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The Occurrence of Postoperative Cognitive Dysfunction (POCD) – Systematic Review

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Summary

Aim. The aim of this systematic review was to summarize the present literature on cognitive dysfunctions in adults after surgical procedures.

Methods. MEDLINE: PubMed, OVID, Web of Science, EBSCO databases have been searched using relevant key words. The literature on cognitive dysfunctions after surgical procedures has been reviewed and the risk factors of POCD occurrence have been analyzed.

Results. The results from seven articles describing neuropsychological studies of 2,796 patients have been analyzed. The tests were conducted within a very short time after the procedure (7 days), within a short time (3 months) and within a long-term perspective (12–60 months). POCD within a very short time after the operation occurred with a different frequency: from 17 to 56% with a tendency to resolve over time (3–34.2%). POCD risk factors have been identified: advanced age, insulin resistance, a short education period. The type of surgical procedure, anesthesia or microembolization related to CPB, does not influence the occurrence of POCD.

Conclusions. It seems that one should focus on searching risk factors outside the procedures, and that certain recommendations should be developed regarding perioperative proceedings which might be beneficial for patients at risk of the impairment of their cognitive functions after a surgical procedure.

Key words: surgical procedure, cognitive functioning anesthesia

Introduction

Surgical procedures and general anesthesia are associated with a number of complications [1, 2]. Postoperative cognitive dysfunction (POCD) is considered to be one of them [3]. POCD does not have one unified international definition [4]; some authors assume that it is a new deficit involving a cognitive function (or several cognitive functions), occurring after surgery. It can last for several days to several months [5].

Mild cognitive disorder (F06.7) is the closest definition available in ICD-10. Despite the lack of a unified definition of POCD, the authors agree that patients with POCD require longer hospitalization and readjustment in their domestic environment [4, 6, 7]. Such a patient loses the ability to acquire information, his/her language functions decline and so does abstract thinking, visual-spatial analysis, the understanding and assessment of situations and incidents, counting and problem solving skills. In consequence, his/her ability to cope with his/her personal, professional and social matters worsens. The influence of cognitive dysfunctions on routine everyday activities (e.g., taking medications) increases the risk of death [3, 8]. Some patients cannot return to their environment, and require specialist care, which has socioeconomic implications [6, 8, 9].

For many years POCD has been believed to be specific for cardiac-surgical patients, which was associated with the use of extracorporeal circulation [6, 10]. Nowadays, it is believed that POCD can occur at the same rate both after cardiac and non-cardiac surgeries and can be caused by an undiagnosed factor [11, 12].

POCD is a disorder which usually passes with time and mostly affects older people but can occur at any age [13]. The number of extensive operations of seniors will continue to increase among the ageing communities of highly developed and fast developing countries [5, 9, 12]. Therefore, the awareness and knowledge of perioperative personnel should involve cognitive dysfunctions.

Postoperative memory impairment

It was already in 1955 that long-term cognitive dysfunctions appeared after a surgical procedure and anesthesia. Most anesthetic techniques involve the reversible impairment of central nervous system (CNS), which means that CNS depression is a part of anesthesia. The agents administered intravenously during a general anesthesia induce an inhibiting effect on the brain stem reticular system and interact with specific receptors such as: opioid receptors or GABA (γ-aminobutyric acid). Neither the molecular mechanism nor the specific target point of routinely used anesthetics is known at present. It seems that synapse is the most important point of action at the cellular level. According to unitarist theory, all anesthetics induce an effect via the same mechanism, whereas according to the alternative approach, there are different effecting mechanisms for different groups of anesthetics. According to the Meyer-Overton rule, the strength of the effect of a desensitizing anesthetic depends on its solubility in lipids. At the molecular level, anesthetics can directly affect the lipid bilayer or receptor proteins of neurotransmitters, or the borderline between lipids and proteins [14].

