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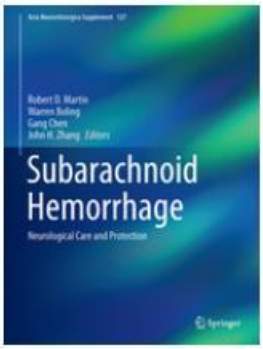

Subarachnoid Hemorrhage

Neurological Care and Protection

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Summarizes the latest studies on acute and delayed neurovascular injuries after subarachnoid hemorrhage

Covers new pilot treatments, clinical trials, academic and industrial interactions

Discusses animal models used to study acute and delayed neurovascular events

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Chapter 28: Intraarterial Administration of Verapamil for the Prevention and Treatment of Cerebral Angiospasm Mikeladze KG, Okishev DN, Belousova OB, Konovalov AN, Pilipenko YuV, Ageev IS, Kaftanov AN, Shekhtman OD, Kurdyumova NV, Tabasaransky TF, Okisheva EA, Eliava SS, Yakovlev SB

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Summary

From 2013 to 2017, at the Burdenko Institute of Neurosurgery, intraarterial verapamil for treatment of cerebral vasospasm following intracranial hemorrhage after aneurysm rupture was administered to 35 patients (total 75 procedures). The age from 8 to 77 years. All ruptured aneurysms were treated: in 26 cases with open approach – clipping, in 9 cases with endovascular occlusion. The procedure was carried out from 0-11 days after the operation. Severity of spasm was assessed by angiography and TCDU. Efficacy of the administration was assessed by TCDU one hour after the procedure, and by clinical evaluation of the patient's condition. The dose of verapamil was 15-50 mg (on average 40 mg) per procedure/per carotid pool and depended on the data of TCDU, clinical and radiological picture. The procedure was performed repeatedly (1-5 times) according to the indications and depending on the patient's condition, with an interval of 24 hours. The procedure was effective as a preventive measure for care of patients in the initial stage of cerebral ischemia and was ineffective with a formed focus of ischemia. Endovascular administration of verapamil for treatment of cerebral vasospasm is a safe technique which positively affects the overall recovery of such patients.

Key words

Intracranial aneurysm; cerebral angiospasm: verapamil; subarachnoid hemorrhage; intraarterial administration of verapamil

Introduction

One of the main complications after subarachnoid hemorrhage is a spasm of the cerebral vessels with subsequent delayed secondary ischemia of brain tissue, which significantly worsens the clinical outcome [1]. A large number of treatment options were introduced for this complication, but none of them has been very successful [2, 3]. Hence, the search for an effective method for the prevention and treatment of angiospasm still continues. In a

number of clinics intraarterial administration of vasodilator drugs, in particular verapamil (IAV), has shown some promising results. It should be noted that there is no single protocol describing the exact time of initiation of therapy, frequency of administration, exact dosing and other features of the procedure. However, the presence of sufficiently large series of patients for whom the positive effect of intraarterial administration of vasodilators has been shown enabled this method to be included in the latest guidelines for the treatment of patients after SAH (Class IIa, Level of Evidence B) [2]. In this article a retrospective series of 35 patients was analyzed, in which IAV was used.

