Dobrovolskyi V. V., Stoyanov O. M., Mashchenko S. S. Possibility of therapy of acute ischemic stroke by polyphenols of flavonoid group. Journal of Education, Health and Sport. 2019;9(1):388-395. eISNN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.2579346 http://ojs.ukw.edu.pl/index.php/johs/article/view/6639

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part B item 1223 (26/01/2017).
1223 Journal of Education, Health and Sport eISSN 2391-8306 7

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 03.01.2019. Revised: 11.01.2019. Accepted: 31.01.2019.

POSSIBILITY OF THERAPY OF ACUTE ISCHEMIC STROKE BY POLYPHENOLS OF FLAVONOID GROUP

V. V. Dobrovolskyi, O. M. Stoyanov, S. S. Mashchenko

Department of Neurology, Odessa National Medical University, Odessa, Ukraine

Abstract

Objective - to study neuroprotective effect of Quercetin in ischemia-reperfusion injury in acute ischemic stroke.

Materials and methods. The study included 98 patients with acute ischemic stroke. All patients: main and control group, received standard treatment in accordance with the clinical protocol order Ministry of Health of Ukraine from 03.08.2012, № 602. Patients of the main group (n=68) on the back of the base further treatment was administered quercetin (Corvitin lyophilisate injection solution) course of 10 days according to the scheme: 500 mg of the drug diluted in 100 ml of 0.9% of the physiological solution intravenously twice a day for the first five days and once a day for the next five days. Patients in the control group (n=30) - quercetin is not appointed. Assessment by GCS, NIHSS, Barthel served in the 1st, 3rd, 5th, 10th day of the disease.

Results. Simultaneously with the standard treatment, intravenous administration of quercetin, positively influenced the regression of focal neurological symptoms on the NIHSS and Barthel scales in patients with acute ischemic stroke, increased the proportion of patients in the consciousness or with its minor impairments in the GCS, ie contributed to an earlier “awakening” in acute ischemic stroke.

Conclusions. Neuroprotective effect of quercetin (Corvitin lyophilisate injection solution) can be explained by its polytropic, antioxidant, anti-inflammatory, membrane-stabilizing effect in ischemia-reperfusion.

Keywords: **stroke, reperfusion injury, quercetin.**

ВОЗМОЖНОСТИ ТЕРАПИИ ОСТРОГО ИШЕМИЧЕСКОГО ИНСУЛЬТА ПОЛИФЕНОЛАМИ ФЛАВОНОИДНОЙ ГРУППЫ

В. В. Добровольский, О. М. Стоянов, С. С. Мащенко

Кафедра неврологии, Одесский национальный медицинский университет, Одесса, Украина

Цель - изучить нейропротекторное действие кверцетина при ишемически-реперфузионном повреждении в остром периоде ишемического инсульта.

Материалы и методы. В исследование были включены 98 пациентов с острым ишемическим инсультом. Все пациенты: основная и контрольная группа, получавшие стандартное лечение в соответствии с клиническим протоколом приказа Минздрава Украины от 03.08.2012 г. № 602. Пациентам основной группы (n = 68) назначали кверцетин в дозе 500 мг, разведенный в 100 мл 0,9% физиологического раствора внутривенно капельно два раза в день в течение первых пяти дней и один раз в день в течение следующих пяти дней. Пациентам контрольной группы (n = 30) - кверцетин не назначается. Оценка по ШКГ, NIHSS, Barthel служила в 1-й, 3-й, 5-й, 10-й день заболевания.

Результаты. Одновременно со стандартным лечением, внутривенное введение кверцетина, положительно влияло на регрессию очаговых неврологических симптомов по шкалам NIHSS и Barthel у пациентов с острым ишемическим инсультом, увеличивало долю пациентов в сознании или с его незначительными нарушениями по ШКГ, т.е. способствовало более раннему «пробуждению» при остром ишемическом инсульте.

Выводы. Нейропротективный эффект кверцетина (раствор для инъекций лиофилизата корвитина) можно объяснить его политропным, антиоксидантным, противовоспалительным, мембраностабилизирующим действием при ишемии-реперфузии.

