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Review

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Nitric Oxide Donors in the Treatment of Vascular Spasm and Delayed Cerebral Ischemia in Patients with Subarachnoid Hemorrhage

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ABSTRACT Secondary vascular spasm due to non-traumatic rupture of cerebral artery aneurysms is a formidable complication leading to serious disability of patients who face this disease, and in 30–50% of cases leads to death. Standard therapy used in intensive care units does not have tremendous success in the treatment of this pathology, which encourages scientists around the world to search for new drugs that can improve the outcome and increase the quality of life of patients. At the moment, the most promising non-surgical method of treatment is the use of nitric oxide donor drugs as part of complex therapy. In modern medicine, there are several ways to administer drugs of this group: intravenously, intra-arterially , intrathecally , intraventricularly and by inhalation. The method depends on the type of drug used. Despite the promise of using these dosage forms, there are a number of negative side effects, which, due to insufficient study, limit their widespread use in hospitals. This review contains studies examining the positive and negative aspects of the use of these drugs and the appropriateness of their use.

Keywords: subarachnoid hemorrhage; non-traumatic subarachnoid hemorrhage; nitric oxide; nitric oxide donors; vasospasm

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AH — arterial hypotension
BP — blood pressure
CA — cerebral angiospasm
cAMP — cyclic adenosine monophosphate
cGMP — cyclic guanosine monophosphate
CD 45 — differentiation antigen 45
EMR — evoked motor response
GFAP — glial fibrillary acidic protein
GOS — Glasgow Outcome Scale
GSNO — nitrosoglutathione
H–H — Hunt–Hess scale
IA — intracranial aneurysms
ICA — internal carotid artery
ICP — intracranial pressure
iNO — inhaled nitric oxide (II)
LBFV — linear blood flow velocity
MAP — mean arterial pressure
MMSE — Mini-Mental State Examination
mRS — modified Rankin scale
PDA — phorbol diacetate
PDE — phosphodiesterase
PET-CT — positron emission tomography
$PtiO_2$ — partial pressure of tissue oxygen
SAH — non-traumatic subarachnoid hemorrhage
SIN-I — linsidomine
SN — sodium nitrite
SNAP — S-Nitroso-N-acetylpenicillamine
SNP — sodium nitroprusside
SOD — superoxide dismutase
TCDS — transcranial Doppler sonography
VS — vascular spasm

Cerebral vasospasm (CVS) and delayed cerebral ischemia are the main causes of unfavorable treatment outcome in patients with ruptured cerebral aneurysms [1, 2].

The pathogenesis of cerebrovascular accidents and cerebral ischemia is complex and includes a large number of elements. One of the leading mechanisms of cerebrovascular accident development is a decrease in the plasma and intracellular concentration of endothelial vasorelaxing factor (NO) during subarachnoid hemorrhage (SAH) [3, 4].

In this review, we will consider drugs that affect nitric oxide (NO) metabolism, used in clinical or experimental practice in SAH.

All drugs that affect NO metabolism can be divided into the following groups according to their mechanism of action: NO donors, inhaled NO, endothelin-1 antagonists, phosphodiesterase (PDE) inhibitors and NO synthesis precursors (table) [5, 6].

Table

Drugs that affect nitric oxide metabolism

Item No.	Preparations		Mechanism of action
1	NO Donors	Nitrosothiols	Nitrosothiols or thioesters of nitrous acid are the transport form of NO in the blood [7]
		Nitrates	The effects are due to the cleavage of NO from the nitrate group.
		Non-nitrate NO donors (molsidomine)	The effects are mediated by metabolites (mainly linsidomine, which releases NO), which stimulate soluble guanylate cyclase.
2	Inhaled NO		A highly reactive gas that undergoes a nitrosylation reaction with the SH groups of amino acids in serum albumin, forming S -nitrosoprotein. NO binds to hemoglobin to form S -nitrosohemoglobin (Hb– S NO) and nitrosohemoglobin (Hb–NO). Oxygenated nitrosohemoglobin, releasing oxygen in arterioles and capillaries, changes its isoform, which leads to the release of NO
3	Precursors of NO synthesis	L-arginine	Substrate for NO synthesis in the vascular wall. When interacting with NO synthase, it releases NO with the formation of L-citrulline.
4	Endothelin-1 antagonists	Clazosetan	Physiological antagonist of NO and one of the strongest phase constrictors. By blocking endothelin-1 receptors, clazosentan promotes relaxation of vascular wall myocytes
5	Phosphodiesterase inhibitors	3rd type (Cilostazol)	Increases intracellular concentration of cyclic adenosine monophosphate, which leads to relaxation of smooth muscles due to increased NO effect
		5th type (Sildenafil)	Slows down the breakdown of cyclic guanosine monophosphate. Increased intracellular cyclic guanosine monophosphate levels result in relaxation of arteriolar smooth muscle cells and vasodilation

Note: NO — nitric oxide

NITROSOTHIOLS

These substances are physiological metabolites that serve as depots/carriers of NO. A selection of studies using these dosage forms was carried out, carried out mainly on animal models and published in single versions in foreign literature.