Materials and methods

During the past 6 years (2012–2017) at the Acad. N.N. Burdenko Institute of Neurosurgery, this method (IAV) has been implemented. This paper is a retrospective analysis of the results of treatment of 35 patients who underwent one or several procedures of IAV into cerebral vessels. The criteria for inclusion into analysis were: the first (or only) IAV procedure within two weeks after the last SAH; total dose of verapamil per procedure ≥ 15 mg; follow up – not less than three months after discharge. Verapamil was intraarterially administered at the concentration of 0.25 mg / ml at an average rate of 10 ml per minute. The dosage was selected empirically and depended on the severity of vasospasm. The drug was administered in a manual mode, based on hemodynamics and in some cases on intracranial pressure monitoring data. The condition of patients before the verapamil injection was analyzed according to: the Hunt-Hess score at the time of admission, the severity of hemorrhage by Fisher's scale, the time (day) of the operation after SAH, the presence and nature of ischemic foci on CT, the patient's state according to the modified Rankin scale, the fact of the deterioration of the clinical state at the time of the procedure, and some other parameters. The following data concerning the IAV procedure were recorded: the day of the first procedure after SAH, the amount and doses administered, transcranial Doppler ultrasound (TCDU) data in dynamics, angiographic data in dynamics, parameters of hemodynamics during treatment. “Angiographic spasm” of the vessel was calculated in percentage relative to the standard average size for the internal carotid artery on both sides – 4 mm, for the middle cerebral artery on both sides –3.2 mm, for the larger anterior cerebral artery – 2.6 mm, for the main artery – 3 mm [4, 5]. In accordance, mild (0-30%), moderate (30-60%) and severe (more than 60%) angiographic spasms were differentiated [6]. The outcomes of the treatment were evaluated based on the presence of new foci of ischemia after the completion of IAV. The patient’s status was analyzed according to the modified Rankin scale at the time of discharge and more than 3 months after discharge.

Results

The average age in the analyzed group of 35 people was 46.7 ± 14.5 years (from 8 to 77 years); gender – 13 males, 22 females. In 26 cases surgery was performed, in 9 cases – endovascular intervention. All the patients analyzed in this study had an "angiographic spasm". The overwhelming majority, these were severe cases – 77.2% of patients, had III or higher grade of Hunt-Hess scale. A massive SAH, whose degree according to the Fischer scale was classified as 3-4, was observed in 90.6% of patients (see Table 1). Each patient was operated within the first two weeks. The median day of the operation was the fourth, all patients were operated at the earliest possible time. In 12 cases, primary decompression was performed during the surgical intervention, in three cases delayed decompression according to vital indications was done. In 14 patients, external ventricular drainage was used for the first few days after the operation. Ischemic foci before the IAV were observed in 8 patients; in 7 of those patients the foci were secondary to the developed angiospasm (not associated with intraoperative damage of any artery). Three patients had ischemic foci due to complete obstruction or stenosis of an arterial branch during surgery. Assessment of the clinical state of the patient by the time of the first IAV does not seem very informative, since most of the patients received some form of sedative therapy: 82.9% of patients were grade V of the modified Rankin scale. Nine patients were operated due to obvious clinical deterioration. The first IAV procedure was performed on different days within two weeks after SAH (on average 7.4 ± 3.2.days after SAH). The number of procedures ranged from one (minimum) to five (maximum). In some cases, if the condition improved after the first procedure, the next one was performed in one day or even later .The total dose of verapamil per course: the average value – 78.6 (15 to 220) mg, median 55 (32.5, 107.5) mg. In total, 75 IAV procedures were performed in all patients. The total dose of verapamil per procedure: 36.7 ± 9.7 (15 to 50) mg. In a number of cases, verapamil was administered only to the angiographically or clinically most spasmodic vascular bed, in other cases to all beds prophylactically. Administration to one bed was performed in 12 cases, to two – in 48 cases, to three – in 15 cases. Quite often typical changes in hemodynamics in the form of lowering blood pressure and bradycardia were observed. The fall of systolic blood pressure by more than 11 mm Hg and / or a decrease in heart rate by 5 beats per minute was observed in 43 cases (57.3%). A drop in the arterial blood pressure by more than 50 mm Hg was observed in 8 cases (10.7%), a decrease in heart rate by more than 20 beats / min in 8 cases (10.7%). Obviously, these reactions should be considered in view of the fact that many patients simultaneously received inotropic support. It should be noted that no complications directly related to hemodynamic fluctuations were observed. In 8 cases, invasive ICP monitoring was performed. In one case, an uncontrolled rise in ICP was observed, requiring urgent decompressive craniotomy.