It has been believed for many years that the effects of medications do not last longer than their pharmacological effects, and that the brain functions return to the initial status from before the surgical procedure. More and more evidence has proven this not to be true. Changes in brain functioning after anesthesia are prolonged or permanent neurological and neuronal changes occur. The brain seems to be particularly susceptible to changes in young and old-aged people. The earliest manifestation of neuron destruction in the brain is the worsening of the higher cortical functions, such as memory and recall. One of the difficulties in studying the effect of anesthetics upon cognitive dysfunction is the fact that anesthesia is hardly ever or almost never an independent procedure. Scientific research confirms that one of the mechanisms of the formation of cognitive dysfunctions can be the stress response to a surgical procedure [15]. Certain factors occurring during hospitalization – noise, isolation, harsh lighting, sleep disorders, and limitation of mobility – can result in a sensory overload and cause anxiety and, subsequently, an impairment of cognitive functions in elderly people [16].

The occurrence of cognitive dysfunctions can also be triggered by an immunological response of the body to the surgery causing the release of TNFα, which damages the blood–brain barrier. This causes the migration of macrophages to CNS (hippocampus) [17].

Risk factors

The risk factors of POCD can be divided into the following types, related to:

– the patient (e.g., advanced age, low level of education, coexisting brain vascular diseases, insulin resistance, genetic factors, coexistence of depression) [3, 18–22];
– the surgery (extensive surgery, intraoperative complications, the duration of the extracorporeal circulation) [19, 23];
– the anesthesia (prolonged anesthesia effects) [18, 19, 24].

The assessment of cognitive functions

Neuropsychological tests are considered to be among the objective methods of the assessment of cognitive functions (Table 1) [25–39]. A complete assessment of cognitive functions is extremely difficult. Conducting a full neuropsychological examination is tedious and straining for the patient. A number of factors can influence the obtained results, e.g., the impairment of sensory organs, the medications taken (e.g., opioids), an increased susceptibility to weariness, the motivation for performing the test, the level of emotional tension and the mood [41]. The tests should be performed at the same time of the day, in the same surroundings, by the same researcher. It is not recommended to perform tests when the patient still requires the administration of opioid medications. The significance of the assessment of the patient's performance before surgery has to be emphasized in order to determine the level of earlier intellectual functioning of the examined person [30, 41]. The usefulness of neuropsychological tests may be limited unless the interpretation of results is corrected for age, level of education, type of work and interests, and also unless the data can undergo a precise methodological and statistical analysis [30].

The aim of the study

The aim of this systematic review was to summarize the presently available literature on the impairment of cognitive functions of patients who have undergone a surgical procedure.

Method

This systematic review has been prepared according to the latest standards for systematic reviews published by the Institute of Medicine [42].

Research strategy

The content of the electronic literature and abstract databases available in: PubMed/MEDLINE, OVID, Web of Science, EBSCO, was searched. Key words such as ‛surgical procedure’, ‛cognitive dysfunctions’, ‛impairment of cognitive functions’, ‛cardiac surgery’ and ‛non-cardiac surgery’ were used for the verification. The search was limited only to the scientific studies conducted on people and published in English and Polish during the last 9 years (2008–2017). During the search, single key words and their combinations, separated by AND, OR, or both, were typed in. The number of quotations obtained after each search was scanned and reduced using the inclusion criteria which involved patients after surgical procedures whose cognitive functions had been assessed. 754 results were obtained. Full access was obtained to 112 articles, whereas 47 articles were subjected to a preliminary analysis in terms of the inclusion criteria based on their summaries. Eventually, 7 articles, to which full access (the whole paper) had been obtained, were included in the review.

Inclusion and exclusion criteria

It was decided that the analysis should consider the articles which:

– involved the examination of the level of cognitive functions before a surgery, afterwards and at least 3 months after the surgery; also the studies which were based on neuropsychological tests recommended in the statement [43] were considered for inclusion for comparative purposes.

