REVIEW ARTICLE

Postoperative cognitive disorders: an update

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Abstract
Background: Cognitive dysfunction is a common complication after surgery. It is a major cause for increased, sometimes long-term, morbidity and mortality.
Methods: In this narrative review we performed a literature search regarding postoperative cognitive decline regarding risk factors, the type of surgical intervention, potential neuroprotective effects of anesthetic drugs, and associated quality of life and healthcare costs.
Results: Several risk factors are implicated in postoperative cognitive impairment. Cardiac surgery and specific orthopedic interventions are associated with a higher incidence of postoperative cognitive disorders. Results regarding the neuroprotective effects of anesthetics agents are still controversial but promising. Postoperative cognitive alterations are a major public healthcare issue as they impair the everyday quality of life, and expand the yearlong expenses.
Conclusions: Postoperative cognitive disorders are devastating, potentially life-threatening complications. High-suspicion, especially in high-risk patients and operations, and adoption of available neuroprotective strategies may prove lifesaving. HIPPOKRATIA 2018, 22(4): 147-154.

Keywords: Cognitive dysfunction, risk factors, cardiac surgical procedures, neuroprotection

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Introduction

A significant proportion of cognitively normal patients undergoing surgery will develop symptoms of cognitive impairment postoperatively[1,2]. The most common types are postoperative delirium (POD) and postoperative cognitive dysfunction (POCD)[1,3]. Although the exact etiology of POD/POCD is still obscure, several risk factors have been recognised[1,4]. Moreover, certain types of operations are accompanied by higher risk, rendering patients more vulnerable to POD/POCD[1,3].

Postoperative cognitive impairment is associated with increased morbidity and mortality[5,6]. Furthermore, it may lead to complete loss of independence and expand the yearlong expenses[3,7,8]. Although there is still no treatment for this complication, several studies suggest potential neuroprotective effects of the anesthetic drugs[9]. The existing evidence remains promising but controversial[9,10].

Methods

We aimed at accumulating existing evidence regarding POD/POCD with respect to the risk factors, type of surgery, neuroprotective effects of the anesthetic agents, the quality of life, and healthcare costs. We used the PubMed, the online bibliographic database of the US National Library of Medicine. The following terms in free-text combinations were used: postoperative delirium; postoperative cognitive dysfunction; postoperative cognitive decline; anesthesia; postoperative cognitive disorders; cardiac surgery; non-cardiac surgery; focusing on the last decade (2008-2018). A manual selection by two authors ensured that only relevant articles were included. Duplicate and irrelevant articles were excluded from further analysis (Figure 1, Table 1).

Definitions

Postoperative cognitive disorder is a broad definition, including several forms of cognitive dysfunctions. The most common types are POD and POCD[1,3]. Postoperative cognitive alterations are classified based on their onset and severity and are characterized by troubles on thinking and perception (Table 2)[2,8,11].

POD is an acute dysfunction in cognition, that is not explained by a preexisting neurocognitive disorder or severe reduction in arousability[2,3,8]. Altered attention is the core symptom of POD and stands for the inability to direct, focus, sustain, or shift attention[1-3]. Impaired memory, disorientation or perceptual disturbances may also be present[1-3]. The alterations of cognitive capacity in