In 20 cases an improvement in the neurological status was observed immediately after the IAV procedure. An analysis of angiographic spasm was possible for 30 patients, with moderate or pronounced narrowing of the lumen of the main vessels. The severity of spasm was evaluated at its worst state during the treatment period of the most affected vascular bed. Separately, the severity of spasm for MCI (M1 segment) was assessed. With repeated administration, the dynamics of angiographic spasm was evaluated in 16 cases. In 68.8% (11 cases) progression of spasm was noted, and only in 12.5% of cases (2 patients) its regression was noted as a result of procedures. At that in one of these two patients the IAV course was started on day 10, and in the other – on day 13; hence, the regress of spasm could be attributed to the natural course of the disease. In 6 cases, an angiographic control of the effectiveness of the IAV procedure was performed 30 minutes after the administration; in all the cases an increase in the diameter of the vessels was recorded to varying degrees. The effect of enlarging the lumen of the vessels was more pronounced for the most spasmodic areas. TC USDG after the procedure (approximately an hour later) showed the decrease in LCA for CMA by 20-40% (on average by 27%) in all cases, with the difference disappearing the next day. Angiographic spasm of the peripheral bed was observed in 21 patients (70%). Treatment outcomes were analyzed for all 35 patients (see Table 2). At the time of discharge, only 28.6% (10 people) had favorable outcomes. In the long-term (after the third month of observation), most patients were compensated, and favorable outcomes were noted in 74.3% of cases. New ischemic foci (delayed ischemia) after starting the IAV course occurred in 12 cases (34.3%). Of the 4 patients who died, only one died due to the progression of angiospasm, while the IAV course for him was started only after the appearance of an ischemic focus due to the progression of angiospasm. Causes of death of three other patients: postoperative ischemic changes, exacerbation of severe somatic pathology and sepsis followed by detection of pathogens on the central catheter. When comparing outcomes with different parameters, a number of clinically relevant facts were identified. There was no correlation between the immediate and distant outcomes with the severity of the condition on the Hunt-Hess scale upon admission. It should be noted that none of the three patients with the Hunt-Hess score “5” die. Out of 10 patients with a Hunt-Hess score of 4-5, in the long-term period only two patients had adverse outcomes (mRs 4-6). Eight patients underwent the IAV after the appearance of secondary ischemic foci as a consequence of angiospasm. These were quite severe patients, in the nearest postoperative period, the mRs score for each of them was at least 4,with the significant difference from the rest of the group ($p = 0.09$). In the long-term period, three of them were restored to grade 3 of mRs; nonetheless the outcomes in this group were significantly worse than in patients without secondary ischemia before IAV ($p <0.05$).

In six of these eight patients subsequently occurrence of new secondary ischemic foci or expansion of the ischemic zone was observed, which also significantly distinguishes this group of patients from other patients ($p = 0.01$). Of the 9 patients whose IAV was initiated due to the clinical worsening, only one patient had a satisfactory outcome (mRs-3). In this group of patients, there was also a significant difference in the immediate outcomes with respect to other patients ($p < 0.05$). Also, in four of these patients, secondary ischemic foci appeared after the procedure. In assessing the correlation of outcomes with angiographic data (angiographic spasm), a significantly worse outcome – by more than 70% ($p = 0.02$) – was observed in the nearest future in case of spasm of at least one vascular bed. All other attempts to detect a correlation have not yielded meaningful results. The progression of spasm in repeated angiography (11 patients) was not accompanied by a worse clinical outcome or a greater probability of secondary ischemia. We will only note here that among 8 patients with a moderate spasm only one had a secondary ischemic focus, while among 22 patients with a marked angiographic spasm secondary foci appeared in 9 patients. Of the 20 cases in which we observed angiographic spasm of peripheral vessels, 9 patients developed secondary ischemic foci after the initiation of the IAV course. Among patients without angiographic spasm of peripheral vessels, secondary ischemia did not occur in any case.

