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Prevention of Recurrent Ischemic Stroke

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Relevance of the problem *The problem of stroke prevention has not only medical, but also the most important social significance, since stroke is one of the most common causes of mortality and disability. In Uzbekistan, the incidence of stroke and mortality from it remain among the highest in the world; more than 50 thousand strokes are registered annually in our country, among which ischemic strokes are more common (60–75%) [1,3]. In the United States, about 800 thousand strokes are registered annually, while recurrent strokes account for 250 thousand and are accompanied by a higher incidence of mortality and disability than the first stroke [20].*

The problem of stroke prevention is not only medical, but also of critical social importance, since stroke is one of the most common causes of mortality and disability. In *Uzbekistan,* the incidence of stroke and mortality from it remain among the highest in the world; more than 50 thousand strokes are registered annually in our country, among which ischemic strokes are more common (70–85%) [1,3]. In the United States, about 800 thousand strokes are registered annually, while recurrent strokes account for 250 thousand and are accompanied by a higher incidence of mortality and disability than the first stroke [10].

The likelihood of stroke increases more than tenfold in individuals who have had a stroke or transient ischemic attack (TIA), so stroke prevention is most important in this population [1–4,10,14]. In this group of patients, the risk of myocardial infarction and mortality from cardiovascular diseases also increases significantly [14]. Prevention of recurrent ischemic stroke should begin as soon as possible after the development of the first stroke or TIA. It is based on the correction of its risk factors and includes both medicinal and non-medicinal means of prevention. The most significant correctable risk factors for cerebral infarction include smoking, alcohol abuse, arterial hypertension, atherosclerotic stenosis of the carotid arteries, increased blood cholesterol levels, heart disease and diabetes mellitus [1,3,4,10].

Elderly patients benefit most from preventive therapy because they have more risk factors for stroke than young and middle-aged patients. At the same time, the risk of complications in elderly patients is higher than in middle-aged patients, so preventive therapy in the elderly should be carried out with extreme caution, taking into account their existing somatic diseases [10].

Non-drug methods of prevention Quitting smoking is accompanied by a gradual significant reduction in the risk of ischemic stroke, and after 5 years of abstinence from smoking, the risk of stroke in a former smoker differs little from its risk in a person who has never smoked. Even in older people with a very long history of smoking, stopping smoking or reducing the number of cigarettes smoked has been proven to be effective in preventing myocardial infarction and ischemic stroke [20]. Stopping alcohol abuse gradually reduces the risk of stroke in former alcoholics. Moderate consumption of alcohol (no more than a bottle of beer, a glass of wine or 30 ml of strong drinks per day) slightly reduces the risk of ischemic stroke, which may be associated with a decrease in platelet aggregation, a decrease in the content of cholesterol and fibrinogen in the blood serum [17]. However, in patients who have suffered an ischemic stroke or TIA, drinking even moderate doses of alcohol has not been proven to reduce the risk of recurrent stroke.

Low physical activity increases the risk of stroke, and regular physical activity reduces the risk of stroke [14,10]. The effect of regular physical exercise is associated with its beneficial effect on body weight, blood pressure, serum cholesterol and glucose tolerance. Persons who have had a stroke are advised to refrain from significant physical activity, but moderate exercise and regular walking in the fresh air are not contraindicated and, apparently, can have a positive effect in preventing recurrent cerebral infarction. If, due to movement disorders, the patient cannot move after a stroke, a regular set of physical exercises at home is recommended.

A balanced diet is of great importance in the prevention of recurrent ischemic stroke [14]. For a patient who has suffered an ischemic stroke or TIA, it is advisable to eat enough fruits and vegetables, vegetable oil, and limit the consumption of foods rich in cholesterol. Diabetes mellitus requires strict control of blood glucose levels, diet, and the use of sulfonylureas or insulin. Reducing excess weight is advisable in patients who have suffered an ischemic stroke or TIA to achieve optimal body weight (body mass index from 18.5 to 24.9 kg/m2) by reducing calorie intake and increasing physical activity [20].