In a study by Kiriş T. et al. (1999), SNAP (S-Nitroso-N-acetylpenicillamine) was administered intravenously to a SAH model in 37 rabbits at a dosage of 15 μg/kg/min. During the experiment, the scientists concluded that after the administration of SNAP, the severity of spasm (according to microscopic morphometry) decreased by 56% compared to the comparison group [8].

Sehba F.A. et al. (1999) studied the effect of intra-arterial administration of nitrosoglutathione (GSNO) on the severity of cerebral vasospasm and cerebral ischemia in a model of endovascular perforation of the internal carotid artery in rats. The authors observed an increase in cerebral blood flow according to laser Doppler flowmetry 60 minutes after GSNO administration by 40–100% compared to the comparison group [9].

Data have been obtained on the positive effect of diazenium thiolates (diethylenetriamine, DETA) on cerebral blood flow and CVS in experimental SAH in various animal models (Wolf EW et al. (1998), Gabikian P. et al. (2002), Pradilla G. et al. (2004), Clatterbuck R.E. et al . (2005)) [10–13].

However, there are no certified medicinal forms for these physiological metabolites, which limits their use in clinical practice.

NITRATES

This group of drugs includes nitroglycerin (glyceryl trinitrate), isosorbide dinitrate, isosorbide mononitrate, sodium nitroprusside (SNP) and nicorandil. The main clinical indication for all drugs is the relief of hypertension, antianginal action in angina pectoris and acute myocardial infarction. These drugs are not used in routine practice for the treatment of brain damage in SAH. However, there are a large number of experimental and clinical studies on the use of nitrates in patients with ruptured intracranial aneurysms.

Experimental data

Matsui T. et al. (1994) used nicorandil (nicotinamine nitrate) for the treatment of cerebral vasospasm in vivo under experimental SAH conditions on 12 dogs. Animals were administered nicorandil intravenously for 6 hours a day at a dose of 10 mcg/kg/min. To assess the effectiveness of nicorandil, animals were administered phorbol diacetate (PDA), which is a potent vasoconstrictor, on the 7th day. Contractility of the basilar artery was measured. According to the results of the study, in animals receiving nicorandil, a decrease in vascular wall contractility to 60% of the initial lumen was noted according to angiography, while in the comparison group this figure was 90%. The researchers considered the results of contractility reduction to be promising, however, to date, we have not encountered data on the successful use and implementation of nicorandil in patients with ruptured intracranial aneurysms (IA) in clinical practice [14].

In a study by Pluta M. et al . (2005) the effect of intravenous sodium nitrite was studied on the SAH model in 14 monkeys. The authors observed the development of SAH on the 7th day of the experiment in all 8 animals of the comparison group - according to digital subtraction angiography, while after the introduction of sodium nitrite, vasospasm did not develop in any of the 6 animals. With bolus administration of sodium nitrite in 3 animals, the authors noted a temporary decrease in blood pressure (BP). After the introduction of sodium nitrite, all animals noted an asymptomatic increase in the content of methemoglobin in the blood to a maximum of 2.1% [15].

Lilla N. et al. (2016) studied the effectiveness of intravenous administration of SNP in rats with experimental SAH. The authors assessed cerebral perfusion blood flow using dual-channel laser Doppler flowmetry. After experimental SAH, animals were administered SNP and an increase in cerebral blood flow was observed 15 minutes after SAH by 10–20% compared to the comparison group. In addition, the authors noted a decrease in the severity of ischemic damage to the brain tissue according to morphological examination data, as well as a decrease in the number of damaged neurons in the hippocampal zone compared to the comparison group by an average of 5% [16].

In addition to systemic use, data on selective intrathecal administration of nitric oxide donors in an experiment are presented. Marbacher S. et al. (2008) presented the results of intrathecal administration of nitroglycerin in combination with nimodipine in 55 white rabbits with experimental SAH. The animals were divided into six groups: group 1 with saline administered intrathecally, group 2 without SAH, in which nitroglycerin was administered intrathecally, group 3 of animals without SAH, with nimodipine administered intrathecally, group 4 of animals with SAH, saline administered intrathecally, group 5 of animals with SAH with nitroglycerin administered intrathecally, group 6 of animals with SAH, nimodipine administered intrathecally. Nitroglycerin and nimodipine were administered intrathecally as a constant infusion using an osmotic pump installed subcutaneously. The severity of SAH was assessed based on the results of cerebral angiography on day 5 after SAH. In the group of rabbits with SAH that

received intrathecal saline, the vessel diameter narrowed by 19.85±2.94% on the 5th day. In 11 rabbits in the group with SAH that used nitroglycerin, the vessel diameter decreased by 5.93±5.20% on day 5, while in the group of rabbits with SAH that received intrathecal nimodipine, the vessel diameter narrowed by only 0.55±2.66% on the day 5 of constant infusion. According to the study, nimodipine was found to be somewhat more effective than nitroglycerin in the treatment of cerebral angiospasm [17].

