Review
https://doi.org/10.23934/2223-9022-2021-10-4-750-759

Endovascular Methods of Prevention and Treatment of Vascular Spasm Due to Rupture of Cerebral Aneurysms: Pros and Cons

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ABSTRACT This review highlights current approaches to endovascular therapy of cerebral angiospasm in non-traumatic subarachnoid hemorrhage due to a ruptured cerebral aneurysm (CA). The main clinical guidelines for the management of patients withchemoangioplasty rupture are highlighted, clinical studies on the use of balloon angioplasty, intra-arterial administration of various vasodilators are presented, the advantages and complications of using various techniques are described.

Keywords: cerebral aneurysm, nontraumatic subarachnoid hemorrhage, cerebral angiospasm, endovascular treatment, balloon angioplasty, chemoangioplasty

For citation Prirodov AV, Bakharev EYu, Kalinkin AA. Endovascular Methods of Prevention and Treatment of Vascular Spasm Due to Rupture of Cerebral Aneurysms: Pros and Cons. *Russian Sklifosovsky Journal of Emergency Medical Care.* 2021;10(4):750–759. https://doi.org/10.23934/2223-9022-2021-10-4-750-759 (in Russ.)

Conflict of interest Authors declare lack of the conflicts of interests

Acknowledgments, sponsorship The study has no sponsorship

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AA – arterial aneurysm
ACA – anterior cerebral artery
BP – blood pressure
CA – cerebral aneurysm
CT – computed tomography
ICA – internal carotid artery
ICP – intracranial pressure
LBFV – linear blood flow velocity
MCA – middle cerebral artery
MRI – magnetic resonance imaging
PCA – posterior cerebral artery
PDE – phosphodiesterase
SAH – subarachnoid hemorrhage
TBA – transluminal balloon angioplasty

Cerebral vascular spasm is the main cause of poor outcome in patients with ruptured cerebral aneurysms. Angiospasm (angiospasm) develops in response to blood entering the subarachnoid space and leads to delayed cerebral ischemia. Until now, there is no single algorithm that would completely prevent the development of angiospasm and cerebral ischemia.

Among the endovascular techniques aimed at increasing the lumen of the artery in cerebral vascular spasm, the methods of selective intra-arterial injection of various vasodilators into spasmodic arteries (chemoangioplasty) or mechanical dilatation of spasmodic vessels (transluminal balloon angioplasty) have now been applied.

Transluminal balloon angioplasty (TBA). The essence of the technique is to dilate the spasmodic section of the artery with a balloon catheter. For the first time this technique was proposed by Zubkov Yu.N. et al. (1984), after that it was recognised and adopted worldwide [1]. There is a very large amount of data in the literature on the positive therapeutic and even preventive effect of this intervention in reducing the severity of symptomatic spasm [2–4].

However, balloon angioplasty can be accompanied by a number of severe complications: rupture of a spasmodic vessel, its dissection, reperfusion syndrome with the development of cerebral edema or hemorrhagic impregnation of the ischemic zone, as well as migration of clips or microcoils [1, 3]. Nonspecific complications may be complications arising after endovascular access: formation of a pulsating hematoma in the area of femoral artery catheterization, retroperitoneal hematoma, etc. (Table 1).

Table 1

Complications after transluminal balloon angioplasty (data taken from the article by Newell D. et al. (1999) [5])

Author, year	Number patients, *n*	Clinical improvement, %	Complications, *n*
Higashida et al., 1992	28	61	2 vessel ruptures
Zubkov Yu.N. et al., 1993	95 (52 - symptomatic angiospasm)	86.5	4.5%
Coyne et al., 1993	13	31	1 rebleeding
Eskridge et al., 1995	50 (46 - symptomatic angiospasm)	61	1 occlusion, 2 vessel ruptures, 2 rebleeds
Firlik et al., 1997	13	92	intracranial hemorrhage
Bejjani et al., 1998	31	74	2 intracranial hemorrhages, 1 retroperitoneal hematoma

More recent work demonstrates the safety and efficacy of TBA in patients with angiographic and clinical signs of angiospasm. Patel A.S. et al. (2017) presented the results of using angioplasty in 52 patients with symptomatic angiospasm due to a ruptured cerebral aneurysm (CA). The use of TBA contributed to clinical improvement immediately after the procedure in 78.8% of cases, a satisfactory outcome of treatment 3 months after discharge was achieved in 61.5% of patients. No complications of TBA were observed in this series of patients [6].

