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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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Содержание:

EFFECT OF INVESTIGATIONAL COMBINATIONS OF NEUROPROTECTANTS ON THE LEVEL OF S 100 AND NSE PROTEIN IN THE BLOOD SERUM OF PATIENTS WITH MODERATE AND SEVERE ISCHEMIC STROKE

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Abstract.

Ischemic cerebral stroke (ICS) is a devastating neurological pathology associated with enormous comorbidity and mortality.

Preliminary experimental screening of cerebroprotective agents with different mechanisms of action was performed: Edaravone, Cerebrolysin, Choline alfoscerate, Citicoline, Mexidol, the most effective combinations of cerebroprotectors were identified, followed by their screening for efficacy in clinical conditions by neuron-specific enolase (NSE) and S100 protein, as one of the main biochemical markers of brain damage in acute ischemic stroke.

Different combinations of neuroprotectants identified as the most effective in experimental screening differed in their ability to correct serum levels of S100 and NSE protein in ischemic stroke in clinical settings.

The lowest effectiveness in the correction of neuroglioproliferative processes was recorded when using only conventional therapy (CT), which was determined according to the Order of the Ministry of Health of Ukraine of 03.08.2012 № 602, without the use of neuroprotectors. Whereas, the use of a neuroprotective combination/complex (NPC) (cerebrolysin + citicoline) in the treatment of ischemic strokes in terms of the effectiveness of correction of neuroglioproliferative processes was 1,7-2,7 times ($p<0.01$) higher than conventional therapy, and 1,2-1,4 times ($p<0.05$) higher than treatment that included the use of a neuroprotective combination - cerebrolysin + mexidol.

Key words. Ischemic stroke, neuroprotectant, neuron-specific enolase, S100 protein.

Introduction.

Ischemic cerebral stroke (ICS) is the second leading cause of dementia and the third leading cause of death worldwide. More than half of the 18 million people who suffer from stroke every year have permanent motor impairment, which is the result of irreversible neuronal loss and causes disability of a patient with ICS. This disease is a social burden for all countries, and the number of cases of ICS is constantly increasing with the growth of the world's population [1-3].

The COVID-19 pandemic and the military invasion of Ukraine by the Russian Federation have caused major changes in the system of medical care for ICS, including untimely consultation and reduced and sometimes impossible timely intravenous thrombolysis and mechanical thrombectomy procedures [4,5]. To date, it remains unclear whether combinations of various cerebroprotective agents can improve the course of acute stroke or not [6]. At the same time, many literature sources indicate the effectiveness of individual neuroprotectors when used in ICS.

For example, the study by X.L. Xue, T. Zhang, W.Y. Zhao et al. showed a significant improvement in the 21-day treatment outcome when cerebrolysin was used to correct the effects of ischemic stroke [7]. A meta-analysis by N.M. Bornstein, A. Guekht, J. Vester et al. in 2018 (1879 patients) showed the advantage of cerebrolysin over placebo in terms of both neurological deficits and clinically significant improvement in patients' functional capacity on the 90th day after the onset of ICS [8].

In the study by A. Mehta, R. Mahale, K. Buddaraju et al. in 2019, 20 patients after ischemic stroke received citicoline intravenously/ orally with a mean baseline National Institutes of Health Stroke Scale (NIHSS) score of 14.0 ± 4.3 with a significant improvement in NIHSS scores on day 11 and 90 days after stroke [9]. The results of a meta-analysis of a randomized clinical trial of oral citicoline among 1372 patients with ICS revealed a statistically significant effect of citicoline on overall recovery (25.2% *vs.* 20.2%) [10]. In a study by Indian scientists S. Ghosh, K.S. Das, T. Nath et al. reported better results and a higher probability of complete recovery after treatment with citicoline in all types of strokes [11].

A study by K.M. Sinha, K.H. Anuradha, R. Juyal et al. showed that patients treated with edaravone had a significant reduction in NIHSS after 90 days [12]. A comparative study of edaravone/citicoline conducted by M. Mitta, D. Goel, K.K. Bansal, P. Puri showed that the use of edaravone leads to a better result 90 days after ischemic stroke, while the total use of edavarone with citicoline was not studied [13]. The mechanism of action of edavarone in ischemic stroke is aimed at glutamate excitotoxicity and prevention of calcium inflow, reduction of blood-brain barrier damage; tendency to develop cerebral edema; neutrophil migration, affecting secondary inflammation, as well as oxidative and nitrite/nitrate stress [12,13].

