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PRACA KAZUISTYCZNA/CASE REPORT

Neurorehabilitation in the Early Recovery Period of Ischemic Stroke. Pharmacology Support

Neurorehabilitacja we wczesnym okresie udaru niedokrwiennego mózgu. Wsparcie farmakologiczne

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Denys N. Khramtsov[1], Olexandr N. Stoyanov[1], Tetiana N. Muratova[1], Olexandr R. Pulyk[2]

[1]Odessa National Medical University, Odesa, Ukraine
[2]Uzhhorod National University, Uzhhorod, Ukraine

SUMMARY

Aim: The aim of the study was to evaluate the clinical outcome in the use of neuroprotective agents in the acute period of ischemic stroke.
Material and Methods: The study was performed on the basis of the stroke of the Center for Reconstructive and Rehabilitation Medicine (University Clinic) of the Odessa National Medical University. A retrospective analysis of clinical outcomes of 115 patients with acute stroke was conducted.
Results: An average NIHSS score at discharge was 4.1±0.1 points when treated with no refinery, then it reached 3.6±0.1 points when using peptidergic drugs, and 3.4±0.1 when using D-fdf. 3.1±0.1 points. When using D-FDF, the MMSE score was 3.5±0.1 points, whereas when using cholinergic agents, this index did not exceed 26.9±1.5 points, and when using peptidergic agents - 26.8±1.4 points.
Conclusion: The use of neuroprotective agents positively affects the effectiveness of neuro-rehabilitation in patients with acute stroke. The best results in three months after the hospitalization were obtained for peptidergic agents and D-fructose-1,6-diphosphate.

Key words: stroke, neuroprotection, neurorehabilitation, treatment

STRESZCZENIE

Cel: Celem badania klinicznego była ocena efektywności rehabilitacji poudarowej przy dołączeniu środków neuroprotekcyjnych w ostrym okresie udaru niedokrwiennego mózgu.
Materiał i metody: Badanie przeprowadzono na oddziale udaru mózgu Centrum Medycyny Rekonstrukcyjnej i Rehabilitacyjnej (Klinika Uniwersytecka) Narodowego Uniwersytetu Medycznego w Odessie. Przeprowadzono analizę retrospektywną wyników klinicznych u 115 pacjentów z udarem mózgu.
Wnioski: Udowodniono, że stosowanie środków neuroprotekcyjnych ma pozytywny wpływ na skuteczność neurorehabilitacji pacjentów po udarze. Trzy miesiące po hospitalizacji najlepsze wyniki uzyskano u pacjentów ze wsparciem lekami peptydergicznymi i D-fruktozo-1,6-difosforanem.

Słowa kluczowe: udar mózgu, neuroprotekcja, neurorehabilitacja, leczenie

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INTRODUCTION

According to WHO, stroke remains the second most common cause of death (12% of all deaths) and the leading cause of disability. In 2013, nearly 6.5 million people died from stroke in the world, and in ten years the number of stroke deaths will increase to 7.8 million per year [1]. After a stroke, a third of patients die within the first year and about a third of patients remain dependent on outside help forever. Due to the severe socio-economic impact of a stroke, the prevention and treatment of acute cerebrovascular pathology in the majority of developed nations are formally recognized as a priority for health [1, 2].

According to the indicators of incidence of acute disorders of cerebral circulation and mortality from stroke, Ukraine ranks as one of the first places in Europe (Fig. 1). According to official statistics, 100-110 thousand cases of stroke occur every year (more than a third of them are of working age patients) [2]. The death rate reaches 138.0 cases per 100,000 population, which corresponds to close to 55,500 deaths per year [1-3].

Since the late 1990s, the Stroke Unit has been the "gold standard" for stroke care [4-6]. The priority for organizing and expanding the stroke block network in Europe was proclaimed by the Helsingborg Consensus in 1996 and 2006

and the recently approved Munich Consensus 2018, which adopted a plan for action to prevent and treat stroke by 2030, with final approval expected in May 2020. According to this document, by 2030, the absolute number of new stroke cases in Europe should be reduced by 10%, and at least 90% of all patients with stroke should receive first-line care in stroke units [3] (Figure 1).