Antiplatelet drugs

Antiplatelet therapy is one of the leading areas in the secondary prevention of ischemic stroke [1,2,4,9,15,20]. Antithrombotic agents reduce the aggregation ability of platelets, thereby preventing the development of ischemic stroke and other cardiovascular diseases . For the secondary prevention of ischemic stroke, the following antiplatelet agents have been proven effective : acetylsalicylic acid, clopidogrel (Plavix), MB - dipyridamole and ticlopidine [1,2,4,7,9,15,20]. A meta -analysis of studies assessing the effectiveness of antiplatelet drugs in patients who suffered an ischemic stroke or TIA showed that long-term (for three years) use of antiplatelet drugs reduces the risk of recurrent stroke, myocardial infarction and acute vascular death by an average of 20 % [9].

The most well-known and widely used antiplatelet agent is acetylsalicylic acid (ASA). The main mechanism of the antiplatelet effect of ASA is the irreversible inhibition of platelet cyclooxygenase , as a result of which the synthesis of cyclic endoperoxides (PGH2 and PGD2), which are precursors of a powerful vasoconstrictor and inducer of platelet aggregation - thromboxane A2 , is reduced . In addition to reducing the synthesis of thromboxane , taking ASA leads to a decrease in the formation of prostacyclin.

ASA for secondary prevention of cerebral infarction is currently recommended in a dose of 75 to 325 mg per day [20]. A meta-analysis of several randomized trials showed that regular use of ASA reduces the risk of stroke, myocardial infarction or vascular death by an average of 13% [9,15]. When using small (75–160 mg), medium (160–325 mg) and high (500–1500 mg) doses of ASA, there were no significant differences in the incidence of stroke, but when using low doses, complications from the gastrointestinal tract were less common [9].

A relatively new group of antiplatelet drugs is represented by thienopyridine derivatives – clopidogrel (Plavix) and ticlopidine . They suppress platelet aggregation caused by ADP and other inducers of platelet adhesion, thereby providing a strong antiaggregation effect.

Ticlopidine is used 250 mg 2 times. The use of ticlopidine reduces the risk of recurrent ischemic stroke by 35.5% [12]. A comparison of the effectiveness of ticlopidine and ASA [13] showed that ticlopidine is more effective than ASA in preventing stroke: within three years of treatment, stroke or death (from any cause) developed in 17% of patients taking ticlopidine , and in 19% of patients taking ASA (the reduction in the risk of stroke and death when comparing ticlopidine and ASA was 12%). A comparison of the side effects of these drugs has established that taking ASA is often complicated by gastrointestinal discomfort and bleeding, while the use of ticlopidine is complicated by inhibition of bone marrow function (hematopoiesis), rash and diarrhea. Since treatment with ticlopidine is often complicated by leukopenia and thrombocytopenia, when taking it, regular monitoring of a complete blood count is required (every 2 weeks during the first 3 months of treatment) and discontinuation of the drug if complications develop.

Clopidogrel (Plavix) is a derivative thienopyridine , which is chemically similar to ticlopidine but has significantly fewer side effects. It has been shown that taking 75 mg clopidogrel reduces the incidence of stroke, myocardial infarction or acute vascular death more significantly than taking 325 mg ASA [7]. A prospective observation of almost 20 thousand patients who had suffered an ischemic stroke, myocardial infarction or had peripheral arterial disease showed that in the group of patients receiving 75 mg of clopidogrel per day, stroke, myocardial infarction or acute vascular death occurred 8.7% significantly less often. than in the group of patients receiving 325 mg of ASA. The analysis shows that when treating 1,000 patients over three years, ASA prevented 19 new events and clopidogrel prevented 24 new events (26% reduction). Neutropenia , a common complication of ticlopidine , was observed in only 0.1% of cases when taking clopidogrel and in 0.17% of cases when taking ASA [7]. Thus, clopidogrel (Plavix) has a safety profile comparable to ASA and, as the results of the CLASSICS study showed, it is 2 times safer than ticlopidine in terms of hemorrhagic complications [15]. Monoterpy clopidogrel at a dose of 75 mg is indicated for patients who have suffered an ischemic stroke, starting from day 7 for a course of 12 months. Adding ASA to clopidogrel in patients after stroke does not provide clinical benefits and increases the risk of bleeding [10]. However, combined antiplatelet therapy with clopidogrel (Plavix) and ASA is recommended for patients who have suffered a TIA or ischemic stroke and have recent coronary events (angina pectoris, myocardial infarction) or have undergone coronary artery stenting [10,11]. Dipyridamole is another antiplatelet agent used for secondary prevention of ischemic stroke. The results of the study showed that the combination of ASA 50 mg/ day . and MV- dipyridamole 400 mg/ day . reduces the risk of stroke by 22.1%, which significantly exceeds the effectiveness of isolated administration of 50 mg of acetylsalicylic acid [11].