In a study of choline alfoscerate in 2484 patients with ICS and TIA, the drug improved functional recovery [14]. In addition, a multicenter RCT demonstrated a positive effect of choline alfoscerate on cognitive function [15].

The team of authors I.A. Strelnikova, A.A. Svetkina, O.V. Androfagina in 2020 published the results of their own clinical trial, in which mexidol treatment in the acute and early recovery periods of ICS has a positive effect on the regression of neurological symptoms, increasing the likelihood of achieving independence in everyday life by 3.34 times, reducing neurodynamic disorders and improving memory [16]. The results of a 2020 clinical trial demonstrated a decrease in blood levels of total cholesterol and low-density lipoprotein β, and a decrease in the severity of hypercoagulability in patients with ICS with the use of mexidol [17].

As shown in the above studies, cerebroprotective agents with different mechanisms have neuroprotective properties, and there are no studies that would confirm or refute the feasibility of combining cerebroprotective agents with different mechanisms to reduce disability and mortality from acute ischemic stroke.

Materials and methods.

A randomized prospective controlled trial of the use of the most effective NPCs in patients with ischemic CVA was conducted at the Vinnytsia City Clinical Emergency Hospital from 2021 to 2023 in the intensive care units of the neurological department and anesthesiology departments with intensive care beds (ADICB) № 1 and 2.

The main criterion for patient selection was the presence of moderate to severe ischemic stroke with deep stunning, soporas, or coma, i.e., patients requiring intensive care in the intensive care unit. The neuroimaging of ICS was confirmed by spiral computed tomography. A total of 90 patients with acute ischemic stroke participated in the study. The control group consisted of 25 people.

The study patients to determine the therapeutic effect of the studied NPCs were randomized by the method of random numbers into 6 groups of 15 patients each, a total of 90 patients, including 43 men and 47 women. The average age was 67.93 ± 1.67 years and an additional group of 25 healthy people, including 12 men and 13 women. The average age was 65.04 ± 1.67 years. The study groups did not differ in age, severity, or other baseline parameters that could affect the final results of the study.

Distribution of study groups of patients:

1. Healthy individuals - 25 people
2. Patients with moderate ischemic stroke (IS) who received conventional therapy (moderate ischemic stroke + conventional therapy (CT)) - 15 people
3. Patients with moderate ischemic stroke who received conventional therapy and a complex of neuroprotectants №1 (NPC №1) - (moderate ischemic stroke + CT + NPC №1) - 15 people
4. Patients with moderate ischemic stroke who received conventional therapy and a complex of neuroprotectants №2 (NPC №2) - (moderate ischemic stroke + CT + NPC №2) - 15 people
5. Patients with severe ischemic stroke who received conventional therapy (severe ischemic stroke + CT) - 15 people
6. Patients with severe ischemic stroke who received conventional therapy and a complex of neuroprotectants №1 (NPC №1) - (severe ischemic stroke + CT + NPC №1) - 15 people
7. Patients with severe ischemic stroke who received conventional therapy and a complex of neuroprotectants №2 (NPC №2) - (severe stroke + CT + NPC №2) - 15 people

Neuroprotective complexes (NPCs) were studied: NPC №1 (cerebrolysin + mexidol) and NPC №2 (cerebrolysin + citicoline) were administered intravenously in similar doses and regimens according to the manufacturer's instructions immediately after confirmation of the diagnosis by spiral computed tomography (SCT), and then daily every 24 hours for 7 days. The control group included patients who received only conventional therapy.

Biochemical studies of the content of biochemical markers of neurodegradation (NSE) and neuroglioproliferation (S100 protein) in the blood serum of patients with ischemic stroke [18,19] were performed in dynamics: 1) upon admission to the hospital (before treatment); 2) after 3 days of treatment - as of the 4th day of treatment; 3) after 6 days of treatment - as of the 7th day. The content of S100 and NSE protein in the blood serum was determined by enzyme-linked immunosorbent assay using the CanAg S100 EIA Kit (Fujirebio Diagnostics Inc., Goteborg, Sweden) according to the manufacturer's instructions, using an automatic STAT FAX 303/PLUS analyzer. The studies were conducted in the research clinical diagnostic laboratory of the Pirogov National Medical University, certified by the Ministry of Health of Ukraine (certificate of recertification №049/15 of March 02, 2015).

