TRANSIENT ISCHEMIC ATTACK: MANAGEMENT TACTICS AND ANTIPLATELET THERAPY FOR THE PREVENTION OF CEREBRAL INFARCTION

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Summary: Despite the significant progress achieved in the treatment and prevention of acute cerebral circulatory disorders (ONMC), strokes remain one of the main causes of mortality and the leading cause of disability worldwide. The new procedure for providing medical care to patients with ONMC, regulating the creation of specialized departments for ONMC patients, increased the number of patients hospitalized in a timely manner for stroke, decreased the frequency of deaths and disability.
Keywords: Transient ischemic attack, Cerebral infarction, Ischemic stroke, antiplatelet drugs.

Difficulties remain in organizing care for patients with transient ischemic attacks (TIA) all over the world. Due to the short duration of the existence of symptoms in most cases, patients do not attach importance to them, do not seek medical help, so the registration of TIA remains incomplete. According to international statistics, the incidence of TIA reaches 50-100 people per 100 thousand population [20]. Meanwhile, timely recognition of TIA is extremely important, because it allows to provide effective assistance aimed at preventing the development of gross motor, speech and other disorders depending on the location of the lesion, as well as to carry out secondary prevention of stroke. TIA, according to the clinical classification developed by E.V. Schmidt, adopted in the Russian Federation, is a variant of transient cerebrovascular accident (PNMC) [15]. TIA is traditionally defined as an acute cerebrovascular accident (ONMC) with a short-term (not exceeding 24 hours) impairment of brain functions in the form of focal and/or cerebral symptoms, followed by complete regression of symptoms and the absence of signs of cerebral infarction according to neuroimaging data [4, 5, 8, 11]. Do not forget that TIA is a critical condition, which is clinically impossible to distinguish from a cerebral infarction before the symptoms pass (or before the expiration of 24 hours).

It is known that the risk of ischemic stroke after TIA increases by 4-10% in the first two days, and by 10-20 in the next 3 months. Thus, TIA can be considered a predictor of stroke. Usually TIA precede atherothrombotic stroke (up to 50% of cases), less often – cardioembolic (in 10% of cases) or lacunar (in 20% of cases), other patients develop hemorrhagic stroke.

The most significant risk factors for TIA are arterial hypertension, hypercholesterolemia, diabetes mellitus, smoking, excessive alcohol consumption, overweight, sedentary lifestyle. The most common etiological factors of TIA are [1, 6, 11, 12, 24, 31, 33]: %. In the presence of extracranial carotid artery stenosis exceeding 70% of the diameter, the risk of stroke in the first 2 years after TIA reaches 28%.

• atherosclerosis of the carotid, vertebral arteries and large branches of the basin of these arteries, which leads to arterio-arterial embolism, and symptomatic carotid stenosis of more than 50% of the artery lumen, leading to the development of hemodynamic insufficiency;
• anomalies of development (inflection, doubling, hypo- or aplasia) of the carotid or vertebral arteries, coarctation of the aorta;
• angiopathies caused by arterial hypertension, diabetes mellitus or other causes;
cardiogenic embolism;
• dissection of the carotid or vertebral artery;
• coagulopathy;
• extravasal compression of vertebral arteries by pathologically altered cervical vertebrae;
• use of sympathomimetics.

In more rare cases, TIA may be caused by vasculitis, including specific, blood diseases, antiphospholipid syndrome, venous thrombosis, migraine, oral contraceptives or other causes. The development of TIA is caused by an acute, but reversible (without the development of a heart attack) critical decrease in blood supply to a part of the brain in a certain arterial basin. The key point in the pathogenesis of TIA is precisely reversible local cerebral ischemia, which develops with a decrease in cerebral perfusion below 18-22 ml per 100 g/min. (at a rate of 50-60 ml per 100 g/min.), which is the functional threshold of ischemia. In case of a further drop in perfusion below the threshold of irreversible changes (8-10 ml per 100 g / min.), a brain infarction develops. In general, the mechanisms of TIA development are similar to the pathogenesis of ischemic stroke. The clinical outcome of ischemic type ONMC (TIA or cerebral infarction) mainly depends on the localization of the lesion and the rate of development of the pathological process, the state of collateral circulation and rheological properties of blood [4, 5, 9, 17].