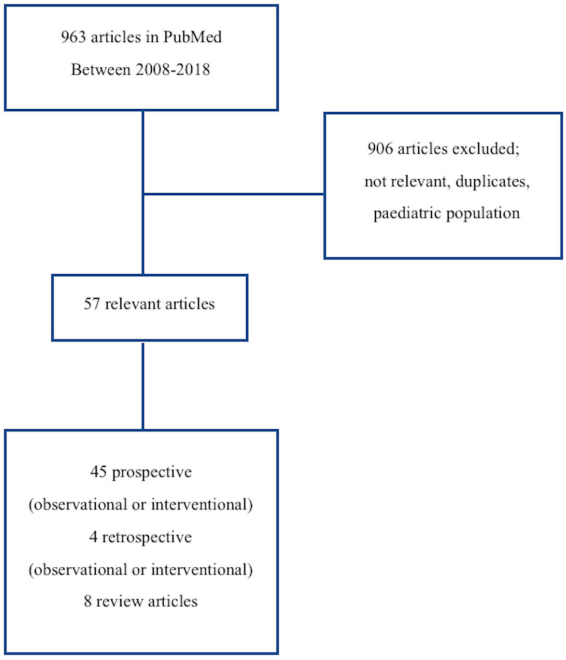

Figure 1: Flow chart of the recovered and analyzed articles from PubMed regarding studies for postoperative cognition dysfunction with respect to risk factors, the type of surgical intervention, potential neuroprotective effects of anesthetic drugs, and associated quality of life and healthcare costs, focusing on the last ten years (2008-2018).

patients suffering from POD develop within the first few days and fluctuate throughout the day[2] Confusion Assessment Method (CAM) is a widely used screening tool for delirium[3,12]. It has been used for research in the Greek population[12,13].

POD is classified based on the changes in psychomotor behavior. There are four categories: hypoactive, hyperactive, mixed variation, and sub-syndromal[1,2,11]. Hypoactive delirium presents with slow mentation and decreased movement in a lethargic state[1,2,11]. This type of POD is often under-diagnosed or misdiagnosed, and those patients are experiencing higher mortality[1]. On the other hand, hyperactive delirium is characterized by agitation, restlessness, and hyper-vigilance, combined with more prominent circadian rhythm abnormalities[2]. Subsyndromal delirium stands for elderly patients who are experiencing one or more symptoms of but do not meet the defined diagnostic criteria for POD[1]. At this point, it would be worth saying that maybe sub-syndromal type of POD could be the answer regarding the under-diagnosed status of this well recognized public health problem.

Additionally, POD may be further classified with respect to the time point of diagnosis in relation to surgical intervention[1-3]. However, the evidence is controversial. Strom and Rasmussen[1] suggest that the first 24-72 hours after surgery should be considered as "lucid interval" distinct from cognitive emergence phenomena due to transition from anesthesia to wakefulness[1,2]. On the other hand, Rengel et al[3] suggest the following classification. The mental status changes during emergence from general anesthesia stand for emergence delirium[3]. Post-anesthesia care unit (PACU) delirium covers the cognitive impairment after emergence but before the discharge from a PACU[3]. The fluctuating status that meets the diagnostic criteria of delirium from the PACU to the ICU or ward is defined as emergence delirium[3]. Both opinions are well documented and established[1,3]. As there is a significant association between POD and increased mortality, the diagnosis of delirium in the preoperative settings proves to be of paramount importance[2,3]. That said, clinicians should be aware of the "sub-syndromal" POD during the whole preoperative period.

Contrary to POD, there is no formal definition for POCD[2]. Based on experts and current literature, it is defined as a newly diagnosed cognitive deterioration arising postoperatively[1,2,8,11]. The diagnosis of POCD should be based on both pre- and postoperative screening with the appropriate psychometric tests[1,2,8,11]. Experts suggest that the need for thorough diagnostic screening has contributed to the lack of code on the International Classification of Diseases (ICD-10) for POCD. Subsequently, POCD is not listed in the Statistical Manual of Mental Disorders (DSM)[2]

POCD is a prolonged and subtle, and affects several cognitive domains [1,8]. More specifically, memory, executive function, attention, verbal fluency, and/or visual-spatial performance may be impaired[1,8]. Contrary to the more acute nature of POD, POCD may develop within seven days to one year postoperatively[1,2,8,11]. Several screening tools with respect to main cognitive domains have been validated for the Greek population such as the Stroop test, the Trail-making test, and the Rey auditory verbal learning test[12,14].