Similar data were presented by *Schacht H. et al*. (2020) [7]. After the use of TBA in 35 patients, the authors observed a statistically significant positive angiographic and clinical effect. In one case, the authors noted the development of MCA dissection after TBA, which led to extensive cerebral infarction.

According to a meta-analysis by *Li K. et al*. (2019), TBA has a significant positive clinical and angiographic effect and reduces the incidence of cerebral infarction by 31% [8]. In addition, with the use of TBA, the frequency of repeated endovascular interventions is lower than with chemogioplasty. The frequency of complications with the use of TBA was less than 1% [8]

Transluminal balloon angioplasty (TBA) is included in the clinical guidelines of the American, Japanese, and Korean neurosurgical communities as an effective treatment for symptomatic cerebral vascular spasm when conservative methods fail (induced hypertension) [9–11]. A significant limitation of this technique is the diameter of the spasmodic vessel: with spasm of the arteries of the distal bed (less than 1.5–2 mm in diameter), it turns out to be technically impossible to insert a balloon catheter into them. It is believed that this technique has a longer effect (compared to chemoangioplasty). Balloon angioplasty is the method of choice for segmental spasm of the internal carotid artery (ICA), proximal parts of the middle, anterior and posterior cerebral arteries

(MCA, ACA and PCA) by more than 50%, as well as with the ineffectiveness of chemoangioplasty, as a more "aggressive" vasodilation technique [12–14].

Chemoangioplasty. Unlike TBA, it is used to restore the patency of not only the proximal, but also the distal sections of spasmodic cerebral arteries. There are two types of chemoangioplasty, which differ in the method of drug administration: selective catheterization of a narrowed segment of the cerebral arteries with subsequent administration of drugs, or the administration of drugs into a catheterized artery of the neck, in the pool of which a spasm has occurred. Selective administration of vasodilators can reduce the concentration of the drug and the severity of systemic side effects. Currently, chemoangioplasty is recommended for patients with symptomatic angiospasm in the absence of the effect of systemic use of nimodipine and induced hypertension as the next stage of therapy [9–11, 13].

There are data in the literature on the use of papaverine, verapamil, nimodipine, nicardipine as vasodilators for chemoangioplasty in patients with angiospasm due to ruptured arterial aneurysm (AA). However, we did not find data on the conduct of multicenter randomized trials on endovascular methods for the prevention and treatment of angiospasm. In addition to the above drugs, there is information about the use of fazudil hydrochloride, magnesium sulfate, milrinone and collforsin daropate, but there is much less data on their use. The main characteristics and mechanisms of action are presented in Table 2 [15].

Table 2

The main vasodilators used for chemoangioplasty in patients with angiospasm due to ruptured arterial aneurysm [15–33]

A drug	Mechanism of action	Disadvantages and complications
Papaverine	Phosphodiesterase - inhibitor	Systemic hypotension, neurotoxicity, seizures, negative effect on cerebral metabolism, paradoxical vasoconstriction, increased intracranial pressure
Nimodipine	Calcium (Ca^{2+}) channel antagonist	Hypotension, increased intracranial pressure, decreased cardiac output, edema of the basal ganglia, infectious complications (with prolonged continuous infusion)
Nicardipine	Calcium (Ca^{2+}) channel antagonist	Systemic hypotension
Verapamil	Calcium (Ca^{2+}) channel antagonist	Systemic hypotension, bradycardia, increased intracranial pressure
Fasudil hydrochloride	Rho-associated protein kinase inhibitor	Seizures, intracranial hemorrhage
Milrinone	Phosphodiesterase - inhibitor	Cardiac complications
Forskolin	phosphodiesterase inhibitor	Headache, palpitations

Next, we review the largest studies on the use of various vasodilators for chemoangioplasty.

