

Current aspects in postoperative cognitive dysfunctions, including otolaryngological procedures

Rogowska A. *, Wygnał N.¹, Simonienko K.¹, Kwiatkowski M.¹, Kuryga D.²

1. Department of Psychiatry, Medical University of Białystok, Poland

2. Department of Otolaryngology, Medical University of Białystok, Poland

ABSTRACT

Area disorders typically affect executive function, memory, attention, and verbal processing. Factors known to influence postoperative cognitive impairment are: age, preoperative cognitive functioning, and type of anesthesia. Current research into POCD is focused on cardiac and gastric surgery. A rapidly developing surgical technique is endoscopic surgery; specifically, endoscopic transnasal surgery, where a “dry” operating field is required. To date there is little research assessing the impact of this type of surgery on the development. POCD. In the current study we determine the possibility of occurrence of POCD, and investigate its prevention, in the aforementioned surgical situation. General ways to show existing research on

POCD in the context of skull base surgery. Hypothetically, less tissue injury is associated with less inflammatory reaction and thus with the reduction of cognitive dysfunctions. Analysis of operating methods (such as derating RR and HR) and their potential impact on POCD. POCD is a temporary postoperative disorder and correlates with poor recovery after surgery. The causes of POCD are multifactorial; however, the immune response following surgery may be the initial factor to initiate the damage-causing ischemic response. Careful anesthesiological and surgical procedures lower the likelihood of POCD.

Key words: Cognitive disorders, memory disorders, endoscopy, anesthesiology, postoperative complications

***Corresponding author:**

Department of Psychiatry
Medical University of Białystok
16-070 Choroszcz, Poland
Tel./ Fax: +48857193977; e-mail: anna_rogowska@o2.pl

Received: 19.08.2015

Accepted: 1.12.2015

Progress in Health Sciences

Vol. 5(2) 2015 pp 193-199

© Medical University of Białystok, Poland

INTRODUCTION

A common and clinically important complication of surgery is postoperative cognitive dysfunction, or POCD. POCD is a mild form of ischemic brain damage that occurs in the postoperative period and is characterized by impaired concentration and memory problems, which may persist for months or even years after the surgery. Studies of POCD are extensive, encompassing multiple surgical specialties ranging from cardiac surgery to minor outpatient interventions. Significant well-known risk factors for the development of POCD include: type of surgery, duration and type of anesthesia administered during surgery, advanced patient age, history of alcohol abuse, and use of anticholinergic medications. At present, the incidence of POCD is difficult to determine because formal criteria for correct diagnosis and evaluation are lacking. Many studies have attempted to systematize the definition of POCD and its timing. There is general agreement that POCD consists of subtle disruptions of thought processes, which may have a significant impact on the patient's health; however, a precise definition is yet to be established.

Early POCD, i.e. that which is observed within the first few days of surgery, has previously been assessed using the Post-operative Quality of Recovery Scale [1]. The results of this study indicate that although the disorder is transient in nature, for most patients the cognitive impairment fails to resolve within 3 days post-surgery.

Previous POCD studies focused on cardiac surgery because, until recently, cognitive impairment after cardiac surgery was considered to result from physiological disturbances associated with the cardiopulmonary bypass technique. In 2011, a study was conducted in 644 patients, which indicated that cardiac surgery and associated procedures were principal predictors of early (up to 7 days after surgery) POCD [2]. Research has since shown that the immune system is a key element in the pathogenesis of POCD after cardiac surgery [3]. Also in support of this hypothesis, are the findings of a recent study that suggest inflammatory neuronal changes may be fundamental in the mechanism of postoperative cognitive dysfunction [4]. The relationship between the choice of anesthesia and the occurrence of POCD has also been studied, and epidural anesthesia was found to be safer and less likely to result in POCD than general anesthesia [5].

There are increasing possibilities for a large number of minor surgical interventions to be carried out on an outpatient basis. Although the benefits of such procedures are well established, outpatient surgery presents another challenge: the expectation of prompt recovery soon after surgery. Cognitive complications, including delirium and POCD, have

been reported to be less common in outpatient surgery [6].