The pathophysiology of ischemic stroke is complex and has not yet been sufficiently studied [7]. With a prolonged reduction of cerebral perfusion, irreversible ischemic damage to brain tissue develops. The zone of the nucleus of the infarction of the brain is surrounded by ischemic tissue – the area of the penumbra, in which energy metabolism is still preserved, but functional changes of neurons are already being occurred. Under unfavorable conditions, the infarction zone may increase than brain edema raises. Both cytotoxic and ionic mechanisms, as well as vasogenic swelling, play a role in the development of edema. Against this background, the processes of glutamate and calcium-induced excitotoxicity are realized, the processes of lipid peroxidation are enhanced, the production of nitric oxide and free radicals is increased. Activation of glia ischemia results in a secondary local inflammatory process that enhances the permeability of the blood-brain barrier. The described changes are accompanied by activation of apoptosis [7, 8]

The management of patients after acute stroke involves the use of a whole range of different medical methods, including drug therapy, at all stages of the rehabilitation process, starting with the acute period of the disease, when the patient's rehabilitation potential is largely determined. As the process of stroke recovery is multicomponent and multidisciplinary, drug therapy consists of basic (correction of essential vital functions) and reperfusion therapy (use of anticoagulants, antiplatelet agents and tissue plasminogen activators); neuroprotection (prevention, interruption and reduction of adverse effects on the brain), as well as secondary prevention and treatment of post-stroke conditions, along with neurorehabilitation measures [9].

The results of numerous clinical trials have led to a change in the concept of neuroprotection in stroke. Any measures aimed at reducing neuronal losses in acute ischemic stroke (reperfusion, antithrombotic agents, normalization of physiological functions) can be considered as indirect neuroprotection [9, 10]. In a more narrow sense, neuroprotection is considered to be the use of drugs that act directly on brain cells (cytoprotection) and can play an independent role in the treatment of ischemic stroke in the acute stage [10, 11, 12, 13]. However, the clinical efficacy of various neuroprotective agents is still a matter of debate [5, 9].

AIM

The aim of the study was to evaluate clinical outcomes with the use of non-protective agents in the acute ischemic stroke period.

MATERIAL AND METHODS

The study was performed at the stroke unit of the Center for Reconstructive and Rehabilitation Medicine (University Clinic) of the Odessa National Medical University. A retrospective analysis of clinical outcomes of 115 patients treated for ischemic stroke during 2017-2019 was conducted. Inclusion criteria:

