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Advanced Issues of Carotid and Vertebral Artery Stenting in Acute Ischemic Stroke (Literature Review)

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Abstract Cerebrovascular diseases are the leading cause of mortality and a major cause of persistent neurologic and physical disorders in adults. Carotid endarterectomy has been the gold treatment standard for asymptomatic significant carotid stenosis. Carotid artery stenting (or implantation of a stent into the carotid artery) has developed rapidly over the past 30 years. The authors analyzed an evidence base of carotid artery and vertebral artery stentings, tandem atherosclerotic lesion of the main cerebral arteries, complications associated with arterial stenting and others reported in world literature. Intravascular interventions provide adequate revascularization of stenosed and occluded main and cerebral vessels of the brain. The ultimate clinical outcome of these interventions is a reduction in mortality and disability in patients with ischemic stroke.

Keywords Cerebrovascular diseases, Carotid endarterectomy, Carotid artery stenting, Atherosclerotic lesion, Revascularization

1. Introduction

Cerebrovascular diseases are the leading cause of mortality and a major cause of persistent neurologic and physical disorders in adults. Ischemic stroke is the most common among cerebrovascular diseases, with approximately 15-20% of all ischemic strokes occurring as a result of atherosclerotic stenosis of the carotid artery, especially the internal carotid artery [1-3]. Significant carotid stenosis (stenosis of 70% or more) occurs in approximately 0.5% of patients aged 60-79 years, while at age 80 years and older it occurs in approximately 10% of patients [4]. Most patients have no cerebral symptoms in the presence of carotid artery stenosis. Symptomatic carotid artery stenosis is defined as stenosis of the internal carotid artery with cerebral symptoms on the ipsilateral side. It is an important cause of ischemic stroke and patients with symptomatic carotid artery stenosis are at high risk of recurrent strokes.

Carotid revascularization prevents recurrent ischemic stroke in patients with significant symptomatic carotid stenosis. Carotid endarterectomy (CAE) has been the gold treatment standard for asymptomatic significant carotid stenosis for more than 60 years [5]. Carotid artery stenting (CAS) (or implantation of a stent into the carotid artery) has developed rapidly over the past 30 years and is increasing in incidence because it is less invasive than carotid endarterectomy with less risk of surgical complications [6].

There is a strong association between the occurrence of stroke and carotid artery stenosis, which can cause cerebral embolism, transient ischemic attack (TIA), or thromboembolic stroke. TIA is a warning sign often followed by ischemic stroke. Significant symptomatic carotid stenosis is responsible for 20% of all ischemic stroke cases [7]. Duplex ultrasound is an available first-line imaging modality to assess the hemodynamic status of the carotid arteries. The information obtained is very important in the choice of treatment tactics [8]. Ultrasound may be used to diagnose significant carotid stenosis if the maximum systolic velocity exceeds 250 cm/sec or the end-diastolic velocity exceeds 120 cm/sec. Lipid-rich and heterogeneous ultrasound structure of the plaque indicates its instability and a high probability of its covering rupture [9-10].

Other non-invasive imaging techniques include computed tomography (CT), CT-angiography, magnetic resonance imaging (MRI), and MR-angiography (MRA). These techniques can be used if the carotid artery stenosis is far from its bifurcation and cannot be diagnosed by duplex ultrasonography [11-12]. In cases of significant symptomatic stenosis (≥70%), carotid artery revascularization by stenting is the generally accepted standard of treatment to reduce the further risk of ischemic stroke. To assess the anatomy of the aortic arch, as well as the morphology of the carotid arteries of patients with planned CAS, MRI or CT-angiography should be performed beforehand [13].

Endovascular treatment based on the use of mechanical thrombectomy has become the gold standard for patients with acute ischemic stroke associated with occlusion of large cerebral vessels [14-15]. Mechanical thrombectomy is particularly efficient in the treatment of embolic occlusions.

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However, in practice, atherothrombotic occlusions in situ are often found, and in such conditions, the underlying atheroma cannot be eliminated only by mechanical thrombectomy [4,16-20]. It greatly complicates the treatment of strokes due to occlusion of large cerebral arteries associated with their atherosclerotic lesions. Carotid artery stenting is the method of choice in such situations [21-22].

2. Evidence Base of Carotid Artery Stenting

The efficiency of carotid artery interventions has been studied for the past 4 decades. For instance, there were studies that compared the efficiency of CAE with drug therapy in patients with symptomatic carotid artery stenosis in the eighties of the last century and asymptomatic stenosis - in the nineties. Multicenter studies comparing the efficiency of CAE with carotid artery stenting in patients with symptomatic carotid artery stenosis were conducted in the 2000s and asymptomatic stenosis - in the 2010s.