Further categorization of POCD proves to be impossible due to currently limited understanding[1,2]. However, its complex nature should not be overlooked. Some patients will only experience mild symptoms, such as slight-although lifelong-memory loss[1]. Compared to more pronounced cognitive deterioration such as inability to process information or concentrate, mild symptoms may easily be overlooked or perceived as normal ageing[1]. When acknowledged in the everyday clinical practice, combined with the lack of diagnostic certainty, concerns could be raised. Do anesthetists underdiagnose their patients with POCD, underestimating the great impact of this common complication? High suspicion index for subjective symptoms or behavioral changes and appropriate screening perioperatively seems mandatory.

Dementia is a common diagnosis in the aged population, and several types have been recognized. The most prevalent form (60% of cases) is Alzheimer's disease[15]. According to DSM-5 criteria, dementia is classified as a major neurocognitive disorder, being characterized by a significant decline in cognition (one or more domains), not explained by delirium or another mental disorder, which impairs everyday activities of daily living[2,15]. The

Table 1: Studies in the literature that report adequate data regarding postoperative cognitive dysfunction (POCD)/postoperative delirium (POD) presented in chronologically ascending order.

Study	Study type	Type of surgery	Results-Significant variables for outcomes
Monk, 2008[20]	Prospective	Major noncardiac	POCD was higher at 3 months in elderly patients (p <0.001); Lower educational level, previous cerebral vascular accident POCD at discharge were independent risk factors for POCD at 3 months; POCD at hospital discharge and 3 months were found to increase the mortality risk at 3 months and 12 months respectively
Hudetz, 2009[63]	Randomised	Cardiac	Ketamine attenuates POCD at 1 week (p <0.001)
Mack, 2009[64]	Randomised	Vascular	Low dose intraoperative magnesium therapy protects against POCD/POD (P<0.01)
Mathew, 2009[16]	Randomised	Cardiac	Lidocaine infusions during and after cardiac surgery do not reduce the rate of POCD (p =0.97); Higher doses were independent predictors of POCD (p =0.004)
Mitchell, 2009[66]	Randomised	Cardiac	Lidocaine was not prove to be neuroprotective
Slater, 2009[27]	Prospective	Cardiac	Intra-operative cerebral oxygen desaturation is associated with increased risk of POCD/POD (p =0.024)
Steinmetz, 2010[71]	Prospective	Noncardiac	No significant difference was detected
Evered, 2011[37]	Prospective	Cardiac Orthopaedic	The incidence of POCD in elderly patients at 7 days (p <0.01); higher after CABG than THJR; independent at 3 months (p =0.24); CV risk factors were not predictive of POCD
Siepe, 2011[53]	Randomised	Cardiac	Normal perfusion pressures during normothermic CPB (80-90 mmHg) is associated with less early POCD/POD (p =0.017)
Ballard, 2012[68]	Randomised	Abdominal Orthopaedic	Intraoperative monitoring of anaesthetic depth and cerebral oxygenation may reduce the POCD (p <0.05)
Kline, 2012[21]	Retrospective	Non-cardiac	Elderly undergoing surgery experience an increased rate of atrophy in hippocampal and gray matter (5-9 months)
Saczynski,2012[39]	Prospective	Cardiac	POD is associated with more prolonged cognitive decline within 12 months after cardiac surgery
Chan, 2013[69]	Randomized double blind	Major noncardiac	BIS-guided anesthesia decreased the risk of POCD at 3 months (10.2% vs. 14.7%, p =0.025)
Krüger, 2013[55]	GERAADA registry	Acute Aortic Dissection type A	Steroid administration may be associated with improved neurological outcomes
Lamy, 2013[43]	Prospective	Cardiac	At 1 year after CABG there was no significant difference between off-pump and on-pump CABG to the neurocognitive function
Mathew, 2013[65]	Randomised	Cardiac	Magnesium administered during and after cardiac surgery does not reduce POCD (p =0.93)
Mu, 2013[40]	Prospective	Cardiac	High serum cortisol level in 1st postoperative morning associated with increased risk of cognitive dysfunction 7 days after CABG (p =0.003)
