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Carotid Endarterectomy for Thrombosis of the Internal Carotid Artery in Patients With COVID-19

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Abstract: Analysis of the results of emergency carotid endarterectomy (CEE) against the background of internal carotid artery (ICA) thrombosis in the acute period of acute cerebrovascular accident (ACVA) in patients with COVID-19. During the COVID-19 pandemic (April 1, 2020-May 1, 2021), 43 patients with ICA thrombosis and a positive polymerase chain reaction (PCR) result for SARS-CoV-2 were included in this prospective study. In all cases, CEE was performed in the acutest period of ACVA. These patients were included in group 1. The comparison group was represented by 89 patients who underwent CEE in the acute period of stroke, in the period before the

The authors have no conflicts of interest to disclose.

The work has no funding.

Curr Probl Cardiol 2022;00:101252

0146-2806/\$ – see front matter

<https://doi.org/10.1016/j.cpcardiol.2022.101252>

COVID-19 pandemic (April 1, 2019-March 1, 2020). According to laboratory parameters, patients with COVID-19 had severe coagulopathy (with an increase in D-dimer: 3832 ± 627.2 ng/mL, fibrinogen: 12.6 ± 3.1 g/L, prothrombin: 155.7 ± 10 , 2%), inflammatory syndrome (increased ferritin: 646.2 ± 56.1 ng/mL, C-reactive protein: 161.3 ± 17.2 mg/L, interleukin-6: 183.3 ± 51.7 pg/mL, leukocytosis: 27.3 ± 1.7 10^9 /L). In the hospital postoperative period, the groups were comparable in terms of the incidence of deaths (group 1: 2.3%, $n = 1$; group 2: 1.1%, $n = 1$; $P = 0.81$; OR=2.09; 95 % CI=0.12-34.3) myocardial infarction (group 1: 2.3%, $n = 1$; group 2: 0%; $P = 0.7$; OR = 6.3; 95% CI=0.25-158.5), CVA (group 1: 2.3%, $n = 1$; group 2: 2.2%, $n = 2$; $P = 0.55$; OR = 1.03; 95% CI=0,09-11.7). ICA thrombosis and hemorrhagic transformations were not recorded. However, due to severe coagulopathy with ongoing anticoagulant/antiplatelet therapy, patients with COVID-19 more often developed bleeding in the operation area (group 1: 11.6%, $n = 5$; group 2: 1.1%, $n = 1$; $P = 0.02$; OR = 11.5; 95% CI = 1.3-102.5). In all cases, the flow of hemorrhagic discharge came from the drainage localized in the subcutaneous fat. This made it possible to remove skin sutures in a dressing room, suturing the source of bleeding and applying secondary sutures under local anesthesia. Emergency CEE in the acute period of stroke is an effective and safe method of cerebral revascularization in case of ICA thrombosis in conditions of COVID-19. (Curr Probl Cardiol 2022;00:101252.)

Introduction

It has been more than 2 years since the new coronavirus infection reached pandemic status. The clinical spectrum of this pathology varies from an asymptomatic form to a severe disease characterized by hypoxemic respiratory failure, community-acquired polysegmental pneumonia, septic shock, and systemic multiple organ failure.^{1,2} COVID-19 is often accompanied by hypercoagulability, micro- and macrovascular thrombotic angiopathy.³ This conclusion is confirmed

by the laboratory profile observed in these patients, with a significant increase in D-dimer, prothrombin, fibrinogen.⁴ In addition, an aggravating factor is systemic hyperinflammation with an increase in pro-inflammatory cytokines (tumor necrosis factor, interleukin-6, interleukin-1 β), which can contribute to the development of intravascular coagulopathy.⁵ In a study by Klok F.A. et al reported a cumulative incidence of thrombotic complications in 49% of patients with COVID-19 in infectious hospitals.⁶ According to a systematic review by Cheruiyot I et al, 27 studies described arterial thrombosis of various locations in patients with COVID-19. Among them, special emphasis was placed on the carotid arteries, the proportion of which was 24%.⁷ It should be noted that in patients without COVID-19, thrombosis of the internal carotid artery is quite rare (about 1.6% of the total). In 92% of cases, as a rule, neurological symptoms are observed. In 17.1%, a repeated ischemic event is recorded within 30 days after the manifestation.⁸ Thus, a significant increase in the frequency of diagnosing this condition has raised the question of choosing effective and safe methods of treatment.