First stage: comparative analysis of the CAE efficiency with drug therapy. This time period includes the results of 3 multicenter trials: the NASCET (North American Symptomatic Carotid Endarterectomy Trial), the ECST (European Carotid Surgery Trial), and a small VA309 trial by the Veterans Affairs Cooperative Studies Program 309 Trialist Group. The NASCET and ECST studies randomized men and women with carotid artery stenosis up to 50%, whereas the VA309 study included only men with stenosis ≥50% [23-27]. The results of all 3 trail studies proved a significant reduction of stroke risk after CAE in patients with stenosis ≥70%.

Based on the results of the NASCET study, long-term differentiated results of the development of ischemic stroke after CAE were obtained depending on the degree of carotid artery stenosis. Thus, patients with stenosis ≥70% had an absolute reduction in the risk of ipsilateral stroke after carotid artery surgery of more than 15% ($p<0.001$), while those with stenosis 50-69% had a 6.5% risk of stroke ($p=0.045$). Patients with less than 50% stenosis had a 3.8% risk of ipsilateral stroke ($p=0.16$) [27].

The results of the ECST study proved the efficiency of CAE in preventing the development of ischemic stroke (IS). Patients with carotid artery stenosis ≥80% after CAE had a lower risk of IS compared with the control group. The long-term results of 3-year follow-up showed that the incidence of ipsilateral stroke and perioperative death was 6.8% in patients with CAE versus 20.6% in patients receiving drug therapy ($p<0.001$) [24].

The results of the VA309 trial showed a significant reduction in the incidence of ipsilateral stroke and transient ischemic stroke after CAE in patients with carotid artery stenosis >70% - 7.9% vs. 25.6% in patients receiving drug therapy ($p<0.010$) [28-29].

An important conclusion of the conducted 3 studies was the lack of benefits of CAE in the prevention of IS in patients with minor or moderate carotid artery stenosis with a degree of narrowing of 30-49%.

The second stage: Due to the improvement of medical technologies, more and more attention is being paid to minimally invasive methods of treatment. Carotid artery stenting is one of these methods. The advantages of this method are the use of mini-incisions, reduced postoperative complications and shorter length of hospital stay. CAS can be performed through both transfemoral and transradial accesses [29-31].

The first studies evaluating the efficiency of percutaneous interventions on the carotid arteries indicated a high incidence of strokes, mainly due to different levels of professional training and competence of endovascular specialists [32-34].

Six randomized multicenter studies comparing the efficiency and safety of CAS and CAE in patients with symptomatic carotid artery stenosis were conducted:

1. CAVATAS (Carotid Stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study);
2. SAPPHIRE (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy);
3. EVA-3S (Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis);
4. SPACE-1 (Stent-supported Percutaneous Angioplasty of the Carotid artery versus Endarterectomy);
5. ICSS (International Carotid Stenting Study);
6. CREST-1 (Carotid Revascularization Endarterectomy vs Stenting Trial);

The CAVATAS study is the first large randomized clinical trial comparing the clinical efficiency of CAE and transluminal angioplasty for carotid artery and vertebral artery stenosis. An important conclusion that negatively influenced the further development of endovascular treatments was the absence of statistically significant differences in the incidence of ipsilateral stroke during the 5-year follow-up period: 11.3% of patients with endovascular intervention versus 8.6% with CAE ($p>0.05$) [35].

The design of the subsequent 3 randomized trials SPACE, EVA-3S and ICSS was also aimed at comparing the efficiency of CAS and CAE in patients with symptomatic carotid artery stenosis [36-41]. In addition, a subgroup analysis of patients with symptomatic carotid artery stenosis was performed for the SAPPHIRE and CREST studies, which included patients with symptomatic and asymptomatic carotid artery stenoses [42-45]. During the SPACE-1 study, the use of devices to protect against distal embolism began, but at the beginning of the study, the frequency of using these devices was low. However, in the next four trials, this figure increased to 72-100% [38,40,42,46]. A reduction in perioperative strokes has been noted as a result of the use of "traps" [47-50]. The incidence of 30-day postoperative complications as death, development of ischemic stroke and TIA, ranged from 3.9% to 9.3% in patients who underwent CAE and from 2.1% to 9.6% in patients who underwent CAS.