Clinically, TIA is manifested by transient symptoms of cerebral ischemia, depending on the localization of the pathological process, such as:
• loss of vision in one or both eyes;
• paresis in the arm and/or leg and/or facial muscles;
• impaired sensitivity in the arm and/or leg and/or facial muscles;
• disturbance of balance and/or coordination of movements;
• speech disorder;
• epileptic seizures;
• loss of consciousness;
• memory impairment, psychomotor agitation, behavior disorder.

The average duration of a TIA episode is 8-14 min., most TIAs are resolved within 1 hour or earlier. According to V.A. Parfenov, the duration of TIA symptoms less than 1 hour was noted in 43.5%, from 1 to 3 hours – in 45.7%, more than 3 hours – in 10.9% of patients. TIA occur in the carotid basin almost 4 times more often than in the vertebrobasilar [10]. In most cases, the diagnosis of TIA is determined retrospectively, because at the time of examination of the patient by a neurologist, his focal symptoms regress spontaneously [28, 31, 33]. In this regard, it is necessary to carefully collect anamnesis and knowledge of the clinical manifestations of TIA by doctors of various profiles. TIA can be repeated often or develop once.

Verification of the diagnosis of TIA is based on:
• assessment of the clinical picture;

• determination of the etiology of TIA by echocardiography (EchoCG) and/or duplex scanning of the vessels of the neck and brain, if necessary – angiographic examination;
• exclusion of cerebral infarction using neuroimaging methods (CT or MRI), which must be carried out even with complete regression of symptoms.

The main objectives of the diagnosis of TIA are:
• exclusion of cerebral infarction in the first 3 hours from the development of TIA;
• exclusion of other diseases having a clinical picture similar to TIA;
• determination of the etiology of TIA (differentiation of embolic and non-embolic TIA, TIA in carotid and vertebral stenosis) in order to start targeted prevention of cerebral infarction in a timely manner.

Computed tomography (CT) or magnetic resonance imaging (MRI) of the head is indicated for all patients who, based on the clinical picture, have a suspicion of TIA. If the patient is hospitalized within 1-6 hours after TIA, CT or MRI should be used to exclude a cerebral infarction, as well as a subdural hematoma or brain tumor.

Duplex scanning (DS) is used to assess blood flow in cerebral vessels by qualitative audiovisual and quantitative characteristics. DS allows to diagnose various pathological vascular processes based on direct echographic signs, including atherosclerosis, vasculitis, angiopathies, vascular anomalies, aneurysms, etc. The advantages of DS include the possibility of detecting early preclinical signs of the disease, assessing changes in hemodynamics in real time with the detection of not only organic, but also functional disorders of blood flow.

Magnetic resonance angiography (MRA) or CT angiography is indicated when DS does not give a reliable result. Carotid angiography is a standard diagnostic procedure before performing carotid endarterectomy. It is also indicated for patients with TIA in the event that DS and MRI (CT angiography) give contradictory results, or if their implementation is impossible.

EchoCG is indicated when the cardioembolic mechanism of TIA is suspected in cases where the data of anamnesis and / or objective examination indicate the possibility of cardiological pathology when the patient's age exceeds 45 years, as well as when the results of a study of the vessels of the neck, brain and blood tests did not reveal the cause of TIA. The basic principles of management of patients with TIA before the end of the episode of PNMC do not differ from the tactics of management of a patient with a brain infarction. If the symptoms associated with TIA persist for several hours and the patient has time to seek help, then he is subject to hospitalization in a specialized department for patients with ONMC for emergency indications in order to conduct differential diagnosis with ischemic stroke. This also applies to patients who have undergone TIA for the first time in their lives, if no more than 48 hours have passed since the regression of neurological symptoms. In the case of a longer time interval (more than 48 hours have passed since the end of the TIA), the patient is examined and treated on an outpatient basis. The examination includes MRI of the head, as well as ECG, DS and EchoCG. Repeated TIA, which developed during the next 12 hours of the outpatient examination period, forces a change in management tactics and serves as an indication for emergency hospitalization. Patients who have undergone repeated TIA are subject to emergency hospitalization. The main diagnostic tasks during hospital stay, as mentioned above, are the exclusion of cerebral infarction, differential diagnosis and the establishment of the etiology of TIA.

