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Hemodynamic Status and Efficacy of the Drug «Edaravon» in Acute and Chronic Disorders of Cerebral Circulation

Yu. A. Musaeva¹

ABSTRACT

Background. The article presents the results of an open longitudinal study of two parallel groups, in which the effect of the drug «Edaravon» on the clinical course of acute ischemic stroke and secondary hemodynamic effects were studied.

Material and methods. Group 1 patients (n=20) received traditional therapy for ischemic stroke and Group 2 patients (n=20) received «Edaravon» 2 times a day and traditional therapy for ischemic stroke for 10 days.

The results showed that adding «Edaravon» to conventional therapy for ischemic stroke effectively reduced cerebral oedema, which plays an important role in the processes of early and late neuronal damage.

Conclusion. Treatment contributed to a significant improvement in the clinical course of the disease, a rapid reduction of the perifocal oedema zone, which was confirmed by the reduction of neurological deficit, according to clinical scales and the results of Dopplerography.

Keywords: ischemic stroke (stroke), USDG, LVBF (linear velocity of blood flow).

INTRODUCTIONS

Up to 6 million people die from stroke every year in the world, and about 5 million remain disabled after a stroke dependent on outside help. [9]

Despite significant correlations between risk factors and stroke, the practical system of stroke prevention faces quite serious difficulties due to the multifactorial nature of the aetiology and pathogenesis of stroke. According to international epidemiological studies, stroke occupies a leading place in the structure of both mortality and disability of the population and is a serious medical and socio-economic problem for society [8,9,10].

Statistical studies conducted in a number of World Health Organization (WHO) countries, including Uzbekistan, indicate a rejuvenation of strokes and an increase

in the proportion of young women and an increase in cases of new strokes among rural residents.

The European Regional Bureau of the World Health Organization believes that the creation of a modern system of care for stroke patients will reduce mortality during the first month of the disease to 20% and ensure independence in daily life 3 months after the onset of the disease at least 70% of surviving patients.

The most common is ischemic stroke. Considering the concept of a “therapeutic window, the postponement of irreversible brain damage in acute vascular catastrophe has been proven. In ischemic stroke, the early appointment of neuroprotectors in combination with reperfusion allows us to expect a greater effect from therapy. Most often, mild and moderate are encountered, in most

¹ **Corresponding Authors:** PhD, Associate Professor of the Department of Neurology and Medical Psychology of the Tashkent Medical Academy, Tashkent, Uzbekistan. e-mail: yulduz76m@gmail.com

cases amenable to correction and recovery with the alternate appointment of appropriate therapy.”

The purpose of the study. To evaluate the effectiveness of the effect of the cytoprotection of the neuropeptide nature of edaravone on cognitive impairment in patients with ischemic stroke and chronic cerebral ischemia combined with cardiac pathology.

MATERIAL AND METHODS

To assess the effect of complex therapy with the inclusion of the drug Edaravone on the clinical course of the disease with the study of secondary hemodynamic effects in acute ischemic stroke, a clinical and neuroimaging study was conducted. Clinical observation was carried out on the basis of the Intensive Neurology department of the 1st clinic of the Tashkent Medical Academy.

The study involved 80 patients with acute ischemic stroke aged 30 to 73 years (average age 59.3 ± 6.58 years). All patients were admitted to the clinic during the acute period of the disease.

Those included in the study were divided into 2 groups. Patients of the 1st group made up the main group (40) who received edaravone by 20 ml drip for 10 days, patients of the control group (20) who did not receive edaravone in complex treatment were observed in the same order according to scales like the main group.

Neurological deficit was assessed according to the Scandinavian Scale and the NIHSS scale (National Institutes of Health Stroke Scale), computed tomography examination of the arterial and venous component of cerebral hemodynamics according to transcranial Dopplerography.

RESULTS & DISCUSSIONS

In our patients with hemispheric ischemic stroke, the clinical picture of the lesion of the carotid basin was characterized by the predominance of focal symptoms: central paresis of the VII and XII pairs of cranial nerves, the presence of mono/hemiparesis or hemiplegia, the appearance of pathological reflexes, reflexes of oral automatism in combination with sensitive disorders in the form of superficial or total mono- and hemi anaesthesia. The defeat of the dominant hemisphere was accompanied by aphotic, gnostic, and practical disorders. General cerebral symptoms were noted in patients with severe stroke: impaired consciousness and secondary dislocation stem syndrome.