Thrombosis of the internal carotid artery in patients with COVID-19 most often develops against the background of hemodynamically significant stenosis and unstable atherosclerotic plaque.⁸ However, among patients who do not suffer from a new coronavirus infection, this condition rarely manifests itself in occlusive thrombosis. This pattern is explained by aggravating factors that accompany the course of COVID-19: endothelitis and hypercoagulability.⁸ Due to the lack of sufficient experience in the treatment of this pathology, the optimal tactics of revascularization has not yet been developed. However, there are reports that in case of peripheral arterial thrombosis, open thrombectomy, endovascular thromboextraction, thrombolysis are accompanied by a high frequency of repeated thrombosis and limb amputations.¹ Thus, the use of these techniques in the treatment of patients with occlusive thrombosis of the internal carotid artery will be associated with the risk of new thrombosis and acute cerebrovascular accident. But it must be borne in mind that the listed methods of treatment do not “turn off” one of the main components of the development of this process - the inflamed endothelium. If it is possible to cope with hypercoagulability due to medical support, then within the framework of thrombosis of the internal carotid artery, the most optimal method of revascularization is the removal of the thrombus and the adjacent atherosclerotic plaque along with the endothelium through carotid endarterectomy.^{9,10} Thus, within the framework of this pathology, we should talk about the effectiveness of carotid

endarterectomy in the most acute period of ischemic stroke in patients with COVID-19.

The criteria for selecting patients for emergency CEE in "non-covid" surgery have been repeatedly put forward and substantiated: unstable atherosclerotic plaque with a high risk of distal embolization; the diameter of the ischemic focus in the brain, not exceeding 2.5 cm; the absence of a pronounced neurological deficit (stupor, coma); hemorrhagic stroke; hemorrhagic transformation; acute coronary syndrome.^{8,11-14} But in the absence of an alternative, these parameters can be used in the context of COVID-19 as well. There were no other indications/contraindications for revascularization in this cohort of patients to date. In the world literature, there are only a few reports of individual clinical cases of effective/ineffective attempts of cerebral revascularization against the background of COVID-19.^{8,15-18} Thus, due to the lack of large studies on the results of emergency carotid endarterectomy in the acute period of ischemic stroke in patients with a new coronavirus infection, the optimal treatment strategy has not yet been developed.

The aim of this study was to analyze the hospital results of emergency carotid endarterectomy against the background of thrombosis of the internal carotid artery in the acute period of ischemic stroke in patients with COVID-19.

Materials and Methods

During the COVID-19 pandemic (April 1, 2020-May 1, 2021), this prospective, open, comparative study included 43 patients with thrombosis of the internal carotid artery and a positive result of the polymerase chain reaction for the presence of SARS-CoV-2. In all cases, carotid endarterectomy was performed in the acute period of ischemic stroke. These patients were included in group 1. The comparison group was represented by 89 patients who underwent carotid endarterectomy in the most acute period of ischemic stroke, in the period before the COVID-19 pandemic (April 1, 2019-March 1, 2020).

The inclusion criteria for the study were: (1) The presence of acute thrombosis of the internal carotid artery in patients with COVID-19; (2) Hemodynamically significant stenosis of the internal carotid artery (more than 60%) and/or unstable atherosclerotic plaque; (3) The most acute period of ischemic stroke (within a day after the development of ischemic stroke); (4) Positive result of the polymerase chain reaction for the presence of SARS-CoV-2; (5) Viral pneumonia of 1-3 degrees according to multislice computed tomography of the chest in patients with COVID-

19; (6) The diameter of the ischemic focus in the brain, not exceeding 2.5 cm according to computed tomography; and (7) Local thrombosis of the internal carotid artery with retrograde filling of the artery.

Criteria for exclusion from the study: (1) Severe neurological deficit over 25 points on the National Institute of Health Stroke Scale; (2) Systemic multiple organ failure; (3) Sepsis; (4) Unstable hemodynamics requiring inotropic support; (5) Acute coronary syndrome; (6) Severe course of COVID-19; and (7) Viral pneumonia of the 4th degree according to computed tomography of the chest, requiring mechanical ventilation.

To visualize the affected area of the internal carotid artery, computed tomography with angiography of the precerebral arteries was performed. The choice of treatment tactics was carried out by a multidisciplinary consultation (cardiovascular surgeon, endovascular surgeon, neurosurgeon, cardiologist, neurologist, infectious disease specialist, anesthesiologist-resuscitator). The operation was performed under local anesthesia. In both groups, eversion carotid endarterectomy was performed with preservation of the carotid glomus.

The anastomosis was performed using a 6/0 polypropylene suture. Wound drainage was performed with the installation of 2 active drains in the paravasal space and subcutaneous fat.

