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Динамика изменения когнитивных функций у пациентов, перенесших вмешательства на каротидном бассейне

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АННОТАЦИЯ

Введение. Среди европейского населения в 715 млн человек ежегодно регистрируется около 1,4 млн инсультов. Приблизительно 87% инсультов являются ишемическими, среди них атеросклероз сонных артерий составляет около 20%. Для предотвращения развития ишемического события головного мозга, связанного с атеросклерозом брахиоцефальных артерий, разработаны различные варианты оперативного лечения, среди которых каротидная эндартерэктомия (КЭАЭ) и стентирование сонных артерий (ССА). КЭАЭ и ССА достоверно снижают риск повторного инсульта, связанного с атеротромбозом, но при этом уровень изменения когнитивных функций, восстановления церебрального функционального дефицита широко не исследованы. На данный момент нет рандомизированных исследований и мета-анализов, соответствующих всем стандартам проведения данных исследований, относительно изменения когнитивных функций у пациентов, перенесших вмешательства на сонных артериях. Имеются результаты отдельных медицинских центров, осуществляющих аналогичные вмешательства, причем данные не однозначные: ряд авторов отражают улучшение когнитивных функций, другие же не отмечают различий или даже указывают на ухудшение.

Заключение. В настоящем обзоре литературы освещен вопрос, который касается оценки изменения послеоперационного когнитивного дефицита у пациентов, перенесших КЭАЭ или ССА. Рассмотрены сравнения в контексте когнитивной церебральной функции в послеоперационном периоде эндартерэктомии или стентирования, оценка неврологического статуса у пациентов, перенесших острое нарушение мозгового кровообращения в анамнезе либо без него, различные варианты анестезии, техники выполнения КЭАЭ.

Ключевые слова: *каротидная эндартерэктомия; стентирование сонных артерий; когнитивные функции после каротидной эндартерэктомии; когнитивные функции после стентирования сонных артерий*

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Dynamics of the Alterations of Cognitive Functions in Patients with Past Interventions on the Carotid System

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ABSTRACT

INTRODUCTION: Among the European population of 715 million people, 1.4 million cases of strokes are recorded annually. Of them, approximately 87% are ischemic strokes, and approximately 20% were accounted for by atherosclerosis of the carotid arteries. To prevent an ischemic cerebral event associated with atherosclerosis of brachiocephalic arteries, different surgical techniques have been developed including carotid endarterectomy (CEAE) and carotid artery stenting (CAS). CEAE and CAS reliably reduce the risk of recurrent stroke associated with atherothrombosis, but with this, the level of alterations of cognitive functions and the restoration of cerebral functional deficit have not been widely studied. At present, no randomized studies and meta-analyses have met all the standards of conducting research concerning alterations in cognitive functions in patients with past interventions on carotid arteries. Some medical centers have performed such interventions, but data are not unambiguous: some authors describe the improvement of cognitive functions, whereas others do not note any differences or even see signs of impairment.

CONCLUSION: This literature review highlights an issue concerning the assessment of the alteration of postoperative cognitive deficit in patients with past CEAE or CAS. Comparisons in the context of cognitive cerebral functions in the postoperative period of endarterectomy or stenting and assessment of neurological status in patients with or without a history of acute cerebrovascular accident, different variants of anesthesia, and CEAE techniques are considered.

Keywords: *carotid endarterectomy; carotid artery stenting; cognitive functions after carotid endarterectomy; cognitive functions after carotid artery stenting*

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ECO•VECTOR

LIST OF ABBREVIATIONS

EDP — end diastolic pressure
CAS — carotid artery stenting
CCA — common carotid artery
CEA — carotid endarterectomy
CI — confidence interval
ICA — internal carotid artery
MCA — medial cerebral artery
MRI — magnetic resonance imaging

INTRODUCTION

Among the European population of 715 million people, 1.4 million strokes and 1.1 million deaths caused by it, are recorded annually, which makes stroke the second most common cause of death. Here, more than half the patients who survived stroke, depend on other people for their everyday activity [1–3]. About 87% of strokes are ischemic ones [4], among them atherosclerosis of the carotid arteries is recorded with more than 20% frequency [5].