The EVA-3S study reported lower rates of ipsilateral stroke in patients with CAE (6.2% CAE compared with 11.1% of cases in patients with stenting; $p=0.03$), which was

mainly explained by a higher number of periprocedural complications in the stenting group. CAE was found to be safe in patients over 70 years of age, whereas perioperative risk for CAS increased with age [51].

There have been 4 randomized multicenter studies comparing the efficiency and safety of CAS and CAE in patients with asymptomatic carotid artery stenosis.

1. SAPPHIRE (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy). The study included patients with both symptomatic and asymptomatic carotid artery stenosis;
2. CREST-1 (Carotid Revascularization Endarterectomy vs Stenting Trial). The study included patients with both symptomatic and asymptomatic carotid artery stenosis;
3. ACT-1 (Asymptomatic Carotid Trial);
4. SPACE-1 (Stent-supported Percutaneous Angioplasty of the Carotid artery versus Endarterectomy);

The ACT-1 study randomized 1453 patients with asymptomatic carotid artery stenosis for CAE and CAS in a 1:3 ratio [52]. The CREST-1 study included 1181 patients with asymptomatic stenoses, and the SAPPHIRE study included 237 patients [42-45].

The results of the ACT-1 and CREST-1 studies did not reveal differences in the incidence of perioperative complications in the form of IS, AMI and death between patients with both CAE and CAS [52]. In CAE, the complication rate was 2.6% and in the CAS group it was 3.3% ($p< 0.60$). In the CREST study, the risk of perioperative complications was 3.6% in CAE patients and 3.5% in CAS patients. One of the main conclusions of the ACT-1 and CREST studies was that the incidence of long-term stroke among asymptomatic patients was significantly lower than in other studies where CAE was analyzed. The CREST study demonstrated that the 10-year stroke rate was 10.1% in asymptomatic patients who underwent CAE and 9.6% in those ones who had CAS ($p= 0.95$). According to the ACT-1 trial, stroke was developed 5 years after CAE in 2.7% and in 2.2% of patients with CAS. The SAPPHIRE trial, which included patients with asymptomatic carotid artery stenosis, found high 3-year stroke rates of 29.2% and 21.4% in patients who underwent CAE and CAS, respectively. The high rate of stroke is explained by the fact that patients at high risk of IS were randomized according to the study design.

3. Evidence Base of Vertebral Artery Stenting

In contrast to treatment algorithms for carotid artery stenosis, optimal treatments for symptomatic vertebral artery stenosis have not been fully developed yet [55-56]. In general, the predominant treatment strategy for symptomatic vertebral artery stenosis includes medication, surgery and endovascular intervention techniques. Optimal drug therapy includes control of risk factors (smoking cessation, moderate to high physical activity and treatment of obesity), antiplatelet therapy (aspirin, clopidogrel), hypolipidemic drugs (statins) and individualized management of patients with arterial hypertension or diabetes mellitus [57]. Despite the use of warfarin or aspirin in combination with modification of vascular risk factors, a high risk of ischemic stroke caused by symptomatic stenosis is still existing [58]. The results of the well-known WASID (Warfarin–Aspirin Symptomatic Intracranial Disease) study showed that ischemic stroke was observed in 106 (19.0%) patients, of which in 77 (73%) patients the ischemic zone was located in the territory of the stenotic artery, after the therapy with aspirin or warfarin [59-60]. Besides, multivariate analysis revealed a positive correlation between significant vertebral artery stenosis (>70%) and the risk of subsequent stroke in the area of symptomatic intracranial artery stenosis [60]. Alternative treatment methods are needed for this purpose. Surgical strategies for symptomatic vertebral artery stenosis include transposition of the vertebral artery into the common carotid artery, vertebral artery endarterectomy and implantation of the vertebral artery into the subclavian artery [61-62]. Previous studies have shown that the complication rate for transposition of the vertebral-carotid artery is 4.5% with a mean follow-up of 8.8 months [63].

Another retrospective study also showed that transposition of the vertebral artery into the carotid artery is associated with less risk than carotid artery reconstruction [64]. However, these surgeries require a high level of technical skills. In addition, surgical revascularization often requires general anesthesia and longer operative time than endovascular therapy, which can be performed under local anesthesia. An important point is that the benefit of surgical treatment of vertebral artery stenosis remains unclear. The lack of evidence-based studies confirming the efficiency of surgical revascularization on the one hand, and the rapid progress of endovascular treatment methods on the other hand, is the reason why endovascular methods are increasingly preferred. Endovascular treatment of vertebral artery stenosis appears to have high technical success rates, low complication rates and stable long-term outcomes [55]. Contraindications for vertebral artery stenting are high risk of periprocedural complications and restenosis in case of stenosis of the distal and proximal parts of the vertebral artery [64].