Radtke, 2013[70]	Prospective	Noncardiac	Intraoperative neuromonitoring is associated with a lower incidence of POD (p =0.036)
Sauër, 2013[5]	Randomised	Cardiac	At 7.5 years follow-up off-pump CABG had a similar or even better cognitive performance compared PCI (p <0.01)
Colton, 2014[56]	Retrospective	-	Propofol does not have long-term effects on intracranial hypertension
Ellard, 2014[33]	Retrospective	Vascular	POD after vascular anesthesia is similar with regional or general anesthesia (p =0.56)
Fang, 2014[28]	Prospective	Microvascular decompression	Higher doses of dexamethasone increases the incidence of early POCD
Kok, 2014[50]	Pilot study	Cardiac	No significant difference in cerebral oxygenation; CPB identified as independent risk factor for development of late cognitive dysfunction (p =0.027)
Krenk, 2014[36]	Prospective	Orthopaedic	The incidence of early, but not late, POCD after total hip and knee replacement seems to be lower after a fast-track approach
Mahajan, 2014[61]	Randomised	Neurosurgery	Neuroprotection with propofol at the time of clipping during aneurysm surgery was not adequate
Ottens, 2014[29]	Randomised	Cardiac	Treatment group did not differ in the incidence of POCD 1 (p =0.09) or 12 (p =0.24) months postoperatively
Papadopoulos, 2014[67]	Randomised	Orthopaedic	Postoperative ondansetron administration seems to protect; might improve cognitive function in pts undergoing hip fracture surgery under GA
Saporito, 2014[57]	Prospective	ICU +/- major	Early POD is very common after major surgery, even without known risk factors (p <0.02)
Shi, 2014[59]	Animal study	-	Propofol exerts neuroprotection against ischemic brain damage
Wang, 2014[62]	Randomised	-	Propofol-Dexmetomidine combination exerts a stronger neuroprotection against ischemia repercussion
Zhang, 2014[60]	Animal study	-	Propofol has a neuroprotective effect on hippocampal injury induced by hypoxia
Zhu, 2014[30]	Prospective	Orthopaedic	Perioperative blood transfusion >3 RBCs = independent risk factor for POCD in aged patients following total hip replacement surgery (p <0.05)
Hudetz, 2015[47]	Randomised	Cardiac	RIPC prevented deterioration of short-term POCD (p <0.05) but there were no results in POD (p =0.54)
Tachibana2015[22]	Pilot study	Major surgery	Elderly patients undergoing desflurane anesthesia have significant better quality of emergence (p <0.05)
Cereghetti, 2017[31]	Retrospective	Cardiac	Known risk factors for POD are also predictive of prolonged duration of POD
Chen, 2017[32]	Randomized	Orthopaedic	GA is associated with higher cognitive decline compared to combined general anaesthesia (p =0.005)
Del Felice, 2016[54]	Prospective	Cardiac	A decline in hematocrits level <12 % represents a threshold for cognitive decline
Dokkedal, 2016[24]	Prospective	All types	A statistically significant decrease (-0.27; 95% CI, -0.48 to 0.06) in cognitive function was present in twins with at least one major surgery
Micha, 2016[12]	Randomised	Major noncardiac	Sevoflurane has a negative influence on postoperative cognition
Rappold, 2016[23]	Prospective	Noncardiac	Postoperative cognitive decline 1 month after surgery was associated with higher plasma concentrations of the biomarker GFAP
Tzimas, 2016[25]	Prospective	Orthopaedic	Repeated exposure of elderly patients to GA might lead to prolonged cognitive impairment
Abrahamov, 2017[48]	Prospective	Cardiac	The location and intensity BBB disruption is correlated with POCD
Glumac, 2017[49]	Randomised	Cardiac	Preoperative dexamethasone reduced the inflammatory response and the risk of early POCD
Kok, 2017[42]	Prospective	Cardiac	Postoperative cognitive dysfunction could be solely attributable to CPB
Knipp, 2017[52]	Prospective	Cardiac	Silent brain infracts did not impact early or late cognitive performance
Todd, 2017[17]	Prospective	Orthopaedic	Older people with sleep disruption are at higher risk of POD
Tzimas, 2018[13]	Randomised	Orthopaedic	The choice of anesthesia does not influence the emergence of POCD in elderly patients undergoing hip fracture surgery
Zhang, 2018[19]	Sub-analysis Randomised	Cancer surgery	Vitamin D deficiency increases the risk of early POCD