Fathi A.R. et al. (2011) in a similar study confirm the effectiveness of intrathecal nitroglycerin use using the model of experimental SAH in 46 white rabbits. The authors did not note the development of systemic arterial hypotension (AH) and intracranial inflammatory complications during the experiment. Nevertheless, the authors emphasize the need to adhere to strict aseptic rules to prevent possible intracranial infectious complications during drainage of the subarachnoid space [18].

Thus, experimental data were obtained that demonstrated the positive effect of nitric oxide donors on cerebral blood flow.

Clinical data

Some of the first clinical data concerning the use of nitrates in 3 patients with SAH were presented by Allen G.S. et al. (1976). Patients with ruptured cerebral aneurysms were given intravenous infusion of SNP with phenylephrine. The severity of SAH was assessed using digital subtraction cerebral angiography. The authors observed dilation of the lumen of cerebral arteries in all patients. However, the authors encountered such an unfavorable effect as an increase in intracranial pressure (ICP) [19].

Iwanaga H. et al. (1995) presented a clinical study of the effect of intravenous nitroglycerin and dopamine on ICP and cerebral oxygenation in 11 patients with ruptured cerebral aneurysms who were operated on in the first 72 hours after SAH. The study included patients with stage II–III severity of the condition according to the Hunt–Kosnik scale, and stage 2–3 hemorrhage severity according to Fisher. To assess cerebral blood flow, the arteriovenous oxygen difference method and the cerebral perfusion pressure index were used. The arteriovenous oxygen difference index was calculated using the formula:

O_2 content = O_2=Hb×1.39×SpO_2+PO_2×0.0031

The arteriovenous oxygen difference is the difference between the oxygen content in arterial blood and the jugular bulb.

Before the introduction of nitroglycerin, the average ICP values were measured, which were 11.91 ± 5.3 mm Hg. Ten minutes after the introduction of nitroglycerin with dopamine, an increase in ICP was observed with peak values of 14.64 ± 5.93 mm Hg, followed by a decrease to normal values. Nitroglycerin infusion did not statistically significantly affect the arteriovenous difference in oxygen and SBP. However, with an increase in the nitroglycerin dosage of more than 1.5 μg/kg/min, a statistically significant decrease in cerebral perfusion pressure was noted. The authors suggested that the studied treatment method may be effective in patients without intracranial hypertension (ICP below 24 mm Hg), but, in their opinion, this hypothesis requires further study [20].

In a literature review, Rose J.C. et al. (2004) stated that the use of intravenous NPIs, especially in the form of prolonged infusion, is undesirable due to increased ICP and high toxicity [21].

In the study by Oldfield E.H. et al. (2013), 18 patients with ruptured cerebral aneurysms were given intravenous sodium nitrite at doses of 132.5 mg/kg/h, 198.8 mg/kg/h, and 265 mg/kg/h for 14 days. The choice of drug dosage was based on the authors' previous studies. The patients were divided into three cohorts, with 6 people in each (3 comparison groups, 3 study groups). The authors found that sodium nitrite (SN) at the indicated doses was safe and did not cause systemic hypertension. The level of methemoglobinemia did not exceed 3.3%. Due to the small number of patients in each cohort, the authors did not evaluate the effect of therapy on the treatment outcome [22].

It should be noted that hypertension and increased ICP significantly limit the systemic use of nitrates in patients with ruptured intracranial artery. In this regard, nitrates were used intrathecally in a number of studies.

Pathak A. et al. (2003) conducted a study in which 8 patients with massive SAH (Hunt–Hess (H–H) III–IV, Fisher III scale) were given intraventricular and intracisternal SNP as an adjunct to 3H therapy, nimodipine, and lumbar drainage in all patients. NNP was administered at a dosage of 4–5 mg every 4–12 hours. In case of a decrease in blood pressure, the SNP dosage was reduced to 2 mg. The presence and degree of ischemia and cerebral vasospasm were recorded using CT perfusion and transcranial Doppler sonography (TCDS). Of the 8 patients, a favorable outcome was observed in 7 patients, one

patient died due to symptomatic SAH, despite a decrease in the linear blood flow velocity (LBFV). The authors observed systemic hypertension in one patient, which required a reduction in the dosage of the drug administered intrathecally [23]. In a similar study, Kumar R. et al. (2003) observed hypertension against the background of intraventricular administration of SNP in 2 patients out of 10, which required discontinuation of SNP administration [24]. Similar data were published by Thomas J.E. et al. (2002). The authors describe the development of systemic hypertension in one of 10 patients after intraventricular administration of SNP, which required its immediate discontinuation [25].