Interestingly, the type of anesthesia used has also been hypothesized to influence the development of POCD. However, previous studies, including those specifically related to outpatient interventions, failed to provide sufficient evidence to conclude whether intravenous anesthesia (propofol) vs. inhalational reduces the risk of delayed cognitive dysfunction [7]. Cerebral oxygen saturation (SCO₂), which represents oxygen balance in the brain, has also been shown to be an effective prognostic factor for POCD [8].

The frequency of perioperative cognitive dysfunction (POCD) in orthopedic patients varies from 16% to 45% [9]. Certain studies indicate that the possibility of monitoring patients using near infrared spectroscopy (NIRS) during lumbar spine surgery in a prone position may be helpful in reducing the risk of POCD.

Current techniques and physician awareness of POCD risk are expected to increase pressure on the need for optimization of surgical and anesthesiological procedures. In the current article we review the literature related to POCD, with a particular focus on specific risk factors in otolaryngological surgery.

Definition and differential diagnosis

POCDs are transient clinical phenomena defined by Bedford as "adverse cerebral effects of anesthesia on old people" [10]. In 2008, Chung and Assmann published case studies of two young people with POCD, confirming that POCD may in fact occur at any age [11]. After ambulatory surgeries, these patients caused serious road accidents in the direct postoperative phase. According to recent data, 40% of patients older than 60 years of age suffer from POCD after surgery; however, in the 3 months following surgery only 10% of patients older than 60 are diagnosed with POCD [12]. Impairments in attention, memory, executive functions, and some verbal functions extends the recovery period after surgery and negatively affects the patient's ability to function effectively in family and society. Nowadays, as the result of the development of modern surgical techniques, which enable doctors to carry out extensive surgeries in increasingly older patients, POCD is likely to occur much more frequently.

Cognitive functions are mental activities used for spatial orientation, to acquire information about oneself, to analyze a situation, to formulate conclusions, and to make decisions and execute action [13]. The most frequent symptoms occurring in the course of POCD are memory and spatial orientation disturbances, as well learning, thinking, attention and speech disorders. POCD must be distinguished from delirium, central anticholinergic syndrome, dementia, and akinetic crisis [14].

Epidemiology

Most studies of POCD published to date relate to cardiac surgery, particularly that requiring cardiopulmonary bypass. Current research on the effects of anesthesia on cognitive abilities focuses on: the type of anesthesia, whether it is local or general, duration, and type of formulation used. The age of respondents and their preoperative cognitive functioning also is also of interest.

Data concerning the incidence of POCD vary, since they depend on the definition of POCD, the patient sample and control group, the measurement method used, and the method of statistical evaluation [14-16]. Krenk [17] presented data showing that POCD may refer to all age groups, but in patients older than 60, the symptoms persist longer and lead to the limitation of normal activity. Monk [18] reported that on the day of hospital discharge, POCD had been diagnosed in 36.6% of patients aged 18–39, 30.4% of those 40–59 years old, and 41.4% of patients older than 60. All patients had undergone extensive surgeries (i.e. surgery scheduled under general anesthesia that was expected to last 2 h or longer); however, none underwent cardiac surgery. Three months after discharge, POCD was still reported in 12.7% patients older than 60. Previous studies reported that a higher incidence of the disorder is typically observed in certain patient groups, e.g. those with cardiovascular disease or subclinical dementia [19-21].

Many years of research has confirmed that POCD is a temporary phenomenon. In most patients diagnosed with POCD, cognitive impairment lasts for up to 3 months after the operation. For the minority of patients, POCD symptoms may be sustained for far longer, potentially becoming a permanent condition which will have a major impact on quality of life. Steinmetz [22] documented, following an 8.5-year study, that POCD is correlated with increased mortality rate, disability leading to premature disability benefits, and additional social encumbrances for society. It is important to identify early signs of cognitive impairment. Monk [18] also reported risk of death is increased if POCD was observed when patients were being discharged from hospital (Cox proportional Hazard Ratio 1.63).