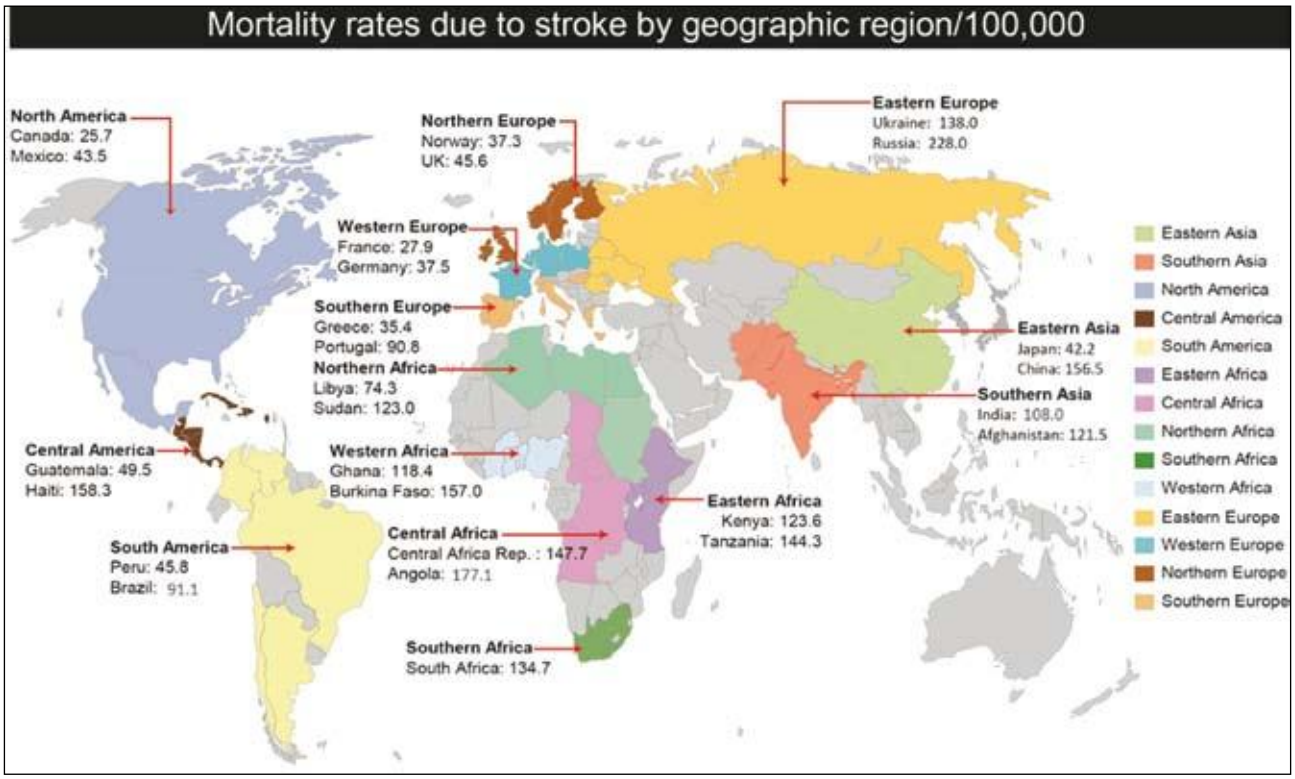

Figure 1. Stroke Mortality in the World (WHO, 2017) [5]

NIHSS at the time of admission - 5-15 points, consent to participate in the study. Exclusion criteria: severe stroke, multiple organ failure, presence of severe comorbidity, hyperphosphatemia, refusal to participate in the study.

Treatment efficacy was evaluated by changes in NIHSS and mRS at the time of discharge, and further evaluated the dynamics of indicators on the MMSE and CGI-I scales after three months [14]. Statistical processing was performed using the non-parametric Wilcoxon-Mann-Whitney test using the Statistica 13.0 software (TIBCO, USA) [15].

RESULTS AND DISCUSSION

The average age of the patients who participated in the study was 56.2±1.8 years. Among the patients, men (65 or 56.5%) were slightly predominant, 50 were women (43.5%). The average NIHSS score at the time of admission was 12.2±0.9 points. The level of adaptive capacity of the body in patients was significantly reduced - an average of 2.1±0.1 per mRS. Symptoms of moderate cognitive deficits were found in 36.5% of patients, the mean MMSE score was 24.6±1.2.

According to the medical records, the majority of patients received certain neuroprotective drugs (Figure 2), including peptidergic (cerebrolysin, actovegin, cortexin, cerebrocurin), cholinergic (cyticolin, choline alfoscerate), macroergic precursors (D-fructose-1,6-diphosphate, D-FDP). Only 9.6% of patients did not have prescriptive medications in their appointments, infusion therapy contained predominantly volumetric controls, as well as drugs for the correction of electrolyte exchange disorders and, if necessary, antihypertensive agents.

When evaluating the effectiveness of treatment, depending on the type of used neuroprotective compounds (Table 1), it was found that in three months after hospitalization the best results were obtained with the use of peptidergic agents and D-FDP.

Thus, if the average NIHSS score at discharge was 4.1±0.1 points when treated with no refinery, then it reached 3.6±0.1 points when using peptidergic drugs, and 3.4±0.1 when using D-fdf. 3.1±0.1 points. As for the mRS score, it was virtually indistinguishable in patients receiving different neurorehabilitation treatment (p>0.05), which may be explained by the small number of observations.