Ключевые слова: **инсульт, реперфузионное повреждение, кверцетин.**

Introduction

One of the main goals of treatment of ischemic stroke - the restoration of blood flow in the ischemic area of the brain to maintain its viability, it was found that the production of reactive oxygen species increased. The results of reperfusion can be detrimental, since oxidative stress is quickly replaced by reoxygenation [1]. Reperfusion can be associated with an early increase in the blood-brain barrier permeability and, consequently, with secondary reperfusion injury, and an unfavorable outcome [2]. Reperfusion injury of ischemic tissues was first described by cardiologists in cases of successful thrombolytic therapy of acute myocardial infarction due to recanalization of thrombosed coronary artery. It can manifest itself in the form of reperfusion arrhythmias, which are often fatal (ventricular fibrillation), myocardial stunning phenomena, microvasculature vascular injury and the absence of coronary blood flow restoration at the tissue level (no-reflow phenomenon), accelerated development of necrosis cardiomyocytes whose function was disrupted by previous ischemia [3, 4, 5]. With the introduction into neurological practice of thrombolytic therapy of acute ischemic stroke, the problem of protecting the brain (ischemic "penumbra" zone) from reperfusion injury is becoming more urgent. The development of such damage is based on interrelated and complementary mechanisms: adverse effects of reoxygenation of ischemic tissue with the formation of free oxygen radicals ("oxygen paradox"), excessive intake of calcium ions from the extracellular space into the cell, followed by a disturbance of mitochondrial function, a decrease in adenosine triphosphate production, and a progressive increase in the zone necrosis ("calcium paradox"), mechanical damage to cells during the restoration of blood flow [6, 7].

The data of experimental and clinical studies of recent years indicate the possibility of preventing reperfusion injury in cardiology with the use of drugs that have membrane-protective properties (trimetazidine, quercetin) prior to thrombolysis, which leads to the limitation of the necrosis zone, increased electrical stability of the myocardium and, consequently, occurrence of fatal complications.

Quercetin is a modulator of enzyme activity. At the heart of biochemical and pharmacological effects of quercetin is a selective inhibitory effect on a number of important enzymes of the cell, which makes it possible to place it in a series of specific bioregulators of many enzyme processes [8]. Probably the inhibitory effect of quercetin is due to its ability to

bind to active ATP-binding sites of enzymes such as protein kinases, mitochondrial ATPases, myosin, Na+/K+ and Ca2+ plasma ATPases, topoisomerase II. Another important property of quercetin, and its metabolites, is participation in intercellular transport, due to activity with respect to ATP-dependent transport P-glycoproteins [9, 10, 11].

Quercetin has antioxidant properties due to the ability to inhibit lipoxygenase and cyclooxygenase, inhibiting the excessive formation of leukotrienes [12].

There is every reason to believe that inhibition of enzymes such as phospholipase A2 and lipoxygenase, as well as slowing of prooxidant processes, are the most important links in the pathogenetic therapy of ischemic stroke in the acute period and prevention of reperfusion syndrome.

Excess of active forms of oxygen acts as a cause of destruction of membranes, violation of permeability of barriers, death of brain cells, expansion of the necrosis zone. In this regard, the use of drugs with antioxidant properties for cerebroprotection is pathogenetically justified. The above data indicate the need to search for new optimal approaches that significantly reduce the risk of development of reperfusion injury in the acute period of ischemic stroke.

Materials and methods

The study included 98 patients from the Odessa Regional Clinical Hospital in the acute period of ischemic stroke.

The criteria for including patients in the study were:

- Age not older than 85 years;
- The sudden emergence of focal neurological symptoms, characteristic of the lesions of both the carotid and vertebrobasilar blood supply reservoirs of the brain, lasting more than 24 hours;
- Excluded hemorrhagic character of stroke on CT;
- First diagnosed ischemic stroke;
- Absence of diseases on account of which it was possible to attribute this clinical exacerbation and the appearance of neurologic symptoms.

The exclusion criteria were:

- The presence of a previous history of a stroke;
- The level of impaired consciousness on the Glasgow scale is less than 7 points;
- Duration of neurologic focal symptoms is less than 24 hours;
- Oncological diseases.