Diagnostic methods

POCD is diagnosed using psychometric tests. The recommendations of the 1995 consensus indicate the results of several tests should be considered in the diagnostic process, and these are described in Table 1. In long-term studies, tests such as the Stroop Test, paper and pencil memory tests, or fourfold tests are typically used [23]. Interestingly, there is evidence to suggest that the selection of tests and the order in which they are administered, may have a significant impact on study outcomes [24]. It is recommended that tests evaluating the level of

predisposition to anxiety and depression be used in parallel, as these conditions may subsequently affect cognitive function.

Table 1. Methods used in neuropsychological evaluation

Test	Definition
Rey Auditory Verbal Learning Test	Assesses the level of verbal learning and memory. It gained great popularity due to the simplicity and ease of testing and comprehensibility for most age groups.
Trail Making Test: A and B (TMT)	Assesses concentration, divisibility, mental flexibility and variability comments.
Grooved Pegboard Test	A test of manual dexterity and motor coordination.
Digit Span Test	Assesses the capacity and efficiency of working memory.
Wisconsin Card Sorting Test (WCST)	Measures executive function, understood as human oversight functions.
Stroop Test	The original version tests reading speed, verbal memory and executive functions.

Full neuropsychological assessment often lasts more than 2 hours. This presents another difficulty, as the stress associated with surgery can falsify the actual performance level of cognitive ability [25].

The Short Cognitive Performance Test (SKT) is a potential alternative [26]: it can be performed within 15 minutes and is based on the speed of processed information. It examines changes in cognitive abilities such as attention, concentration, and memory. The test is simple and attractive, and is therefore greatly popular among researchers [27]. Chung [28] uses a driving simulator to gain quick diagnostics of cognitive disturbances.

The Post-operative Quality of Recovery Scale (PQRS) is also used in many studies. The Postop QRS is a measurement tool to assess many factors influencing the post-surgical convalescence [29, 30]. It is a frequently used method, which takes only 5 to 6 minutes to conduct. The results obtained from this survey show the condition of the patient, but cannot be used to indicate the presence of neuropsychological disorders.

Pathogenesis and risk factors for POCD

The mechanism underlying the development of cognitive dysfunctions after a surgery and anesthesia is not clear. As mentioned above, animal experiments indicate that the immune response occurring as a result of surgery may play a role. In a study of mice undergoing surgery, Terrando [31] proved that the activation of the TNF α /NF- κ B-dependent inflammatory cascade and consequent cytokine release leads to a disturbance of the integrity of the blood-brain barrier. This facilitates macrophage migration to the hippocampus and results in a weakening of memory functions. Both TNF α (tumor necrosis factor) and NF- κ B (a protein complex that acts as a transcription factor) play a key role in regulating the immune response to infection [32]. The study also demonstrated that activation of anti-inflammatory anticholinergic signal cascade blocks this mechanism and cognitive functions remain unimpaired.

Clinical observations indicate that POCD more often occurs after extensive surgeries in which general anesthesia was used, after re-surgery, and following operative complications. These observations support the idea that the inflammatory component is a significant factor in the development of cognitive disorders.

The impact of the drugs used in general anesthesia on cognitive functions depends on the pharmacodynamics and pharmacokinetics of these substances; however, what is clear is the shorter the drug action, the shorter the duration of POCD immediately after surgery. At present, there is no evidence to suggest that these drugs cause "chronic" POCD. Twin studies have not provided any evidence of neurotoxicity of the applied anesthetics [33]; in addition, there are no data proving that POCD occurs less frequently following local anesthesia, as compared to general anesthesia.

A patient's age is a very important risk factor for POCD. The ability of the central nervous system to compensate in response to anesthesia decreases with age. Imaging examinations performed in elderly people often reveal ischemic foci without clinical symptoms (silent brain ischemia), which is predisposes these patients to POCD [34]. Another risk factor is alcohol abuse, as shown by Hudetz [35] in a randomized study. Low education level also corresponds to high likelihood of POCDs [23, 36]. The significance of genetic factors is also a subject of discussion [16].