POCD: postoperative cognitive dysfunction, CABG: coronary artery bypass grafting, THJR: total hip joint replacement, CV: cardiovascular, POD: postoperative delirium, PCI: percutaneous coronary intervention, CPB: cardiopulmonary bypass, RBCs: red blood cells, GFAP: glial fibrillary acid protein.

Table 2: The main characteristics of postoperative cognitive disorders.

Type of Postoperative Cognitive Disorders		Diagnostic methods normed in Greece	Clinical Course	Prognosis
Postoperative Delirium	Thinking and perception Fluctuating consciousness	Delirium Scales- Confusion Assessment Method	Acute onset within few days	Reversible if the underlying condition treated
Postoperative Cognitive Dysfunction	Thinking and perception Newly diagnosed postoperatively Subtle, manifold Unaffected consciousness	Pre- and post-operative psychometric testing	Gradual onset within 7 days to 1 year	Prolonged impairment May be reversible in months
Dementia	Major neurocognitive disorder Decline in one or more cognitive domains No other diagnosis better explains the symptoms	Dementia tests- Mini Mental Status Examination	Progressively over years	Poor prognosis No treatment available

four diagnostic criteria for a major neurocognitive disorder are i) Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains, ii) Interference with independence in the daily activities, iii) Not exclusively in the context of a delirium, and iv) No other diagnosis better explaining the symptoms[2].

Mini-mental state examination (MMSE) is a brief screening tool for the clinical examination of patients with dementia. MMSE is validated in Greek population[15] and assesses orientation, registration, attention, recall, and language. It should be highlighted that dementia develops progressively and is a lifelong condition with poor prognosis[11].

Risk Factors

The exact etiology of POD/POCD is still obscure. However, various risk factors are acknowledged to be associated with their development[1,4]. Advanced age, fewer years of education, and lower preoperative cognitive test scores are identified as strong, non-modifiable risk factors for POCD/POD[1,16]. Moreover, sleep disruption, preoperative vitamin-D deficiency, and diabetes mellitus have also been recognized as independent risk factors for POCD (1.26-fold higher risk for POCD)[16-19]. Regarding the advanced age, it should be noted that patients older than 60 years are suffering from POCD more than twice as often compared to younger patients[20]. A possible explanation could be that older patients have many co-morbidities (cerebral, cardiac, and vascular diseases) which lead to a greater cerebral white matter damages[5,21-23]. Furthermore, advanced age raises the possibility of repeated exposure to surgery and anesthesia, which is reported to lead to statistically increased postoperative cognitive dysfunction[24,25] which means that older patients are facing the risk of less cognitive reserve, which may lead to a failure of resilience of the perioperative stress.