To prevent the development of an ischemic brain event associated with atherosclerosis of the brachiocephalic arteries, different variants of surgical treatment have been developed including carotid endarterectomy (CEA) and carotid artery stenting (CAS). ESCT, NASCET, SVACS studies evidence the reduction of the risk of stroke in surgical treatment compared to optimal medicinal therapy in patients with carotid stenosis, and provide indications for surgical treatment [6–8].

To note, *CEA reliably reduces the risk of repeated stroke associated with atherothrombosis, but the level of alteration of cognitive functions, restoration of cerebral functional deficit in this case have not been widely investigated*. This literature review highlights a problem of assessment of alterations of postoperative cognitive deficit in patients with past CEA and CAS.

This study **aimed** to analyze and generalize the data on alterations of cognitive functions in patients with the previous interventions on the carotid pool.

To achieve the preset goal, analysis of literature was performed in search systems PubMed, Google Scholar, Science Direct, Scopus, Elibrary in English and Russian languages with use of the keywords: carotid endarterectomy, carotid artery stenting, cognitive functions after carotid endarterectomy, cognitive function after carotid artery stenting, cognitive decline after carotid endarterectomy, cognitive function after carotid endarterectomy, cognitive decline after carotid artery stenting, cognitive function after carotid artery stenting.

In the review, the studies are analyzed where alterations of cognitive functions and of neurologic deficit are considered in the long-term postoperative period in patients who had CEA and CAS.

General Information about the Problem of Studying Cognitive Functions

The effect of CEA and CAS *on reduction of the risk of repeated stroke* in the vascular pool of interest has been proven long ago. However, the influence of these interventions *on the alteration of cognitive status of the patient* is not yet completely known. Currently, there are no results of randomized studies and meta-analyses meeting all the standards of implementation of such investigations (PRISMA, QOUROM, etc.) of cognitive functions of patients with previous interventions on the carotid arteries. Neither this question is included in the control points of protocols for assessment of patients in the postoperative period in CREST, ASCT, ACAS large studies concerning the problem of atherosclerotic lesion of the carotid arteries [9–11].

Limitations in Studying Cognitive Functions

Considering the cognitive functions in patients who underwent interventions on the carotid pool, it is worth noting a number of limitations in the analysis of the functional cerebral reserve. Among the patients, the following groups can be distinguished:

- patients who *suffered a disorder of the cerebral circulation* of the atherothrombotic event type;

- patients in whom *ischemic circulatory disorder was not verified*, but who have disorders in cerebral perfusion leading to the so called circulatory encephalopathy affecting cognitive functions.

In our opinion, it is reasonable to consider postoperative alterations in these groups of patients separately due to different genesis of disorders in the functions of neurons: in some patients acute lesion of the brain tissue predominates, while in others — chronic perfusion deficit.

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Methods of evaluating the cognitive functions are also of high significance. Most commonly, different scales of evaluation of cerebral functions are used.

In the USA, the following tests are predominating:

- Trail Making Tests A / B);
- Processing Speed Index (PSI);
- Wexler Intelligence Scales — third Edition (WAIS-III);
- Boston Test, Working Memory Index (WMI);
- Wexler Memory Scales (WMS-III);
- Hopkins Verbal Learning Test, Association of Controlled Spoken Words.

In European countries, other testing systems are used:

- Montreal Cognitive Scale (MoCA-test);
- Brief Mental Status Assessment Scale (MMSE);
- Frontal Dysfunction Battery Test (FAB);
- the Raven matrix;
- Schulte test.

It is important to emphasize *different approaches to assessment of the brain cognitive functions used by researchers*.

To analyze these parameters, different scales can be used, but not a single one is validated as assessment of cognitive functions particularly in patients with the past surgical intervention on carotid arteries and is associated with atherothrombotic and other carotid-dependent disorders of brain perfusion. With this, scales may have certain limitations. For example, the Brief Mental Status Assessment Scale (MMSE) tests the dominant hemisphere of the brain, which may give different data because of hemispheric asymmetry in patients who have suffered circulatory disorders [12].