Prevention of POCD

When assessing the need for extensive surgeries, especially in elderly people, the benefits and potential negative consequences should always be properly balanced and the potential occurrence of POCD should be taken into account. In such

situations it is useful to determine the patient's preoperative cognitive status.

POCD occurs more often and is more intensive after extensive surgeries (e.g. cardiac surgery, using cardiopulmonary bypass). To try to prevent cognitive disorders, it is important to prevent intra- and postoperative complications. To what extent minimally invasive surgical techniques prevent cognitive disorders has not yet been studied; however, hypothetically, less tissue injury is associated with less inflammatory reaction and thus should correlate with a reduction in cases of cognitive dysfunctions [18,37]. As mentioned above, generally, it is assumed that the shorter action of the anesthetic, the shorter the duration of POCDs. Remembering this, we should critically analyze the present premedication practice; for example, midazolam (dormicum), which may result in cognitive disorders. In his publication, Dressler [33] demonstrated that after 1 or 2 hours of general anesthesia with propofol/remifentanyl and premedication with midazolam, memory disorders occurred on the first day after surgery [38]. With regard to the modern concept of perioperative proceedings, which assumes early patient cooperation after the surgery (fast-track treatment), the above-mentioned limitations of cognitive functions receive negative evaluation. On the other hand, we still do not have evidence that techniques other than general anesthetics reduce the incidence of POCD [39].

In many areas of surgery, progress is connected with the development of endoscopic techniques, which often create special requirements for general anesthesia. Endoscopic transnasal surgery, in which bleeding during the surgery must be kept low, is a special challenge. Little bleeding and good visibility in the operating field has been achieved by maintaining a low heart rate (HR) and gradually lowering the mean arterial blood pressure (MAP) [40]. The anesthetics used in such endoscopic surgeries were propofol and remifentanyl or sevoflurane and esmolol [41]. The influence of controlled hypotension during endoscopic procedures on middle cerebral artery peak systolic velocity was additionally evaluated when good, bloodless conditions of the operating field were achieved [42]. More than half of patients operated standard flow rate fell below the lower limit of normal and end-diastolic velocity was below the limit of even 60% of patients in these conditions, as is apparent from earlier studies could be a risk of ischemic brain tissue. Previous studies have demonstrated a correlation between middle cerebral artery peak systolic velocity and cerebral blood flow; as such, it is possible that increased risk of cerebral ischemia might have occurred in these conditions. No neurological disturbances were found in any of the patients in the postoperative period; however, cognitive functions need to be monitored in patients

who have undergone this kind of surgery. Other works by the same research team indicate that lowering the middle cerebral artery peak systolic velocity was directly caused by a reduction of the hemodynamic parameters of the cardiovascular system, not the set of drugs used for general anesthesia. Although lowered RR (blood pressure) and HR (Heart Rate) parameters were maintained within the limits commonly regarded as safe, the blood flow velocity occasionally dropped below the lower limit of the normal range and blood flow velocity parameters lowered unevenly, which (according to some scholars) may prove approximating the phase of failure of cerebral blood flow autoregulation mechanisms [43]. In another study [44], the serum concentration of S-100 and NSE (neuron-specific enolase) proteins was evaluated, as these are considered to be markers of nervous tissue injury. Increased concentration of NSE was found in 5 of 6 patients who had a drop of middle cerebral artery peak systolic velocity below the lower limit of the normal range. Although neurological complications were not observed, the results of the presented studies point to the need to evaluate the possibility of POCD occurring in patients treated with transnasal endoscopic surgery. In this case, POCD may be connected, not with the extensiveness of the operation but rather with potential hemodynamic disorders and perfusion.

Developments in the cerebral circulation during several hours of free maintenance of heart function and hypotension should be the subject of further studies. Could rate evaluating the safety margin used methods of intraoperative anesthesia, and their impact on the further functioning of the patient. It is important that future studies on this disorder focus on measures to prevent the occurrence of POCD. Although many studies have attempted to elucidate whether electroencephalography (EEG) monitoring of the depth of anesthesia may contribute to limiting POCD [45, 46], to date this question remains unanswered and should be the subject of future studies.