The effect of drug neuroprotection on the level of cognitive deficits is noteworthy. When using D-FDF, the MMSE score was 3.5±0.1 points, whereas when using cholinergic agents, this index did not exceed 26.9±1.5 points, and when using peptidergic agents - 26.8±1.4 points. These values are almost

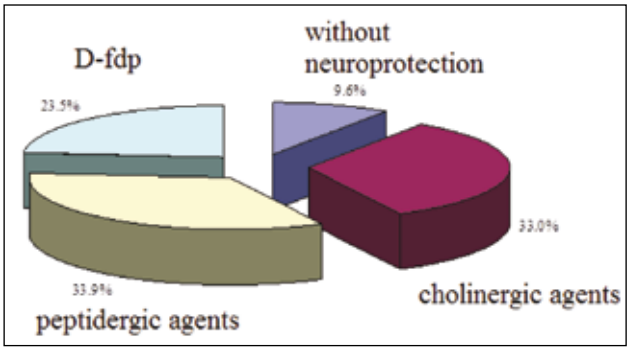

Figure 2. Distribution of patients according to the use of neuroprotective compounds

indistinguishable from the level achieved in patients who have not received special neuroprotective agents (p> 0.05), but the demonstrated trend is noteworthy.

With regard to the CGI index, at the end of treatment, it averaged 3.3±0.1 points in patients who did not receive refineries, while in patients receiving cholinergic agents it equaled 2.5±0.1 points, peptidergic agents - 2.6±0.1 points, and when using D-fdp - 2.5±0.1 points (p <0.05), which corresponds to significant changes in the state of the cognitive sphere and general social adaptations.

In our opinion, the positive effect of D-fdp on neurorehabilitation, which can be explained by the optimization of various physiological processes, including energy metabolism, ATP synthesis, oxygen transport to tissues (2,3-diphosphoglycerate), regulation of the activity of glycolysis, pH maintenance of blood and urine, is worthy of note.

The nutritional deficiency of phosphorus inherent in patients with ischemic stroke can be successfully corrected by the introduction of actively metabolized metabolites such as fructose-1,6-diphosphate. In vitro and in vivo biochemical studies also indicate that D-fdp interacts with cell membranes at pharmacological doses, accelerates the uptake of potassium cells from circulating blood, and stimulates an increase in the intracellular supply of high-energy phosphate and 2,3-diphosphoglycerate.

The principles of action of cholinergic and peptidergic agents are somewhat different - according to current ideas, the enhancement of cholinergic and peptidergic stimulation of brain structures promotes neuroplastic changes. Increased cholinergic transmission and reduction of transmitter dysfunction increases the affinity of GABA receptors and

Table 1. The results of treatment depending on the type of used neuroprotective agents

Indices	With neuroprotective agents			Without neuroprotective agents
	Cholinergic agents	Peptidergic agents	D-fdp	
NIHSS	3,8±0,2	3,6±0,1*	3,4±0,1*	4,1±0,1
mRS	0,9±0,1	0,9±0,1	0,9±0,1	1,0±0,1
MMSE	26,9±1,5	26,8±1,4	27,0±1,3	25,7±1,4
CGI-I	2,5±0,1*	2,6±0,1*	2,5±0,1*	3,3±0,1

Note: * differences with non-refined group were statistically significant (p <0.05)

limits NMDA receptor hypersensitivity. Such stimulation of the mechanisms of neuroplasticity and natural neurogenesis leads to structural and functional neuroreparation, which is the key to rapid and successful rehabilitation after the stroke.

CONCLUSIONS

The use of neuroprotective agents has a positive effect on the effectiveness of the neurorehabilitation of patients with ischemic stroke.

The best results are obtained for peptidergic agents and D-FDP.

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ADDRESS FOR CORRESPONDENCE:
Denys N. Khramtsov
Odessa National Medical University,
Valikhovskiy lane, 2, Odesa, 65082, Ukraine
phone: +380973126185
e-mail: dionis_hr@live.ru

ORCID ID and AUTHORS CONTRIBUTION
0000-0002-5289-5542 – Denys N. Khramtsov (A, B, C, D, E, F)
0000-0002-3375-0452 – Olexandr N. Stoyanov (D, E, F)
0000-0001-6573-6180 – etiana N. Muratova (B, D, E, F)
0000-0002-8717-047X – Olexandr R. Pulyk (C, E, F)

A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of article