysfunction in the elderly: ISPOCD1 study. *The Lancet, 351*(9106), 857-861. http://dx.doi.org/10.1016/S0140-6736(97)07382-0

Monk, T. G, Weldon, B. C, Garvan, C.W., Dede, D. E, van der Aa M. T., Heilman, K. M, et al. (2008). Predictors of cognitive dysfunction after major noncardiac surgery. *Anesthesiology, 108*(1), 18-30. http://dx.doi.org/10.1097/01.anes.0000296071.19434.1e

Morrison, R., Magaziner, J., Gilbert, M., Koval, K., McLaughlin, M., Orosz, G., S et al. (2003). Relationship between pain and opioid analgesics on the development of delirium following hip fracture. *J Gerontol A Biol Sci Med Sci, 58*(1), 76-81. http://dx.doi.org/10.1093/gerona/58.1.M76

Newman, M., Grocott, H., Mathew, J., White, W., Landolfo, K., Reves, J., et al. (2001). Report of the substudy assessing the impact of neurocognitive function on quality of life 5 years after cardiac surgery. *Stroke, 32*(12), 2874-2881. http://dx.doi.org/10.1161/hs1201.099803

Newman, S., Stygall, J., Hirani, S., Shaefi, S., & Maze, M. (2007). Postoperative cognitive dysfunction after noncardiac surgery. *Anesthesiology, 106*(3), 572-590. http://dx.doi.org/10.1097/00000542-200703000-00023

Oztürk, L., Pelin, Z., Karadeniz, D., Kaynak, H., Cakar, L., Gözükirmizi, E. (1999). Effects of 48 hours sleep deprivation on human immune profile. *Sleep Res Online., 2*(4), 107–111.

Pandharipande, P. P, Pun, B. T., Herr, D. L., Maze, M., Girard, T. D, Miller, R. R, et al. (2007). Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA, 298*(22), 2644-2653. http://dx.doi.org/10.1001/jama.298.22.2644

Pandharipande, P., Sanders, R., Girard, T., McGrane, S., Thompson, J., Shintani, A., et al. (2010). Effect of dexmedetomidine versus lorazepam on outcome in patients with sepsis: An a priori-designed analysis of the MENDS randomized controlled trial. *Crit Care, 14*(2), p.R38. http://dx.doi.org/10.1186/cc8916

Planel, E., Krishnamurthy, P., Miyasaka, T., Liu, L., Herman, M., Kumar, A., et al. (2008). Anesthesia-induced hyperphosphorylation detaches 3-repeat tau from microtubules without affecting their stability in vivo. *J Neurosci, 28*(48), 12798-12807. http://dx.doi.org/10.1523/JNEUROSCI.4101-08.2008

Prough, D. (2005a). Anesthetic pitfalls in the elderly patient. *J Am Coll Surg, 200*(5), 784-794. http://dx.doi.org/10.1016/j.jamcollsurg.2004.12.010

Prough, D. (2005b). The proper study of mankind is man'-rather, men and women undergoing anesthesia and surgery. *Anesthesiology, 103*(3), 451-452. http://dx.doi.org/10.1097/00000542-200509000-00002

Pugsley, W., Klinger, L., Paschalis, C., Treasure, T., Harrison, M. & Newman, S. (1994). The impact of microemboli during cardiopulmonary bypass on neuropsychological functioning. *Stroke, 25*(7), 1393-1399. http://dx.doi.org/10.1161/01.STR.25.7.1393

Rasmussen, L. (2006). Postoperative cognitive dysfunction: Incidence and prevention. *Best Pract Res Clin Anaesthesiol, 20*(2), 315-330. http://dx.doi.org/10.1016/j.bpa.2005.10.011

Rasmussen, L., Larsen, K., Houx, P., Skovgaard, L., Hanning, C. & Moller, J. (2001). The assessment of postoperative cognitive function. *Acta Anaesthesiol Scand, 45*(3), 275-289. http://dx.doi.org/10.1034/j.1399-6576.2001.045003275.x

Roach, G., Kanchuger, M., Mangano, C., Newman, M., Nussmeier, N., Wolman, R., et al (1996). Adverse cerebral outcomes after coronary bypass surgery. *New Engl J Med, 335*(25), 1857-1864. http://dx.doi.org/10.1056/NEJM199612193352501

Sanders, R. & Maze, M. (2011). Contribution of sedative-hypnotic agents to delirium via modulation of the sleep pathway. *Can J Anesth, 58*(2), 149-156. http://dx.doi.org/10.1007/s12630-010-9421-2

Shaw, P., Bates, D., Cartlidge, N., French, J., Heaviside, D., Julian, D. et al. (1987). Neurologic and neuropsychological morbidity following major surgery: comparison of coronary artery bypass and peripheral vascular surgery. *Stroke, 18*(4), 700-707. http://dx.doi.org/10.1161/01.STR.18.4.700