CONCLUSIONS

POCD is both widespread and common. Its occurrence depends on a variety of factors. POCD is difficult to define and the exact investigational strategy remains uncertain due to the extensiveness of the phenomenon. Most studies conducted so far agree that the risk of POCD increases concurrently with the patient's old age, diseases of central nervous system, cardiovascular disorders and extensive surgery. POCD is a temporary postoperative disorder and correlates with poorer recovery after the surgery. Importantly, careful anesthesiological and surgical procedures lowers the likelihood of POCD. The dynamically developing area of minimally invasive surgery, especially endoscopic transnasal

surgery in which a "dry" operating field is required, calls for research into the occurrence of POCD following this type of surgery and methods of prevention. The management strategy for POCD should be multimodal, and involve close cooperation of the anesthesiologists, surgeons, geriatric specialists, psychologists and the patient's family members. This network will promote early rehabilitation and avoid loss of autonomy by postoperative patients. Future clinical research should concentrate on factors that are likely to provide a better understanding of POCD.

Conflicts of interest

The authors declare no conflicts of interest.

Funding

No sources of support provided.

REFERENCES

1. Newman S, Wilkinson DJ, Royse CF. Assessment of early cognitive recovery after surgery using the Post-operative Quality of Recovery Scale. *Acta Anaesthesiol Scand*. 2014 Feb;58(2):185-91.
2. Evered L, Scott DA, Silbert B, Maruff P. Postoperative cognitive dysfunction independent of type of surgery and anesthetic. *Anesth Analg*. 2011 May;112(5):1179-85.
3. van Harten, AE, Scheeren, TWL and Absalom AR. A review of postoperative cognitive dysfunction and neuroinflammation associated with cardiac surgery and anaesthesia. *Anaesthesia* 2012;67:280-293.
4. Hovens IB, Schoemaker RG, van der Zee EA, Absalom AR, Heineman E, van Leeuwen BL. Postoperative cognitive dysfunction: Involvement of neuroinflammation and neuronal functioning. *Brain Behav Immun*. 2014 May;38: 202-10.
5. Shi HJ, Xue XH, Wang YL, Zhang WS, Wang ZS, Yu AL. Effects of different anesthesia methods on cognitive dysfunction after hip replacement operation in elder patients. *Int J ClinExp Med*. 2015 Mar 15;8(3):3883-8.
6. Rasmussen LS, Steinmetz J. Ambulatory anaesthesia and cognitive dysfunction. *Curr Opin Anaesthesiol*. 2015 Aug 25.
7. Ortiz AC, Atallah AN, Matos D, da Silva EM. Intravenous versus inhalational anaesthesia for paediatric outpatient surgery. *Cochrane Database Syst Rev*. 2014 Feb 7;2:CD009015.
8. Ni C, Xu T, Li N, Tian Y, Han Y, Xue Q, Li M, Guo X. Cerebral oxygen saturation after multiple perioperative influential factors predicts the occurrence of postoperative cognitive dysfunction. *BMC Anesthesiol*. 2015 Oct 26;15 (1):156.

