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Carotid endarterectomy on the course of the acute period of ischemic stroke and chronic cerebral ischemia

Abstract

Background: Carotid endarterectomy (CE) is currently the main surgical treatment and preventative measure for ischemic stroke (IS) in patients with atherosclerotic stenosis and carotid artery occlusion; however, there are no clear opinions regarding the effect of CE on the course of the acute period of IS and chronic cerebral ischemia (CCI).

Methods: The study included 186 patients aged 45–81 years. The study population comprised two observation groups: group I included 131 patients with internal carotid artery (ICA) stenosis of more than 60% with unstable atherosclerotic plaque who underwent CE, and group II included 55 patients with ICA stenosis 60% with stable atherosclerotic plaque who did not undergo surgical treatment. The SPSS 21 package was used for statistical analysis.

Results: The results of the NIHSS, Rankin, and Rivermead scales after 12 months indicated a significant positive dynamic of the neurological status in patients in the first group (2.33 ± 0.30 in the first group and 0.89 ± 0.12 in the comparison group, $p < 0.05$). In the acute period of IS, CE performed according to indications led to a decrease in neurological symptoms (80.9% of patients scored 0–3 points on the NIHSS scale), a decrease in the degree of disability, and an increase in mobility in patients.

Conclusion: In patients who underwent the operation, disability was significantly lower 1 year after IS.

Keywords: Carotid endarterectomy, Ischemic stroke, Atherosclerotic stenosis.

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Carotid endarterectomy (CE) is currently the only cerebral revascularization method with a relatively low incidence of postoperative complications. The effectiveness of CE compared to conservative therapy has been confirmed with the help of numerous clinical studies showing the feasibility of surgical treatment methods. During the study, recommendations were developed regarding the indications and contraindications for performing CE in so-called symptomatic and asymptomatic patients, as well as the developments regarding the surgical technique of the intervention. Studies such as the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) have demonstrated the advantages of active surgical tactics for more than 70% of internal carotid artery (ICA) stenoses accompanied by neurological symptoms (1, 2). The ECST did not find an advantage of CE over drug therapy for symptomatic stenoses of 60–70% (50–67% stenosis according to NASCET criteria), due to approximately the same frequency of neurological complications in both groups (3). The NASCET study, showed that with the same degree of ICA stenosis, the risk of stroke over the next 2 years with an ulcerated plaque is 30%, while that without ulceration – is 17%, which indicates that surgeons in such cases choose active tactics (4). Moreover, there is evidence that non-stenosing complicated plaques are highly likely to cause cryptogenic stroke (5).

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To date, according to the recommendations of the American Heart Association, the American Stroke Association, and the Canadian Neurological Society, it has been determined that the preoperative risk tolerance for “symptomatic” patients should be no more than 6%, while that for “asymptomatic” patients should not be more than 3%. The life expectancy of such patients will be ≥ 5 years.

After uncomplicated thrombolysis, patients with significant carotid stenosis may be candidates for CE.

Based on the Danish and Swedish Vascular Registry, the Finnish capital region, researchers presented the results of patients who underwent surgery for symptomatic carotid artery stenosis (6-8). Some patients successfully underwent thrombolytic therapy before CE (6-8). These studies confirmed that CE can be performed within the recommended first 2 weeks after the onset of IS symptoms (8). CE is currently the primary surgical treatment and prevention of IS in patients with atherosclerotic stenosis and carotid artery occlusion. Despite numerous studies, including international randomized multicenter studies, there is currently no consensus on the timing of CE surgery in the acute period of IS. Moreover, there are few studies on the further course of the disease in operated patients in the short and long term. Additionally, there are no clear opinions regarding the effect of CE on the course of the acute period of IS and chronic cerebral ischemia. However, several issues remain unclear; for example, what tactics should be preferred for symptomatic moderate (50–69%) stenoses of the ICA. Together, these factors determined the purpose and methods of this study.