Pachl J. et al. (2005) presented the results of treatment of 16 patients with ruptured cerebral aneurysms who underwent injection of NNP into the basal cisterns to prevent angiospasm and cerebral ischemia (H–H I–IV, Fisher II–IV). The drug was administered from the first day after the aneurysms were excluded from the blood flow. With this therapy, the authors did not observe the development of cerebral perfusion insufficiency according to computed tomography (CT) perfusion in any case, and an increase in LBFV according to TCD due to angiospasm was noted in 3 patients. Side effects included headache, vomiting, and increased blood pressure. A good outcome was noted in 56.25% of patients — one point according to the Glasgow Outcome Scale (GOS), 2 points in 12.5%, 3 points in 25%, and 4 according to GOS in 6.25%. There were no fatal outcomes in the study group [26].

Agrawal A. et al. (2009) studied the effect of intraventricular administration of SNP in 10 patients with SAH who had severe cerebral angiospasm - according to TCDS data. The result was a significant decrease in LBFV in patients receiving SNP compared to a comparison group of 10 people. Good outcome was observed in 70% of patients. Complications in the form of systemic hypertension and vomiting were observed in 30% and 60% of patients, respectively. The authors did not note an increase in ICP against the background of SNP administration. One patient from the SNP group died due to acute myocardial infarction [27].

Thus, a number of side effects (systemic hypertension, increased ICP) significantly limit the use of nitrates in patients with ruptured IA. Even local (intrathecal) use of nitrates does not completely exclude their effect on systemic hemodynamics. Most published studies are single-center, non-randomized studies with a small number of patients.

PRECURSORS OF NITRIC OXIDE SYNTHESIS

The amino acid L-arginine is a substrate for the synthesis of nitric oxide in the vascular wall, from which free nitric oxide and L-citrulline are released under the influence of NO synthase. A number of studies have been aimed at studying the effects of introducing L-arginine into the bloodstream in SAH.

Kajita Y. et al. (1994) presented the results of intrathecal administration of L-arginine in combination with superoxide dismutase (SOD) in a dog model of SAH. SOD was used to prevent oxidation of nitric oxide by superoxide anion. Basilar artery lumen was measured using angiography. L-arginine was administered in amounts of 10 mmol/l and 100 mmol/l on days 4 and 7 after induction of SAH during angiography.

L-arginine on the 4th day, the lumen of the basilar artery increased to 30±1.5% in contrast to the comparison group. After administration of the same dose of L-arginine on the 7th day, the lumen of the artery increased to 15.2±2.1% in comparison with the comparison group. The addition of SOD did not affect the vasodilating effect of L-arginine [28].

There are experimental data on the use of L-arginine in a study in monkeys by Pluta R.M. et al. (2000). After implantation of a blood clot into the blood supply area of the right middle cerebral artery, animals were administered L-arginine intracarotid and intravenously. After a single intracarotid administration of the drug, the lumen of the arteries increased significantly for 3 minutes according to cerebral arteriography, but this effect quickly regressed. In animals that were administered L - arginine intravenously for 14 days, no increase in the lumen of the arteries was detected. Thus, neither intra-arterial nor intravenous administration reduced the frequency and severity of the development of delayed cerebral vasospasm (CVS) [29].

L-arginine use is described in the works of Göksel H.M. et al. (2001) and Ozüm U. et al. (2007) with intra-arterial and intrathecal administration.

Göksel HM et al. (2001) used intracisternal L-arginine in a rabbit model with SAH. The drug was administered on the 4th day after experimental SAH for 60 minutes, measuring the cerebral blood flow velocity in the right internal carotid artery (ICA) using transorbital Doppler sonography. As a result,

after intracisternal administration of L-arginine, dilation of the artery and a decrease in the LBFV in the ICA from 53.3±2.61 cm/s to 17.65±0.74 cm/s after 60 minutes were observed. The LBFV in the ICA in the control group without SAH averaged 25.6±0.65 cm/s [30].