9. Tomaszewski D. Biomarkers of Brain Damage and Postoperative Cognitive Disorders in Orthopedic Patients: An Update. *Biomed Res Int.* 2015;402959.
10. Bedford PD. Adverse cerebral effects of anaesthesia on old people. *Lancet.* 1955 Aug 6;269(6884):259-63.
11. Chung F, Assmann N. Car accidents after ambulatory surgery in patients without an escort. *Anesth Analg* 2008;106:817-20.
12. Rundshagen I. Postoperative cognitive dysfunction. *Dtsch Arztebl Int.* 2014 Feb; 111 (8):119-25.
13. Warwas K, Szwed K, Borkowska A. Zaburzenia funkcji poznawczych po operacjach chirurgicznych. *Neuropsychiatria i neuropsychologia.* 2010;5(2):64-70. (Polish)
14. Newman S, Stygall J, Hirani S, Shaefi S, Maze M. Postoperative cognitive dysfunction after noncardiac surgery. *Anesthesiology.* 2007 Mar; 106(3):572-90.
15. Avidan MS, Evers AS. Review of clinical evidence for persistent cognitive decline or incident dementia attributable to surgery or general anesthesia. *J Alzheim Dis.* 2011;24:201-16.
16. Ghoneim MM, Block RI. Clinical, methodological and theoretical issues in the assessment of cognition after anaesthesia and surgery: a review. *Eur J Anaesthesiol.* 2012 Sep; 29(9):409-22
17. Krenk L, Rasmussen LS, Kehlet H. New insights into the pathophysiology of postoperative cognitive dysfunction. *Acta Anaesthesiol Scand.* 2010;54:951-6.
18. Monk TG, Weldon BC, Garvan CW, Dede DE, van der Aa MT, Heilman KM, Gravenstein JS. Predictors of cognitive dysfunction after major noncardiac surgery. *Anesthesiology.* 2008 Jan; 108(1):18-30.
19. Müllges W, Berg D, Schmidtke A, Weinacker B, Toyka KV. Early natural course of transient encephalopathy after coronary artery bypass grafting. *Crit Care Med.* 2000 Jun;28(6):1808-11.
20. Selnes OA, Grega MA, Bailey MM, Pham LD, Zeger SL, Baumgartner WA, McKhann GM. Cognition 6 years after surgical or medical therapy for coronary artery disease. *Ann Neurol.* 2008 May;63(5):581-90.
21. Kline RP, Pirraglia E, Cheng H, De Santi S, Li Y, Haile M, de Leon MJ, Bekker A, Bekker A. Surgery and brain atrophy in cognitively normal elderly subjects and subjects diagnosed with mild cognitive impairment. *Anesthesiology* 2012 Mar;116(3):603-12.
22. Steinmetz J, Christensen KB, Lund T, Lohse N, Rasmussen LS, ISPOCD Group: Long-term consequences of postoperative cognitive dysfunction. *Anesthesiology.* 2009 Mar;110(3): 548-55.
23. Moller JT, Cluitmans P, Rasmussen LS, et al. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. *International Study of Post-Operative Cognitive Dysfunction. Lancet* 1998; 351(9106):857-61.
24. Cognitive Dysfunction after On-Pump Operations: Neuropsychological Characteristics and Optimal Core Battery of Tests. *Stroke Research and Treatment* 2014;302824.
25. Sandi C. Stress and cognition. *Wiley Interdiscip Rev Cogn Sci.* 2013 May;4(3):245-61.
26. Lehfeld H1, Erzigkeit H. The SKT-a short cognitive performance test for assessing deficits of memory and attention. *Int Psychogeriatr.* 1997;9 Suppl 1:115-21.
27. Lehfeld H, Erzigkeit H. The SKT - a short cognitive performance test for assessing deficits of memory and attention. *Int Psychogeriatr.* 1997;9(1):115-21.
28. Chung F, Kayumov L, Sinclair DR, Edward R, Moller HJ, Shapiro CM. What is the driving performance of ambulatory surgical patients after general anesthesia? *Anesthesiology* 2005 Nov;103(5):951-6.
29. Newman S, Wilkinson DJ, Royse CF. Assessment of early cognitive recovery after surgery using the Post-operative Quality of Recovery Scale. *Acta Anaesthesiol Scand.* 2014 Feb;58(2):185-91.
30. Lindqvist M, Royse C, Brattwall M, Warrén-Stomberg M, Jakobsson J. Post-operative Quality of Recovery Scale: the impact of assessment method on cognitive recovery. *Acta Anaesthesiol Scand.* 2013 Nov;57(10):1308-12.
31. Terrando N, Eriksson LI, Ryu JK, Yang T, Monaco C, Feldmann M, Jonsson Fagerlund M, Charo IF, Akassoglou K, Maze M. Resolving postoperative neuroinflammation and cognitive decline. *Ann Neurol* 2011;70: 986-95.
32. Schütze S, Wiegmann K, Machleidt T, Krönke M. TNF-induced activation of NF-kappa B. *Immunobiology.* 1995 Jul;193(2-4):193-203.
33. Stratmann G. Neurotoxicity of anesthetic drugs in the developing brain. *Anesth Analg.* 2011 Nov;113(5):1170-9.
34. Ito A, Goto T, Maekawa K, Baba T, Mishima Y. Postoperative neurological complications and risk factors for pre-existing silent brain infarction in elderly patients undergoing coronary artery bypass grafting. *J Anesth.* 2012 Jun;26(3):405-1
35. Hudetz JA, Iqbal Z, Gandhi SD, Patterson KM, Hyde TF, Reddy DM, Hudetz AG, Warltier DC. Postoperative cognitive dysfunction in older patients with a history of alcohol abuse. *Anesthesiology.* 2007 Mar;106(3):423-30.
36. Ancelin ML, De Roquefeuil G, Ledesert B, Bonnel F, Cheminal JC, Ritchie K. Exposure to