Papaverine. One of the first results ofchemoangioplasty with papaverine was presented by *Kassell N.F. et al.* (1992), *Kaku Y. et al*. (1992). These studies included no more than 10–12 patients and demonstrated the preliminary efficacy and safety of the technique [33, 34]. Angiographic resolution of angiospasm occurred in 34 spasmodic segments of cerebral arteries out of 37, regression of neurological symptoms in 8 out of 10 patients, no complications were noted. Similar results were published by *Clouston J.E. et al*. (1995), however, the authors described a case of monocular blindness in 1 patient out of 14 [35].

There is evidence of the effect of papaverine on systemic hemodynamics, intracranial pressure (ICP). *McAuliffe W. et al.* (1995) during chemoangioplasty with papaverine in 21 patients with angiospasm due to rupture of thechemoangioplasty, a statistically significant increase in ICP, heart rate and blood pressure (BP) was noted. In addition, we observed a trend towards a decrease in cerebral perfusion pressure in all examined patients. Nevertheless, regression of angiospasm was found in 76% of patients, and clinical improvement in 52% [18].

Sawada M. et al. (1997) studied the effectiveness ofchemoangioplasty with papaverine in 46 patients at various dosages and observed a positive angiographic and clinical effect. However, the authors noted that the

introduction of a papaverine solution at a concentration above 0.4% may be accompanied by a transient increase in neurological symptoms, and therefore exceeding these dosages is not recommended [36].

Polin R. et al. (1998) presented the results of the use of papaverine in 31 patients with symptomatic angiospasm. However, according to the authors, no advantages were observed in the use of chemoangioplasty with papaverine when using statistical analysis, and the treatment outcomes after 3 months did not differ in the study and control groups [37].

Firlik K.S. et al. (1999) on the material of 15 patients with angiospasm with intra-arterial use of papaverine observed regression of angiospasm in 78% of patients, improvement in cerebral blood flow in 46% and regression of neurological symptoms in 26% of patients. However, when chemoangioplasty was performed in the vertebrobasilar region, 4 patients with hemorrhage due to chemoangioplasty rupture developed arterial hypotension and focal neurological stem symptoms [16].

Among the complications and side effects of chemoangioplasty with papaverine, the following observations are described in the literature. *Tsurushima H. et al.* (2000) described a case of seizures and paradoxical aggravation of angiospasm [17].

Carhuapoma JR et al. (2001) presented a clinical observation in which a patient with symptomatic angiospasm after chemoangioplasty was observed to develop a convulsive syndrome [19].

Andaluz N. et al. (2002) [14] published the results of combined endovascular treatment (TBA and chemoangioplasty with papaverine) in 50 patients with chemoangioplasty rupture. The authors noted that in the combined treatment of TBA and chemoangioplasty with papaverine, clinical outcomes are worse. The use of chemoangioplasty with papaverine for widespread spasm in both carotid pools is accompanied by a significant increase in ICP and worsens the outcome of treatment [14].

Smith W. et al. (2004) reported the result of 5 patients who experienced significant neurological deterioration after selective angioplasty with papaverine in chlorobutanol solution for angiospasm. After the procedure, patients underwent magnetic resonance imaging (MRI) of the brain, which revealed specific lesions in the cerebral cortex. The authors concluded that the use of a solution of papaverine in chlorobutanol is not recommended for angioplasty and is accompanied by a negative clinical and radiological effect [38].

Horsman A. et al. (2019) studied cerebral metabolism in 10 patients with angiospasm due to rupture of thechemoangioplasty, who underwent intra-arterial administration of papaverine. A positive angiographic effect was observed in 80% of patients. At the same time, the patients showed an increase in ICP, a decrease in glucose levels in the brain tissue, and an increase in lactate levels, which gradually recovered and improved relative to the initial level within 10 hours after the procedure. Thus, intra-arterial infusions of papaverine immediately after the procedure had a negative effect on brain metabolism, which was leveled within a few hours [39].

Thus, it can be concluded that papaverine can successfully lead to regression of angiographic angiospasm and radiological angiospasm, however, its use may be accompanied by a number of clinically significant side effects.

Nimodipine. One of the first results in the literature on the use of nimodipine for intra-arterial administration in angiospasm in patients with subarachnoid hemorrhage (SAH) was presented by *Biondi A. et al*. (2004) and *Hui C. et al*. (2005) [40, 41]. *Biondi A. et al*. used nimodipine infusion into the ICA in 25 patients with angiospasm due to ruptured cerebral aneurysms [40]. Angiographic resolution of angiospasm was noted in 12 patients (48%), clinical improvement in 19 (76%). 3 months after treatment, a satisfactory outcome was noted in 18 patients (72%). No complications of manipulation were observed.