The average score on the NIHSS scale was 19.3 - 1.4, on the Scandinavian scale – by 22.4%) of patients who

used Edaravon, already on the 3rd day of the disease. In patients who did not use Edaravon, by the 3rd day of the disease, the positive dynamics were statistically insignificant. (Table 1)

Table 1
Assessment of the neurological status of patients with ischemic ACA according to clinical scales in the dynamics of the disease

Scale, points	Patients with ischemic stroke				
	Before treatment (n=20)	Those who did not use edaravon (n=20)		Who used Edaravon (n=20)	
		3rd day (n=20)	10th day (n=20)	3rd day (n=20)	10th day (n=20)
NIHSS	19,3±1,4	17,5±1,6 $p_1 > 0,05$	14,7±1,5 $p_1 < 0,05$	12,1±1,2 $p_1 < 0,001$ $p_1 < 0,05$	10,4±1,3 $p_1 < 0,001$ $p_1 < 0,05$
Scandinavian scale	30,0±2,2	31,6±2,4 $p_1 > 0,05$	37,5±2,9 $p_1 < 0,05$	38,7±2,5 $p_1 < 0,01$ $p_2 < 0,05$	46,5±3,1 $p_1 < 0,001$ $p_2 < 0,05$

p_1 – reliability in relation to patients before treatment; p_2 – reliability in relation to patients who have not used Edaravon.

Comparative analysis showed that on the 10th day of the disease, the positive tendency to decrease neurological deficit was statistically significantly higher in patients receiving edaravone (see Table 1). Thus, the clinical score on the NIHSS scale decreased by 29.51%, and on the Scandinavian scale - increased by 24% ($p < 0.05$) compared to with patients not treated with Edaravon.

It was shown that in patients who did not receive Edaravon, even in the presence of positive neurological dynamics and a decrease in the hypodense zone according to computed tomography, there is a preservation or an increase in the zone of perifocal edema.

The study of cerebral hemodynamics was carried out with an assessment of the effect of Edaravon on the arterial (middle cerebral artery (MCA), anterior cerebral artery (PMA), posterior cerebral artery (PCA), main artery (CCA)) and venous (internal jugular vein (VJI)) components.

Analysis of the results showed that signs of asymmetry of blood flow with hypoperfusion in the affected basin prevail statistically significantly ($p < 0.05$) in hemispheric stroke (Table 2).

Local change in blood flow velocity with signs of turbulence, as well as a moderate increase in linear blood

flow velocity (LVBF) by PMA, significantly increasing with compression of the contralateral common carotid artery (CCA) and a significant increase in the LVBF of the PCA during compression of the homolateral CCA with a decrease in the response of the MCA in response to the compression test were observed in 45.71%.

Table 2
Dopplerographic indicators of intracranial hemodynamics in the examined patients

Groups of surveyed	Arteries		Parameters			
			LSK, cm/s	PI	RI	
Control (n=30)	MCA	Left	86,4±8,2	0,85±0,12	0,55±0,11	
		Right	84,2±8,4	0,82±0,11	0,53±0,11	
	ACA	Left	73,6±4,3	0,84±0,13	0,53±0,15	
		Right	72,6±4,2	0,87±0,13	0,52±0,15	
	PCA	Left	63,2±7,5	0,84±0,12	0,55±0,16	
		Right	60,4±7,8	0,80±0,14	0,52±0,18	
	CCA		56,8±4,6	0,80±0,12	0,49±0,15	
Edaravon recipients: before (numerator) and after (denominator) treatment	MCA	Left	63,4±6,4* 85,5±5,5	1,19±0,12* 1,02±0,14	0,96±0,15* 0,72±0,08	
		Right	60,9±6,2* 83,3±5,3	1,14±0,13* 0,88±0,06	0,95±0,18* 0,76±0,06	
	ACA	Left	58,4±6,5* 72,6±5,2	1,27±0,15* 0,85±0,08	0,94±0,13* 0,71±0,05	
		Right	57,3±6,3 74,2±6,3	1,26±0,14* 1,04±0,13	0,92±0,13* 0,73±0,09	
	PCA	Left	48,8±4,5 55,4±6,8	1,22±0,13* 1,01±0,15	0,97±0,12* 0,85±0,12	
		Right	49,6±4,7 56,9±7,1	1,20±0,12* 1,02±0,14	0,96±0,12* 0,87±0,13	
	Those who did not receive Edaravon (n=20): before (numerator) and after (denominator) treatment	MCA	Left	62,5±5,2* 71,5±4,3 ₁	1,17±0,13* 1,12±0,13	0,99±0,14* 0,95±0,07 ₁
			Right	61,6±5,4* 69,3±4,4 ₁	1,15±0,12* 1,13±0,10 ₁	0,94±0,15* 0,92±0,05 ₁
		PCA	Left	57,3±6,3* 58,4±4,7 ₁	1,25±0,14* 1,12±0,11 ₁	0,92±0,14* 0,87±0,05 ₁
			Right	59,2±6,2 64,6±6,3	1,24±0,15* 1,14±0,12	0,93±0,15* 0,81±0,13
		ACA	Left	45,7±4,3 50,1±5,4	1,23±0,12* 1,00±0,17	0,94±0,13* 0,88±0,15
			Right	47,2±4,5 52,3±5,1	1,21±0,13* 1,01±0,16	0,95±0,14* 0,89±0,13
CCA			40,3±3,7* 36,7±4,5	1,16±0,13* 1,09±0,14	0,91±0,12* 0,87±0,14	