Methods

The present study is a case-control study, all new cases of the study included 186 patients aged 45–81 years (average age: 65.46 ± 1.03 years), comprising 131 men (70.4%) and 55 women (29.6%). At the same time, patients aged 51–60 years, that is, of working age, also constituted a significant proportion of the population (22.6%). All patients were admitted, during the acute period of IS, to the neurological department No.24 at Samara City N. I. Pirogova Clinical Hospital No.1. All patients provided their written informed consent to participate in the clinical study. Coded personal data were used when processing the study results. The study included patients diagnosed with hemispheric IS in the territory of the right or left internal carotid artery resulting from existing stenosis due to atherosclerotic processes. The exclusion criteria were the presence of concomitant mental and oncological diseases. The study population comprised two observation groups:

group I included 131 patients with ICA stenosis of $\geq 60\%$, considering the presence of clinical symptoms and the detection of especially dangerous embologenic atherosclerotic plaques (types I, II, and III, with an ulcerated or uneven contour, with intimal flotation, mural thrombus and hemorrhage into the plaque); and group II (comparison group) included 55 patients who also had stenotic lesions of the ICA and IS but did not undergo surgical treatment. The comparison group included patients with ICA stenosis of 60% with morphologically stable atherosclerotic plaques. The study groups were comparable in terms of sex and age, and the data had a normal distribution. Most patients had several concomitant diseases, which, in turn, were risk factors for the development and progression of cerebral atherosclerosis. The highest frequency of detection was arterial hypertension (97.8%), followed by coronary heart disease (71.0%), chronic heart failure (67.2%), and dyslipidemia (61.8%).

All studied patients were admitted to the admission and diagnostic unit of the hospital, where they were examined by a neurologist. The patients in both groups underwent computed tomography (CT) of the brain and an electrocardiogram, as well as blood tests for platelets, glucose, activated partial thromboplastin time, international normalized ratio, and prothrombin. In group I, CT angiography was also conducted. Brain CT was performed using Siemens SOMATOM Definition AS 64 (Munich, Germany) and J-Optima CT 660 (Chicago, Illinois, USA) helical CT machines according to the standard technique. Ultrasound diagnosis of the carotid arteries was performed on all patients upon admission to the hospital. The patients in group I also underwent Doppler ultrasound 3–6 months after surgery. The Vivid E9 XD Clear (Chicago, Illinois, USA) was used. Other tests, studies and consultations with various specialists were performed – if necessary. All patients received standard therapy for IS, as determined by decrees of the Ministry of Health and Social Development of the Russian Federation No. 389n dated July 6, 2009, which was named “On approval of the Procedure for providing medical care to patients with acute cerebrovascular accident,” No. 357n as of 2011, and No. 928n as of 2012. In group I, the atherothrombotic type of IS was dominant (98 cases (74.8%)), while IS of an unspecified nature was observed in 33 (25.2%) patients. In group II, the stroke was of an unspecified nature in 44 (80.0%) patients and atherothrombotic in 11 (20.0%) patients. Neurological symptoms were assessed using the National Institutes of Health Stroke Scale (NIHSS), and the functional state of patients was studied using the Rankin scale and the Rivermead mobility index. The SPSS 21

package (License No. 20130626-3) was used for statistical analysis. Comparisons between two independent groups were performed using the Mann–Whitney–Wilcoxon test, and comparisons between related groups were performed using the paired Wilcoxon test. For qualitative features, the analysis of contingency tables was performed by calculating Pearson's χ^2 statistics (chi-square) with the Yates correction for continuity with the dimension of the table 2×2 . In this research, we present the mean (M) and its standard error (m) – $M \pm m$ as descriptive statistics. The graphs show the mean and its 95% CI, and the box plots show the median and quartiles. Differences were considered statistically significant at $p \leq 0.05$. Logistic regression analysis was used as a mathematical method to study the influence of various factors on the prognosis of neurological function recovery in the studied patients. The predictors of the model were the anamnesis data, clinical examination results, and the results of a patient survey.

Results

All patients included in the study had neurological disorders characteristic of hemispheric IS: damage to the VII and XII pairs of cranial nerves, motor disorders (hemiparesis), sensory disorders (hemihypesthesia), speech disorders (motor and sensory aphasia), and dysarthria. A study conducted in the acute period of IS showed that both groups had comparable neurological symptoms in terms of presence and severity. Most patients had one or more concomitant somatic pathologies. The frequency of concomitant pathologies was comparable between groups I

and II. All patients underwent laboratory blood and urine tests. According to the main indicators of the blood test, the patients in the main and comparison groups were comparable.