The following articles were excluded from the analysis:

– opinions, letters to editor, conference reports, case studies, research on animals, and articles published in languages other than English and Polish;
– studies pertaining to patients after neurosurgical operations or with a brain injury;
– studies concerning the same or an overlapping case record of a group of patients described in an article already included in the review; in such a case we

used only the latest article which involved both the new data and the data reported earlier.

The eligibility of each article found was independently assessed on the basis of its full text by two reviewers, using the above-mentioned selection criteria. When the opinions of two reviewers on accepting an article to be eligible were divergent, then it was consulted with a third reviewer.

Gathering data

Both reviewers independently assessed the articles which had been selected by means of a standardized data gathering form, in order to register the required data, such as: the first author, year of publication, number of participants undergoing the surgical procedure and number of participants in the control group, neuropsychological tests used in the research, the results of the cognitive function impairment.

The quality of the research was assessed on the basis of four criteria:

1) the availability of data regarding the patients' cognitive performance at the beginning of the research;
2) the use of neuropsychological tests for the assessment of cognitive functioning;
3) the description of inclusion and exclusion criteria;
4) the correction of the assumptions which might affect the cognitive result, such as age and sex.

The above quality criteria have been selected as they are commonly used ones (number 3 and 4) and they are specific for the examination verifying the neurocognitive results (number 1 and 2).

Results and discussion

The prevalence of POCD occurrence after surgical procedures differed greatly between authors – from 17% in [45] to 56% in [45] (Table 2). POCD in the early postoperative period (7 days) occurred more often than in the later period (after 3 months) after different kinds of surgical procedures – both cardiac and non-cardiac surgery [3, 11, 56]. The results obtained from the analysis of the selected research are presented in Table 2. The drop in the POCD rate after 3 months (or a longer period) could be related to the improvement of the patient's general health condition –elimination of the cause of malaise and lack of disease symptoms led to better results during testing [40]. Furthermore, in a long-term period following the surgery there was no longer need to relieve the pain with opioids, which also affected cognitive functions. Monk et al. [3] have indicated that 3 months after a surgery the number of elderly persons (over 60 years of age) suffering from cognitive decline was over two-fold higher than that of middle-aged and younger individuals (12.7% vs. 5.6% vs. 5.7%). Still, the occurrence of POCD at discharge and 3 months after the surgery correlated with a higher risk of death within one year after the surgery (10.6% vs. 2.1% for patients who did not suffered from POCD) [3].

The results showing different POCD prevalence were associated with the fact that the authors selected their research tools and the time intervals between tests at their own discretion, that the tests were not conducted in a control group, and due to the possibility of ʻlearning' from the tests through repetitions during research [6, 23, 40, 45, 46]. In 1998 the, results of the multi-institutional International Study on Postoperative Cognitive Dysfunction (ISPOCD), lasting 1.5 years, were published. It was the first remarkable study which considered the ʻlearning effectʻ of standardized neuropsychological tests and the natural deviations of the results of these tests [47]. The ʻlearning effect' could be avoided by using different sets of words/numbers in particular tests [34, 38].

The type of surgery and anesthesia did not influence the prevalence of POCD. Evered et al. [11] have explored what influence the type of anesthesia and the scope of the surgery had upon the POCD occurrence. The risk of POCD after 3 months following an operation (coronary artery bypass grafting – CABG vs. total hip joint replacement – THJR vs. coronary angiography – CA) was in each group at a similar level. Significantly more patients experienced POCD within a short time (7 days) after CABG ($p < 0.01$), which was consistent with the results of research of other authors [43, 49]. Van Dijk et al. [55] also suggested that the type of the surgery did not induce any effect on deterioration and the maintaining of cognitive impairment within a long-term perspective (5 years), which might indicate the possibility of nonspecific risk factors (e.g., the susceptibility of the patient) [11, 50].

Early reports on the use of a cardiopulmonary bypass (CPB) indicated a high rate of complications after surgical procedures involving its use [51]. The imperfections of surgical techniques and equipment have caused the occurrence of neurological complications such as ischemic stroke or air microembolism [52]. The results of neurological complications – affecting cognitive processes – could suggest that the use of CPB was related to POCD. Liu et al. [44] indicated the lack of influence of the use of extracorporeal circulation and associated microembolism on the occurrence of cognitive dysfunctions.

