Chapter

The Treatment of Acute Stroke

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Abstract

Stroke is a major public health issue, because of its high incidence rate, high case fatality rate, risk of residual physical and neuropsychological disabilities, and direct and indirect costs. Many strokes are preventable and treatable in the acute stage, provided that patients are admitted soon enough. The term stroke covers a wide range of heterogeneous disorders, depending on the severity of the clinical presentation, from transient deficits to severe cases with coma and early death; the underlying mechanism, i.e., cerebral ischemia, parenchymal hemorrhage, subdural hemorrhage, or subarachnoid hemorrhage (SAH); and the cause, i.e., atherosclerosis, cardioembolism, small-vessel occlusion, rare vasculopathies and undetermined causes in cerebral ischemia, or vascular malformations, cerebral amyloid angiopathies, small-vessel diseases, rare vasculopathies and undetermined causes in parenchymal hemorrhages. This chapter will focus only on acute cerebral ischemia and parenchymal hemorrhage. We will cover the general assessment of stroke patients, the complications that can occur in the acute stage, the treatment of acute stroke, and finally a few situations that require specific managements and where evidence-based data are scarce.

Keywords: cerebral ischemia, parenchymal hemorrhages, thrombolytic therapy, complications

1. Introduction

This chapter focuses on the treatment of acute cerebral ischemia and intracranial hemorrhage, which are two types of stroke. Stroke is characterized by a sudden loss of brain function with no established cause other than vascular origin. This applies to both ischemic stroke and intracranial hemorrhage.

1.1 The diagnosis of stroke

Acute stroke suggests the following signs:

- Sudden onset of symptoms and development of the clinical picture in a few seconds or minutes with further stabilization or improvement.

- Focal neurological symptoms associated with damage to certain parts of the brain: motor deficits (weakness or immobility of the limbs on one side of the body (hemiplegia or hemiparesis) or an isolated limb), loss of sensitivity (decreased sensitivity in various parts of the body), aphasia, agnosia, and vision disorders.

- Symptoms suggesting a loss of function: limb tremors, convulsions, paresthesias, visual hallucinations, and flashes before the eyes.

- Headache, nausea and vomiting, dysphagia, dysarthria, dysphonia, diplopia, ataxia, hiccups, one-sided acute hearing loss, respiratory disorder, convulsive syndrome, and transient loss of consciousness may be clinical manifestations of a stroke localized in the brain stem.

- Symptoms such as loss of consciousness, dizziness, general weakness, confusion, urinary incontinence, syncopal condition, and tinnitus do not indicate the development of a stroke if they are not associated with focal neurological symptoms.

For the differential diagnosis of ischemic and hemorrhagic strokes, it is necessary to conduct a neuroimaging study [1]. This is the most important stage of diagnosis, because patients with ischemic and hemorrhagic strokes require different therapies in the acute period and various measures of secondary prevention [2].

Magnetic resonance imaging (MRI) is the most appropriate diagnostic method for patients with acute cerebral circulation disorders due to the following reasons [3]:

1. T1- and T2-weighted images and fluid-attenuated inversion recovery (FLAIR) sequences allow the differentiation of old foci and foci of nonvascular origin.

2. Diffusion-weighted images allow the identification of new ischemic foci. Low brain blood flow causes the development of cytotoxic cell edema and, as a result, a decrease in the movement of extracellular fluid, which is displayed as a hyperintensive signal on diffusion-weighted images, and a decrease in the water diffusion coefficient. These changes appear earlier than changes in T1 and T2 and FLAIR.

3. T* sequences are used to detect hemorrhages.

4. Time-of-flight (TOF) MR angiography can be used to visualize the occlusion of extra- and intracranial arteries.

When MRI is not available in an emergency or cannot be performed due to contraindications (established rhythm driver, claustrophobia, psychomotor agitation), an emergency computed tomography (CT) scan of the brain is performed without contrast. CT scan reveals an intracranial hemorrhage in the form of a hyperintensive zone in the brain parenchyma. **Figure 1** shows a non-contrast CT scan with a spontaneous hyperdensity of the right cerebral hemisphere, due to a deep intracerebral hemorrhage (ICH). In the early stages of acute cerebral ischemia, CT signs of ischemia may be absent. But within 3 hours, you can see signs of ischemia, for example, the disappearance of a clear border of gray and white matter. With the occlusion of the middle cerebral artery, CT signs will appear in the form of a hyperintensive zone. CT with contrast allows you to visualize the anatomy of the arteries and perfusion.

The most common causes of ischemic stroke are common atherosclerosis, atrial fibrillation (AF), occlusion of small perforating arteries of the brain, pathology of heart valves, and infectious diseases, in young patients—cerebral artery dissection.

Intracerebral hemorrhages in most cases are the result of the damage to small cerebral vessels due to chronic arterial hypertension or amyloid angiopathy.