In 2017, a meta-analysis of 10 clinical trials involving 672 patients showed no significant difference between percutaneous transluminal angioplasty and medical treatment for symptomatic vertebral artery stenosis [57]. Thus, larger randomized controlled trials are needed to determine the real benefits of endovascular therapy in patients with vertebral artery stenosis.

Stenotic lesions mainly occur in the proximal vertebral artery, but may also affect the distal vertebral artery or even the basilar artery [65]. Historically, attention to vertebral artery stenosis and generally to ischemia in the posterior circulation vessel basin has been minimal because it was considered less severe than ischemia in the anterior circulation vessel basin. To date, the safest and most efficient treatment for symptomatic vertebral artery stenosis has not

been developed yet. Currently, the predominant therapy for symptomatic vertebral artery stenosis is medication and the possibility of endovascular therapy. However, the benefit of drug treatment for symptomatic vertebral artery stenosis remains controversial [62]. Over the past decade, there have been several randomized clinical trials comparing the safety and efficiency of endovascular therapy combined with drug treatment or drug treatment alone for vertebral artery stenosis [66-69]. The SAMMPRIS (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis) study showed that endovascular therapy combined with medical treatment for severe intracranial artery stenosis (from 70% to 99%) leads to a worse outcome compared to patients receiving medical treatment alone [67]. It should be noted that stenotic lesions in patients included in the SAMMPRIS study were localized intracranially.

In the VISSIT (Vitesse Intracranial Stent Study for Ischemic Stroke Therapy) study, the sample size of patients with vertebral artery stenosis was not defined, making the study insufficient to confirm the benefit of endovascular therapy in patients with vertebral artery stenosis [69].

More representative clinical trials on vertebral artery stenosis are the VAST (Vertebral Artery Stenting Trial) and the VIST (Vertebral Artery Ischaemia Stenting Trial) studies [67-68]. The results of the VAST study showed a higher rate of periprocedural vascular complications in the stenting group, while data from the VIST study showed that, in contrast, stenting of extracranial vertebral artery stenoses was safer with a low complication rate [66,68]. A comprehensive meta-analysis using data from the SAMMPRIS, VIST and VAST trials also showed that stenting can help for extracranial vertebral artery stenosis [70].

4. Tandem Atherosclerotic Lesion of the Main Cerebral Arteries

In 20-30% of patients with acute ischemic stroke due to occlusion of a major intracranial vessel, there is additional concomitant high-grade stenosis or occlusion of the extracranial part of the internal carotid artery on the ipsilateral side. Such a lesion is termed a “tandem” lesion, which is considered an unfavorable outcome factor in patients with acute ischemic stroke. The unfavorable prognosis is due to the low efficiency of thrombolytic therapy. In tandem cerebral artery lesions, favorable outcome is achieved in only 30% and mortality is up to 50% [70-71].

Endovascular therapy is considered as an alternative treatment method in which the clot is mechanically removed through endovascular access. The efficiency and safety of the endovascular method in patients with occlusion of large arteries of the anterior circulation has been proved. Endovascular therapy achieves a higher recanalization rate and better functional outcome compared with thrombolytic therapy alone. This technique has found widespread use and was quickly incorporated into national stroke treatment guidelines [73-75]. Endovascular therapy has also been shown to promote good functional outcome in patients with concomitant lesions of the extracranial part of the internal carotid artery [76-77]. In patients with significant stenosis of the extracranial part of the internal carotid artery, balloon angioplasty is performed to access the intracranial arteries for thrombectomy. However, balloon angioplasty does not result in definitive treatment of the stenotic and occlusive lesion, as recurrence or residual stenosis of the extracranial portion of the internal carotid artery is often observed [78].

There is no clear answer in the current literature to the question of whether extracranial stenting of the internal carotid artery should be performed in tandem lesions of the main arteries in the acute stage of ischemic stroke. Guidelines recommend CAE within 2 weeks of the first event to prevent a recurrent event, but it is based on studies comparing the efficiency of CAE and CAS in a different population of patients with subacute non-disabling ischemic stroke [75,78,79-81]. The safety of immediate internal carotid artery stenting combined with endovascular treatment is not fully studied. Dual antiplatelet therapy, which is used with stenting, potentially increases the risk of bleeding complications in patients with acute stroke. In addition, whether stenting of the extracranial internal carotid artery should be performed before or after recanalization of the occluded cerebral artery is not fully studied [24,83-84,86-87].