Price et al. [45] indicated that the type of cognitive dysfunction did influence instrumental activities of daily living (IADL). Isolated memory disturbances affected the level of functioning in everyday life to a lesser extent – individuals whose scope of impairment covered executive functions or both executive and memory functions performed significantly worse. The deterioration within these two spheres affected not only the level of cognitive dysfunction but also the individual's performance in his/her domestic environment. This, in turn, could have influenced one's health recovery [45].

When analyzing the research results, it was confirmed that the presence of diabetes was not a POCD risk factor ($p = 0.47$ [46]; $p = 0.96$ [44]; $p = 0.1$ [11]). This complied with the results of Kadoi et al. [53] of 2005, who examined the relation between type 2 diabetes and cognitive dysfunctions. 6 months following surgery POCD occurred significantly more frequently in those individuals who required insulin therapy ($p < 0.01$) and who suffered from diabetic retinopathy ($p < 0.01$) [53], thus it was not the coexistence of diabetes but its complications which influenced the occurrence of cognitive dysfunctions. Probably, this resulted from the damaging effect of hyperglycemia causing microangiopathy, which led to the risk of brain stroke [54].

The level of education seemed to have a protective effect upon one's cognitive performance – the longer the education, the better the test results [3, 55, 56]. This can be explained using the concept of 'cognitive reserve' – a number of people are able to function on the same level in spite of pathological changes in their body. The duration of one's education and occupational activity (and also actively spent free time in older age) may increase this reserve, thus making some people less susceptible to changes [56–58].

A remarkable number of authors indicated that age was a risk factor of POCD [3, 11, 24, 44, 59]. Evered et al. [11] showed that, regardless of the type of surgery, age predetermined the occurrence of POCD 3 months after the surgery, which predisposed a search for POCD causes not related to the procedure itself (related to the patient). This was confirmed by research conducted earlier by Moller et al. [24], in which age was a factor of long-term cognitive impairment. These results are consistent with the current theory that the occurrence of POCD is associated with future cognitive decline amongst seniors [46].

A number of scientists used *the Mini–Mental State Examination* (MMSE) before a surgery. MMSE is, however, a tool which does not always disclose subtle changes within cognitive functions – for this reason, some patients might have mistakenly qualified to the group without cognitive dysfunctions, which affected the further interpretation of the research result [12, 56]. Avidan et al. [12] emphasized the necessity to avail sensitive tests for the preoperative assessment of the patients and control group participants – they have proven that those who were diagnosed with mild cognitive dysfunctions (in the preoperative period), manifested a deterioration of cognitive functions in a long-term perspective. Silbert et al. [46] compared the test results of the group of persons suffering from cognitive dysfunctions before the surgery with the group in which such dysfunctions were not found – in the long-term perspective the first group was exposed to a 9-fold higher risk of POCD after 12 months from the surgery (9.4% vs. 1.1%).

As it has already been said before, the patient's mood may affect the results of neuropsychological tests. In the course of depression some of the cognitive functions may become impaired (e.g., attention, memory, executive functions, and also psychomotor functions – information processing is slowed down) [28]. The symptoms of depression significantly affect the patient's functioning, which translates into the results of neuropsychological tests. The Beck Depression Inventory is a popular method for mood assessment. Although the influence of mood on cognitive functions is commonly known, only a number of authors chose to assess this parameter [3, 45, 56].

Research on genetic risk factors could also be found in the literature [4, 60, 61]. Mathew et al. [59] described the genetic variants of the inflammatory response of the body leading to postoperative cognitive dysfunctions. On the other hand, Shoair et al. [4], during their studies, have come to the conclusion that the risk of POCD 3 months after the surgery increased among patients with a particular genotype (APOE – 4).

These studies had, however, certain limitations – a small study group and no possibility to generalize the results.