One should also note such a phenomenon as "*learning syndrome*" which is memorizing separate parts of the test by the patient, which frustrates its objectiveness and increases the scoring being interpreted as improvement of the brain functions. An important aspect that permits to avoid this phenomenon, is changing statements of the scale, without changing its essence, for example, substitution of some words with other ones. Of much importance is the time interval between tests: a small interval is more likely to lead to incorrect validation of the test, which will influence the resultant score of the patient.

One should separately consider *operator-dependent factors* understood as different periods of assessment of functions. Some researchers analyze functions in 1, 3, 6, 12 months [13, 14], others only in 12 months [15], and some use only 5-year follow-up period, which may be associated with subjectivity of assessment [15]. Each scale or test has certain instructions for a testing person, but they do not imply clear indications, which may lead to ambiguous interpretation of test/results. This may affect the end result, i*f patients were tested by different operators*, especially within the same work.

Evidences of Improvements of Cognitive Functions

We studied more than 40 works of different authors, where alterations of cognitive functions were investigated in patients with the previous interventions on the carotid arteries. Table 1 presents generalization of research works devoted to this problem and considering it both from the point of view of comparison between CAS and CEA, and assessment of neurologic status of symptomatic and asymptomatic patients after use of different surgical techniques, etc.

Table 1. Studies Demonstrating Improvement of Cognitive Functions after Intervention on Carotid Arteries

Authors, Year of Publication	Number and Type of Investigated Patients, Follow-up Period	Main Results of Investigation	Limitation of Investigation	Notes
Whooley J. L., et al., 2020 [14]	81 patients, asymptomatic: 53 — CEA; 17 — CAS; 11 — control group. General anesthesia. *Follow-up period:* 1, 6, 12 months.	Patients of control group showed 11% impairment of parameters of Trail Making Test. Patients of surgical groups showed 14% improvement.	In 12 months only 45 patients were examined, a stable improvement was only in Trail Making Test B.	Improvement of parameters in Trail Making Test B was observed in patients with improvement of blood flow in MCA as compared to patients without it (54.5 ± 40.0 vs. 6.1 ± 32.3, p = 0.001).
Nakamizo A., et al., 2020 [15]	95 patients: 59 — symptomatic, 36 — asymptomatic. All underwent CEA. General anesthesia. *Follow up period:* from 3 to 9 years, on average 6.5 years.	Improvement of cerebral functions reliably associated with EDP in the CCA on the operated side, and with pulsation index.	Different follow-up period in all patients, no comparison of symptomatic and asymptomatic patients.	Pulsation index is noted to be more associated with changes of FAB scale, and EDP — with Cognistat scale.

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Belov Yu.V. et al., 2018 [16]	100 patients, asymptomatic: 66 — eversion CEA; 23 — classic CEA; 11 — classic CEA with use of temporary intraluminal shunt. General anesthesia. *Follow-up period:* 1 day, 7 days, 3 months, 6 months.	No statistically significant differences of cognitive testing of patients in subgroups of eversion and classic methods were found ($p > 0.05$). Improvement of cognitive functions by 6 months — 78% of operated patients.	Short follow-up period.	Existence of serious depressive disorders in patients in the immediate postoperative period significantly increases the risk of development of postoperative cognitive dysfunction.
Migliara B., et al., 2012 [17]	39 patients: 33 — symptomatic; 6 — asymptomatic. All underwent eversion CEA. Local anesthesia. *Follow-up period:* 1 day, 1 month.	Improvement of cognitive functions in a month after surgery. No cognitive deficit in the first day after the operation that in other studies may be associated with general anesthesia.	Short follow-up period, no comparison with the group of general anesthesia, small sample.	–
Ghogawala Z., et al., 2013 [18]	24 asymptomatic patients, CEA. Follow-up period: 1, 6, 12 months.	100% of patients with improvement of blood flow in MCA showed a significant improvement of attention in comparison with 56% of patients without improvement of blood flow in MCA ($p = 0.06$). Clinically significant improvements in all 4 cognitive areas were observed in 1 year ($p < 0.01$).	Small sample, MRI-angiography was performed only in 1 month.	Of interest are the data on improvement of perfusion through MCA and improvement of cognitive deficit.
Turowicz A., et al., 2021 [19]	105 patients, asymptomatic: 70 — CEA; 20 — CAS; 15 — control group. *Follow-up period:* 6 months.	Improvement of cognitive functions irrespective of the type of intervention.	Small amount of used non-validated scales, short follow-up period.	Neuropsychological assessment shows improvement in 5 out of 7 cognitive domains in MoCA-test, CANTAB test showed improvement of visual memory, learning, work of memory and executive functions in CEA group. In CAS group, MoCA-test score increased from 24.39 to 26.28 ($p = 0.0016$). These patients also demon-strated a significant improvement of visual functions, learning and executive functions in CANTAB-test.
Kougias P., et al., 2015 [20]	60 patients, asymptomatic: 31 — CEA; 29 — CAS. *Follow-up period:* 6 weeks, 6 months.	In 6 weeks, the speed of cognitive processing and motor function were better in CAS group in comparison with CEA. The attention, memory and visual-spatial skill tests were similar in patients with CAS and CEA in 6 weeks and 6 months. With this, both groups showed a stable improvement of cognitive functions.	Small sample, scales not validated, short follow-up period.	–