5. Complications Associated with Arterial Stenting. Embolic Stroke

Examination of patients undergoing CAS with transthoracic Doppler ultrasound showed the presence of microembolization in almost all procedures. Although diffusion-weighted MRI showed new foci of ischemia in only 10-50% of cases, most patients had no symptoms of ischemic stroke. Researchers reported that the use of a proximal balloon-type embolic protection device (EPD) showed a lower incidence of embolic complications than the use of distal protection devices [88-90]. Based on experience and improved tools, especially the active use of EPDs, recent studies have shown a 3% reduction in the rate of cerebral complications [90-91].

6. Hyperperfusion Syndrome

Dilatation of the carotid artery stenosis by stent placement quickly eliminates chronic pressure drops in patients, so a large flow of high blood pressure blood is delivered to the brain parenchyma without adaptation. In most patients cerebral vasoconstriction is observed due to activation of cerebral vascular autoregulation mechanisms and the increased perfusion pressure is restored to normal within a few minutes. However, in some patients it is impaired due to prolonged excessive reduction in cerebral blood flow, which can lead to a persistent increase in intracranial pressure (lasting from hours to days), thereby causing hyperperfusion syndrome [92]. The main manifestations of this complication are

headache, vomiting, local convulsions and varying degrees of loss of consciousness due to increased intracranial pressure. This complication can lead to fatal cerebral hemorrhage. These data indicate contralateral carotid artery occlusion, circle of Willis, almost complete stenosis with excessive blood flow reduction. Hyperperfusion syndrome is also developed in case of simultaneous stenting of both carotid arteries. Hyperperfusion is usually developed within a few days after stent implantation, but in some cases symptoms are developed immediately after the procedure. Because this complication can have very serious consequences, it is important to take preventative measures. It is better to avoid simultaneous stenting of both carotid arteries and try to keep SPB below 140 mmHg during and after the procedure.

7. Brain Bleed

Brain bleed can be a fatal complication of CAS; it occurs in approximately 0.7% of all cases and is often preceded by hyperperfusion [93]. A brain bleed is usually associated with excessive anticoagulant therapy, impaired blood pressure control, unskillful manipulation of the conduit, intracranial aneurysm, and reperfusion of a recently developed massive ischemic stroke. Intracranial hemorrhage after CAS usually occurs within a few hours after the procedure and has catastrophic consequences. If sudden loss of consciousness occurs after complaints of a sudden severe headache, cerebral hemorrhage should be suspected. If it occurs, the operator should immediately stop the procedure and perform intracranial artery angiography to determine whether blood is leaking from the blood vessel or whether there is localized insufficient blood supply. In case of brain bleed, anticoagulant therapy with protamine sulfate should be weakened and a CT scan of the brain should be performed.

8. Spasm and Dissection of the Carotid Artery

Carotid artery spasm is usually associated with carotid artery tortuosity, filter device placement, and excessive guidewire manipulation. However, the condition usually improves when the guidewire is removed or nitroglycerin is injected into the carotid artery, which is in a state of spasm.

Although carotid artery dissection is rare, it is a serious complication that can occur due to severe intracranial tortuosity or over-handling of instruments. Additional causes of delamination include overinflating the distal part of the stent after stenting and intensive manipulation of the guiding catheter. Carotid artery dissection requires immediate additional stenting.

9. Stent Thrombosis

Stent thrombosis is a very rare complication that can be prevented with the help of appropriate antiplatelet drugs, the choice of an appropriate stent size and balloon dilation after stenting. Double antiplatelet therapy with aspirin and clopidogrel should be prescribed long before the procedure. If the duration of treatment is not suitable, an initial loading dose should be taken before the procedure. The therapy should be continued for more than 4 weeks after the procedure. Since late stent thrombosis is known to be more common in radiation-induced stenosis, longer antiplatelet therapy should be considered in this situation.

10. Conclusions

Further development of medical technologies contributes to the improvement of safer minimally invasive endovascular treatments of acute ischemic stroke.

Intravascular interventions provide adequate revascularization of stenosed and occluded main and cerebral vessels of the brain.

The ultimate clinical outcome of these interventions is a reduction in mortality and disability in patients with ischemic stroke.

Conflict of Interests' Statement

The authors declare no conflict of interest.

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