The diagnosis of ischemic stroke was established according to the standard method based on the analysis of the clinical picture, the history and additional examination methods (instrumental (computed tomography, magnetic resonance imaging, duplex scanning of the main arteries of the head and neck), laboratory). The neurological status was assessed by the Glasgow Coma Scale, according to Teasdale G.M., Jennett W., 1974, the NIHSS scale (Stroke Scale of the National Institutes of Health, Brott T. et al., 1989), the Barthel Daily Activity Index F. Mahoey, D. Barthel, 1965, S. Granger et al., 1979, D. Wade, 2000) 24 hours after the onset of the stroke, and then on days 3, 5 and 10.

All patients, the main and control groups, received standard treatment (support of respiratory and cardiovascular activity, correction of hypertension and hyperglycemia, infusion therapy), thrombolytic or anticoagulant therapy, treatment of cerebral edema, symptomatic therapy (in accordance with the clinical protocol of the Ministry of Health of Ukraine No. 602 of 03.08.2012).

In the main group, basal treatment was additionally assigned to Quercetin (Corvitin lyophilisate injection solution) with a course of 10 days according to the scheme: 500 mg of the drug diluted in 100 ml of 0.9% physiological solution intravenously twice a day for the first five days and once a day for the next five days. Quercetin was not assigned to the control group. The statistical treatment was carried out using the t-test of the Student ($p<0.05$). Differences were considered reliable at a significance level of $p <0.05$.

Results

When assessing the results of treatment in the study and control groups, there was a positive dynamics in the recovery of consciousness, regression of focal neurological symptoms.

Table 1. Main demographic and clinical characteristics of patient groups

Index	Main group (N = 68)	Control group (N = 30)
1	2	3
Age (years)	70,3±5,2	69,5±7,2
Male	47,06% (32)	46,7% (14)
Female	52,94% (36)	53,3% (16)
Hypertonic disease	77,9% (53)	83,3% (25)
Atrial fibrillation	39,7% (27)	33,3% (10)
Diabetes	14,7% (10)	10% (3)
Hypercholesterolemia	79,4% (54)	93,3% (28)
The subtype of ischemic stroke according to the TOAST criteria (Adams H.P. et al, 1993)		

1	2	3
Cardioembolic	*38,2% (26)*	*33,3% (10)*
Atherothrombotic	*52,9% (36)*	*56,7% (17)*
Lacunar	*8,8% (6)*	*10% (3)*
Stroke in the carotid zone	77,9% (53)	80% (24)
Stroke in the vertebrobasilar zone	22,1% (15)	20% (6)
Glasgow Coma Scale	9,2±1,2	9,8±1,6
NIHSS	11,3±1,4	10,2±2,1
Barthel's index	28,4±1,5	32,1±2,2

The dynamics of patients' condition for 10 days is reflected in Table 2.

In patients of the main group, starting from the 5th day, a more pronounced effect of normalizing the level of consciousness was noted. Significant differences were also revealed in the dynamics of recovery of the neurological deficit.

Table 2. Dynamics of average total indicators on different scales

Time of examination after a stroke onset	Glasgow Coma Scale		NIHSS		Barthel's index	
	Main group	Control group	Main group	Control group	Main group	Control group
24 hours	9,5±1,4	9,8±1,6	11,3±1,4	10,2±1,1	29,4±2,4	32,1±2,2
3rd day	11,5±1,6	11,2±1,0	8,7±1,6	9,5±1,2	53,1±1,6	51,8±1,4*
5th day	13,2±0,8*	11,8±0,6*	6,5±0,9*	7,9±1,0*	63,7±1,6*	59,4±1,2*
10th day	14,3±0,9*	12,4±1,1*	5,2±1,1*	7,6±1,3*	73,1±1,4*	70,4±1,5*

* $p<0,05$.

The best recovery of neurological deficit with the use of quercetin was observed in patients who underwent lacunar or atherothrombotic stroke, in comparison with cardio-embolic (Table 3).

Table 3. Dynamics of mean total values on the scale of NIHSS in patients with different subtypes of ischemic stroke in the main group

Time of examination after a stroke onset	The subtype of ischemic stroke			
	cardio-embolic	atherothrombotic	lacunar	The total (average) indicator
5th day	8,2±1,1	6,2±0,9	5,0±0,8	6,5±0,9*
10th day	6,1±1,1	4,9±1,1	4,5±1,1	5,2±1,1*

* $p<0,05$.