During the ultrasound examination, the common, external, internal carotid, and vertebral arteries in the extracranial section, subclavian arteries, and brachiocephalic veins from both sides were examined. Among the revealed changes, the intima-media complex thickness (IMT) increased to 1.3 cm or more with the loss of differentiation into layers, mainly in vessel bifurcations. In the study group, the IMT was 1.09 ± 0.03 cm, whereas that in the comparison group was 1.03 ± 0.03 cm. In the subclavian arteries, the blood flow was mostly of the main type, whereas in both vertebral arteries, it was antegrade. The local blood flow velocity (LBV) increased in areas of luminal narrowing or arterial bends. Stenosis of the right ICA was found in $74.58\% \pm 3.51\%$ of patients, and stenosis of the left ICA was found in $74.0\% \pm 2.42\%$ of patients.

Figure 1 shows an example of the detection of complete thrombus occlusion of the ICA. Foci of cerebral ischemia, as a rule, were localized in the area of the right or left MCA; however, they also occurred in the territory of the ACA, and multifocal foci were detected predominantly in the territory of the PCA (table 1). As can be seen, the patient groups were comparable in terms of the localization of ischemic foci. Regarding the size of the foci, one of the sizes (the size of focus 1) was significantly larger in the study group, while there were no differences in other sizes and areas of the lesion (table 2). The focus area was calculated as $3/4$ of the product of the first two dimensions.

Table 1. Localization of ischemic foci on CT in patients of the study groups

Parameters		Comparison group		Study group		X ²	p
		Abs.	%	Abs.	%		
Sex	M	33	60.0	98	74.8	3.40	0.07
	F	22	40.0	33	25.2		
Right MCA	No	30	54.6	71	54.2	0.00	1,00
	Yes	25	45.5	60	45.8		
Left MCA	No	29	52.7	69	52.7	0.00	1,00
	Yes	26	47.3	62	47.3		
Right MCA+PCA	No	54	98.2	128	97.7	0.00	1,00
	Yes	one	1.8	3	2.3		
Left MCA+PCA	No	53	96.4	130	99.2	0.61	0.43
	Yes	2	3.6	1	0.8		

Parameters		Comparison group		Study group		X ²	p
		Abs.	%	Abs.	%		
Right ACA	No	55	100.0	128	97.7	0.24	0.62
	Yes	-	-	3	2.3		
Left ACA	No	53	96.4	128	97.7	0.00	0.98
	Yes	2	3.6	3	2.3		

Note: ACA – anterior cerebral artery, MCA – middle cerebral artery, PCA – posterior cerebral artery.

Table 2. Comparative analysis of the size and area of the ischemic foci in the studied groups

Parameters	Comparison group (in mm)	Study group (in mm)	p
Focus size No.1	19.64±3.55	23.17±2.41	0.04
Focus size No.2	13.25±1.74	16.14±1.63	0.13
Focus size No.3	16.07±3.08	20.41±3.14	0.10
Focus area	328.69±111.15	353.81±62.07	0.06

Note: Focus area has 3 sizes – No.1 (axial section), No.2 (frontal section), No.3 (sagittal section).

A total of 131 patients underwent CT angiography. Figure 2 shows CT angiography and CT of the brain of a patient with stenosis of the left ICA. In this study, the following types of surgery were used: open CE (33 cases), eversion CE (81 cases), resection of the carotid artery tortuosity with its redressing (9 cases), and prosthetic repair of the internal carotid artery (8 cases). Often, the final decision on the type of surgery was made only during the surgery; 65 interventions were made on the right side, and 66 interventions were made on the left. Bilateral CE was performed in 19 patients. In the first week of IS surgery, 69 patients underwent surgery, while in the second, third, and fourth weeks, 10, 23, and 3 patients did, respectively. Twenty-six patients were operated on more than 4 weeks after IS; most (19 cases) were repeat surgeries on the opposite side.

After hospital discharge, all patients in the post-stroke period continued rehabilitation activities in a health resort, or else on an outpatient basis in their neighborhood or at home. Patients included in the study were monitored during consultations and examinations, and they were advised to carefully monitor their blood pressure. All patients used the same standard methods of drug (including neuroprotectors and vitamins) and non-drug (including physiotherapy, massage, and exercise therapy) rehabilitation. All patients underwent pharmacological prevention of recurrent CVA (hypotensive, anticoagulants, and statins) and treatment of

concomitant somatic diseases. A comprehensive assessment of neurological status, emotional, cognitive functions, and quality of life was performed 12 months after IS. During the observation period, the patients included in the study did not have acute cardiovascular events (repeated CVA and myocardial infarction), and none died.