Until recently, according to current recommendations , a patient who has suffered an ischemic stroke or TIA should be prescribed an antiplatelet drug. The drugs of choice are: ASA, clopidogrel (Plavix) and MB- dipyridamole [1,3,4,20]. Clopidogrel and the combination of ASA and MB- dipyridamole showed their advantage over ASA in reducing the risk of ischemic events. In 2018 , at the European Stroke Conference, the results of the PR FESS study were presented , the purpose of which was to directly compare the effectiveness and safety of the long-acting dipyridamole (DP)/ASA combination and clopidogrel . The PRoFESS study did not confirm the comparability of ASA+MB-DP and clopidogrel . The primary endpoint of the study (comparability with clopidogrel in terms of effectiveness in preventing recurrent stroke) was not achieved. The incidence of secondary endpoints (stroke, MI and vascular death) was comparable in the clopidogrel and ASA+DP groups. In the ASA+DP group, the absolute incidence of intracranial bleeding increased by 0.4% (a significant increase in relative risk by 42% compared with clopidogrel). The incidence of headache (causing treatment discontinuation), dizziness, and fainting was higher in the ASA+DP group. Experts do not plan major changes to the International Guidelines for the treatment of stroke in connection with the completed study. The drugs of choice for antiplatelet agents will apparently remain ASA, Plavix , and a combination of ASA and MB- dipyridamole [27].

Indirect anticoagulants The development of TIA or ischemic stroke due to cardiogenic embolism is observed in approximately 20% of cases [10]. The most common causes of cardiogenic embolism of the cerebral arteries are atrial fibrillation (half of all cases), pathology of the heart valves (a quarter of cases), and the formation of an intraventricular thrombus (a third of cases) [13]. In this group of patients, the administration of indirect anticoagulants is more effective than the use of antiplatelet agents [10].

The use of indirect anticoagulants is indicated for patients with atrial fibrillation, intraventricular thrombus, recent (up to three months) myocardial infarction, rheumatic lesion of the mitral valve, artificial heart valve and other pathology dangerous for the recurrence of cardioembolic stroke. The dose of warfarin is adjusted gradually based on the international normalized ratio (INR), which is maintained at 2.5 (2–3). In patients who have suffered a cerebral infarction due to atrial fibrillation, when taking warfarin and maintaining MHO at 2–3, ischemic events develop annually in only 8% of cases with a relatively low incidence of major bleeding (2.8% per year).

In cases where the administration of indirect anticoagulants in patients who have suffered a cardioembolic TIA or stroke is not recommended due to the high risk of possible complications, such as gastric bleeding, the use of antiplatelet agents (ASA or clopidogrel if ASA is intolerant) is indicated. A comparative study of the effectiveness and safety of ASA and clopidogrel (ACTIVE-A) in patients with atrial fibrillation who are unable or unwilling to take oral anticoagulants for stroke prevention is - ongoing [26].

Antihypertensive therapy

Normalization of blood pressure is one of the most effective areas of secondary prevention of ischemic stroke [1,4,8,10]. Increase in systolic blood pressure by 12 mm Hg , and diastolic blood pressure by 5 mm Hg . is associated with an average 34% increased risk of stroke. This dependence is observed not only in patients with arterial hypertension, but also in patients with normal blood pressure after a stroke [8]. Elderly patients have almost twice the effect of normalizing blood pressure than young patients, since they have a significantly higher risk of developing a recurrent stroke [8]. As non-medicinal methods of lowering blood pressure, it is recommended to reduce salt intake from food, and in case of excess weight, to achieve and maintain ideal body weight, which requires reducing the total calorie content of food and regular physical activity (therapeutic exercises, walking), the intensity of which varies from person to person. For patients with stage II–III (moderate or severe) arterial hypertension, various antihypertensive drugs can be effective, taking into account individual indications for their use and concomitant diseases in a particular patient. However, to normalize blood pressure in such patients, as well as in patients with stage I (mild) arterial hypertension, the effectiveness of only some antihypertensive drugs has been proven: the diuretic indapamide [16], a combination of the angiotensin-converting enzyme inhibitor perindopril and indapamide [16], the angiotensin II receptor blocker eprosartan [22].