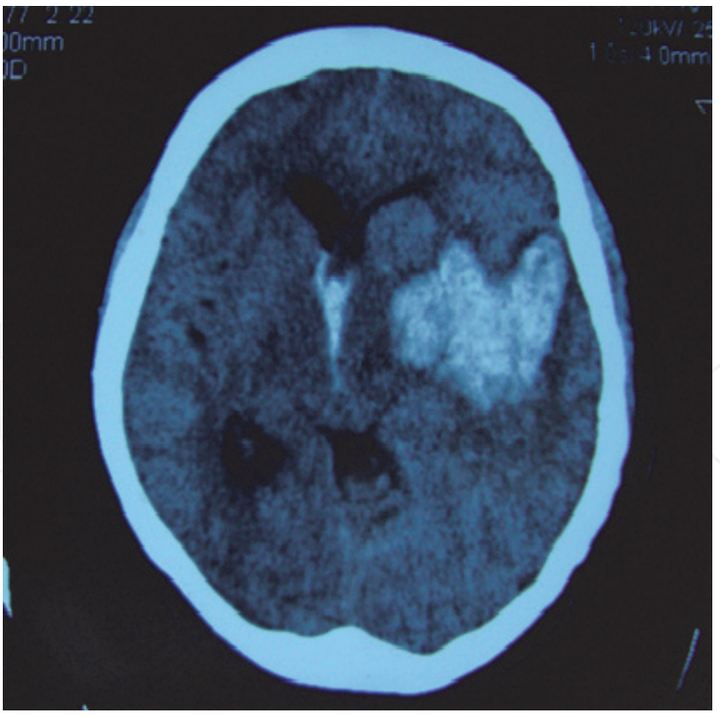

Figure 1.
Non-contrast CT scan shows a spontaneous hyperdensity of the right cerebral hemisphere.

1.2 Examination of patients with acute stroke

For all patients in the acute stage, the following examinations should be carried out, which will determine the treatment plan: a thorough collection of anamnesis to determine the presence of hypertension, medications used, alcohol abuse, and substance abuse and a family history of stroke, oncology, and trauma; a clinical examination; blood test to detect polycythemia and plateletemia, erythrocyte sedimentation rate (ESR) to detect vasculitis, and the level of glycemia to detect diabetes or hypoglycemia, and coagulation tests. Cardiac assessment including electrocardiogram (ECG) and echocardiography (EchoCG) is quite important in all cases and Holter in selected cases. ECG recording to detect heart attacks, atrial fibrillation, continuous ECG monitoring to detect arrhythmias; monitoring of systolic, diastolic, and mean blood pressure (BP) by noninvasive method; dopplerography to detect stenoses and dissections of cervical and intracranial vessels; transthoracic EchoCG to detect blood clots, tumors, valve pathology, vegetations on the valves, reduction of ejection fraction, and the presence of an open oval window. Neuroimaging methods include MRI and CT of the brain to detect caverns, intracranial venous thromboses, cerebral microhemorrhages, arteriovenous malformations (AVM), tumors, and indirect signs of unknown injuries. Additional examinations are prescribed depending on the initial results obtained, the patient's age, and the presumed etiology of the stroke: angiography (usually MR, CT angiography) and specific biological tests when it comes to specific causes, such as antinuclear antibodies, etc.

There are neurological complications that occur in the acute phase of stroke in any type in the form of convulsive syndrome; hyper- and hypoactive delirium, especially with a pre-existing decrease of cognitive functions and the development of metabolic or infectious complications; as well as intracranial hypertension.

Nonspecific complications include bedsores, pneumonia, urinary tract infection, hyponatremia due to inadequate secretion of antidiuretic hormone (ADH), deep vein thrombosis, and pulmonary thromboembolism. They are more likely to

develop in patients with severe neurological deficits. Hyponatremia is a common accompaniment during the acute stage of stroke. Its relevance to the clinical presentation, treatment and prognosis should be mentioned.

1.2.1 Protocol of hypernatremia correction in patients with stroke

Hypernatremia: Na >145 mmol/l (the main reason—central DI)
Criteria: polyuria: rate of diuresis >3 ml/kg/hour
Hypernatremia: >145 mmol/l
Urine specific gravity: <1005

Infusion therapy:

Base 75–100 ml/hour monitoring of sodium concentration every 6 hours.
Fluid deficit replenishment: in case of polyuria—compensation of fluid loss.

If ineffective, symptoms of diabetes insipidus (DI) persist—ADH

Desmopressin: 2–4 mcg per 24 hours
Vasomirin (nasal spray): 10 mcg

1.2.1.1 Fluid loss calculation

Total body fluid = 0.6 × body weight
Free water deficit = (0.6 × body weight) − (0.6 × body weight) × (140/Na act)
Example: body weight = 75 kg, Na = 154 mmol/l
Free water deficit = 0.6 × 75 − [0.6 × 75 × (140/154)] = 45 − 40.9 = 4.1 l

1.2.2 Protocol of hyponatremia correction in patients with stroke

Hyponatremia: Na < 135 mmol/l
If Na <125 mmol/l, there is a high risk of neurological disorders.

1. Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

   A. No neurological deterioration

   B. Acute neurological deterioration

   - Hyponatremia: no longer than 24 hours acute not prolonged reducing the level of sodium
   - Negative fluid balance: IV 3% NaCl—4 ml/kg during 15–30 min
   - 2/3 of physiological need for fluid + furosemide 1 mg/kg
   - Intravenous (IV): only sodium solutions
   - Monitoring: fluid balance, diuresis, sodium in plasma/urine, and urine specific gravity

2. Central salt wasting syndrome

A. Restoring of fluid deficit

B. Positive sodium balance

C. Rehydration

D. HyperHAES: 0.25 ml/kg/hour or 0.9%NaCl

E. Fludrocortisone: 0.4 mg per 24 hours

F. Acute hyponatremia correction rate (<48 h): ≤24 mmol/l/24 hours

G. Chronic hyponatremia correction rate (>48 h): ≤0.5 mmol/l/hour, but ≤10 mmol/l/24 hours

H. In the presence of an accompanying potassium deficit: ≤4 mmol/l/25 hours

2. Treatment of acute stroke

2.1 General principles of the therapy

Stroke patients should be treated in specialized departments. For every 24 patients treated in a specialized rather than general ward, one death and one disability are prevented [4]. This does not depend on the age, type, and severity of stroke [4, 5]. Therefore, specialized departments are very important for the treatment of stroke patients [1, 4]. For all strokes with persistent neurological deficits, the treatment aimed at stabilizing the patient's condition, controlling vital functions, and actively curating problems that may worsen recovery is indicated. This is the main component of the stroke treatment program [6, 7].

In the detection and treatment of emergency life-threatening conditions (risk of aspiration, epileptic status, respiratory failure, etc.), the patency of the upper respiratory tract should be ensured in the case of deprivation of consciousness to the level of coma, respiratory failure of central origin, or local causes leading to respiratory disorders.

The stabilization of most physiological parameters, blood pressure, saturation (more than 93%), glycemic level (less than 180 mg), body temperature (below 37.50°C), and hydration, is necessary in the first few days to prevent negative dynamics in the penumbra zone.

A normal respiratory function with adequate blood oxygenation is necessary in the acute period of stroke to maintain an adequate oxygen delivery to brain cells, but there is no conclusive evidence that all patients with stroke receive oxygen therapy with a positive result [4]. In cases of hypoxemia, improved blood oxygenation is achieved by oxygen therapy via a nasal catheter and noninvasive or invasive ventilation.

Complications of acute stroke include neurogenic stressful cardiomyopathy, paroxysmal sympathetic hyperactivity, atrial fibrillation, acute heart failure, myocardial infarction, and sudden death [1, 2]. The frequency of these complications explains the need for a constant monitoring for 2–3 days.

Many stroke patients are in a state of dehydration, which leads to a worse outcome of the disease [1, 2]. Despite limited clinical data, the administration of

infusion therapy (0.9% sodium chloride solution) is considered part of the overall treatment of stroke, especially in patients with an increased risk of dehydration due to depression of consciousness or respiratory disorders. Experience in the treatment of hyperglycemia recommends avoiding the introduction of glucose solutions in the early period of stroke and strict control of the level of glycemia [4].

According to the literature, there are no mechanisms for autoregulation of cerebral blood flow in the penumbra zone. Therefore, a decrease in blood pressure in the first hours after a stroke before the penumbra zone appears can cause significant hypoperfusion, which worsens the development of the ischemia zone. Therefore, in the acute period, it is not necessary to aggressively treat arterial hypertension if there are no concomitant life-threatening conditions, such as aortic dissection or intracranial hematoma [2, 4].

In practice, blood pressure correction is usually started when the systolic blood pressure exceeds 220 mm Hg and diastolic blood pressure exceeds 120 mm Hg. However, in many clinics, antihypertensive therapy is performed only in cases of heart failure, acute renal failure, aortic arch dissection, or malignant hypertension. When conducting a thrombolytic therapy (TLT), it is common practice to maintain blood pressure below 185 mm Hg. The intravenous administration of labetalol (10 mg bolus, followed by an infusion of 0.1–0.3 mg/kg/hour) or urapidil (12.5 mg bolus for 20 seconds, followed by an infusion of 6–30 mg/hour) is often used.

Hyperglycemia occurs in 60% of stroke patients who have not previously suffered from diabetes [2, 7]. Hyperglycemia after a stroke is usually associated with a large volume of infarction and cortical damage and is associated with an adverse outcome of the disease [4]. Currently, the routine use of insulin infusions in patients with moderate hyperglycemia is not recommended. The European Stroke Association recommends maintaining glycemia below 180 mg/dl (10 mmol/l) [4].

Body temperature control: hyperthermia is associated with an increase in the size of the infarction zone and a worsening of the outcome of the disease [8]. Fever is associated with a worse clinical outcome [9]. When the body temperature increases, it is necessary to quickly exclude concomitant infections and, if necessary, treat them.

2.1.1 Prevention of acute stroke complications

The prevention of trophic disorders in the form of bedsores is carried out by establishing an early enteral nutrition through a nasogastric probe with an adequate calorie of nutritional mixtures: early mobilization, anti-bedsore mattresses, suitable beds, and nursing care.

Aspiration pneumonia: diagnosis of dysphagia (special examination of the function of swallowing by doctors, nurses, or speech therapists) [10, 11] or use of a nasogastric probe if necessary.