Statistical processing of the study results was performed in the licensed standardized package "Statistica 13,3 for Windows" and included analysis of the nature of the distribution of characteristics by the Shapiro-Wilk W test and analysis of differences by the Mann-Whitney test for nonparametric data and the Wilcoxon rank sum test to assess changes in intragroup dynamics $p < 0,05$ was considered significant.

Results.

The activity of neurodegradation by the level of NSE in the blood depending on the severity of ischemic stroke (Table 1). It turned out that in the blood serum of healthy subjects, the serum level of NSE was low, its median was 0,648 ng/ml, and the interquartile range P_{25}-P_{75} was 0,450-0,843 ng/ml.

In moderate ischemic stroke, there was a significant increase in the mean serum NSE level by 7,1 times ($p<0.001$) compared with healthy subjects: the median was 4,57 ng/ml, and the interquartile range P_{25}-P_{75} was 4,11-4,97 ng/ml.

In patients with severe ischemic stroke, the intensity of neurodegeneration by serum NSE level was significantly higher by 1,6 times ($p<0,001$) compared with that of moderate severity. Thus, in patients with severe ischemic stroke, the median serum NSE level was 7,22 ng/ml, and the interquartile range P_{25}-P_{75} was 6,39-7,85 ng/ml.

The applied pharmacotherapy reduced the severity of neurodegeneration in patients with ischemic strokes with varying efficacy (Table 2). Conventional therapy had the least effect on the activity of neurodestruction in ischemic stroke. It was found that in patients with moderate ischemic stroke, the use of conventional treatment on days 4 and 7 was accompanied by a significant decrease in serum NSE levels by 21,1 and 38,6 % ($p<0,05$), respectively, compared with the pretreatment level. In severe ischemic stroke after 3 days and 6 days of conventional treatment, the serum NSE content significantly decreased by 30,8 and 43,6 %, respectively ($p<0,01$).

The inclusion of the combination of NPC №1 in conventional treatment significantly increased the effectiveness of correction of neurodegeneration processes. In patients with moderate ischemic strokes, the use of this treatment regimen was accompanied by a significant decrease in serum NSE levels by 41,1% (as of day 4) and 53,9% (as of day 7) compared with the pretreatment level. In patients with severe ischemic strokes, the inclusion of the combination of NPC №1 caused a statistically significant decrease in serum NSE levels after 3 days and 6 days of treatment by 46,1 and 56,5 %, respectively ($p<0,01$). The effectiveness of the combination of conventional treatment with NPC №1 in terms of reducing the serum level of NSE was 1,3-2,0 times higher ($p<0,05$) than conventional treatment.

Table 1. *Serum NSE content in healthy subjects and patients with ischemic strokes of varying severity (M±m).*

Patient groups		n	NSE, ng/ml
1	Healthy individuals	25	0,652±0,043
2	Ischemic stroke of moderate severity	45	4,60±0,10*
3	Ischemic stroke of severe degree	45	7,23±0,16*#

Notes:
*1. * - significance of differences (p<0,05) relative to healthy individuals.*
2. # - significance of differences (p<0,05) in relation to patients with moderate ischemic stroke.

Table 2. *Serum NSE content in patients with ischemic strokes of varying severity during treatment (M±m; n=15).*

Duration of the study	NSE, ng/ml		
	Patient groups		
	Conventional therapy	Conventional therapy + NPC №1	Conventional therapy + NPC №2
Ischemic stroke of moderate severity			
Before treatment	4,56±0,17	4,60±0,18	4,63±0,15
After 3 days of treatment	3,60±0,21*	2,71±0,20*#	2,06±0,18*#&
After 6 days of treatment	2,80±0,19*	2,12±0,21*#	1,54±0,14*#&
Ischemic stroke of severe degree			
Before treatment	7,15±0,27	7,24±0,31	7,30±0,28
After 3 days of treatment	4,95±0,24*	3,90±0,18*#	3,08±0,14*#&
After 6 days of treatment	4,03±0,19*	3,15±0,16*#	2,28±0,18*#&

Notes:
*1. * - significance of differences (p<0.05) relative to the pretreatment index.*
2. # - significance of differences (p<0.05) compared to the group of patients receiving conventional therapy.
3. & - significance of differences (p<0.05) compared to the group of patients who received conventional therapy combined with NPC №1.