$p < 0.05$, and the reliability of indicators in relation to those who received edaravon: $1 - p < 0.05$.

In 26.15% of patients with ACA against the background of hypertension, a moderate increase in LVBF with an increase in the index of peripheral resistance and vascular tone was registered (Table 2).

In 32% of patients of this group, the source of collateral circulation was the pool of the contralateral PMA.

In these patients, the blood flow rate in the supra-block artery did not change during compression of the same-named CCA, which indicated that the distal part of the internal carotid artery was filled from another source of blood circulation and confirms the presence of collateral circulation at the intracranial level.

In a smaller number (5%) of patients, the arteries of the vertebrobasilar basin were the source of blood circulation. The magnitude of the antegrade direction of blood flow in the supratrochlear artery did not change with sequential compression of both CCAs.

The study of the venous component of cerebral blood flow indicates the presence of signs of difficulty in venous outflow from the cranial cavity associated with general hemodynamic changes against the background of ACA. Patients showed signs of a decrease in LVBF and average blood flow rate (by >26%) with a decrease in peripheral indices ($p < 0.001$), a violation of the phase curve, indicating an overflow of the venous system with difficulty in blood outflow (Table 3).

Table 3
Indicators of blood flow in the VJI in the examined

Parameters		Control group (n=30)	Those who received edaravone (n=20), before treatment	Those who did not receive Edaravon (n=20)
LVBF, cm/s	Right	27,8±1,05	20,5±1,02* 28,3±1,05	21,5±1,03* 24,2±1,04 ₂
	Left	25,3±1,01	22,6±0,98* 27,5±1,08	22,4±0,99* 24,3±1,06 ₁
PI	Right	0,75±0,04	0,55±0,03* 0,72±0,01	0,57±0,02* 0,67±0,02 ₁
	Left	0,76±0,02	0,52±0,04* 0,75±0,02	0,56±0,03* 0,67±0,03 ₁
RI	Right	0,47±0,03	0,35±0,02* 0,51±0,01	0,33±0,02* 0,45±0,02 ₂
	Left	0,45±0,02	0,33±0,01* 0,53±0,01	0,35±0,01* 0,40±0,03 ₁

The reliability of indicators in relation to the norm: *—

*The reliability of indicators in relation to the norm: * – $p < 0.001$, the reliability of indicators in relation to those who received Edaravon 1 – $p < 0.05$; 2 – $p < 0.01$.*

A dynamic study of cerebral hemodynamics showed that when Edaravon was included in therapy for ischemic ACA, there was a statistically significant improvement in the arterial and venous components of cerebral blood flow. Thus, in patients receiving Edaravon, LVBF significantly increased with a decrease in vascular tone and peripheral resistance (see Table. 2), indicating an improvement in arterial perfusion in brain tissue. Simultaneously with the improvement of the arterial component of cerebral hemodynamics, venous outflow also improved, which was expressed in a significant increase in LVBF and average blood flow velocity with an increase in venous tone — indicators PI (pulsation index) and RI (resistance index) (Table. 3), due to the venotonizing properties of edaravon. Serious side effects of the use of Edaravon, requiring the withdrawal of the drug, were not noted.