A relationship between hypothermia and cognitive dysfunctions has been proven in animal model studies [62]. There were, however, no studies which would examine the influence of perioperative hypothermia on cognitive dysfunctions in people.

Conclusions

The identification of risk factors could become beneficial for persons who indicate a deterioration in terms of their cognitive functions in the preoperative period or for whom the surgery would be a ‘catalyst’ of cognitive dysfunctions.

It is recommended to talk to the patient and his/her family about the possibility of cognitive dysfunctions after the surgery. The patient’s carers are often surprised with the postoperative changes in the patient’s cognitive functions, and explaining the essence of these changes could reduce stress associated with the surgery.

When examining cognitive dysfunctions, it is important to ensure optimal conditions for testing. The assessment of the mood or sleep quality of the patients subjected to the tests can significantly influence the interpretation of the results.

Efforts should be taken towards creating an international definition of postoperative cognitive dysfunctions, and towards an agreement on the standardization of tests used for the assessment of postoperative cognitive dysfunctions.

Table 1. **The most frequently used neuropsychological tests for the assessment of selected cognitive functions**

Test	Abbreviation	Characteristic
Mini-Mental State Examination	MMSE	A simple screening tool evaluating a number of cognitive functions: time and place orientation, operational memory, concentration and numeracy, verbal abilities (naming, understanding commands, reading and writing) and construction praxis [31].
Montreal Cognitive Assessment	MoCA	Screening tool for detecting mild cognitive impairment (MCI); it is used to assess cognitive functions such as short-term memory, visual-spatial functions, executive functions, language functions, verbal fluency, attention, naming, abstracting and allopsychic orientation [32].
Wechsler Adult Intelligence Scale	WAIS	Intelligence test, which consists of 11 sub-tests. In Poland, the WAIS-R (PL) version is used [33].
Wechsler Memory Scale	WMS	It consists of a series of short subtests. It assesses the memorizing of words and pictures, meaningful and abstract material, direct and deferred memory. Five indicators are obtained: general memory, verbal and non-verbal material memory, attention/concentration and delayed recall [27].

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Trail Making Test A and B	TMTA, TMTB	The Trail Making Test is a test that assesses the ability to focus on the visual and spatial material. It also assesses the ability of visual search, the ability to switch attention between various stimuli, which is considered one of the manifestations of executive functions [34].
Rey Auditory Verbal Learning Test	RAVLT	It consists in learning a list of unrelated words, which should be recalled after a short and long (about 30 minutes) break. There are numerous variations of this test (e.g., PALT – Paired Associate Learning Test – it consists in memorizing pairs of unrelated words) [34].
Grooved Pegboard	GPB	It assesses psychomotor functions. The test may show a deficit in the coordination of upper limbs (for dominant and non-dominant hands) – as many as possible special pins should be inserted within 30 seconds to the horizontal grooves inside the wooden base (time is calculated for right and left hand) [35].
Visual Retention Test	VRT	The Benton Visual Retention Test consists in drawing one figure or a set of three geometrical figures directly after their presentation – it measures direct visual memory [34].
Controlled Oral Word Association Test	COWAT	A short clinical trial, which consists in generating as many words as possible from a given semantic category (semantic fluency) or words beginning with a specific letter (phonetic fluency) by the examined person within 1 minute [34].
Stroop Colour Word Test	SCWT	It is used to study executive processes through the so-called interference effect – consists in naming the color of the printed word being the name of a different color (e.g., the word 'blue' printed in yellow, etc.) [36].
Digit Symbol Substitution Test	DSST	One of the WAIS sub-tests; it is used to measure the ability to learn new skills and the ability to concentrate as well as visual-motor coordination. In clinical practice, its result is treated as an indicator of the general indicator of information processing [30, 37].
Boston Naming Test	BNT	The set contains of 20 pictures depicting commonly used objects, rare and abstract items; the number of correctly named items is assessed; attention is paid to the number of invalid names, agrammatisms and paraphrases [38].
Symbol Digit Modalities Test	SDMT	For numbers 1–9 the appropriate symbols are assigned. The subject has to copy them into the table in the right order [39].