Hui C. et al. (2005) presented preliminary results of the use of chemoangioplasty with nimodipine in 9 patients, which was accompanied by angiographic resolution of angiospasm and had no side complications [41].

Hanggi D. et al. (2008) published the results of the treatment of 26 patients who underwent selective administration of nimodipine into spasmodic arteries, which reduced the severity of angiospasm according to angiography in 43% of patients, achieved clinical improvement and improved cerebral perfusion in 76%. The authors noted that hypotension after the use of nimodipine was observed in 6 patients, but this did not affect the outcome of treatment. According to the authors, chemoangioplasty with nimodipine was more effective than chemoangioplasty with papaverine [42]. On the other hand, *Kerz T. et al*. (2012) found that intra-arterial administration of papaverine leads to vasodilation in 100% of cases, while the administration of nimodipine did not cause vasodilation in 16% of cases [43]. Thus, data on the comparative efficacy of nimodipine are contradictory.

According to *Cho W.S. et al*. (2011),chemoangioplasty with nimodipine was performed in 42 patients with angiospasm, which made it possible to achieve regression of the angiographic pattern of angiospasm in 50% of patients after one session of chemoangioplasty [44]. The rest of the patients required 2–3 chemoangioplasty sessions. In 82.2% of patients, regression of angiospasm was noted, which in 68.3% of cases was accompanied by a decrease in neurological deficit. Ischemic changes in the substance of the brain were found in 21.4% of patients, mortality was 2.4%. The authors did not note any complications of the technique that affected the outcome of treatment.

Kim S.S. et al. (2012) published the results of chemoangioplasty with nimodipine in 29 patients with angiospasm due to chemoangioplasty rupture [45]. Intra-arterial administration of the drug at a dose of 1 to 3 mg in 82% of patients was accompanied by an expansion of spasmodic cerebral arteries by 40% or more, which led to a regression of the neurological deficit. However, in one patient, despite the expansion of the spasmodic artery, the authors revealed a worsening of the clinical condition. Treatment outcomes were not presented in this article.

Ott S. et al. (2014), using chemoangioplasty with nimodipine in 30 patients with angiospasm due to chemoangioplasty rupture, determined that this method of administration led to an improvement in cerebral perfusion and restoration of oxygen tension in the brain tissue [46]. In 83% of patients, the authors noted satisfactory outcomes of treatment.

According to *Narayan V. et al*. (2018), continuous intra-arterial infusion of nimodipine in patients with clinical signs of cerebral ischemia allowed resolution of angiospasm angiographically in 95.7% of cases and contributed to the regression of clinical signs of angiospasm in 87% of patients [47].

Despite the fact that, according to most authors of chemoangioplasty, nimodipine is a safe and effective treatment for angiospasm in patients with SAH due to rupture of the cerebral chemoangioplasty, some researchers have noted possible complications with intra-arterial administration of the drug. Yes, *Ryu C.W. et al*. (2011) presented 2 clinical observations, when intra-arterial administration of nimodipine was accompanied by edema of the basal ganglia, which significantly worsened treatment outcomes [22]. *Kieninger M. et al*. (2018) described the following negative consequences in patients who received continuous infusion of nimodipine for a long time (more than 5 days): hypotension requiring correction with sympathomimetics, cardiac complications, an increase in the number of infectious complications, and an increase in ICP [24].

According to *Adami D. et al*. (2019), in patients with severe angiospasm after rupture of the chemoangioplasty, the frequency of new ischemic lesions after chemoangioplasty with nimodipine in combination with TBA is 6%, and in 3% of cases, recurrent stroke is associated with the consequences of endovascular treatment, which significantly levels the effectiveness of interventional treatment [23].

Thus, at the moment, a large number of single-center studies have been accumulated showing the effectiveness of chemoangioplasty with nimodipine with an acceptable number of side effects. It is likely that multicenter randomized trials are required to clarify the indications and methods for performing chemoangioplasty using this vasodilator.