Deep vein thrombosis and pulmonary embolism: low-molecular-weight heparins (LMWH) in prophylactic doses reduce the risk of thromboembolic complications without affecting mortality [2]. Their use slightly increases the risk of intracranial hemorrhages. The use of LMWH is recommended only if the patient has risk factors for deep vein thrombosis and pulmonary embolism, such as lower limb immobilization, in the first few hours after a stroke [2], and not earlier than 24 hours in patients with intracranial hemorrhage [9]. A recent study of Clots in Legs Or sTockings after Stroke (CLOTS) [12] has shown that an intermittent pneumatic compression reduces the risk of deep vein thrombosis and can improve stroke survival in patients who cannot go to the toilet with an assistant.

Rehabilitation: it is an important issue both in acute phase and in chronic phase. Points to be covered are position turning to avoid pressure sores, chest physiotherapy to minimize lung complication, swallowing assessment and training, limb movements to prevent deep vein thrombosis, speech therapy, early mobilization,

etc. All should be started as early as possible. Rehabilitation should begin as soon as the patient's condition stabilizes: passive measures to minimize contractures, bedsores, and pneumonia. A coordinated multidisciplinary approach to patient management with the help of constantly trained staff is important, which leads to a reduction in mortality and disability.

2.2 Thrombolytic therapy

The intravenous administration of a recombinant tissue plasminogen activator (tPA) increases the chances of a favorable outcome approximately 8 times within 3 months if performed in the first 90 minutes, 2 times when performed within 91–180 minutes after a stroke, and 1.4 times when performed in 181–270 minutes [6, 13]. The mortality does not change when administered up to 270 min after stroke onset, but increases with later administration of tPA [6]. Indications and contraindications for thrombolytic therapy are noted in **Tables 1** and **2**, respectively.

Hemorrhagic transformation is more often observed in patients with large strokes and of old age [7]. The earlier the tPA is introduced, the more likely the beneficial effect is, and despite the fact that the probability of a favorable effect is also present when used later than 3 hours from a stroke, it is significantly reduced. The dose is 0.9 mg/kg (10% intravenous bolus, 90%—within an hour microjet). In Japan, the recommended dose is lower—0.6 mg/kg. Thus, thrombolytic therapy is recommended as early as possible after the onset of a stroke, no later than 4.5 hours. Restrictions apply both to contraindications [increased risk of hemorrhage, delay of more than 4.5 hours, blood pressure (BP) above 185 mm Hg, blood glucose above 4 G/l] and strict rules of use (only by a doctor trained in the management of stroke patients and only in the stroke department) [6].

Other ways to achieve rapid recanalization are currently being investigated and do not change the existing recommendations: other thrombolytic drugs, MRI patient selection criteria, intra-arterial thrombolytic therapy, and ultrasound-assisted intravenous thrombolysis. Mechanical thrombextraction is considered a promising technique in addition to intravenous thrombolysis in patients with proximal occlusions. In patients receiving oral anticoagulants, mechanical thrombectomy is often the only recommended recanalization strategy.

2.3 Antithrombotic therapy

Aspirin at a starting dose of 300 mg and then 75–150 mg daily prevents 9 cases of disability and death per 1000 patients. Aspirin should be prescribed 24 hours after any thrombolytic therapy. Recently, a Clopidogrel in High-Risk Patients with Acute Nondisabling of Cerebrovascular Events (CHANCE) study showed that patients with small strokes and transient ischemic attack (TIA) who received a loading dose of clopidogrel for 24 hours, against the background of aspirin, and then for 90 days on 75 mg of aspirin and 75 mg of clopidogrel had better outcomes without the risk of bleeding.

No. of wording
1. Stroke, ischemic type
2. The time from the symptoms onset to the thrombolysis procedure less than 4.5 hours
3. Age from 18 years and older (after 80 years with caution, individual decision about TLT, taking into account the perceived risk)

Table 1.
Indications for thrombolytic therapy.