CONCLUSION

Thus, the results of the study showed that the use of Edaravon effectively reduces cerebral edema, which plays an important role in the processes of early and late neuronal damage in acute ischemic stroke. The use of Edaravon is accompanied by a significant improvement in the clinical course of the disease, a rapid decrease in the zone of perifocal edema, which is confirmed by a decrease in the severity of neurological deficit, according to clinical scales and computed tomography. Edaravone exhibits a pronounced ability to bind reactive oxygen species and free radicals, including peroxynitrite. The use of Edaravon improves effective intracerebral blood flow because of improved venous outflow, which, in turn, improves arterial perfusion of the brain.

ETHICAL STANDARDS OF RESEARCH – the authors declare that all studies were reviewed and approved by the Bioethics Committee of the Ministry of Health of the Republic of Uzbekistan. All patients gave written informed consent to participate in the study.

CONFLICT OF INTEREST - The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT - The original contributions presented in the study are included in

the article material, further inquiries can be directed to the corresponding authors.

CONSENT FOR PUBLICATION - The study is valid, and recognition by the organization is not required. The authors agree to open the publication.

AVAILABILITY OF DATA AND MATERIAL - Available

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**EDARAVON PREPARATINING MIYA QON AY-
LANISHINING O'TKIR VA SURUNKALI KASAL-
LIKLARIDA SAMARADORLIGI VA GEMODI-
NAMIK HOLATI**

**Musaeva Yulduz Alpisovna
Toshkent Tibbiyot Akademiyasi
ABSTRAKT**

Dolzarbligi. Maqolada Edaravon preparatining o'tkir ishemik insultning klinik kechishiga va ikkilamchi gemodinamikaga ta'siri o'rganilgan ikkita parallel guruhning ochiq tadqiqot natijalari keltirilgan.

Material va tadqiqot. 1-guruhdagi bemorlar (n=20) ishemik insult uchun an'anaviy terapiya, 2-guruhdagi bemorlar (n=20) kuniga 2 marta Edaravon va 10 kun davomida ishemik insult uchun an'anaviy terapiya oldilar.

Natijalar shuni ko'rsatdiki, ishemik insultning an'anaviy terapiyasiga edaravon qo'shilishi erta va kech neyron shikastlanish jarayonlarida muhim rol o'ynaydigan miya shishini samarali ravishda kamaytiradi.

Xulosa. Davolash kasallikning klinik kechishini sezilarli darajada yaxshilashga, perifokal shishlar maydonining tez pasayishiga yordam berdi, bu klinik shkalalar va Doppler ultratovush tekshiruvi natijalariga ko'ra nevrologik etishmovchilikning pasayishi bilan tasdiqlandi.

Tayanch iboralar: ishemik insult(II), UTDG, QOCHT(qon oqimining chiziqli tezligi)

**СОСТОЯНИЕ ГЕМОДИНАМИКИ И
ЭФФЕКТИВНОСТЬ ПРИМЕНЕНИЯ
ПРЕПАРАТА ЭДАРАВОН ПРИ ОСТРЫХ И
ХРОНИЧЕСКИХ НАРУШЕНИЯХ МОЗГОВОГО
КРОВОБРАЩЕНИЯ**

**Мусаева Юлдуз Алписовна
Ташкентская Медицинская Академия
АБСТРАКТ**

Актуальность. В статье представлены результаты открытого продольного исследования двух параллельных групп, в котором изучено влияние препарата Эдаравон на клиническое течение острого ишемического инсульта и вторичные гемодинамические эффекты.

Материалы методы. Больные 1-й группы (n=20) получали традиционную терапию при ишемическом инсульте, 2-й группы (n=20) – препарат Эдаравон 2 раза в сутки и традиционную терапию при ишемическом инсульте в течение 10 дней.

Результаты показали, что добавление Эдаравон к традиционной терапии при ишемическом инсульте эффективно уменьшает отек головного мозга, играющий важное значение в процессах раннего и позднего нейронального поражения.

Заключение. Лечение способствовало значительному улучшению клинического течения заболевания, быстрому уменьшению зоны перифокального отека, что подтверждено уменьшением неврологического дефицита, по данным клинических шкал и результатам доплерографии.

Ключевые слова: ишемический инсульт, УЗДГ, ЛСК (линейная скорость кровотока).