Nicardipine. The first use data for chemoangioplasty was published by *Badjatia N. et al* . (2004) [48]. Intra-arterial administration of nicardipine in 18 patients with clinical and instrumental signs of angiospasm made it possible to reduce angiographically pronounced angiospasm in all patients, to reduce the mean linear blood flow velocity (LBFV) in the MCA from 277.4±80.8 to 212.8±65.7 cm/s and achieve improvement in neurological status in 42.1% of patients. Among the undesirable effects, the authors noted an increase in ICP in 6 patients, and in 5 cases, the increase was quickly corrected, which did not lead to clinical deterioration.

Tejada J.G. et al. (2007) evaluated the effectiveness of chemoangioplasty with nicardipine in 11 patients with severe angiospasm and severity of the condition upon admission to the hospital according to the *Hunt-Hess* III-IV scale. [49]. Against the background of superselective administration of the drug at a dose of 10 to 40 mg, positive angiographic changes in angiospasm were observed in all patients, and regression of symptomatic angiospasm was observed in 10 out of 11 patients.

Linfante I. et al. (2008) published the results of treatment of 22 patients with angiospasm afterchemoangioplasty rupture, who were treated with balloon angioplasty andchemoangioplasty with nicardipine. The authors observed a positive angiographic effect in all patients, in 50% of cases the treatment outcome was satisfactory. However, despite the effectiveness of nicardipine in the treatment of angiospasm, intra-arterial administration of the drug may be accompanied by a decrease in blood pressure. The authors did not observe an increase in ICP after chemoangioplasty [25].

Shah Q.A. et al. (2009) presented the results of combined intra-arterial administration of magnesium sulfate and nicardipine in the treatment of angiospasm in 14 patients with SAH [50]. Against the background of the treatment, the researchers observed a positive angiographic effect in 68% of cases. Satisfactory results of treatment were noted in 12 out of 14 patients. No complications of the technique were noted.

A major study was published in 2010 by *Schmidt U. et al.* (2010). The authors performed chemoangioplasty with nicardipine, milrinone or in combination in 73 patients with symptomatic angiospasm. An increase in the diameter of spasmodic arteries was noted in 93% of patients, in-hospital mortality was 11%. However, despite the effectiveness of the technique, the authors noted the development of hypotension, which required the use of sympathomimetics. Comparative efficacy of milrinone and nicardipine has not been performed [26].

According to *Rosenberg N. et al*. (2011): intra-arterial administration of nicardipine in 30 patients with angiospasm in SAH caused a decrease in blood pressure in 44% of patients, which required sympathomimetic therapy [27].

Pandey P. et al. (2012) presented the results of treatment of symptomatic angiospasm in 27 patients with ruptured cerebral aneurysms. The authors managed to achieve angiographic resolution of spasm in 86.1% of cases, clinical improvement in 81.5%. A satisfactory outcome at discharge was observed in 62.9% of cases [51].

Park E. et al . (2017) performed chemoangioplasty with nimodipine or nicardipine in 27 patients with symptomatic angiospasm, which resulted in clinical improvement in 51.9% of patients. Comparative efficacy of nimodipine and nicardipine has not been performed [52].

Thus, it can be concluded that intra-arterial nicardipine is effective for the treatment of symptomatic angiospasm. However, this treatment may be accompanied by an increase in ICP and hemodynamic instability.

Verapamil. For the first time, the results of the use of verapamil as a drug for chemoangioplasty in 29 patients with SAH were presented by *Feng L. et al*. (2002) [53]. The use of verapamil was accompanied by an increase in the diameter of spasmodic arteries by an average of 44% and regression of neurological manifestations of angiospasm in 29% of patients. The authors did not note an increase in ICP and the development of hemodynamic disorders (bradycardia, hypotension). It should be noted that the dosage of verapamil administration in this study did not exceed 3 mg per procedure.

Keuskamp J. et al. (2008), studying the administration of high doses of verapamil (more than 20 mg per procedure) in 10 patients, showed that the technique was not accompanied by systemic hypotension, increased ICP and contributed to the regression of the angiographic and clinical picture of angiospasm [54].