Silbert, B., Scott, D., Evered, L., Lewis, M. & Maruff, P. (2007). Preexisting cognitive impairment in patients scheduled for elective coronary artery bypass graft surgery. *Anesth Analg, 104*(5), 1023-1028. http://dx.doi.org/10.1213/01.ane.0000263285.03361.3a

Smith, P., Newman, S., Ell, P., Treasure, T., Joseph, P., Schneidau, A., & Harrison, M. (1986). Cerebral consequences of cardiopulmonary bypass. *The Lancet, 327*(8485), 823-825. http://dx.doi.org/10.1016/S0140-6736(86)90938-4

Stockton, P., Cohen-Mansfield, J. & Billig, N. (2000). Mental status change in older surgical patients: cognition, depression, and other comorbidity. *Am J Geriatr Psychiatry, 8*(1), 40-46. http://dx.doi.org/10.1097/00019442-200002000-00006

Taggart, D., & Westaby, S. (2001). Neurological and cognitive disorders after coronary artery bypass grafting. *Curr Opin Cardiol, 16*(5), 271-276. http://dx.doi.org/10.1097/00001573-200109000-00003

Tononi, G. & Cirelli, C. (2006). Sleep function and synaptic homeostasis. *Sleep Med Rev, 10*(1), 49-62. http://dx.doi.org/10.1016/j.smrv.2005.05.002

Tung, A. (2010). Anaesthetic considerations with the metabolic syndrome. *Br J Anaesth, 105*(Supplement 1), pp.i24-i33. http://dx.doi.org/10.1093/bja/aeq293

Vacas, S., Degos, V., & Maze, M. (2012). Forced Wakefulness Enhances Neuroinflammation in Postoperative Mice. Retrieved from http://epostersonline.s3.amazonaws.com/asa2012/asa2012.0040012.NORMAL.pdf

Vacas, S., Terrando, N., & Degos, V. (2011). Forced Wakefulness Disrupts Memory in Adult Mice. Retrieved from http://www.asaabstracts.com/strands/asaabstracts/abstract.htm;jsessionid=316C1047882383871616051C649E68C9?year=2011&index=10&absnum=2509 [Accessed 28 Mar. 2016].

Van Dijk, D., Spoor, M., Hijman, R., Nathoe, H., Borst, C., Jansen, E., et al. (2007). Cognitive and cardiac outcomes 5 years after off-pump vs on-pump coronary artery bypass graft surgery. *JAMA, 297*(7), 701-708. http://dx.doi.org/10.1001/jama.297.7.701

Walker, M. (2008). Cognitive consequences of sleep and sleep loss. *Sleep Med, 9*, S29-S34. http://dx.doi.org/10.1016/S1389-9457(08)70014-5

Wang, Y., Sands, L., Vaurio, L., Mullen, E. & Leung, J. (2007). The effects of postoperative pain and its management on postoperative cognitive dysfunction. *Am J Geriatr Psychiatry, 15*(1), 50-59. http://dx.doi.org/10.1097/01.JGP.0000229792.31009.da

Williams-Russo, P., Sharrock, N. E., Mattis, S., Szatrowski, T. P., Charlson M. E. (1995). Cognitive effects after epidural vs general anaesthesia in older adults. *JAMA, 274*(1), 44-50. http://dx.doi.org/10.1001/jama.1995.03530010058035

Xie, Z., Dong, Y., Maeda, U., Alfille, P., Culley, D., Crosby, G. et al. (2006). The common inhalation anaesthetic isoflurane induces apoptosis and ancreases Amyloid β protein levels. *Anesthesiology, 104*(5), 988-994. http://dx.doi.org/10.1097/00000542-200605000-00015

Xie, Z., Dong, Y., Maeda, U., Moir, R., Xia, W., Culley, D., et al. (2007). The Inhalation anesthetic isoflurane induces a vicious cycle of apoptosis and Amyloid β-protein accumulation. *J Neurosci, 27*(6), 1247-1254. http://dx.doi.org/10.1523/JNEUROSCI.5320-06.2007

Yıldızeli, B., Oğuzhan Özyurtkan, M., Batırel, H., Kuşcu, K., Bekiroğlu, N., & Yüksel, M. (2005). Factors associated with postoperative delirium after thoracic surgery. *Ann Thorac Surg, 79*(3), 1004-1009. http://dx.doi.org/10.1016/j.athoracsur.2004.06.022

Zhu, B., Dong, Y., Xu, Z., Gompf, H., Ward, S., Xue, Z., et al. (2012). Sleep disturbance induces neuroinflammation and impairment of learning and memory. *Neurobiol Dis, 48*(3), 348-355. http://dx.doi.org/10.1016/j.nbd.2012.06.022

Copyrights

Copyright for this article is retained by the author(s), with first publication rights granted to the journal.

This is an open-access article distributed under the terms and conditions of the Creative Commons Attribution license (http://creativecommons.org/licenses/by/3.0/).