Note: CAS — carotid artery stenting; EDP — end diastolic pressure; CEA — carotid endarterectomy; MRI — magnetic resonance imaging; CCA — common carotid artery; MCA — medial cerebral artery

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Most publications note the improvement of the brain functions in the long-term period after CEA or CAS, which occurs in 1–3 months after the intervention and is manifested in improvements of the results on different scales.

After CEA, asymptomatic patients show a higher degree of improvement of cognitive functions compared to patients that suffered acute cerebrovascular accident in the operated pool [21].

The work of M. M. Tanashian, et al. specifies a transient decline of cognitive deficit in the first 2 months after surgery, followed by recovery to the initial level by the 2nd month without significant improvement of cognitive status [22]. The authors point to a greater amount of "silent" embolization during stenting in patients with concomitant type 2 diabetes mellitus: 70% of all operations were accompanied by signs of embolization in intraoperative transcranial Doppler ultrasonography. Also, the number of silent foci of ischemia in 2 months after surgery, according to the results of magnetic resonance imaging (MRI) in the group of patients without type 2 diabetes, was 22%, and in the group with diabetes — 50% [22]. It should be explained that silent foci are zones of lesion of the brain tissue in neuroimaging (MRI), which do not give any clinical symptoms [23].

There are ambiguous data of comparison of CAS and CEA in terms of alteration of cognitive functions. A number of authors demonstrate a more stable improvement of function after CEA, which is supported by a higher frequency of distal embolization in case of CAS [24–25]. Others do not note improvement with any particular variant of surgical intervention, or note improvement after CAS emphasizing a negligible distal embolization in stenting and a significantly shorter time of compression of the internal carotid artery (ICA) [19, 20].

The results obtained are probably associated with a small sample of patients, high level of microembolization recorded in transcranial Doppler ultrasonography during CAS, different extent of restenosis after surgical intervention, different duration of "shutdown" of the carotid artery.

Of high interest are the works of J. L. Whooley, et al. and A. Nakamizo, et al., where the authors correlate cognitive deficit with the change in the perfusion state of the cerebral system [14, 15]. J. L. Whooley, et al. note improvement of cognitive functions in the postoperative period [14]. Here, the patients with higher blood flow in the medial cerebral artery (MCA) improved the results in the Trail Making Tests B with higher probability than the patients with no increase in blood flow in MCA. However, no significant relationship was found between improvement of the flow through MCA and tests associated with attention, speech fluency or memory [13].

A. Nakamizo, et al. demonstrate the interrelation between improvement of cognitive deficit, end diastolic pressure (EDP) on CCA and pulsation index: the higher EDP on CCA, the higher the results of Cognistat and FAB neuropsychic tests [15]. EDP below 14.5 cm/s is the most reliable predictor of the lower 25th percentile on the General Assessment Scale Cognistat (sensitivity 83.3%, specificity 61.0%), while the threshold values of pulsation index on CCA 1.76 and 1.83 are the most reliable predictors of the lower 25th percentile of Cognistat total score and FAB total score, respectively (sensitivity — 85.0%, specificity — 54.1%) [14].

Evidence of Impairment or Absence of Improvement of Cognitive Functions

In Table 2, works are given with generalized results of studies demonstrating impairment or absence of impairment of cognitive functions after intervention on the carotid arteries.