Albanese E. et al. (2010) presented data on the use of prolonged intra-arterial infusion of high doses of verapamil (25–360 mg) in 12 patients with clinical signs of angiospasm. The authors observed a positive angiographic effect in the form of complete or partial resolution of angiospasm in all patients, the frequency of new ischemic lesions according to computed tomography (CT) of the brain was 25%, a satisfactory clinical outcome 6–12 months after the hemorrhage was observed in 8 patients out of 11 [20]. There was one case of ICP rise above 20 mm Hg. and 2 cases of hypotension, which required a temporary cessation of the infusion, but these complications did not affect the outcome of treatment.

Stuart R.M. et al. (2011) presented the results of angiospasm therapy in 11 patients with massive SAH due to aneurysm rupture in a severe clinical condition (*Hunt-Hess* grade III–V). The authors studied changes in ICP and changes in metabolism in the brain substance using tissue microdialysis [55]. Against the background ofchemoangioplasty with verapamil, an increase in ICP and glucose concentration in the intercellular fluid was noted without changes in lactate, pyruvate, and local oxygen tension in the brain tissue ($PbrO_2$), which indicated a positive effect of the technique. In 5 patients out of 11, an outcome was observed on the Rankin scale of 1–3 st.

Mikeladze K.G. et al. (2018) presented the results of treatment of 35 patients with ruptured aneurysms who underwentchemoangioplasty with verapamil. Most of the patients (77.2%) were III–V st. gravity by *Hunt-Hess*. The decision on the need to perform angioplasty was made with the development of clinical or increasing instrumental signs of angiospasm. A favorable outcome of treatment was achieved in 74.3% of patients. An unfavorable outcome was noted in 11.4% of patients. In all cases, after an angioplasty session, a decrease in LBFV in MCA by 20–40% was observed. Among the complications of angioplasty, there was the development of systemic hypotension and bradycardia, increased intracranial pressure. In one patient, the rise in ICP was uncontrolled, which required urgent decompressive craniotomy [21].

Thus, data on the use of verapamil for chemoangioplasty in patients with chemoangioplasty rupture are quite limited and are represented by small series of single-center studies, however, all studies indicate a positive effect of this drug with minimal side effects.

Fazudil. The first clinical experience with fasudil for chemoangioplasty was presented by *Tachibana E. et al.* (1999). Intra-arterial administration of fazudil in 10 patients with angiospasm contributed to a positive angiographic effect in 9 patients out of 10, regression of neurological symptoms in 2 symptomatic patients out of 3 and was not accompanied by side effects [57].

According to *Tanaka K. et al.* (2005), chemoangioplasty fazudil in 23 patients with angiospasm due to rupture of the chemoangioplasty contributed to the regression of angiospasm in 100% of cases, clinical improvement in 44.1% of cases and a satisfactory outcome of treatment in 65.2% of cases and was safe [57].

Enomoto Y. et al. (2010) presented the results of angiospasm treatment in 23 patients with superselective intra-arterial infusions of fazudil [29]. Continuous infusion of the drug at a rate of 3 mg/min made it possible to achieve regression of the symptoms of symptomatic angiospasm in 18 out of 22 patients and was not accompanied by side effects, and an increase in the infusion rate caused the onset of convulsive syndrome.

According to *Iwabuchi S. et al.* (2011), selective intra-arterial administration of fazudil in 90 patients made it possible to resolve angiospasm angiographically in 100% of cases, being safe and effective in the treatment of patients with angiospasm [58].

However, *Ishihara M. et al.* (2012) presented a clinical observation of massive intracranial hemorrhage immediately after intra-arterial administration of fasudil [29].

Nakamura T. et al. (2013) compared superselective and nonselective administration of fasudil in 20 patients with symptomatic angiospasm, 11 patients with a similar clinical profile made up the comparison group. Fasudil chemoangioplasty was found to statistically significantly reduce the severity of myocardial infarction according to CT of the brain and the clinical outcome of treatment. Selective chemoangioplasty fasudil had greater clinical efficacy, however, the frequency of seizures in this group of patients was higher than in the control group. No other side effects were noted [59].

It can be concluded that fasudil is highly effective for chemoangioplasty in patients with symptomatic angiospasm due to chemoangioplasty rupture. Among the specific complications, the development of convulsive syndrome was noted.