Discussion

In our study, there were no undesirable events, side effects of the treatment. The results of the study indicated a positive dynamics of regression of the neurological deficit according to the NIHSS scores and the Barthel index, the effect of an earlier "awakening", i.e. increase in the main group of the proportion of patients in consciousness or with a mild degree of its violation on the Glasgow coma scale, starting from the 5th day, in comparison with the control group of patients. The neuroprotective effect of quercetin can be explained by its polytropic, antioxidant, anti-inflammatory, membrane-stabilizing action under ischemia-reperfusion conditions.

Conclusions

Intravenous administration of quercetin (Corvitin lyophilisate injection solution) at the same time as standard treatment with a course of 10 days according to the scheme: 500 mg of the drug diluted in 100 ml of 0.9% of the physiological solution intravenously twice a day for the first five days and once a day for the next five days, positively affects the regression of focal neurologic symptoms on the NIHSS and Barthel index scales in patients in the acute period of ischemic stroke. The use of quercetin allows increasing the proportion of patients in consciousness or mild degree of its violation on the Glasgow scale, i.e. cause an earlier "awakening" in the acute period of an ischemic stroke.

References

1. Lobusheva N.V., Tonshin A.A., Selin A.A., Yaguzhinsky L.S., Nartsissov Y.R. Diversity of neurodegenerative processes in the model of brain cortex tissue ischemia. Neurochem. Int. - 2009, Vol. 54 (5-6). - P. 322 - 329.

2. Podoprigora G.I., Nartissov Y.R., Aleksandrov P.N. Effect of glycine on microcirculation in pial vessels of rat brain. Bull. Exp. Biol. Med. – 2005, Vol. 139 (6). – P675 – 677.

3. David G., Maiisol R. et al. Lethal reperfusion injury in acute myocardial infarction: facts and unresolved issues // Cardiovascular Research. – 2009. – Vol. 83. – P. 165 - 168.

4. Majidi M., Kosinski A.S. Reperfusion ventricular arrhythmia 'bursts' predict larger infarct size despite TIMI 3 flow restoration with primary angioplasty for anterior ST-elevation myocardial infarction // Eur. Heart J. – 2009. – Vol. 30 (7). – P. 757 – 764.

5. Reffelmann T., Kloner R. The «no-reflow» phenomenon: basic science and clinical correlates // Heart. – 2002. – Vol. 87. – P.162 – 168.

6. David R. Van Wagoner, Meredith Bond. Reperfusion Arrhythmias: New insights into the role of the Na+/Ca2+ Exchanger // J. Mol. Cell. Cardiol. – 2001. Vol. 33. – P. 2071 – 2074.

7. Subodh V., Paul W.M. Fundamentals of Reperfusion Injury for the Clinical Cardiologist // Circulation. – 2002. – Vol. 105. – P. 2332 – 2336.

8. Slesarchuk V.Yu. Neyroprotektivnyie svoystva preparatov kvertsetina. // FarmakologIya ta lIkarska toksikologIya. – 2014. - #6 (41). – S. 11 – 18.

9. Chow pharmacokinetics and modeling of quercetin and metabolites / Xiao Chen, Ophelia Q. P. Yin, Zhong Zuo, Moses S. S. // Pharmac. Res. – 2005. – Vol. 22 (6). – P. 892 – 901.

10. Murata K. Antioxidative flavonoid quercetin: implification of intestinal absorption and metabolism / Murata K., Terao J. // Arch. Biochem. Biophys. – 2003. –Vol. 417. – P. 12 – 17.

11. Youdim K. A. Flavonoids and the brain: interactions at the blood-brain barrier and their physiological effects on the central nervous system / K. A. Youdim, B. Shukitt-Hale, J. A. Joseph // Free Radical Biol. Med. – 2004. – Vol. 37 (11). – P. 1683 – 1693.

12. Baraboy V. A. Bioantioksidantyi / V. A. Baraboy. – K. : Kniga plyus. – 2006. – 461 s.