- anaesthetic agents, cognitive functioning and depressive symptomatology in the elderly. *Br J Psychiatry*. 2001;178:360–6.
37. Gameiro M, Eichler W, Schwandner O, Bouchard R, Schon J, Schmucker P. Patient mood and neuropsychological outcome after laparoscopic and conventional colectomy. *Surg Innov*. 2008;15(1):171–8.
 38. Dressler I, Fritzsche I, Spies C, Cortina K, Rundshagen I. Psychomotor dysfunction after remifentanyl/propofolanaesthesia. *Eur J Anaesthesiol*. 2007;24:347–54.
 39. Mason SE, Noel-Storr A, Ritchie CA. The impact of general and regional anesthesia on the incidence of postoperative cognitive dysfunction and postoperative delirium: a systematic review with meta-analysis. *J Alzheimers Dis* 2010; 22:67–79.
 40. Sieskiewicz A, Drozdowski A, Rogowski M. The assessment of correlation between mean arterial pressure and intraoperative bleeding during endoscopic sinus surgery in patients with low heart rate. *Otolaryngol Pol*. 2010;64(4):225-8. (Polish)
 41. Drozdowski A, Sieskiewicz A, Siemiątkowski A. Reduction of intraoperative bleeding during functional endoscopic sinus surgery. *Anestezjol Intens Ter*. 2011;43(1):45-50.
 42. Sieskiewicz A, Lewczuk A, Drozdowski A, Lyson T, Rogowski M, Mariak Z. Is it safe to decrease hemodynamic parameters to achieve bloodless surgical field during transnasal endoscopic procedures? Our experience in fifteen patients. *Clin Otolaryngol*. 2013;38(4): 326-9.
 43. Sieskiewicz A, Lyson T, Piszczatowski B, Rutkowski R, Turek G, Lewczuk A, Drozdowski A, Rogowski M, Mariak Z. Blood flow velocity in the middle cerebral artery during transnasal endoscopic skull base surgery performed in controlled hypotension. *Neurol Neurochir Pol*. 2014;48:181-7. (Polish)
 44. Sieskiewicz A, Groblewska M, Lysoń T, Piszczatowski B, Turek G, Rutkowski R, Mroczko B, Rogowski M, Mariak Z. Neurobiochemical markers of brain ischemia in patients subjected to endoscopic skull base surgery under controlled hypotension. *J Neurosurg Sci*. 2014 May 20.
 45. Farag E, Chelune GJ, Schubert A, Mascha EJ. Is depth of anesthesia, as assessed by the bispectral index, related to postoperative cognitive dysfunction and recovery? *Anesth Analg*. 2006 Sep;103(3):633-40.
 46. Chan MTV, Cheng BCP, Lee TMC, Gin T, and the Coda Trial Group: BIS-guided anesthesia decreases postoperative delirium and cognitive decline. *J Neurosurg Anesthesiol*. 2013 Jan; 25(1):33-42.