Discussion

The search for an effective method of treating angiospasm is one of the pressing problems medical science has yet to solve. To date, no conservative measures have been proposed that significantly affect the development and course of vascular spasm after SAH [2]. One of the effective methods of treating a local spasm is balloon angioplasty. However, this technique allows to eliminate only local spasms of large enough vessels, and is ineffective in case of spasm of distal vessels and has a rather high percentage of complications – up to 7% [6-8]. Intraarterial administration of drugs can provide an instantaneous maximum concentration of the drug in the area suffering from an arterial spasm, and in this connection, a number of studies assess the possibility of this particular method of treatment. For intraarterial administration, various drugs have been used in various studies: papaverine, nimodipine, nicardipine, verapamil, milrinone, fasudil, colforsin daropate [9]. The availability of verapamil, its low price, encouraging results of a number of studies with the minimum number of complications – all these factors led us to use this drug. Verapamil is an antiarrhythmic drug of Class IV according to the Vogan-Williams classification from the group of diphenylalkylamines. Verapamil also reduces the tone of the smooth muscles of the coronary and peripheral arteries, as well as the general peripheral vascular resistance and is the drug of choice for the treatment of

vasospastic angina. Half-life with intravenous injection biphasic: early – about 4 minutes, terminal – 2-5 hours. After IV introduction, antiarrhythmic effect develops within 1-5 min, hemodynamic effects (vasodilation, decrease in blood pressure) – within 3-5 min and maintained for 10-20 min [10, 11]. Little is known about the dynamic and kinetic features after the intraarterial administration. In animal experiments it has been shown that the effect of vasodilation occurs in 30 minutes [12, 13]. Due to temporary effect of vascular dilatation, a number of authors explain the positive effect after the administration of verapamil in SAH by its greater tropicity to resistive arterioles (prearterioles) [13, 14]. The intraarterial administration of verapamil for the treatment of angiospasm was first used in cardiology for the treatment of coronary artery spasm in 1988 [15]. Later, cases of intracoronary administration of verapamil in patients with acute coronary syndrome were described, leading to a statistically significant improvement in coronary blood flow [16]. For the first time, the effect of the intraarterial administration of verapamil on the cerebral blood flow was described by Joshi and co-authors in 1997 [17]. The first series of 29 patients who received the IAV course for cerebral angiospasm was published by Feng in 2002 [18]. Later 5 more original articles describing similar series of patients were published. In each of these studies the authors spontaneously chose the dose of verapamil used. The recommended dose for intravenous administration is 5-10 mg [10]. In published studies on intraarterial administration of verapamil, the dose varied from 3 to 360 mg per procedure for a different period of time. Depending on the effect of treatment, and the severity of spasm, the authors would repeat the procedure multiple times; thus, according to Jun -2010, more than half of the patients underwent repeated injections [6]. Albanese and co-authors followed a different pathway, administering a solution of verapamil with heparin for many hours [19]. In the published works, [20,21,22]. the following evidence of the effectiveness of IAV for the prevention and treatment of spasm was presented: the dilatation of arteries (especially the most spasmodic) 20-30 minutes after IAV and the relatively good results of treatment of patients using IAV. We were unable to find any article containing discussion of comparable groups treated with and without IAV. After analyzing the available data from the literature, we came to the conclusion that verapamil bolus administration is safer at a dosage of up to 20 mg per carotid bed and up to 10 mg per vertebrobasilar bed. Due to the possibility of the thromboembolic complications from the prolonged administration of verapamil, it was decided to forgo it. Thus, the maximum dose of verapamil for the procedure in our cases was 50 mg. In the case of a moderate spasm, we adhered to smaller doses, especially at the initial stage. In all 6 cases of angiographic control, after 30 minutes, the dilatation of the arterial bed was recorded with a tendency to a greater effect on the spasmodic vessels, which is consistent