No. of wording
Cerebral
1. Neuroimaging (CT, MRI) signs of intracranial hemorrhages, brain tumors
2. Hemorrhagic stroke or stroke of an unspecified nature in the anamnes
3. Rapid improvement or mild symptoms by the time of the beginning of TLT (non-invalidizing symptoms) in the absence of data for occlusion of the main vessels
4. Signs of a severe stroke: clinical [score on the National Institutes of Health Stroke Scale (NIHSS) > 25), neuroimaging (based on CT of the brain and/or MRI of the brain in the diffusion-weighted imaging (DWI) mode, the focus of ischemia extends to the territory of a larger basin medium cerebral artery (MCA)]
5. Convulsions at the beginning of a stroke (if there is reason to assume that focal symptoms are represented by Todd's paresis)
6. Previous stroke or severe traumatic brain injury within 3 months
7. Suspected subarachnoid hemorrhage (SAH)
8. Surgical intervention on the brain or spinal cord in the anamnesis
Cerebral and somatic
9. Arterial aneurysms, defects in the development of arteries or veins
10. Tumors with a high risk of bleeding
Somatic
11. Hypersensitivity to any component of the drug
12. Hemorrhagic diathesis
13. Arterial hypertension over 185/110 mm Hg or necessity in intensive reduction of less than these figures
14. Bacterial endocarditis, pericarditis
15. Gastrointestinal or urogenital bleeding during the last 3 weeks. Confirmed exacerbations of peptic ulcer disease of the stomach and duodenum during the last 3 months
16. Liver failure (cirrhosis, active hepatitis, portal hypertension)
17. Acute pancreatitis
18. Present bleeding or extensive bleeding in the recent 6 months
19. Extensive surgery, trauma, delivery, puncture of large vessels, cardiopulmonary resuscitation within the last 10 days
20. Recent myocardial infarction
21. Pregnancy
22. Data on bleeding or acute injury (fracture) at the time of examination
Laboratory
23. Taking indirect anticoagulants (warfarin) if international normalized ratio (INR) >1.3
24. Use of heparin for 48 hours with increased activated partial thromboplastin time (aPTT)
25. Thrombocytopenia less than 100,000/mm^3
26. Glycemia less than 2.8 and more than 22.5 mmol/l
27. With previous administration of new oral anticoagulants (dabigatran, rivaroxaban, apixaban), indicators of aPTT, INR, quantity of platelets, thrombin time, or Xa factor activity should be within normal values. In the absence of the ability to determine the laboratory data, the last intake of a drug from the oral anticoagulant group should be >2 days before the development of stroke (with normal kidney function)
28. Other diseases or conditions with increased risk of bleeding or other complications of TLT (the decision is made by the council of physicians)

Table 2.
Contraindications for thrombolytic therapy.

Low-molecular-weight heparins do not have advantages, because a decrease in the frequency of early recurrent strokes is balanced by an increase in the frequency of hemorrhagic transformations. There is no reason to recommend heparin in the acute stage of ischemic stroke, even in patients with atrial fibrillation.

2.4 Hypothermia and neuroprotection

Experimental studies have shown that potential neuroprotectors are effective, but this is not confirmed in the human population. Many neuroprotective agents have been developed based on a cascade of biochemical events leading to cell death.

We report below the current clinical status of drugs that have been developed as neuroprotective agents (**Table 3**) [14].

Hypothermia is a potential opportunity to provide neuroprotection, but due to side effects and the need for intensive therapy, it can only be used in severe cases, especially in patients with malignant heart attacks, and currently requires randomized trials [8, 15].

2.5 Decompressive neurosurgery

Decompressive neurosurgery (hemispherectomy) reduces mortality and disability in patients younger than 60 years old who recently suffered a massive stroke

Category, mechanism	**Drug name, name of multicenter study, and its results**	**Category, mechanism**	**Drug name, name of multicenter study, and its results**
Ca^{2+} channel blocker	Nimodipine: no benefit (VENUS)	Noncompetitive NMDA antagonist	Dizocilpine, discontinued Dextrorphan, no benefit
Na^{+} channel blocker	Lifarizine, no benefit; lubeluzole, no benefit; fosphenytoin, discontinued	Competitive NMDA antagonist	Selfotel: discontinued
GABA agonist	Clomethiazole: no effect	AMPA/KA receptor antagonist	NBQX, discontinued YM872, RCT
Free radical scavenger	Edaravone, clinical use; ebselen, phase III; NXY059: phase III; tirilazad, discontinued	Metabotropic receptor antagonist	Groups I, II, and III: RCT being planned
Growth factor	bFGF: abandoned AX200 (filgrastim, G-CSF analogue), phase II	LMWH-CoA reductase inhibitor	Lovastatin, phase II; simvastatin, phase III
Growth factors, oxygen delivery	Human chorionic gonadotropin (hCG)/erythropoietin (Ntx-265): phase II	Hemodiluting agent	Albumin: phase III (ALIAS)
Ganglioside	No benefit	Membrane stabilizer	Citicoline (CDP choline): phase III
$MgSO_4$	FAST-MAG: ongoing (IMAGE)	Iron chelator	Deferoxamine mesylate: phase II
Opioid receptor antagonist	Nalmefene: no benefit	Metal ion chelator	DP-b99: phase III
Polyamine receptor antagonist	Eliprodil: discontinued	Antibiotic, pleiotropic protective effects	Minocycline: phase III
Glycine antagonist	ACEA-1021, no benefit; gavestinel, no benefit	Others	Piracetam: phase III

VENUS, very early nimodipine use in stroke; NMDA, N-methyl-D-aspartic acid; GABA gamma-aminobutyric acid; AMPA, amino-hydroxy-methyl-isoxalone propionic acid; KA, kainate; NBQX, 2,3dihydroxy-6-nitro-7-sulfamoyl-benzo [f]quinoxaline-2,3-dione; RCT, randomized controlled trial; bFGF basic fibroblast growth factor; ALIAS, albumin in acute stroke; FAST-MAG, Field Administration of Stroke Therapy—Magnesium; ACEA-1021, 5-nitro-6,7-dichloro-1,4dihydro-2,3-quinoxalinedione.