Regarding the intra-operative risk factors, extensive surgery with prolonged anesthesia is associated with a higher incidence of POD in cardiac surgery [odds ratio (OR) 1.37 for one hour increase][26]. Intra-operative cerebral oxygen desaturation is another identified risk factor[27]. High doses of lidocaine and dexamethasone increase the incidence of early POD/POCD[16,28]. However, high doses of dexamethasone do not increase the risk of POCD one and twelve months postoperatively[29]. Regarding volume replacement strategies, a prospective study on 313 patients who underwent hip replacement surgery demonstrated that blood transfusion with more than three units of red blood cells increased the risk of POCD[30]. Furthermore, the use of hydroxyethyl starch is an independent risk factor for POD compared to the use of albumin[15]. Long surgery duration, high dexamethasone doses, and aggressive volume replacement could be translated into high levels of perioperative stress response aggravating the cognitive impairment[1]. This hypothesis is also supported by the fact that increased levels of C-reactive protein postoperatively were found to increase the incidence of POD (OR 2.16, two-fold increase)[31].

For many years general anesthesia (GA) per se was blamed for POD/POCD, and anesthetists favored the regional techniques, especially for elderly patients[13]. In a recent randomized trial, GA was associated with higher cognitive decline compared to combined epidural and GA[32]. On the other side, various studies concluded that no differences exist between regional and GA concerning the incidence of long-term POCD. The potential neuroprotective effect of regional techniques subsides one week postoperatively[13,25,26,33]. Indeed, Tzimas et al[13] found that the choice of anesthesia (GA versus spinal) does not influence the emergence of POCD thirty days after hip fracture surgery. Experts suggest that both surgery and anesthesia should be considered coincidences masquerading as causes and clinicians should focus on the optimization of the perioperative environment[2-4,11,22].

POD/POCD and non-cardiac surgery

POD and POCD rates demonstrate a wide variation

based on the type of surgery and procedural risk[1,3,34]. Patients undergoing otolaryngology and minor general surgical procedures are exposed to a lower risk for POD, 12 % and 13 % respectively. The prevalence rises in aortic surgery (>29 %), major abdominal (>50 %), and cardiac surgery (<51 %). In patients with hip fractures undergoing surgery, the incidence of POD may be as high as 62 %[4]. Factors such as advanced age, morbidities, the increased risk for fat micro-embolism, and the high blood transfusion requirements may be a possible explanation[3]. Last but not least, the highest incidence of POD has been reported in patients that require admission in the Intensive Care Unit (ICU) and mechanical ventilation. In these settings, 80 % of the patients may develop some form of POD[3,35].

As far as the POCD is concerned, the existing evidence vary depending on the definition, the psychometric tests, and the time frame of assessment[34]. The incidence of POCD reported in the literature is 41-75 % (one week) and 18-45 % (three months)[30]. Major and more invasive procedures such as abdominal and vascular surgery carry a great risk for POCD, contrary to minor and outpatient interventions[34]. Patients undergoing cardiac and specific orthopedic procedures are experiencing the highest risk for short- or long-term POCD[34].

It should be noted that the risk of POCD at three months postoperative, at patients older than 60 years, undergoing any type of major surgery (more than two hours) under GA is 10 %[4]. Contrary it seems that fast track approach may lower the risk of POCD early after total joint replacement. In a prospective multi-center study that included 225 elderly patients who underwent fast track knee and hip arthroplasty the incidence of POCD was 9.1 % (1-2 weeks) and 8.0 % (3 months)[36]. Evered et al[37] demonstrated that the incidence of POCD was higher at seven days postoperatively in patients undergoing cardiac surgery compared to major orthopedic surgery but independent of the type of surgery at three months. This is supporting the current literature hypothesis that other factors, rather than surgery and anesthesia per se, are responsible for POCD/POD[4,22,24].

POD/POCD and cardiac surgery

The first concerns regarding cognitive decline in cardiac surgery date back at the introduction of the cardiopulmonary bypass (CPB)[38]. Not long after that, it was noticed that POD/POCD was more prevalent after cardiac surgery[38-42]. Early research suggested that cognition decline was solely attributable to the use of CPB[42]. However, recent well-designed randomized trials report that the use of CPB should not be blamed for the increased risk of POD/POCD after cardiac surgery[43-45]. Moreover, CPB should not be avoided to prevent POCD, as avoiding CPB was not found to improve cognitive function[5,43-45].