In both groups, when assessing neurological status on the NIHSS, Rankin, and Rivermead scales at admission and discharge from the hospital, the results were hardly distinguishable, but the situation changed after 12 months. The graphs presented in Figures 3, 4, and 5 show that the results of the NIHSS, Rankin, and Rivermead scales after 12 months indicated a significant positive dynamic of the neurological status in patients in the first group. Figures 3–5 contain graphs showing the dynamics of the NIHSS scores, the Rankin scale, and the Rivermead index.

Table 3 presents the quantitative parameters of all studies conducted on the patients in the two observation groups during the acute period of CVA and 1 year after the procedure. In the acute period of IS (upon admission to the hospital or at discharge), the characteristics of patients in the first and second groups were significantly comparable. After 12 months, the situation was different. The NIHSS, Rankin and Rivermead scores in the group of operated patients were significantly higher than those in the comparison group ($p < 0.05$). At the stage of study inclusion, groups I and II were comparable in terms of the

NIHSS scores: 5 (3; 6) and 5 (2; 6), respectively ($p = 0.60$). Additionally, there was no significant improvement in the NIHSS score upon discharge of patients from the hospital, and the results remained comparable: 2 (1; 3) and 3 (1; 4) points ($P = 0.24$). Significant differences appeared only in the late recovery period (1 year after the stroke): 1 (0; 1) and 2 (0; 3) points, respectively ($P = 0.01$). It is possible that these differences appeared earlier after CVA, but they were assessed 12 months after the stroke. In the studied groups, a significant difference was observed between the parameters of the Rankin disability scale upon admission to the neurological hospital, at discharge, and after the end of the

late recovery period. A year after the CVA, a significant difference ($P = 0.01$) in the Rankin score was observed between the groups. For patients in group I, the disability score was significantly lower.

Similar to the analysis on the disability scale, the Rivermead mobility index also showed a difference between the groups in each period of the disease. At the same time, for patients in group I, the score on this scale was significantly higher. The clinical significance of this finding is indicated by a decrease in the disability index and an increase in mobility in patients who underwent CE during the acute period of IS.

Table 3. Summary of the quantitative parameters of all studies conducted in patients in the two groups

Averages	Comparison group	Study group	P
Age	65.98±1.32	64.93±0.69	0.47
NIHSS upon admission	4.71±0.38	5.00±0.27	0.60
Rankin scale upon admission	2.96±0.12	2.93±0.08	1,00
Rivermead index upon admission	6.47±0.41	6.29±0.29	0.82
NIHSS at discharge	2.69±0.31	2.21±0.17	0.24
Rankin scale at discharge	1.98±0.14	1.71±0.08	0.13
Rivermead index at discharge	10.60±0.43	11.66±0.23	0.02
NIHSS after 12 months	2.33±0.30	0.89±0.12	< 0.05
Rankin scale after 12 months	1.51±0.15	0.56±0.08	< 0.05
Rivermead index after 12 months	11.76±0.41	14.11±0.14	< 0.05

Note: NIHSS - National Institutes of Health Stroke Scale

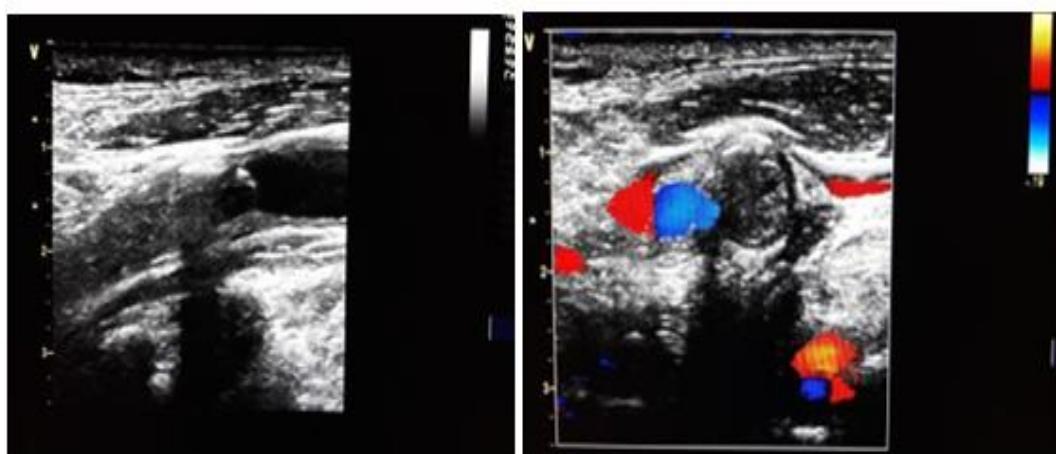


Figure 1. Thrombus occlusion of the left ICA in the longitudinal and cross-sectional directions.
ICA – internal carotid artery