In a study on the SAH model in rabbits, Ozüm U. et al. (2007) studied the effect of L-arginine on the evoked motor response (EMR) rate using transcranial magnetic stimulation. On the 4th day after the induction of SAH, the rabbits were administered 300 mmol L-arginine intracarotidly for 60 minutes. The EMR parameters were measured every 10 minutes after the drug administration. In the L-arginine group, the EMR latency before L-arginine administration was 11.82±0.51 ms and decreased to a minimum of 8.25±0.51 ms at the 60th minute. The amplitude of the EMR was maximal from the 40th to the 60th minute (914.62±201.98–919.12±64.69 mV) with a subsequent decrease (545.62±56.61 mV). The average latency and amplitude in the comparison group were 8.53±0.50 ms and 826.12±47.39 mV. The obtained data indicate a significant improvement in the EMR after intracarotid L-arginine administration, which may indicate improved cerebral perfusion and a decrease in the severity of ischemia against the background of CVS [31].

Ozüm U. et al. (2007) compared intracisternal and intracarotid administration of L-arginine on a rabbit model with induced SAH. Administration of 300 mmol L-arginine into the cistern and into the carotid artery was performed on the 4th day after induction of SAH for 60 minutes. Measurement of the average blood flow velocity was performed using TCDS every 10 minutes. A tendency towards a decrease in the average blood flow velocity after administration of L -arginine was observed in both groups. As a result, 30 minutes after administration of L-arginine into the cisterns and intra-arterially, the average blood flow velocity was at the same level in both the intracisternal and intracarotid administration groups and was approximately 25 cm/s with an initial velocity of 54 cm/s. Thus, no significant differences were observed between intrathecal and intra-arterial administration of L-arginine.

There is no data on the clinical use of L-arginine in patients with ruptured cerebral aneurysms. In summary, it can be stated that the data on the experimental use of NO synthesis precursors are contradictory. Further study of this group of drugs is required [32].

NON-NITRATE NITRIC OXIDE DONORS

The drugs of this group are classified as nitrate-like. They have a similar pharmacological action, but have a chemical structure different from the nitrate group and are metabolized in the liver to form SIN-I A (Linsidomin), which breaks down with the release of nitric oxide. We analyzed a number of publications in which molsidomine was used to prevent and treat cerebral angiospasm in patients with SAH.

In the study by Ehlert A. et al. (2015) the effect of molsidomine on the incidence of ischemic cerebral infarction in patients with ruptured cerebral aneurysms was studied. The study included 74 patients receiving standard therapy with nimodipine. In 54 patients, the development of ischemic stroke was noted in the postoperative period according to TCDS or digital subtraction angiography. Of these 54 patients, 29 patients received combination therapy with nimodipine and molsidomine, and 25 received nimodipine alone. Molsidomine was administered intravenously at a dosage of 20–40 mg for 24 hours under the control of mean arterial pressure (SBP> 65 mm Hg), after which molsidomine was taken orally at a dosage of 8 mg 4 times a day for 14–28 days. In 4 of 29 patients (13.8%) in the molsidomine group and 15 of 25 patients in the nimodipine group, cerebral infarction developed. In the molsidomine treatment group, only one patient out of 29 died, while in the comparison group and in the group of patients with SAH without cerebral angiospasm, the mortality rate was 26.67%. Among the side effects, hypertension was observed in 8 patients in the molsidomine group, which required the administration of norepinephrine in small doses (up to 0.2 mcg/kg/min). In the subgroup analysis, the authors found that the greatest effectiveness of combined therapy with molsidomine and nimodipine was recorded in patients with a severity of III–V on the H–H scale [33].

There are publications describing the combined use of intravenous molsidomine and intrathecal SNP. Ehlert A. et al. (2016) provide a clinical observation of combined intrathecal bolus administration of SeNP and intravenous infusion of molsidomine in a patient with SAH due to a ruptured aneurysm of the right middle cerebral artery in a subcompensated clinical state (H–H III, Fisher IV). For 22 days, starting from the 2nd day after surgery, the patient was administered intravenous molsidomine at a dosage of 1.7 mg/h to 16 mg/h. NNP was administered intrathecal bolus starting from the 9th

day after the development of symptomatic SAH in the form of right-sided hemiplegia and total aphasia. Bolus administration of SNP allowed to stop neurological symptoms on the 10th day after hemorrhage, after which intrathecal administration of nitrates was continued until the 22nd day. The patient was discharged in satisfactory condition (GOS score 5) [34].

Ehlert A. et al. (2020) presented the results of combined intravenous administration of molsidomine and intraventricular bolus administration of SNP in 18 patients with ruptured aneurysms who were in critical condition (H–H stage V). Molsidomine therapy was initiated in the first 12–36 hours after aneurysm rupture at an initial dosage of 1.6 mg/h, followed by an increase over 3 days to 16 mg/h. With the development of CVS according to TCDS data (BFV more than 150 cm/s), in addition to molsidomine therapy, bolus administration of SNP at a dosage of 2–10 mg (on average, 5.6 mg) was performed through an external ventricular drainage. Mortality in the presented group of patients exceeded 70%. Mortality in 2 of 12 patients was caused directly by cerebral ischemia against the background of CA, in 10 of 12 due to other reasons due to concomitant pathology. However, the authors do not provide a detailed analysis of mortality in this study. In one case, mortality was caused by massive intracranial hemorrhage against the background of the introduction of SNP. In 4 patients, the treatment outcome was satisfactory. The authors observed the following complications, side effects and undesirable uses of molsidomine: withdrawal syndrome due to forced cessation of molsidomine administration, atrial fibrillation, asymptomatic methemoglobinemia up to 2.5. The authors concluded that in this cohort of severely ill patients with an extremely unsatisfactory prognosis, the use of this combination therapy can improve the treatment outcome [35].