The PATS study found that taking 2.5 mg of indapamide for two years reduced the risk of recurrent stroke by an average of 28% in patients who had suffered a stroke or TIA [16]. The results of the PROGRESS study showed that in patients who had suffered a stroke or TIA, taking a combination of perindopril 4 mg/ day . And indapamide 2.5 mg/ day . over four years leads to a reduction in the risk of recurrent stroke by an average of 28%. It is important to note that this combination of antihypertensive drugs reduces the risk of recurrent stroke in patients not only with arterial hypertension, but also with normal blood pressure [16].

The MOSES study compared the effectiveness of the calcium channel blocker nitrendipine and the angiotensin receptor blocker eprosartan in patients with systolic arterial hypertension who have had a stroke [12]. During treatment, the target reduction in blood pressure was achieved in approximately 75% of patients when taking both eprosartan and nitrendipine , however, when treated with eprosartan , a significant reduction in the frequency of recurrent strokes was found by 25%, as well as a reduction in overall mortality and all vascular events by an average of 20%. .

Currently, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are - considered as the most effective means of secondary prevention of cerebral infarction [22]. It is likely that the mechanisms by which angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers prevent stroke are not limited to their ability to lower blood pressure. Their antiatherogenic effects, mediated by their effect on the renin-angiotensin-aldosterone system, may be of great importance [10,12] . One arm of the ongoing ACTIVE trial (ACTIVE I) is investigating the role of irbesartan in preventing stroke [16].

The optimal level of blood pressure that should be achieved in patients who have suffered an ischemic stroke or TIA has not been fully determined, but if the patient does not have significant stenosis or blockage of the carotid arteries, one should strive for normal blood pressure (systolic pressure - 120-139 mm Hg. Art ., diastolic pressure – 80–89 mm Hg) [20].

When carrying out antihypertensive therapy, caution is required in patients who have suffered a TIA or ischemic stroke and have severe stenosis or occlusion of at least one carotid artery [19]. In cases in which significant stenosis of the internal carotid artery is detected, consultation with a vascular surgeon is necessary to decide on surgical treatment. In cases where surgical treatment is not performed and the patient remains with significant stenosis or blockage of the carotid and vertebral arteries, one should not strive to normalize blood pressure (below 140/90 mm Hg) , since this is associated with the risk of ischemic complications [19 ,20].

Statins

The effectiveness of statins has now been convincingly proven in patients who have suffered TIA or ischemic stroke [5]. Previously , there was no doubt that if a patient who has suffered an ischemic stroke or TIA suffers from coronary heart disease (myocardial infarction, angina) and (or) diabetes, treatment with statins is indicated to prevent myocardial infarction and mortality from cardiovascular - diseases [10]. One of the latest studies showed that the administration of atorvastatin at a dose of 80 mg per day is effective and safe even in patients who have had a TIA or stroke and do not have either coronary heart disease or high serum cholesterol levels [5].

Carotid endarterectomy and stenting Surgical treatment options - carotid endarterectomy or stenting - are discussed when identifying internal carotid artery stenosis in a patient who has suffered a TIA or ischemic stroke with little or no disability [1,3,4,10].

When deciding on carotid endarterectomy , one should take into account not only the degree of carotid artery stenosis, but also the prevalence of atherosclerotic lesions of extracranial and intracranial arteries, the severity of coronary artery pathology, and the presence of concomitant somatic diseases. It is important to note that the elderly and senile age of the patient is not considered a contraindication to surgical treatment.