Under the conditions of COVID-19, the operating team performed CEE in a specialized outfit: a surgical suit, protective overalls, a disposable surgical gown, 2 pairs of disposable gloves, antiviral goggles or a visor, and an FFP3 respirator.

In the postoperative period, all patients received anticoagulant and antiplatelet therapy, including unfractionated heparin 5000 IU 4 times a day *s/c* + 125 mg acetylsalicylic acid 1 time per day. In the group of patients with COVID-19, according to version 10 (dated February 8, 2021) of the Interim Guidelines for the Prevention, Diagnosis and Treatment of Novel Coronavirus Infection (COVID-19) of the Ministry of Health of the Russian Federation, the following therapy was also implemented: hydroxychloroquine (400 mg in 1 Day 2 (200 mg bid), then 200 mg daily (100 mg bid for 6-8 days), Baricitinib (4 mg bid for 7-14 days), or Tofacitinib (10 mg 2 times a day for 7-14 days), non-steroidal anti-inflammatory drugs.

The hospital postoperative period in the total sample was 12.5 ± 3.5 days. The endpoints were: death, myocardial infarction, ischemic stroke, bleeding, combined endpoint (death + myocardial infarction + ischemic stroke + hemorrhagic transformation).

All patients signed a written consent to participate in the study, as well as a voluntary informed consent of a citizen to use therapy with off-label drugs. The work was carried out in accordance with the standards of good clinical practice (Good Clinical Practice) and the principles of the Declaration of Helsinki, did not contradict the Federal Law of the Russian Federation of November 21, 2011 No. April 1, 2016 N 200n "On approval of the rules of good clinical practice."

Statistical analysis. The type of distribution was determined using the Kolmogorov-Smirnov test. Groups were compared using Pearson's chi-square test with Yates and Mann-Whitney corrections. Differences were assessed as significant at $P < 0.05$. The results of the studies were processed using the Graph Pad Prism software package (www.graphpad.com).

Results

The groups were comparable in many respects. The vast majority corresponded to old age. Males predominated in the total sample. For every fourth patient, this acute cerebrovascular accident has become repeated. However, it should be noted that chronic obstructive pulmonary disease was more often diagnosed among patients with COVID-19, which demonstrated a greater adherence of these patients to the disease of a new coronavirus infection (Table 1).

According to laboratory parameters, it should be noted that in the "pre-Covid period" the measurement of ferritin, D-dimer, interleukin-6 was not included in the study standards. In a cohort of patients with COVID-19, there was a pronounced coagulopathy (with an increase in D-dimer, fibrinogen, prothrombin), an inflammatory syndrome (an increase in ferritin, C-reactive protein, interleukin-6, leukocytosis) (Table 2).

The groups were comparable in terms of severity of stenotic lesions of the internal carotid artery and the time of arterial clamping during carotid endarterectomy (Table 3).

In the hospital postoperative period, the groups were also comparable in terms of the incidence of all adverse cardiovascular events. However, due to severe coagulopathy with ongoing anticoagulant/antiplatelet therapy, patients with COVID-19 were more likely to develop bleeding at the surgical site (Table 4).

In all cases, the hemorrhagic discharge came from the drainage localized in the subcutaneous fat. This made it possible to remove skin sutures in the conditions of the dressing room, with stitching the source of bleeding and applying secondary sutures under local anesthesia.

TABLE 1. Comparative clinical and anamnestic characteristic of patient groups

Indicator	Group 1(with COVID-19) <i>n</i> = 43	Group 2(without COVID-19) <i>n</i> = 89	<i>P</i>	OR	95% Confidence interval
Age, M ± m, y	64.2 ± 5.3	65.7 ± 3.9	0.32	-	-
Male sex, <i>n</i> (%)	31 (72.1)	67 (75.3)	0.85	0.84	0.37-1.93
Postinfarction cardiosclerosis, <i>n</i> (%)	6 (13.9)	15 (16.8)	0.86	0.8	0.28-2.23
Diabetes mellitus, <i>n</i> (%)	3 (6.9)	6 (6.7)	0.75	1.03	0.24-4.36
Chronic obstructive pulmonary disease, <i>n</i> (%)	13 (30.2)	1 (1.1)	<0.0001	38.1	4.78-304.1
Chronic renal failure, <i>n</i> (%)	3 (6.9)	1 (1.1)	0.19	6.6	0.66-65.4
Left ventricular ejection fraction, M ± m, %	60.5 ± 2.5	61.8 ± 2.7	0.45	-	-
Left ventricular aneurysm, <i>n</i> (%)	0	1 (1.1)	0.7	0.67	0.02-17.01
History of percutaneous coronary intervention, <i>n</i> (%)	5 (11.6)	10 (11.2)	0.82	1.03	0.33-3.25
History of coronary artery bypass surgery, <i>n</i> (%)	3 (6.9)	6 (6.7)	0.75	1.03	0.24-4.36
Recurrent acute cerebrovascular accident, <i>n</i> (%)	11 (25.6)	23 (25.8)	0.85	0.98	0.42-2.27
Lung tissue damage, M ± m, %	65.2 ± 13.5	-	-	-	-
SpO ₂ , M ± m, %	87.5 ± 4.8	98.0 ± 1.0	0.001	-	-