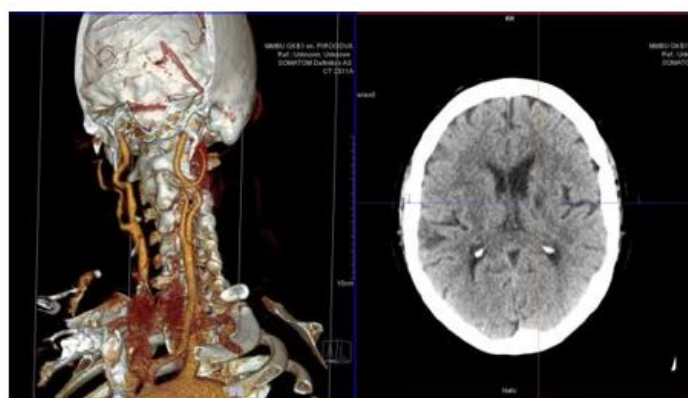


Figure 2. Brain CT and CT angiography of a patient with left ICA stenosis. CT – computer tomography. ICA – internal carotid artery

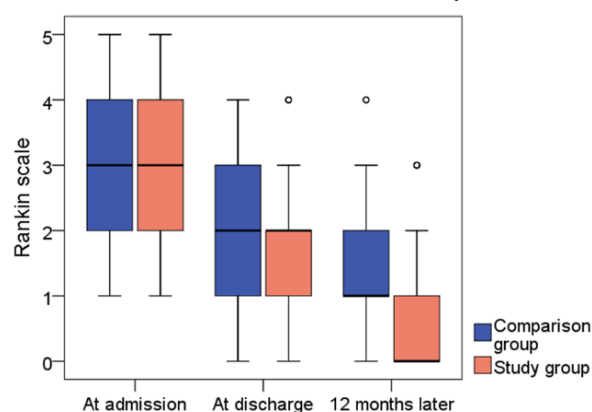


Figure 4. The dynamics of indicators on the Rankin scale

Discussion

We determined indications for CE following the findings of the NASCET study with an (A) level of evidence. According to this study, “symptomatic” patients with stenosis > 60% have absolute indications for the surgical treatment of carotid stenosis provided that the institution has a “stroke + stroke mortality” rate of no more than 3% for patients with a transient ischemic attack (TIA) and 5% for patients who have undergone IS, while the overall mortality should not exceed 2%. Currently, there are no indications for surgery in “symptomatic” patients with less than 50% stenosis (A). CE is indicated for ICA stenosis ranging from 50% to 60% in the presence of a morphologically unstable atherosclerotic plaque with intimal flotation, ulceration, parietal thrombus and plaque hemorrhage, among others, if the patient has had TIA or IS over the last 6 months with neurological symptoms. CE is possible within a few days after the TIA, within 2 weeks after the last episode of CVA in cases of minor strokes (no more than 3 points on the

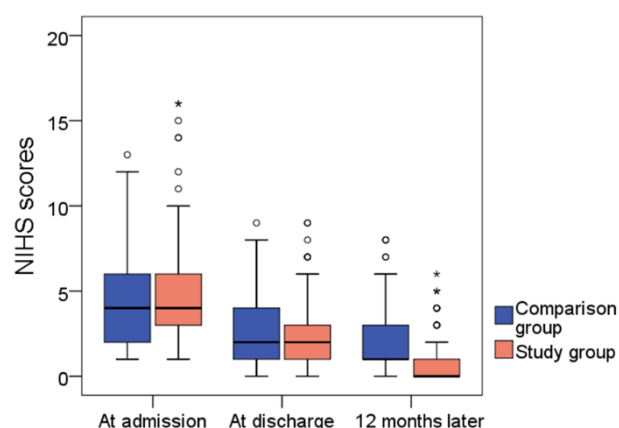


Figure 3. The dynamics of the NIHSS scores. NIHSS – National Institutes of Health Stroke Scale