Table 3.
Neuroprotective drugs developed so far and results of clinical trials.

in the middle cerebral artery basin [16]. In order to be effective, the operation must be performed before the development of a malignant brain attack. The best selection criterion is the volume of damage on a diffusion-weighted MRI within 24 hours; a volume greater than 145 cm^3 is a good predictor of malignant infarction. Therefore, the best candidates for surgical treatment are patients younger than 60 years with a lesion volume of more than 145 cm^3 on diffusion-weighted MRI (6.50). The effectiveness of hemispherectomy is great—every second death is prevented. Results of the Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery II (DESTINY II) study also showed effectiveness in patients over 60 years of age [3].

3. Treatment of intracranial hemorrhage

It is necessary to control blood pressure (BP). Lowering blood pressure in the first hours can prevent or slow down the growth of hematoma, as well as reduce the risk of repeated hemorrhage.

An early decrease in blood pressure can cause cerebral ischemia in low-perfused and hypometabolic regions of the brain adjacent to the hematoma.

European recommendations are based on the evidence of a low level of significance (class 4) [9]:

- No specific drug is recommended.
- In patients with a history of primary arterial hypertension or signs (ECG, changes in the fundus vessels) of chronic hypertension, systolic pressure above 180 mm Hg or diastolic pressure above 105 mm Hg and in patients without a history of hypertension, the target blood pressure is 170/100 or average 125 mm Hg.
- In patients without a history of arterial hypertension (systolic blood pressure above 160 mm Hg and/or diastolic blood pressure above 95 mm Hg), the target blood pressure is 150/90 mm Hg or BP mean 110 mm Hg.
- Avoid lowering blood pressure by more than 20%. These targets should be revised for patients who are being monitored for intracranial pressure (ICP) and are experiencing intracranial hypertension in order to maintain adequate cerebral perfusion pressure (greater than 70 mm Hg).

The INTERACT 2 study recently showed that in patients with intracerebral hematoma, an intensive reduction in blood pressure with targets below 140 mm Hg within an hour slightly improves the outcome and is well tolerated by the patient.

3.1 Prevention of deep vein thrombosis and pulmonary embolism

In patients with intracerebral hematoma, complications such as deep vein thrombosis and pulmonary embolism are feared. A small study conducted on patients with intracerebral hematoma showed that the use of intermittent pneumatic compression is more effective than the use of compression knitwear alone [17]. The CLOTS study [12] showed that the use of compression knitwear is ineffective, but only 232 patients with intracerebral hematoma were included out of 2518 stroke patients. The expediency of using heparin and low-molecular-weight heparins is justified only in cases where the probability of bleeding risk is less than

the possible benefit of prescribing drugs. In clinical practice, low doses of fractionated or low-molecular-weight heparin can be prescribed after 24 hours [16]. According to the results of the CLOTS 3 study [12], intermittent pneumatic compression is effective.

3.2 Intracranial hypertension

ICP negatively affects the functional outcome. The superiority of invasive ICP monitoring over clinical observation and neuroimaging has not been proven. Ways to reduce ICP by medication help to buy time to prepare for surgical decompression, if it is planned. In the acute phase of intracranial hemorrhage, it is recommended to avoid corticosteroids. These recommendations are based on low confidence data. For the medical treatment of ICH, glycerol, mannitol, HAES, and short-term hyperventilation (confidence class 4) are used. For example, mannitol (20%) at a dose of 0.75–1.0 g/kg can be administered as an intravenous bolus followed by 0.25–0.5 g/kg every 3–6 hours, depending on the neurological status and fluid balance.

3.3 Intracranial hemorrhage in patients receiving oral anticoagulants

In the acute stage, every patient with intracranial hemorrhage and an INR greater than 1.4 should receive intravenous vitamin K and drugs that replace the deficiency of clotting factors, despite the reason for taking oral anticoagulants (including patients with artificial valves). The goal is to prevent the growth of hematoma volume. In European protocols, it is recommended to use a concentrated prothrombin complex or SPP together with the intravenous administration of vitamin K [18]. Doses of concentrated prothrombin complex: 10–20 U/kg, if the INR is less than 3.5; or 20–30 units/kg, if the INR exceeds 3.5; together with 10 mg of vitamin K in/B.

Recombinant factor VIIa is not recommended for routine use outside of clinical trials.

There is currently no antidote for patients with intracranial hematoma receiving new oral anticoagulants. This limits the use of these drugs.

There are no specific recommendations for the treatment of hemorrhage on the background of antiplatelet drugs. Studies of the use of thrombosis have not proved its effectiveness [6, 13].

3.4 Thrombolytic therapy

In patients with intracranial hemorrhage with increased ventricles and obstruction of the third and fourth ventricles, according to some data, it is recommended to use a recombinant tissue plasminogen activator inserted directly into the ventricular system, which can improve the functional outcome [9].

3.5 Neurosurgical intervention

The removal of a blood clot should be considered in cases where there is neurological dysfunction or neuroimaging data about occlusion of cerebrospinal fluid spaces subtentorially. According to European recommendations, ventricular drainage and hematoma removal should be performed when the size of the hematoma is more than 2–3 cm in diameter or in the presence of hydrocephalus, even if the favorable outcome is doubtful due to old age or coma.