Milrinone. For the first time, milrinone for intra-arterial administration in patients with ruptured aneurysms was proposed by *Arakawa Y. et al*. (2001) [60]. With combined intra-arterial and intravenous administration in 7 patients, the authors observed a positive angiographic effect in all patients. A satisfactory treatment outcome was achieved in 4 out of 7 patients [60].

Fraticelli AT et al. (2008) studied the efficacy of chemoangioplasty with milrinone in combination with intravenous infusion for 14 days in 22 patients with angiospasm due to chemoangioplasty rupture [30]. The authors observed a positive angiographic effect in all patients (in 5 cases, repeated intra-arterial infusions were required). Only 2 observations (9%) reported an unsatisfactory outcome. Among the side effects of therapy, the need for sympathomimetic support was observed in 2 cases (9%).

According to *Shankar JJ et al* . (2011), the combination of chemoangioplasty and intravenous infusion of milrinone in 14 patients made it possible to achieve satisfactory angiographic resolution of angiospasm without significant side effects [61].

There are data on the combined use of milrinone and nimodipine in patients with symptomatic angiospasm after endovascular exclusion of ruptured chemoangioplasty. *Sherif C. et al*. (2014) published the results of combined chemoangioplasty with nimodipine and milrinone in 16 patients with symptomatic angiospasm due to SAH, not amenable to conservative treatment. The authors performed a combined intra-arterial administration of milrinone and nimodipine, which allowed for regression of angiospasm in 87.5% of cases and neurological improvement in 68.5% of cases, and was not accompanied by side effects [62]. Similar data were presented by *Duman E. et al.* (2017), using a combination of nimodipine and milrinone in 25 patients after endovascular exclusion of thechemoangioplasty, complicated by the development of angiospasm. Regression of angiospasm was noted in 24 cases out of 25 (persistent neurological symptoms due to angiospasm developed in only 1 patient). Among the complications of using the technique, the authors noted the development of two episodes of tachycardia, which were stopped and did not lead to clinical deterioration [31].

Thus, there is a large amount of data in the literature on the use of milrinone for the prevention and treatment of angiospasm in patients with SAH, with many studies demonstrating the successful use of a combination of intra-arterial and systemic administration, as well as a combination with other vasodilators with minimal side effects.

Forskolin. In the literature, there are several references by one group of authors to the use of forskolin in patients with chemoangioplasty rupture for intra-arterial administration, which demonstrate preliminary clinical efficacy [32, 63, 64]. *Suzuki S. et al* . (2010) reported the results of intra-arterial forskolin in 23 patients with chemoangioplasty rupture. A positive angiographic effect was observed in 100% of patients, regression of neurological symptoms in 86%, and a satisfactory outcome of treatment in 66%. Headache and tachycardia were noted as side effects [32]. The same group of authors in 2012 presented the results of prophylactic use of papaverine and forskolin for chemoangioplasty in 231 patients with chemoangioplasty rupture. The outcome of treatment and the frequency of symptomatic angiospasm did not differ depending on the use of papaverine or forskolin. However, the authors noted that in patients with symptomatic angiospasm, forskolin therapy allowed a statistically significant improvement in treatment outcome (34% in the papaverine group, 66% in the forskolin group) and reduced the incidence of cerebral infarction according to MRI (from 85.2 to 65, 1%) [64]. We did not find other data on the use of forskolin in the literature.

CONCLUSION

Endovascular techniques for the treatment of angiospasm are effective in drug-induced "refractory" angiospasm.

Balloon angioplasty can be effective in severe proximal spasm (internal carotid artery, A1 segment of the anterior communicating artery ACA, M1 segment of the middle cerebral artery).

Chemoangioplasty is effective for more severe distal spasm.

Most of the research is devoted to the study of the effectiveness of calcium channel blockers (verapamil, nimodipine, nicardipine) and papaverine.

Chemoangioplasty with papaverine may be accompanied by a number of neurotoxic effects (seizures, uncontrolled intracranial hypertension), and therefore this drug should not be considered as a “drug of choice”.

Randomized trials are required to clarify the indications and standardize the chemoangioplasty technique.

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Received on 04/29/2020

Review completed on 06/08/2020

Accepted on 09/28/2021