A significant risk factor for POD/POCD is surgical trauma leading to systemic inflammatory response syndrome (SIRS)[38,45,46]. The activation of the immune system make the brain more prone to cognitive decline[45]. Ischemia-reperfusion injury, complement activation, heparin neutralization and the contact of blood with the materials of the bypass circuit, contribute to the perioperative SIRS[47]. Moreover, SIRS is responsible for the blood-brain barrier dysfunction leading to cerebral inflammation with a potentially role in POCD pathogenesis[45,48]. Several studies considering the possible therapeutic role of corticosteroids in the systemic inflammation have investigated their potential protective role[29,49]. Low dose dexamethasone (0.1 mg/kg) administration, long (ten hours) before surgery, seems promising[49].

Although CPB per se should not be blamed for POD/POCD after cardiac surgery, CPB related factors pose a significant risk for developing POD/POCD[45,50]. There is a hypothesis that the cerebral micro-emboli along with bad handling of CPB increase the risk for POD/POCD. However, several studies regarding beating-heart surgery were unable to demonstrate a reduction in POCD incidence[43,51,52].

Finally, intra-operative management plays a vital role in postoperative cognitive status. Combined with the aforementioned risks factors that apply to all surgical patients, intra-operative hemodilution, hyper-coagulability, and extreme range of arterial blood pressure may contribute to the high prevalence of POD/POCD[45,53]. Hemodilution has a great impact and a decline in the hematocrit level greater than 12 %, intra-operatively, represents the threshold for cognitive decline[45,54].

POD/POCD and the possible neuroprotective effect of anesthesia

Neuroprotection is a broad term including pharmacological and non-pharmacological interventions[9]. Pharmacological neuroprotection refers to the administration of drugs in order to reduce the clinical effects of cerebral damage. The main mechanisms are the increased tolerance of the brain tissue to ischemia and the change of intracellular response to energy supply deprivation[10].

Thiopental was the first intravenous anesthetic agent tested for its potential ability to protect the brain[9,10]. It was thought that it could reduce the cerebral adenosine triphosphate (ATP) requirements and enhance the brains' tolerance time to ischemia. However, the evidence is still conflicting[9]. A study in patients with acute aortic dissection, receiving thiopental, did not show a reduction in the permanent neurologic damage [55]. In another study, the effect of thiopental on increased intracranial pressure was compared to that of hypertonic saline and was shown that thiopental might decrease the intracranial pressure, but not as effectively as the hypertonic saline[56]. Finally, when compared to propofol, thiopental increased the risk of POD, in adults undergoing major elective surgery[57].

Propofol, the newest intravenous agent, may achieve more promising results on flow-metabolism coupling[10]. It maintains the cerebral blood flow reaction with respect to CO_2 partial pressure changes. The final result is better ischemia handling[10]. Propofol has strong anti-inflammatory properties and reduces the stress-induced

apoptosis[10,58]. Moreover, it increases the neuronal tolerance to hypoxia and may improve the quality of brain recovery[9,58-60]. In a randomized trial that assessed the effect of propofol titrated to burst suppression before and during clipping for intracranial aneurysm, no difference was found between the propofol and control groups regarding cognitive function testing[61]. However, propofol, when combined with dexmedetomidine in rats, shows more promising neuroprotective properties[62]. Based on its anti-inflammatory action, the administration of the optimal dose of propofol, during a more suitable time interval could be the approach to a less impaired postoperative cognition.

Volatile anesthetics have also been investigated regarding their neuroprotective action. Activation of antioxidant enzymes and inhibition of carboxy-terminal modulator protein could be the main pathways[10]. However, data are still lacking, especially regarding potential long-term benefits. Maintenance with desflurane results in a better quality of emergence, and less cognitive impairment after prolonged surgery, compared to sevoflurane[22]. On the other hand, sevoflurane has a negative influence on short- and long-term cognition when compared to propofol[12]. Propofol maintenance is associated with higher cerebral perfusion pressure when compared to volatile agents, but not with better brain relaxation scores[10]. Further data seems mandatory regarding the full neuroprotective spectrum of volatile agents.