TABLE 2. Laboratory indicators

Indicator	Group 1(with COVID-19) n = 43	Group 2(without COVID-19) n = 89	P
Leukocytes, M ± m, 10E9/л	27.3 ± 1.7	5.1 ± 0.6	0.001
Ferritin, M ± m, нг/мл	646.2 ± 56.1	-	-
C-reactive protein, M ± m, мг/л	161.3 ± 17.2	2.5 ± 0.5	0.003
Interleukin 6, M ± m, пг/мл	183.3 ± 51,7	-	-
D-dimer, M ± m, нг/мл	3832 ± 627.2	-	-
Fibrinogen, M ± m, гп/л	12.6 ± 3.1	2.8 ± 0.4	0.01
Prothrombin, M ± m, %	155.7 ± 10.2	93.4 ± 6.9	0.004

In the postoperative period, in all cases, a significant ($P= 0.001$) regression of neurological symptoms was detected: 9.5 ± 1.5 points according to the National Institute of Health Stroke Scale at the time of admission; 5.5 ± 1.0 points on the National Institute of Health Stroke Scale at the time of discharge.

Discussion

A number of studies have shown that diffuse endothelial damage is histologically determined in patients with COVID-19. This condition may be the result of direct viral exposure, which is associated with the presence of overexpression of the angiotensin-converting enzyme 2 receptor, through which SARS-CoV-2 enters endotheliocytes.^{19,20}

Also, the course of COVID-19 is associated with hypercoagulability (increased D-dimer, prothrombin, fibrinogen), which, as a result, reduces the time of clot formation and increases its maximum density.²¹ It is believed that increased blood viscosity is the result of systemic extrapulmonary hyperinflammation and hypercytokinemia, which activate the coagulation cascade.⁵ Endothelitis and hypercoagulation, together with prolonged immobilization of COVID-19 patients (prone position),

TABLE 3. Angiographic and perioperative characteristics

Indicator	Group 1(with COVID-19) n = 43	Group 2(without COVID-19) n = 89	P
% stenosis of the internal carotid artery	78.4 ± 5.3	79.1 ± 6.1	0.34
Clamping time of the internal carotid artery, min	22.5 ± 1.7	21.4 ± 2.4	0.51

TABLE 4. Hospital outcomes

Indicator	Group 1 (with COVID-19) <i>n</i> = 43	Group 2 (without COVID-19) <i>n</i> = 89	<i>P</i>	OR	95% Confidence interval
Death, <i>n</i> (%)	1 (2.3)	1 (1.1)	0.81	2.09	0.12-34.3
Myocardial infarction, <i>n</i> (%)	1 (2.3)	0	0.7	6.3	0.25-158.5
Ischemic stroke, <i>n</i> (%)	1 (2.3)	2 (2.2)	0.55	1.03	0.09-11.7
Hemorrhagic transformation, <i>n</i> (%)	0	0	-	-	-
Bleeding, <i>n</i> (%)	5 (11.6)	1 (1.1)	0.02	11.5	1.3-102.5
Thrombosis of the internal carotid artery, <i>n</i> (%)	0	0	-	-	-
Combined Endpoint, <i>n</i> (%)	4 (6.9)	3 (3.4)	0.31	2.94	0.62-13.78

complete the Virchow triad, providing an explanation for the mechanisms of arterial thrombosis.

Our results showed that all cases of thrombosis of the internal carotid artery were recorded during the stay of patients in the infectious diseases hospital, 5.5 ± 1.5 days after admission. The implemented anticoagulant/antiplatelet therapy did not contribute to the prevention of the process in view of the current endotheliitis. However, due to the fact that patients received heparin and acetylsalicylic acid for several days, the concentration of drugs reached a cumulative effect, which prevented the spread of thrombosis to the intracranial arteries. Thus, the local nature of the lesion with retrograde filling of the internal carotid artery created the conditions for a possible carotid endarterectomy.