After the completion of the TIA, the main efforts should be directed to the prevention of repeated ONMC. The drugs of choice for noncardioembolic TIA are antiplatelet agents, for cardiogenic embolisms – anticoagulants and / or antiplatelet agents. The main way to prevent repeated ONMC in noncardioembolic TIA is long-term daily therapy with antiplatelet agents.

The first-line preparation is acetylsalicylic acid (ASA), prescribed at a dose of 50-325 mg / day. In case of intolerance to ASA or the appearance of side effects, it is advisable to use clopidogrel at a dose of 75 mg / day. In case of recurrence of an episode of ONMC, a combination of ASA at a dose of 50 mg / day is recommended. and dipyridamole 400 mg / day. The combination of clopidogrel with ASA, being more effective than ASA monotherapy, is not recommended for use in most cases due to the increased risk of side effects. The main way to prevent repeated ONMC in cardioembolic TIA is long-term daily therapy with indirect anticoagulants and/or ASA. In addition to this therapy, it is necessary to correct risk factors for TIA and ischemic stroke: arterial hypertension, hypercholesterolemia, heart disease, diabetes mellitus.

With symptomatic carotid stenoses of more than 50% of the artery lumen, carotid endarterectomy is necessary in order to prevent stroke in the shortest possible time. In some cases, with carotid stenoses of more than 70%, it is possible to perform endovascular techniques – balloon angioplasty and stenting of the carotid or vertebral artery.

Antiplatelet drugs are the most popular in the practice of cardiologists and neurologists, which is due to the high prevalence of cardiovascular diseases, as well as a convincing evidence base for the effectiveness of these drugs [3, 7].

According to the unanimous opinion of researchers, the appointment of antiplatelet therapy reduces the number of cases of ischemic stroke [2, 18, 19]. Currently, ASA, clopidogrel, dipyridamole, etc. are used as antiplatelet drugs. ASA for the prevention of cardiovascular diseases began to be used in the 1970s, at the same time, for the first time, information was obtained about a high correlation between the use of ASA and a decrease in the frequency of TIA.

It is known that the leading mechanism of action of ASA is its effect on the cascade of arachidonic acid by inhibiting the enzyme cyclooxygenase-1 (COX-1) of platelets, metabolizing arachidonic acid to endoperoxides. ASA irreversibly acetylates COX-1 near its catalytic center, thereby preventing the formation of arachidonic acid metabolites, and above all such a powerful activator of platelet aggregation as thromboxane A2 [22].

Taking into account the highest degree of activation of the platelet-vascular link of hemostasis in the acute stage of ONMC by ischemic type, the most adequate is the use of ASA during this period.

ASC is the only antiplatelet drug whose effectiveness when prescribed in the acute period of ONMC is confirmed by evidence-based medicine [23, 28, 34]. However, the use of ASA in the acute period of cerebral infarction is not an alternative to thrombolytic therapy and is not recommended in the first 24 hours after thrombolysis [28]. The effectiveness of ASA in the primary prevention of cardiovascular diseases has been evaluated in a number of large studies [27, 32, 34]. In most of them, there is no evidence of the effectiveness of primary stroke prevention using ASA in both healthy individuals and patients with stroke risk factors. The currently available research data on the primary prevention of ischemic stroke allow us to recommend the appointment of small (100 mg/ day) doses of ASA to women aged 45 years

and older who do not have the risk of intracranial hemorrhages and diseases of the gastrointestinal tract (gastrointestinal tract) (class I, level A) [28].

At the same time, other antiplatelet drugs other than ASA are generally not recommended for primary prevention of stroke (Class IV, GCP) [28].

In addition, therapy with small doses of ASA is indicated for individuals who have been diagnosed with asymptomatic stenosis of the internal carotid artery exceeding 50% of the artery lumen (class II, level B) [28], as well as for peripheral artery diseases and diabetes mellitus, even in the absence of a history of ONMC episodes.

The effectiveness of ASA for secondary prevention of ONMC was proved in the late 1970s [26]. Subsequent studies have convincingly confirmed that long-term administration of ASA reduces the frequency of repeated cerebral infarctions [16, 25].