with the results published in the literature. Reduction of the blood flow velocity according to the data of the TCDU was also recorded in all cases. However, both “angiographic” and “ultrasound” improvement in the vast majority of cases was not preserved the next day. Due to the obvious temporary effect of the procedure, we resorted to the repeated administration of verapamil in 60% of cases. To date, we believe that the daily IAV procedures are justified, which is at odds with the recommendations of Jun et al [6] offering treatment every 3 days. We currently consider that the risks and technical difficulties during the IAV several times a day, as well as in the case of prolonged administration of the drug through a fixed catheter exceeds the possible benefits from such treatments. The series described by us included patients with rather severe conditions: grade III or more on the Hunt-Hess scale for 77.2% of patients; SAH 3-4 degrees on the Fisher scale in 90.6% of patients. In this regard, we believe that the results obtained (satisfactory outcomes in 28.6% of cases at discharge, and in 74.3% of cases in the long-term period) indicate the effectiveness of the IAV technique. According to our data, the outcome of treatment is significantly influenced by the presence of secondary ischemic foci due to angiospasm prior to the initiation of intraarterial administration of verapamil. This is due to both the irreversibility of brain necrosis in the field of ischemia, and the limited “therapeutic power” of bolus intraarterial administration of verapamil in the case of unfolded vasospasm. This also explains the worst results of treatment for patients who began intraarterial treatment amid a worsening of the clinical condition. In this regard, in case of massive hemorrhage, we propose to perform the first intraarterial administration of verapamil to all vascular beds already on day 3 or 4 after SAH to ensure a preventive effect. Subsequent administration, in case of a stable clinical status and in the absence of acceleration of blood flow according to USDG, is permissible every other day. The further scheme of treatment, dose and catheterized vessels depend on the individual course of the disease. In the case of severe spasms, it is also acceptable to conduct IAV procedures daily. The duration of the IAV course can be up to 7-9 days. The change in the diameter of the main vessels by the time of repeated intraarterial administration of verapamil is a conditional indicator of the effectiveness of treatment. The presence of spasm of peripheral vessels is often associated with an unfavorable outcome of the disease, which requires consideration of the possible expediency of super selective catheterization for the administration of verapamil. It should be noted that the presence of secondary ischemic foci is not a contraindication to IAV; endovasal treatment can stop the progression of the disease, and favorably affect the penumbra zone. In our series, as in the published literature, the minimal controlled effect of the intraarterial administration of verapamil on systemic hemodynamics is shown. Cases of uncontrolled increase in intracranial

pressure are rare, they are described in several publications [6, 19], were also observed in our series. In this regard, with severe hemorrhages, we recommend IAV in conditions of external ventricular drainage or if a decompressive craniectomy was already performed.

Conclusion

The intraarterial administration of verapamil to cerebral vessels is a simple and safe procedure. The effectiveness of this treatment, in our opinion, is obvious but the degree of its effects is not the same for all patients. We recommend starting the IAV course as a preventive measure from 3-4 days after a massive hemorrhage. Further study and development of a protocol for the intraarterial administration of verapamil – in view of the apparent infeasibility of conducting a randomized study – requires comparison of large normalized retrospective series of patients with or without this treatment.

Conflict of interest statement

The authors declare that they have no conflict of interests

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Tables

Table 1. Distribution of patients upon admission according to the clinical status per Hunt-Hess scale and the degree of hemorrhage per Fisher scale

Hunt Hess				Fisher		
I	1	2,8%				
II	7	20%		II	3	9,4%
III	16	45,7%		III	8	25%

IV	8	22,9%		IV	21	65,6%
V	3	8,6%		No data	3	

Table 2. Immediate and long-term outcomes of treatment according to the modified Rankin scale

Modified Rankin scale	Short-term follow-up patients %			Long-term follow-up patients %		
1	1	2,9%	28,6%	9	25,7%	74,3%
2	2	5,7%		8	22,9%	
3	7	20%		9	25,7%	
4	14	40%	71,4%	2	5,7%	25,7%
5	7	20%		3	8,6%	
6	4	11,4%		4	11,4%	

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