Table 3. *Serum S100 protein content in healthy subjects and patients with ischemic strokes of varying severity (M±m).*

Patient groups		n	S100 protein, ng/ml
1	Healthy individuals	25	0,876±0,051
2	Ischemic stroke of moderate severity	45	4,62±0,18*
3	Ischemic stroke of severe severity	45	6,66±0,18*#

Notes:
*1. * - significance of differences (p<0.05) relative to healthy subjects.*
2. # - significance of differences (p<0.05) in relation to patients with moderate ischemic stroke.

The use of NPC №2 showed the highest efficacy in reducing serum NSE levels in moderate and severe ischemic stroke. In the group of patients with moderate ischemic strokes, the use of conventional therapy in combination with NPK #2 is associated with a significant reduction in serum NSE levels by 55.5% (as of day 4) and 66.7% (as of day 7) compared with the pretreatment level. Under these treatment conditions, in patients with severe ischemic strokes, the decrease in serum NSE levels on days 4 and 7 of treatment was 57.8 and 68.8 %, respectively (p<0.01). The effectiveness of the inclusion of NPC №2 in the pharmacotherapy of ischemic stroke in terms of the degree of reduction of serum NSE levels was 1.6-2.6 times (p<0.01) higher than conventional treatment and 1.2-1.4 times (p<0.05) higher than conventional treatment combined with the use of NPC №1.

In patients with ischemic strokes, along with neurodestruction, activation of neuroglioproliferation processes is recorded, as evidenced by an increase in the serum content of S100 protein (Table 3).

In healthy subjects, the serum S100 protein level was low, with a median value of 0.900 (95% CI 0.489-1.241) ng/mL, and an interquartile range of P_{25}-P_{75} of 0.669-1.077 ng/mL.

In moderate ischemic stroke, a significant increase in the mean serum S100 protein content by 5.3 times (p<0.001) was recorded compared with healthy subjects: the median value was 4.53 (95% CI 2.82-6.51) ng/mL, and the interquartile range P_{25}-P_{75} was 3.65-5.59 ng/mL.

In patients with severe ischemic strokes, the serum level of S100 protein was maximal: the median value was 6.75 (95% CI 4.64-8.63) ng/mL, and the interquartile range P_{25}-P_{75} was 5.66-7.63 ng/mL. On average, the level of S100 protein in the blood serum was 7.6 times (p<0.001) higher than in healthy subjects and 1.44 times (p<0.01) higher than in patients with moderate ischemic strokes.

Table 4. *Serum S100 protein content in patients with ischemic strokes of varying severity during treatment (M±m; n=15).*

Duration of the study	S100 protein, ng/ml		
	Patient groups		
	Conventional therapy	Conventional therapy + NPC №1	Conventional therapy + NPC №2
Ischemic stroke of moderate severity			
Before treatment	4,62±0,29	4,58±0,31	4,65±0,34
After 3 days of treatment	3,85±0,23*	3,12±0,20*#	2,54±0,15*#&
After 6 days of treatment	3,01±0,19*	2,40±0,17*#	1,92±0,16*#&
Ischemic stroke of severe degree			
Before treatment	6,58±0,29	6,67±0,32	6,72±0,35
After 3 days of treatment	5,16±0,19*	4,20±0,21*#	3,57±0,15*#&
After 6 days of treatment	4,37±0,22*	3,56±0,17*#	2,82±0,18*#&

Notes:
*1. * - significance of differences (p<0.05) relative to the pretreatment index.*
2. # - significance of differences (p<0.05) compared to the group of patients receiving conventional therapy.
3. & - significance of differences (p<0.05) compared to the group of patients who received conventional therapy combined with NPC №1.

Different types of pharmacotherapy for ischemic strokes differed in their ability to correct the serum level of S100 protein (Table 4). The lowest efficacy in correcting neuroglioproliferative processes was recorded when using only conventional therapy. In the group of patients with moderate ischemic stroke, the use of conventional therapy for 3 and 6 days caused a significant decrease in the level of S100 protein in the blood serum by 16.7 and 21.8% ($p<0.05$), respectively, compared with the pretreatment level. Under these conditions of therapy in the group of patients with severe ischemic stroke, the decrease in the level of S100 protein in the blood serum on days 4 and 7 was 21.6 and 33.6 %, respectively ($p<0.01$).