In cases of internal carotid artery stenosis, when carotid endarterectomy is contraindicated or the stenosis is located in a place inaccessible to this operation, angioplasty and stent placement can be used . In case of blockage of the internal carotid artery, extra - intracranial anastomosis is not recommended [20]. According to the EUSI guidelines for stroke prevention, carotid stenting should be accompanied by a combination of ASA and Plavix before, during and after stenting for at least 1 month.

In cases of TIA or ischemic stroke caused by severe stenosis (narrowing of 70–99% of the diameter) of the vertebral artery or intracerebral artery, stent placement can be used [10].

Secondary prevention for special conditions In 5–10% of cases, TIA and ischemic stroke are caused by special diseases and conditions for which secondary prevention of stroke has its own characteristics.

For dissection of the carotid or vertebral arteries, indirect anticoagulants and antiplatelet agents can be used for 3–6 months [10]. After 3–6 months, patients taking indirect anticoagulants should be switched to antiplatelet agents. If TIA or ischemic stroke recurs in the affected artery, it is advisable to install a stent [10].

In the case of TIA or ischemic stroke associated with patent foramen ovale, indirect anticoagulants or antiplatelet agents can be used [10]. Relatively often, surgical methods of closing the oval window are used to prevent recurrent ischemic stroke, the effectiveness of which remains insufficiently studied [10].

For hyperhomocysteinemia in a patient who has suffered a TIA or ischemic stroke, drugs containing vitamins B6 and B12 and folic acid can be used as additional therapy to reduce homocysteine levels in the blood serum, but the effectiveness of such therapy remains insufficiently studied [10].

For hypercoagulopathies due to antiphospholipid syndrome or hereditary thrombophilia in patients who have suffered a TIA or ischemic stroke, indirect anticoagulants or antiplatelet agents can be used [10].

For sickle cell anemia in patients who have suffered a TIA or ischemic stroke, antiplatelet agents are recommended; blood transfusions can be used as an additional treatment to reduce the hemoglobin S content to 30–50% (relative to total hemoglobin) [10]. Issues of optimization of secondary prevention Unfortunately , effective prevention of recurrent ischemic stroke is currently carried out only in a small part of patients in our country [2]. Surgical treatment methods and statins are carried out in isolated cases. Among patients with arterial hypertension who have suffered a TIA or ischemic stroke, irregular use of antihypertensive drugs is common , often without strict blood pressure control. Even antiplatelet drugs are constantly taken by only a portion of patients. In cases where a patient taking ASA develops a recurrent ischemic stroke, other antiplatelet drugs are rarely prescribed.

The effectiveness of secondary prevention of ischemic stroke increases significantly when the patient uses all possible effective drugs and non-drugs. The combination of several means of secondary prevention of ischemic stroke (diet, exercise, antiplatelet drugs, statins and antihypertensive drugs) can reduce the risk of recurrent stroke by almost 80%, thereby preventing 4 out of 5 possible strokes [14]. Many patients who have suffered an ischemic stroke or TIA do not prevent recurrent stroke and other cardiovascular diseases because they are not sufficiently informed about effective treatments. Relatively often, patients who have suffered an ischemic stroke do not seek consultation at the clinic after discharge from the hospital. A relatively small proportion of patients are observed in specialized centers (departments) for the rehabilitation of patients after stroke. A significant proportion of patients take courses primarily of drugs that improve cerebral circulation and metabolic processes in the brain, without using antiplatelet agents and other effective methods of secondary prevention of ischemic stroke. An increase in the proportion of patients undergoing dispensary observation after a TIA or ischemic stroke and receiving adequate treatment represents one of the most effective directions in optimizing the prevention of recurrent ischemic stroke.

Thus,

Currently, effective means of preventing recurrent ischemic stroke have been developed: quitting smoking and alcohol abuse, diet, normalization of blood pressure (based on the use of antihypertensive drugs), long-term use of antiplatelet drugs, warfarin (for atrial fibrillation), carotid endarterectomy (for severe stenosis of the internal carotid artery) and taking statins . Unfortunately, in our country, effective means of preventing recurrent ischemic stroke are used in a relatively small proportion of patients. Their widespread introduction into everyday clinical practice can lead to a significant reduction in the incidence of recurrent ischemic stroke and mortality from it in our country.

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