Dynamic monitoring and conservative medical treatment are the first stage in the treatment of patients with intracranial hematoma. A special analysis of subgroups from the STICH study and a recent meta-analysis showed that craniotomy should be considered as a treatment option in cases of depression of consciousness (from 12 to 9 points on the Glasgow scale) [19] or in cases of superficial intracranial hemorrhage (less than 1 cm from the surface and does not reach the basal ganglia) [20–22]. With deep-seated hematomas, craniotomy does not bring a positive result. The STICH II study showed that early surgical treatment did not increase mortality and disability within 6 months, but slightly improved survival in patients with spontaneous intracranial hemorrhage in the absence of intraventricular hemorrhage.

4. Specific clinical situations

4.1 Treatment of stroke due to sinus thrombosis

Sinus thrombosis is the cause of approximately 1% of strokes. It occurs due to the occlusion of the venous sinuses and/or cortical veins. This can lead to a venous infarction with petechial hemorrhages or a perivascular venous infarction. Usually, the cause of sinus thrombosis is congenital and acquired prothrombotic disorders, such as pregnancy and infections, including infections of the central nervous system as well as ear, sinuses, mouth, face, or neck. Also the predisposing factors are various diagnostic and therapeutic procedures, such as surgery, lumbar puncture, jugular vein catheterization, and administration of certain medications, especially oral contraceptives, hormone replacement therapy, steroids, and antitumor drugs [23].

The clinical picture may be different, but sinus thrombosis should be excluded in young patients with recent headache and stroke-like symptoms, transient neurological deficits, convulsions, or lobar intracranial hemorrhages. This is especially true for patients with intracranial hypertension and patients with signs of hemorrhagic infarctions, especially if they are numerous and correspond to certain vascular pools.

The gold standard for diagnosing sinus thrombosis is MRI, which provides direct visualization of occluded veins, sinuses, and blood clots [23]. Sometimes CT is used for diagnostics, but if MRI is available, this is not the method of choice for diagnostics. On CT, you can see a hyperintensive shadow of a blood clot in the occluded sinus, the so-called cord symptom.

4.1.1 Heparin therapy

The available research data on the treatment of venous thrombosis recommend the use of heparin, as it reduces the risk of death and severe disability without the risk of intracranial hematoma. It has been shown that anticoagulant therapy leads to an absolute reduction in the risk of death and disability by 13% and a relative reduction in the risk by 54%, as well as a positive effect of using heparin without increasing the risk of intracranial hemorrhage.

According to European recommendations [18], venous thrombosis should be treated with low-molecular-weight heparins subcutaneously or intravenous heparin; doses are selected by body weight. The presence of intracranial hemorrhage accompanying venous thrombosis is not a contraindication to a heparin therapy [18].

4.1.2 Thrombolytic therapy

There is no data from randomized controlled trials on the efficacy and safety of systemic or local thrombolytic therapy in patients with cerebral vein thrombosis and sinus thrombosis. A recently published systematic review of thrombolytic therapy in patients with cerebral vein thrombosis and sinus thrombosis suggests a favorable effect in comatose patients [24].

According to European protocols [18], there is insufficient data to recommend the use of systemic or local thrombolytic therapy in patients with cerebral vein thrombosis and sinus thrombosis. Thrombolytic therapy may be an option if the patient's condition worsens despite an adequate anticoagulant therapy.

4.1.3 Oral anticoagulants

After the acute phase, they switch to oral anticoagulant therapy. The Target INR is 2.0–3.0. In cases of cerebral vein thrombosis and sinus thrombosis during pregnancy, oral anticoagulants are not prescribed due to their possible teratogenic effects and the ability to penetrate the placenta. In these cases, anticoagulant therapy is continued with heparin. There is no available data from controlled studies concerning the optimal duration of anticoagulant therapy in patients with cerebral vein thrombosis and sinus thrombosis. MRI data from 33 patients showed that recanalization occurs within 4 months after cerebral vein thrombosis and sinus thrombosis, regardless of further anticoagulation therapy [25].

According to European protocols [18], anticoagulants can be prescribed for 3 months if cerebral vein thrombosis occurred due to transient factors and for 6–12 months in patients with idiopathic thrombosis and congenital "moderate" thrombophilia.

4.1.4 Anticonvulsant therapy

The preventive use of anticonvulsants is controversial. Some studies have shown that sensory and motor deficits, parenchymal lesions on MRI/CT, and cortical vein thrombosis can be independent predictors of early symptomatic epileptic seizures [26]. According to European recommendations [18], prophylactic administration of anticonvulsants is possible for patients with local neurological deficits and foci of parenchymal lesions. Treatment can be continued for a year. Despite the fact that 50% of patients with venous thrombosis experience brain edema, mild edema can be relieved by isolated administration of heparin to restore venous outflow. Steroids are not recommended for the treatment of intracranial hypertension due to their unproven effectiveness. In severe cases, with the threat of transtentorial dislocation, surgical decompression is considered the only lifesaving method of treatment.