The use of NPC №1 in the treatment of ischemic strokes significantly increased the effectiveness of correction of neuroglioproliferative processes. Thus, in the group of patients with moderate ischemic stroke, the inclusion of the combination of NPC №1 in conventional therapy was accompanied by a significant decrease in the level of S100 protein in the blood serum on days 4 and 7, respectively, by 31.8 and 47.6% ($p<0.01$) compared with the pretreatment level.

In patients with severe ischemic strokes, the use of pharmacotherapy, which included NPC №1, caused a decrease in the level of S100 protein in the blood serum on days 4 and 7, respectively, by 36.1 and 46.6 % ($p<0.01$). The inclusion of the combination of NPC №1 in the treatment regimen for ischemic strokes was 1.4-2.2 times ($p<0.05$) higher than conventional therapy in terms of the effectiveness of correction of neuroglioproliferative processes.

The use of NPC №2 in the pharmacotherapy of ischemic strokes most effectively corrected neuroglioproliferative processes. Under these conditions, in patients with moderate ischemic stroke, a statistically significant decrease in the level of S100 protein in the blood serum on days 4 and 7, respectively, by 45.4 and 58.7% ($p<0.01$) was observed compared with the pretreatment level. In patients with severe ischemic strokes, the decrease in serum S100 protein level at day 4 and 7 was 46.9 and 58.0%, respectively ($p<0.01$). The use of NPC №2 in the treatment of ischemic strokes in terms of the effectiveness of correction of neuroglioproliferative processes was 1.7-2.7 times ($p<0.01$) higher than conventional therapy, and 1.2-1.4 times ($p<0.05$) higher than treatment with NPC №1.

Conclusion.

Thus, the study demonstrates that the inclusion of NPC №2 (group 3) in the conventional treatment regimen showed the highest efficacy in correcting the processes of neurodegeneration and neuroglioproliferation (according to the dynamics of serum levels of NSE and S100 protein) in patients with moderate to severe ischemic stroke ($p<0.01$). In patients with severe ischemic strokes, the use of pharmacotherapy, which included NPC №1, caused a decrease in the level of S100 protein in the blood serum on days 4 and 7, respectively, by 36.1 and 46.6 % ($p<0.01$). The inclusion of the combination of NPC № 1 in the treatment regimen for ischemic strokes was 1.4-2.2 times ($p<0.05$) higher than conventional therapy in terms of the effectiveness of correction of neuroglioproliferative processes.

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РЕЗЮМЕ

ВЛИЯНИЕ ИССЛЕДОВАТЕЛЬСКИХ КОМБИНАЦИЙ НЕЙРОПРОТЕКТОРОВ НА УРОВЕНЬ БЕЛКА S 100 И NSE В СЫРОВАТКЕ КРОВИ БОЛЬНЫХ НА ИШЕМИЧЕСКИЙ ИНСУЛЬТ СРЕДНЕЙ И ТЯЖЕЛОЙ СТЕПЕНИ

КАРИМУЛИН Р.Ф

Ишемический мозговой инсульт (ИМИ) – это разрушительная неврологическая патология, связанная с огромной коморбидностью и смертностью.

Путем предварительного экспериментального скрининга по показателю летальности различных по механизму действия церебропротекторов: Edaravone, Cerebrolysin, Choline alfoscerate, Citicoline, Mexidol были определены наиболее эффективные комбинации церебропротекторов с последующим их скринингом эффективности в клинических условиях по показателям нейронспецифики. из основных биохимических маркеров поражения головного мозга при остром ишемическом инсульте

Различные комбинации нейропротекторов, определенные как наиболее эффективные при экспериментальном скрининге, отличались по способности корректировать сывороточный уровень белка S100 и NSE при ишемическом инсульте в клинических условиях.

Наименьшая эффективность коррекции нейроглиопролиферативных процессов была зафиксирована при использовании только традиционной терапии (ТТ), которая определялась согласно Приказу Минздрава Украины от 03.08.2012 № 602, без применения нейропротекторов. В то время как использование нейропротекторной комбинации/комплекса (НПК) (церебролизин + цитиколин) в лечении ишемических инсультов по эффективности коррекции нейроглиопролиферативных процессов превышало в 1,7-2,7 раза ($p<0,01$) традиционную терапию, а также в 1,2 -1,4 раза ($p<0,05$) – лечение, которое включало использование нейропротекторной комбинации – церебролизин + мексидол.

Ключевые слова: ишемический инсульт, нейропротектор, нейроспецифическая енолаза, белок S100.