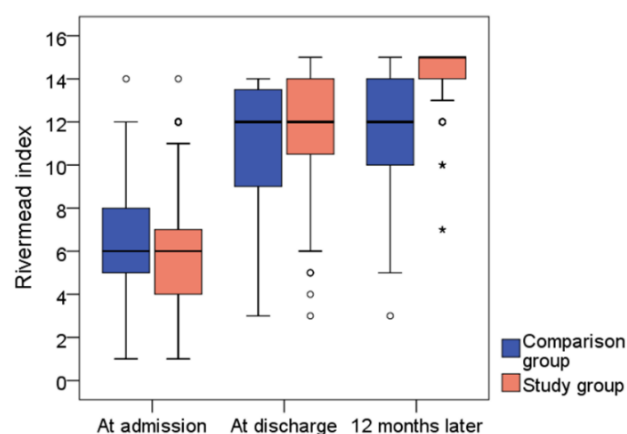


Figure 5. The dynamics of indicators of the Rivermead index

Rankin scale), and within 6–8 weeks in cases of complete strokes (B). The dynamics of neurological status were assessed using the NIHSS, Rankin, and Rivermead scores. Both groups at admission and discharge from the hospital were comparable and hardly distinguishable, but the results of the study after 12 months indicated a more significant positive dynamic of the neurological status in patients in the first group ($p < 0.05$). Moreover, 12 months after the CVA, it is possible to assess the course of chronic cerebral ischemia. In patients in the first group, CE performed in the acute period of IS was found to have a positive effect on the course of chronic cerebral ischemia. There are a few similar studies, similar in research methods but different in the processing of results. A single surgeon experience confirmed early CE for recurrent stroke prevention can be performed safely, at an earlier time (181 stroke patients underwent CE within 72 hours and 13 patients within 5 days) frame than current recommendations 2 weeks (9). In another study the ideal timing for performing CE is between

3 and 7 days from the index event if NIHSS <5 as it is associated with the best rates of improvement in neurological status and durability in the long term. Very early CE (<48 hours) was associated with increased late stroke occurrence (10).

Similar result in the following study: the rate of complications significantly increases, mainly among treated in the very early (<48 hours) period for stroke in evolution or acute/recent stroke and better results in favor of patients operated on between 8 and 14 days (11). Research in this direction should be continued to obtain more precise indications for conducting CE: the time of CE by the hour depending on the neurological symptoms of patients, the degree of stenosis and the morphology of the atherosclerotic plaque. Based on the results of the research, the following conclusions are drawn:

1. The decision to perform CE was made by a multidisciplinary team, including a neurologist, a vascular surgeon, and an anesthesiologist, after determining the indications and considering contraindications for surgery, in accordance with the assessment of the risk/benefit ratio for each patient, and also considering all identified risk factors for the patient in the immediate and late postoperative periods. The indication for surgery is carotid stenosis $\geq 60\%$ or occlusion, as well as the presence of morphologically unstable plaque (ulceration, plaque hemorrhage, intimal flotation, and parietal thrombus). Surgical intervention can be performed within 2–4 weeks from the first day of IS. The surgical technique was selected individually for each case. During the postoperative period, the patients were observed in the intensive care unit for 24 h.

2. In the acute period of IS, CE performed according to indications led to a decrease in neurological symptoms (80.9% of patients scored 0–3 points on the NIHSS scale), a decrease in the disability degree (81.7% of patients scored 0–2 points on the Rankin scale), and increased mobility of patients (73.4% of patients scored up to 12–15 points on the Rivermead scale).

3. One year after IS, the NIHSS, Rankin, and Rivermead scores were significantly higher in operated patients than in those who received only conservative treatment ($p < 0.01$). Limitations of the study. Possible influences of concomitant medication and comorbidities cannot be ruled out. No blinding. Generalizability limited as conducted at a single center, uncertain as to whether study patients were representative of all patients. Perhaps the small number of cases is a limitation of the study for drawing broad conclusions. The degree of drug rehabilitation in the post-stroke period was slightly different among patients.

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Conflict of interests: There is no conflict of interests.

Authors' contribution: The author conceptualized and conducted the study, analyzing and writing the original draft.

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