4.2 Cardiac surgery and strokes

The incidence of strokes in the postoperative period in patients with coronary artery bypass grafting (CABG) is about 2%, and a higher incidence of strokes is observed in patients after valve replacement operations and other cardiac surgeries [3]. The causes of stroke after cardiac surgery include perioperative embolism from the aortic arch or heart chambers, systemic hypoperfusion, ischemia associated with occlusion of large vessels, or a combination of these factors [3]. Risk factors for stroke after cardiac surgery are old age; a history of strokes, hypertension, and diabetes mellitus; the presence of noise in the projection of the carotid arteries; the use of bronchodilators and diuretics; high serum creatinine levels; recovery of large

vessels; the use of inotropes after artificial circulation; and the duration of artificial blood circulation.

Currently, there are no special recommendations for the treatment of patients with stroke after CABG [3]. Moreover, patients with stroke after CABG are treated as patients with acute stroke with loading doses of aspirin (160–320 mg) [3].

4.3 Operations on the carotid arteries and strokes

Carotid endarterectomy is the standard method for treating carotid artery stenosis [3]. It is recommended for 70–99% of patients with symptomatic stenosis. It is confirmed that surgical treatment of asymptomatic stenosis reduces the risk of ipsilateral stroke; however, the absolute advantage of this method has not been proven. Currently, stenting is not recommended for revascularization of the carotid arteries.

The pathophysiological mechanism of stroke in carotid revascularization may be associated with hemodynamic cerebral ischemia or arterio-arterial embolism. The latter mechanism may be more frequent during stenting due to endovascular access.

4.4 Acute coronary syndrome (ACS) and stroke

Intracranial hemorrhage can be a severe side effect of thrombolytic therapy in ACS. The risk of intracranial hemorrhage depends on the previous episodes in the history, age, and mode of thrombolytic therapy. Usually, the risk of intracranial hemorrhage during thrombolytic therapy of acute myocardial infarction is 0.5–1%.

There are no special recommendations for the treatment of ischemic stroke in ACS in European protocols. In the presence of ACS, the protocols of the European Stroke Organization recommend lowering blood pressure [4, 6]. An anticoagulant therapy is not recommended, while a combination of clopidogrel and aspirin is recommended in terms of cardiac causes [4, 7].

4.5 Stroke in patients with atrial fibrillation

Cardio-cerebral embolism is considered to be the cause of at least 20% of ischemic strokes, and non-valvular AF is the most common cause, associated with a fivefold increase in the risk of stroke, and accounts for 25% of all strokes in patients older than 80 years [3]. Long-term thromboprophylaxis is necessary to prevent strokes in patients with AF. Recently, for patients who cannot be treated with warfarin and clopidogrel, it has been shown that clopidogrel and aspirin therapy reduces the risk of vascular accidents [7]. Oral direct thrombin inhibitors such as dabigatran have been shown to be effective in preventing stroke and systemic embolism with a risk of intracranial hemorrhage comparable to that of warfarin. Stroke in patients with AF can be divided into three groups:

1. Ischemic stroke in patients with insufficient therapy, i.e., not receiving anticoagulants, despite scores on the CHADS2 scale greater than 2 [3]

2. Ischemic stroke that developed despite warfarin therapy

3. Intracranial hemorrhage that occurred in a patient receiving anticoagulants

The incidence of intracranial hemorrhage increases 7–10 times compared to patients who do not receive oral anticoagulants and is 1.8% per year in patients at risk of stroke [7].

4.5.1 Treatment

In the acute phase of stroke, heparin is not recommended; its use leads to a slight decrease in repeated strokes, an indefinite decrease in mortality, and a disability with an increase in the frequency of intracranial hemorrhages [7].

4.6 Cerebrocardial syndrome (neurogenic stress cardiomyopathy)

The connection between the brain and the heart reflects a complex multidirectional complex regulation of systemic hemodynamics and organ autoregulation of local perfusion, which is especially pronounced in a cerebral catastrophe. Arrhythmias, in particular AF, often accompany the development of stroke, while myocardial infarction, Takotsubo syndrome, and sudden death are rare, although they are also described in strokes [27–29]. Sometimes stroke patients are found to have high levels of troponin, indicating myocardial damage.

5. Conclusion

To ensure adequate treatment, a rapid diagnosis of stroke and its nature and cause is necessary. Specialized stroke departments allow for effective treatment and specific therapy.

Conflict of interest

The authors declare no conflict of interest.

Notes/thanks/other declarations

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Abbreviations

ACS	acute coronary syndrome
AF	atrial fibrillation
ADH	antidiuretic hormone
aPTT	activated partial thromboplastin time
AVM	arteriovenous malformation
BP	blood pressure
CT	computed tomography
CABG	coronary artery bypass grafting
DI	diabetes insipidus
DWI	diffusion-weighted imaging
ECG	electrocardiogram
EchoCG	echocardiography
ESR	erythrocyte sedimentation rate
LMWH	low-molecular-weight heparins

ICH	intracranial hemorrhage
ICP	intracranial pressure
INR	international normalized ratio
MCA	medium cerebral artery
MRI	magnetic resonance imaging
NIHSS	National Institutes of Health Stroke Scale
SAH	subarachnoid hemorrhage
SIADH	syndrome of inappropriate antidiuretic hormone secretion
tPA	tissue plasminogen activator
TLT	thrombolytic therapy

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