Another issue relates to the urgency of the intervention. The course of the infectious process with severe respiratory failure and polysegmental pneumonia could serve as contraindications for emergency carotid endarterectomy. However, planned hospitalization in a cardiovascular hospital could only be implemented a few weeks after the patient was discharged from the institution and received 2 negative PCR tests for COVID-19. Another difficulty is related to the conversion of medical organizations; including those providing routine angiosurgical cares to the population, into infectious diseases hospitals.¹ Thus, patients were faced with the inability to receive planned revascularization in the shortest possible time due to the long queue for hospitalization in available cardiovascular hospitals. However, patients with thrombosis of the internal carotid artery are characterized by a high risk of recurrent ischemic stroke.^{7,8} Ultimately, the combination of these circumstances was the reason for the emergency carotid endarterectomy.

It should be noted that an important factor in achieving a successful outcome of emergency carotid endarterectomy was the use of local anesthesia during the operation. It was previously reported that patients with polysegmental viral pneumonia are characterized by an increased risk of developing pneumothorax, pneumomediastinum, emphysema when using mechanical ventilation.¹ Thus, the refusal of artificial lung ventilation under local anesthesia prevents the formation of the listed pathology.

Speaking about the choice of the type of carotid endarterectomy, it is necessary to note the importance of the glomus-sparing eversion technique. The rejection of the classical technique with patch implantation is justified by the reduction in the duration of the operation and the risk of restenosis in the mid-term follow-up period.^{22,23} Preservation of the carotid glomus during carotid endarterectomy made it possible to control blood pressure at the level of normotonia in the early postoperative

period. According to the literature, in case of damage to the carotid glomus, against the background of anticoagulant / antiplatelet therapy and hypertensive crisis, the formation of hemorrhagic transformation / intracerebral hematoma is possible with a negative prognosis for the further course of the disease.²⁴⁻²⁶ Thus, the chosen revascularization technique in favor of eversion glomus-sparing carotid endarterectomy has become an important condition for successful revascularization.

Of additional interest may be the method of draining the wound. In elective “non-covid” surgery, we repeatedly used 2 drains for patients with severe hypoaggregation and hypocoagulation.²⁷ Patients with COVID-19, despite the current coagulopathy, are under the influence of heparin and antiplatelet therapy, according to the Interim Guidelines for the Prevention, Diagnosis and Treatment of Novel Coronavirus Infection (COVID-19) of the Ministry of Health of the Russian Federation. Thus, this cohort of patients is at risk of developing acute hematoma in the intervention area after carotid endarterectomy, which is often accompanied by tracheal displacement and respiratory failure.²⁷ For patients with initial respiratory failure on the background of viral pneumonia, this development of events can be fatal. The rationale for the use of 2 drains is as follows: 1. In case of thrombosis/dysfunction of one of the drains, the second one is a safety net and does not allow the formation of an acute hematoma; 2. In view of the fact that the first drainage is installed in the paravasal space, and the second in the subcutaneous tissue, with the development of bleeding, its source can be determined with a further choice of emergency surgical care - removal of skin sutures with local hemostasis in a dressing room, or a complete revision of the wound to paravasal space in the operating room.

A separate emphasis should be placed on the range of hospital complications received. As noted above, in view of the fact that the majority of medical institutions turned out to be converted into infectious diseases hospitals, most patients could not receive the necessary therapeutic assistance in a timely manner.¹ Ultimately, patients hospitalized for COVID-19 often had decompensated cardiac and other pathologies.¹ As part of our work, 2 patients were diagnosed with myocardial infarction, which in 1 case became fatal. These patients were unable to receive the planned myocardial revascularization (percutaneous coronary intervention), which caused coronary circulatory failure with further consequences. In a single case, a recurrent ischemic stroke was diagnosed with regression on the background of conservative treatment. The cause of the condition was a distal embolism during clamping of the common carotid artery with areas of calcification.

The presented work is the first study with a sample of 43 patients, which has no analogues in the world literature. The experience of our medical institution, converted into an infectious diseases hospital, has shown that emergency carotid endarterectomy in the acute period of ischemic stroke is characterized by a low risk of adverse cardiovascular events. Anticoagulant/antiplatelet therapy in combination with removal of the inflamed endothelium during carotid endarterectomy makes it possible to exclude the formation of repeated thrombosis in this group of patients. Thus, glomus-sparing eversion carotid endarterectomy may be the revascularization of choice for patients with COVID-19 in the acute period of ischemic stroke against the background of internal carotid artery thrombosis.

Conclusion

Emergency carotid endarterectomy in the most acute period of ischemic stroke is an effective and safe method of brain revascularization in case of thrombosis of the internal carotid artery under conditions of COVID-19.

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