According to the ESO recommendations, patients who have undergone ONMC are recommended to receive antithrombotic therapy if they are not indicated or contraindicated with anticoagulant therapy. As specific medicines, it is recommended to prescribe a combination of ASA and dipyridamole, as well as monotherapy with clopidogrel, ASA or trifluzal (Class I, level A) [28]. When prescribing ASA, it is important to accurately determine the duration of taking the drug, the dose and frequency of administration, as well as to take into account contraindications and possible side effects. According to the general opinion of researchers, for the prevention of cerebral infarctions after a TIA, ASA drugs should be prescribed for a long time (for 1-2 years or permanently), the frequency of administration is 1 time / day. It is believed that taking ASA reduces the risk of vascular events regardless of the dose (from 50 to 1300 mg / day), although high doses (more than 150 mg / day) increase the risk of side effects. An important advantage of this drug is that in patients with symptomatic atherosclerosis of the intracranial arteries, taking ASA is as effective as oral anticoagulant therapy, but it is accompanied by fewer complications [28].

One of the reasons for choosing a low dose of ASA in order to prevent stroke is the mechanism of action of the drug. It is known that the antithrombotic effect of ASA is associated with irreversible blockade of the enzyme COX-1 of platelets and significant suppression of the production of thromboxane A2. The peculiarity of this enzyme is its high sensitivity to the action of ASA, which is ten times higher than that of COX-2, responsible for the production of prostacyclin in the vascular endothelium. In this regard, ASA in small doses, blocking only COX-1 and leaving COX-2 intact, causes mainly a decrease in the production of thromboxane A2, while the level of prostacyclin – a powerful vasodilator and antiplatelet agent – remains quite high [14]. At higher doses, ASA causes suppression of both isoenzymes.

According to the conducted studies, the optimal dose of ASA, which has an inhibitory effect on platelets and a decrease in the concentration of thromboxane A2, is a dose of 75-150 mg / day. Higher doses lead to simultaneous inhibition of prostacyclin synthesis, and lower doses (less than 50 mg / day.) they do not have a noticeable antiplatelet effect [30]. Secondly, when choosing the optimal daily dose of ASA for the prevention and treatment of ONMC, it is necessary to evaluate the side effects. Like other nonsteroidal anti-inflammatory drugs (NSAIDs), ASA can have a local (due to irritation of the mucous membrane) and systemic (due to a decrease in prostaglandin synthesis) damaging effect on the gastrointestinal mucosa when taken orally, which is fraught with the occurrence of erosions and ulcers, the development of gastrointestinal bleeding. The frequency of these complications depends on the daily dose of the drug. When using a dose of 300 mg / day. it is lower compared to the use

of a dose of 1200 mg / day. In fairness, it should be noted that when using low doses of ASA, the risk of complications is not completely eliminated [23].

Prolonged use of high doses of ASA may increase blood pressure and increase the incidence of hemorrhagic strokes, which is not observed in the treatment of small doses [29]. High doses of ASA can cause liver and kidney dysfunction, allergic reactions, and inhibition of leukopoiesis.

One of the possible ways to eliminate the adverse effects of ASA, in particular on the gastrointestinal mucosa, is the use of dosage forms with an intestinal-soluble shell or the introduction of antacids into the composition of the drug. However, according to available data, the intestinal-soluble shell significantly slows down the absorption of ASA and reduces its bioavailability.

Thirdly, there is a problem of simultaneous long-term administration of ASA and other NSAIDs indicated in connection with the presence of comorbid diseases. In addition, the problem of clinical and laboratory resistance is relevant.

Thus, in order to prevent ONMC, the appointment of ASA should be made for a long time in a small dose using a dosage form that minimizes the adverse effect of ASA on the gastrointestinal mucosa. The above conditions are met by the drug Cardiomagnil. Firstly, it is available in two forms with different dosages (75 or 150 mg of ASA). Secondly, the composition of the Cardiomagnet contains an antacid agent – magnesium hydroxide, which allows for high safety of the Cardiomagnet, preventing the effect of ASA on the gastrointestinal mucosa.

Literature data and our own experience allow us to consider therapy with small doses of ASA as the "gold standard" of antiplatelet therapy, and long-term use of the drug Cardiomagnil at a dose of 75 mg / day. It is recommended for wide application in the practice of outpatient and inpatient medical care for the prevention of cerebral infarction, including in patients who have undergone TIA and suffering from gastrointestinal diseases.

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