Several agents and interventions have also been studied with respect to brain protection. Hudetz et al[63] suggest that ketamine has intense anti-inflammatory action and attenuates POCD after cardiac surgery. Intra-operative magnesium administration may improve the cognitive function of patients undergoing carotid endarterectomy[64]. However, magnesium does not have neuroprotective properties in patients undergoing cardiac surgery[65]. Intravenous lidocaine does not decrease the postoperative cognitive impairment of cardiac patients[66]. Moreover, high doses of lidocaine are independent predictors of POCD[16]. Intravenous ondansetron administration postoperatively seems to protect the cognitive status of patients undergoing hip fracture surgery[67]. Current literature suggests the significance of anesthesia depth monitoring in an attempt to reduce the POD/POCD incidence[68-70]. Two studies have investigated the effects of the level of anesthesia on POCD, and the results are conflicting[70,71]. However, it seems that when the monitoring of the anesthetic depth is combined with the cerebral oxygenation monitoring the results are more promising[68]. It seems that neuroprotection is not a "one-man-show". In order to achieve the best possible results, multimodal interventions may be the best strategy.

Quality of life

POD/POCD may affect multiple aspects of patients' quality of life. Also, it is associated with increased morbidity and mortality[5]. There is a clear link between POD/POCD, impaired postoperative recovery, and prolonged rehabilitation[1-3]. The length of hospital stay rises at least two to five days, and the risk of hospital readmission is increased[3,72]. Moreover, patients with any form of cognitive decline are at a 2- to 5-fold increased risk of major complications such as cardiac arrest, thromboembolic disease and, respiratory failure[3,72].

POD/POCD may lead to increased physical frailty and a 3-fold higher risk for health care institution admission with the potential complete loss of independence[4]. Moreover, 70 % of patients suffering from some form of postoperative cognitive decline will die within five years, compared to 35 % of patients with intact cognition[4]. POD/POCD can lead to great disability and to an unacceptable everyday quality of life. Although it cannot be considered as a direct life-threatening condition, it seems that patients suffering from POD/POCD are facing a significantly increased risk of death within a 5-year time-frame.

Enumerating the actual economic burden

Ongoing research confirms that POD/POCD surpassingly expand the yearlong expenses[3,7,8]. In 2004 the additional healthcare cost was estimated at €2,281 minimum per patient[7,33,69,72,73]. Thinking about the actual expenses, one should keep in mind that every year, 12.5 million individuals over 65 years of age are hospitalized and at least 20 % of them will experience some form of postoperative cognitive disorder[73]. More importantly, the median everyday expenses per patient developing some form of postoperative cognitive dysfunction proved to be 2.5 times higher compared to the everyday costs of the rest surgical patients[73].

Vacas et al[7] described the healthcare-associated costs as "astronomic" as the delirium alone costs at least €139 billion every year in the United States. Those expenses range along with the severity of the underlying disease, and one can compare them with the annual costs for cardiovascular disease and diabetes[7,73]. Additionally, the aforementioned numbers refer strictly to the in-hospital care of these patients and not to the expenses related to morbidity[7]. More specifically, patients suffering from POD/POCD remain in hospital two to five days longer and are experiencing an increased risk of health care institution admission [72]. All the above could be translated into additional costs of €54,752 per patient every year[72].

Conclusion

POD/POCD is a common postoperative complication. Several risk factors have been recognized, and certain types of operations are accompanied by a higher risk of POD/POCD. Given the complex nature of POD/POCD high-suspicion index and the adoption of a multimodal neuroprotective approach could be lifesaving.

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