The use of non-nitrate nitric oxide donors can reduce the severity of systemic hypertension. However, the studies known to us are single-center, non-randomized, and are presented by a single group of authors. Further study of these drugs is required to determine the role of non-nitrate donors in the treatment of patients with ruptured IA.

ENDOTHELIN ANTAGONISTS

Endothelin-1 is a potent vasoconstrictor, a physiological antagonist of nitric oxide. Data on an increase in the concentration of endothelin-1 in the blood plasma of patients with developed cerebral vasospasm due to SAH have been obtained (Bellapart J. et al., 2014). Clazosentan is a drug from the group of endothelin-1 antagonists, which was created directly for the treatment of patients with ruptured cerebral aneurysms [36].

In a series of randomized multicenter studies CONSCIOUS -1, 2, the results of which were presented by Macdonald R.L. et al. (2008, 2011, 2012), it was not possible to demonstrate a positive effect of clazosentan on the outcome of treatment. Clazosentan was administered intravenously at a dose of 5 mg/h in the first 56 hours after SAH up to 14 days of continuous drug administration [37, 38].

Despite the positive angiographic result after taking clazosentan, its use did not have a reliable effect on delayed cerebral ischemia, microcirculatory dysfunction and outcome in patients with ruptured cerebral aneurysms. According to the GOS scale, the outcome of less than 4 points in the first 6 weeks after SAH in the placebo group was observed in 25% of patients, while in the group of patients receiving clazosentan it was observed in 29% [37, 38].

The authors noted a tendency towards a decrease in mortality from cerebral ischemia while taking clazosentan; however, the negative effects obtained and recorded from taking the drug (anemia, hypotension, acute respiratory distress syndrome, pulmonary edema, pneumonia) probably negated its effectiveness [37, 38].

A meta-analysis by Cho S.S. et al. (2019) addressed the use of clazosentan in patients with ruptured IA. The authors, based on data from 2317 patients treated in 2005–2017, concluded that clazosentan reduces the risk of delayed cerebral ischemia, especially at a dosage of 10–15 mg/h. More information and research are needed to further study the effects [39].

Endo H.C. et al. (2022) presented the results of two randomized, double-blind, placebo-controlled multicenter studies in 57 hospitals. In both studies, patients were randomized into two groups: the control group - 111 people and the clazosentan group - 109 people. The drug was prescribed in the first 48 hours after SAH intravenously at a dosage of 10 mg / h for up to 15 days. In patients after aneurysm embolization, angiospasm-associated mortality and overall mortality when taking clazosentan decreased from 28.8 to 13.6%. In patients after microsurgical clipping of aneurysms, the corresponding indicator

decreased from 39.6 to 16.2%. The authors observed serious complications in the clazosentan group, such as: pulmonary edema in 11.9%, cerebral edema in 6%, cerebral angiospasm in 16.1%, cerebral infarction in 15.1%, delayed cerebral ischemia in 19.3%, anemia in 16.5%, and metabolic disorders in 47.7% of patients [40].

At present, the question of the efficacy of clazosentan in patients with ruptured IA remains open, since the data presented in various studies are contradictory.

PHOSPHODIESTERASE INHIBITORS

The PDE5 inhibitor sildenafil does not have a direct relaxing effect on human smooth muscle. Instead, it works by enhancing the effects of nitric oxide by inhibiting phosphodiesterase type 5 (PDE5), which is responsible for the breakdown of cyclic guanosine monophosphate (cGMP). Increased cGMP levels in turn lead to smooth muscle relaxation and increased blood flow [41].

In clinical practice, sildenafil is used in urology for the treatment of erectile dysfunction, as well as in the treatment of pulmonary hypertension.

Han B.H. et al. (2012) studied the efficacy of sildenafil in an experimental model of SAH in 26 mice. In the study group, the authors administered sildenafil to the animals orally twice a day at a dosage of 0.7–5 mg/kg 2 hours after endovascular perforation of the internal carotid artery. The authors noted that the use of sildenafil reduces PDE-5 activity in SAH in the experiment: in the group of animals with SAH, the PDE-5 level was 538.4±118.5 fmol/mg, in the group of animals that received sildenafil therapy - 81.5±110.5 fmol/mg. Also, after taking sildenafil, a decrease in the severity of cerebral angiospasm was observed, according to histological examination of the arterial lumen, and an improvement in the neurological status in animals, which was carried out using specialized scales. Use of sildenafil citrate at a dose of 2 mg/kg did not affect MAP and ICP [42].