Tabela 2. **Systematic review of selected works**

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Author	Type of surgery	Persons undergoing surgical treatment (n[a])	Control group (n[a])	Neuropsychological tests used in the study	Time	POCD definition	Results
Monk et al., 2008	non-cardiac surgery (thoracic, abdominal, orthopedic, minimally invasive – laparoscopic/ superficial reconstructions)	926	182	MMSE (preoperatively, RAVL – VVLT, CST (based on TMT). Beck Depression Inventory (to assess mood), State-Trait Anxiety Inventory	preoperatively, at discharge, 3 months after surgery	Z_{score} [d] ≥ 1.96 in 2 tests or in total	At discharge POCD present in: – 117 (36.6%) of young patients, – 112 (30.4%) people in middle age – 138 (41.4%) elderly patients (> 60 years old)
Price et al. 2008	extensive non-cardiac surgery (thoracic, orthopedic, minimally invasive)	308	56	MMSE (preoperatively), CST based on TMTB, SCWT, LDC, RAVLT – VVLT, Beck Depression Inventory	preoperatively, at discharge, 3 months after surgery	Change by ≥ 1 SD (compared to preoperative results)	At discharge POCD occurred in 186 patients (56%)

Van Dijk et al., 2008	coronary artery bypass grafting – CABG	240	99	RAVLT, GPBd, TMTA, TMTB, SMC, SCWT, SOT, SDMT	preoperatively, 5 years after surgery	Generalized RC[e] ≤ –1.96 or RC ≤ –1.96 in two or more variables	In 34.2% of patients undergoing surgery POCD was present after 5 years of surgery
Avidan et al., 2009	non-cardiac surgery (extensive and non-extensive)	180	395 (healthy and ill persons not subjected to surgical treatment)	WMS (4 sub-tests), VRT, WAIS (2 sub-tests), TMTA, Cross-out Test, BNT	preoperatively, 5 years after surgery	CDR[f] > 0	POCD occurred in 22% of patients undergoing surgery
Liu et al., 2009	coronary artery bypass grafting, CABG (off-pump and on-pump)	227	75	WMS, VRT, PALT, DSST, TMTA, GPBd + nd, WAIS (2 sub-tests)	preoperatively, 1 week after surgery, 3 months after surgery	$Z_{score} \geq 1.96$	PODC was observed in: 55.2% of patients after on-pump CABG 47% of patients after off-pump CABG

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Evered et al., 2011	coronary artery bypass grafting – CABG, total hip joint replacement – THJR; coronary angiography – CA	644	34	NART[b] – preoperatively, CERAD[c] (2 sub-test), TMTA, TMTB, COWAT, GPBd + nd, DSST	preoperatively, 7 days after surgery, 3 months after surgery	RCI[e] < –1.96 in ≥ 2 tests or in total RCI < –1.96	After 7 days from the surgery POCD was observed in: – 17% of patients in the THJR group – 43% of patients in the CABG group
Silbert B. et al, 2015	total hip joint replacement – THJR	271	38	MMSE, CERAD (2 sub-tests), TMTA, TMTB, DSST, COWAT, GPBd + nd	preoperatively, 7 days after surgery, 3 months after surgery, 12 months after surgery	RCI < –1.96 in ≥ 2 tests or total Z_{score} < –1.96	Seven days after surgery, 17% of patients presented with cognitive impairment

[a] – n – the number of people who participated in the research until the end of the trial; [b] – NART – National Adult Reading Test – test used to assess the level of intelligence; [c] – CERAD – Consortium to Establish a registry for Alzheimer's Disease – battery of neuropsychological tests; [d] – standard deviation indicator; [e] – RC(I) – reliability change indicator; [f] – CDR (Clinical Dementia Rating) – a numerical scale used to determine the severity of dementia symptoms

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