Analyzing impairment of cognitive functions or the absence of their improvement, one should mention a number of factors in the postoperative period.

Firstly, in most studies describing a negative effect after surgical intervention, it is noted in the first 1–7 days from the time of surgery. This is a transient phenomenon (regresses by the 1st–3rd months of the postoperative period) that is most probably associated with the cerebral hyperperfusion syndrome or distal microembolization [24–25].

Secondly, studies with longer follow-up periods (more than 2–3 years) indicate reduction of cerebral functions, which, in our opinion, may reflect progression of atherosclerosis, hyalinosis of small cerebral arteries, and also the natural ageing process with the reduction of neuroplasticity.

CONCLUSION

Improvement of cognitive functions in the postoperative period (on average in 6 months) is observed in most studies. There are no works that would indicate their steady decline. Here, reduction of the brain functions manifests either in the early postoperative period (from 1 day to 1 week) as part of the brain hyperperfusion syndrome due to restoration of its blood flow, or in the long-term period (more than 1 year) as the result of progression of atherosclerosis and hyalinosis of cerebral vessels, and also of the natural suppression of the cerebral functions due to ageing.

Table 2. Studies that Demonstrated Improvement of Cognitive Functions after Intervention on Carotid Arteries

Author	Number and Type of Investigated Patients. Follow-up Period	Main Data of Study	Limitations
Zhang H., et al., 2016 [26]	36 patients, symptomatic. All underwent CEA. *Follow-up period:* 1-3 day, 3 months	Buildup of cognitive deficit after surgery (1-3 day), with this, on diffuse weighted MRI no ischemic foci were found. Degree of ICA stenosis (p = 0.029) and duration of ICA compression (p = 0.031) are higher in patients with cognitive disorders immediately after CEA than in patients without them. Here, in 3 months, cognitive disorders remained only in 1 patient, while in others they returned to the preoperative level.	Short follow-up period; only 2 tests were used: MMSE scale and clock drawing test. Twelve patients had pronounced collateral ICA stenosis.
Pettigrew L., et al., 2000 [27]	1659 patients, asymptomatic. All underwent CEA. *Follow-up period:* 5 years	No statistically significant improvement of cognitive functions in 5 years.	Only MMSE scale was used; significant remoteness of the study; long follow-up period.
Chida K., et al., 2009 [28]	60 patients, asymptomatic. All underwent CEA. *Follow-up period:* 1 month	Computed tomography with single-photon emission of N-isopropyl-p-iodamphetamine was performed. Hyperperfusion (CI 95% 1.183-229.447; p = 0.0370) and postoperative decrease in the binding potential of benzodiazepine receptors in the hemisphere (CI 95% 1.003-77.381; p = 0.0496) were significantly associated with postoperative cognitive impairment.	Short follow-up period; no clearly defined criteria for brain hyperperfusion.
Lal B., et al., 2011 [29]	46 patients, asymptomatic: 21 — CAS, 25 — CEA; Follow-up period: 6 months	Both CAS and CEA led to improvement on all scales except PSI scale. When comparing individual tests, CEA led to decrease in memory, while CAS led to decrease in the speed of psychomotor movement after 6 months.	Small sample of patients; short follow-up period.
Bo M., et al., 2006 [30]	103 patients: 51 — asymptomatic, 52 — symptomatic; CEA was performed. Follow-up period: From 30 to 60 months	At the end of research, parameters of MMSE, CLOX1 and CLOX2 scales were significantly lower in patients with symptomatic stenosis of the left ICA (p < 0.001, p < 0.001 и p = 0.002, respectively). According to MMSE scale, patients with symptomatic lesion of the left ICA had a higher risk of reduction of cognitive functions, according to MMSE scale (f = 5.18, p = 0.002) or score on CLOX1 and 2 (f = 5.66, p = 0.001 and f = 4.33, p = 0.006, respectively).	MMSE scale assesses the dominant hemisphere (in right-handers, the left hemisphere), which may distort the results of this study.

Note: ICA — internal carotid artery; CI — confidence interval; MRI — magnetic resonance imaging

ADDITIONAL INFORMATION

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