Mukherjee K.K. et al. (2012) presented their experience of using sildenafil citrate in 72 patients with ruptured cerebral aneurysms and subsequent symptomatic CVS that did not resolve with 3H therapy . Patients received sildenafil citrate orally at a dosage of 100–150 mg every 4 hours. The authors assessed the effectiveness of therapy based on TCDS data (with normalization of LBFV indices within 48 hours after the start of therapy). The authors noted normalization of LBFV in 8 patients (11.1%) and a temporary decrease in LBFV in 4 patients (5.5%). However, in 4 patients, therapy was suspended due to side effects (hypotension, severe headache, visual impairment) [43].

In a two-phase clinical study, Washington C.W. et al. (2015) studied the efficacy and safety of sildenafil in 12 patients with SAH due to rupture of the IA. Five patients were administered sildenafil citrate intravenously at a dosage of 10 mg, and 7 patients were administered 30 mg. All subjects showed a decrease in CAS according to subtraction angiography, without adverse effects from the drug. SBP after administration was short-term reduced by an average of 17% [44].

Dhar R. et al. (2016) studied the effect of sildenafil citrate in 6 patients with ruptured cerebral artery aneurysms. After intravenous administration of 30 mg sildenafil citrate, the authors did not observe changes in regional and global cerebral perfusion (according to positron emission CT tomography) and the diameter of the lumen of cerebral vessels (according to subtraction cerebral angiography) [45].

In a clinical study by Faropoulos K. et al. (2023), the authors studied the effectiveness of sildenafil citrate in the postoperative period on the incidence of cerebral infarction according to brain CT and CT perfusion. The study included 34 patients (17 patients formed the comparison group, 17 patients received sildenafil citrate at a dosage of 20-40 mg). The authors noted that sildenafil administration statistically significantly reduced the incidence of ischemic infarction in patients with ruptured cerebral aneurysms in the postoperative period. However, a detailed analysis of the work reveals that the study groups differed. The comparison group was dominated by patients in a more severe clinical condition - stage III-V on the H-H scale and with more severe forms of hemorrhage on the modified Fisher scale [46].

Thus, data on the effectiveness of PDE5 inhibitors in patients with ruptured cerebral aneurysms are contradictory: on the one hand, there are studies indicating its possible effectiveness, on the other hand, its ineffectiveness, or the scientific level of the presented studies is low.

The phosphodiesterase type 3 inhibitor cilostazol increases the intracellular concentration of cyclic adenosine monophosphate (cAMP), which in turn inhibits protein kinase A, which promotes the

contraction of the actin-myosin complex and leads to the contraction of myocytes, including the vascular wall. An increase in the concentration of cAMP leads to an increase in the biological effects of nitric oxide. In addition to the effect on the metabolism of nitric oxide, this drug has antiplatelet properties.

Cilostazol is used in clinical practice as an antiplatelet agent in the treatment of ischemic stroke and atherosclerotic lesions of the arteries of the lower extremities in intermittent claudication.

There are a large number of studies in the literature devoted to the use of cilostazol in patients with ruptured cerebral aneurysms.

According to the Cochrane meta-analysis by Dorhout Mees S.M. et al. (2003), the use of cilostazol in patients with SAH leads to an improved treatment outcome. However, the positive results are preliminary, and further studies of the effectiveness of cilostazol in patients with SAH are needed [47].

In a randomized, double-blind, placebo-controlled study by Matsuda N.C. et al. (2016), the efficacy of cilostazol was demonstrated in 148 patients with SAH. Patients were randomized into two groups: comparison and study group. The drug was started to be administered orally at a dosage of 100 mg during the first 48 hours after SAH for 14 days. CAS was assessed using digital subtraction cerebral angiography, the presence of cerebral ischemia was determined according to brain CT data, and the outcome of treatment was determined 3 months after SAH according to GOS. In the comparison group, placebo was discontinued in one case due to gastrointestinal bleeding, in the study group, the drug was discontinued in 2 patients due to liver pathology and the presence of an aneurysm of another localization that was not excluded from the bloodstream. When assessing the effect of cilostazol on the outcome of treatment according to the GOS after 3 months, statistically significant data were obtained on the reduction of mortality in the cilostazol group (5.4 versus 17.6%). Among the complications and side effects of the drug, the researchers noted tachycardia up to 120 beats/min in two cases, an increase in the concentration of liver enzymes in the blood plasma in 5 patients [48].

According to meta-analyses by Li L. et al. (2022) and Dayyani M. et al. (2022), in patients with SAH and developed CAS who took cilastozole, the incidence of symptomatic CAS, delayed cerebral ischemia and mortality was reduced [49, 50].

Thus, literature data indicate the effectiveness of cilostazol in patients with ruptured cerebral aneurysms, but at present this drug is not included in domestic and foreign clinical guidelines.

INHALED NITRIC OXIDE (INO)

At present, information on the use of inhaled nitric oxide for the treatment of CAS and cerebral ischemia due to ruptured aneurysms is represented by isolated experimental and clinical data.

Li Y.S. et al. (2013) presented a study examining the effect of inhaled nitric oxide on ischemic brain injury after temporary occlusion of the middle cerebral artery for 1 hour in mice. The animals were divided into control groups and a nitric oxide group. The nitric oxide group was divided into subgroups depending on its concentration in the inhaled mixture (10, 20, 40, 60, and 80 ppm) and the duration of inhalation (5, 8, 16, and 24 hours). Nitric oxide inhalations were started immediately after artery occlusion. The size of the infarction zone and aseptic inflammation were measured by histological and immunohistochemical studies. The authors observed a dose- and time-dependent positive effect of nitric oxide in the form of a decrease in the ischemic zone (for a nitric oxide concentration of 10 ppm, the effect was observed during inhalation for 24 hours, for its concentration of 20, 40 and 60 ppm - at 8 and 16). At the same time, with inhalation of nitric oxide in dosages of 40 and 60 ppm and an inhalation duration of 24 hours, the infarction volume again increased. In the group of animals receiving a nitric oxide concentration of 80 ppm, no significant decrease in the infarction zone was detected in the period of 0-24 hours, which indicates the ineffectiveness of the neuroprotective properties of this dosage. The cerebral infarction zones after nitric oxide inhalation did not exceed the ischemic volume in the animals of the control group. Thus, we can talk about both positive and possible negative effects of inhalation therapy, which depend on the concentration of NO in the inhaled mixture and the duration of inhalation [51].

In the works of Terpolilli N.A. et al. (2015) the effect of inhaled nitric oxide in SAH was demonstrated in an experiment on mice. Nitric oxide inhalations were administered to anesthetized animals in a special chamber for 60 minutes with its content equal to 50 ppm and oxygen content in the air from 30 to 70%. In all animals after SAH the same level of CAS of small arteries and cerebral ischemia was observed according to CT perfusion and subtraction angiography. Against the

background of nitric oxide inhalation, a decrease in the severity of arterial spasm was observed in more than 80% of animals, compared with the control group [52].

Fung et al. (2022) presented the results of clinical use of nitric oxide in 7 patients with ruptured cerebral aneurysms and development of symptomatic vasospasm that was not amenable to standard therapy (induced hypertension, nimodipine intake, hypervolemia with central venous pressure greater than 6 mmHg). Patients were given nitric oxide inhalation for 23 hours a day at a maximum concentration of 40 ppm. The effectiveness of therapy was assessed using digital subtraction cerebral angiography, measurement of partial pressure of tissue oxygen ($PtiO_2$), TCDS, and CT perfusion of the brain. To assess safety, clinical and laboratory parameters were measured (the level of methemoglobin in the patient's venous blood, creatinine, activated partial thromboplastin time, platelets), and ICP levels were monitored. Of the 7 patients, 2 died due to massive cerebral infarction, another 2 patients developed cerebral infarction, and 3 patients were discharged without developing cerebral ischemia. The authors concluded that this type of therapy is safe and requires further study [5].

CONCLUSION

Among the drugs that affect nitric oxide metabolism in patients with non-traumatic subarachnoid hemorrhage due to ruptured cerebral aneurysms, the largest number of publications are devoted to the use of nitrates, endothelin antagonists, and phosphodiesterase type 3 inhibitors. The use of nitrates in patients with subarachnoid hemorrhage is limited by their serious side effects (systemic hypotension, increased intracranial pressure).

Clazosetan, according to the presented randomized studies, is able to reduce the incidence of cerebral ischemia and vascular spasm, but its final impact on treatment outcome has not been determined.

The use of phosphodiesterase type 3 inhibitors (cilostazol) has been the subject of a large number of studies demonstrating the positive effect of this group of drugs on the outcome of treatment. However, phosphodiesterase has not yet been included in published guidelines for the treatment of patients with ruptured aneurysms.

to draw a definitive conclusion about the use of other medicinal substances (non-nitrate nitric oxide donors, L-arginine, inhaled nitric oxide) due to the small number of published studies.

Further study of drugs that affect nitric oxide metabolism appears promising for use in complex therapy of patients with ruptured cerebral aneurysms.

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