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RESEARCH ARTICLE

Neuroprotective Therapy with Citicoline and Piracetam at Acute Cerebrovascular Disease: Clinical and Psychosomatic Effects

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SUMMARY

Contemporary pharmacological market is well developed, suggesting a wide choice of medical preparations for treating various disorders. Particular attention is paid to the group of diseases related to cerebrovascular accidents as the complications and consequences are often unfavorable. A study was conducted in the post-Soviet countries and aimed to determine the effect and efficacy of using neuroprotective drugs in the treatment of cerebrovascular disease, taking into account the psychosomatic effect in patients. Two preparations were chosen for the study, namely, Citicolin and Piracetam. The main purpose was to compare the effectiveness and necessity of these drugs in improving the patients` condition and reducing the effects and mortality. The results of this study and works of other scientists proved a higher efficacy of using Citicolin compared to Piracetam. Among 680 patients (100%) receiving Citicolin as a neuroprotective therapy, 625 (91.9%) patients noted improvement in general condition already after three days. Of 405 patients (100%) receiving Piracetam, the regression of neurological symptoms occurred on the 4th or 5th day of treatment. The improvement of visual functions was noted in 26 patients from Citicolin group and only in 3 patients who received Piracetam as neuroprotective therapy.

Key Words: *Ischemic stroke, citicoline, piracetam, neuroprotective therapy, psychosomatic effect*

Akut Serebrovasküler Hastalıkta Sitikolin ve Pirasetam ile Nöroprotektif Tedavi: Klinik ve Psikosomatik Etkiler

ÖZ

Günümüzün iyi gelişmiş modern ilaç piyasasında çeşitli rahatsızlıkların tedavisi için kullanılabilecek çok çeşitli tıbbi ilaçlar mevcuttur. Genellikle komplikasyonları ve sonuçları ağır olduğundan, serebrovasküler kazalarla ilişkili hastalık grubuna özellikle dikkat edilmektedir. Sovyet sonrası ülkelerde gerçekleştirilen bu çalışmada hastalardaki psikosomatik etki dikkate alınarak serebrovasküler hastalıkların tedavisinde nöroprotektif ilaç kullanımının etki ve etkinliğinin belirlenmesi amaçlanmıştır. Çalışma için Sitikolin ve Pirasetam olmak üzere iki ilaç seçilmiştir. Temel amaç, bu ilaçların hastaların durumunun iyileştirilmesi ile etki ve ölüm oranlarının azaltılmasındaki etkinliklerinin ve gerekliliklerinin karşılaştırılmasıdır. Bu çalışmanın sonuçları ve diğer bilim insanlarının çalışmaları, Sitikolin' in Pirasetam'a kıyasla daha yüksek bir etkinliği olduğunu kanıtlamıştır. Nöroprotektif tedavi olarak Sitikolin alan 680 hastanın (%100) içerisindeki 625 hastanın (%91,9) üç gün sonra genel durumunda iyileşme kaydedilmiştir. Pirasetam alan 405 hastada (%100) ise, nörolojik semptomlarda gerileme, tedavinin 4. veya 5. gününde meydana gelmiştir. Görsel fonksiyonlarda iyileşme Sitikolin grubundan 26 hastada gerçekleşmesine karşın nöroprotektif tedavi olarak Piracetam alan sadece 3 hastada görsel fonksiyonlarda iyileşme kaydedilmiştir.

Anahtar Kelimeler: *İskemik inme, sitikolin, pirasetam, nöroprotektif tedavi, psikosomatik etki*

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INTRODUCTION

To date, cerebrovascular diseases are the second leading cause of death worldwide (World Health Organization, 2018). Cerebrovascular pathology (CVP) is considered the most common non-infectious disease and quite a frequent nervous system disorder. The most complex form of vascular disease is an ischemic stroke, which is characterized by focal lesions of the brain resulting from the disruption of its blood supply. This disorder occurs as a complication of such diseases like atherosclerosis and arterial hypertension.

Ischemic stroke is still believed to be the second leading cause of death in developed countries and the first reason for long-term disability in patients who experienced stroke (World Health Organization, 2018). However, there is still no pharmacological treatment for stroke with proven efficacy or with a favorable risk/benefit ratio for the acute phase of the disease.

Treatment of acute and chronic cerebrovascular disorders should be comprehensive. Basic drugs are antithrombotic agents, hypotensive and hypolipidemic preparations. Also, lifestyle modification with the exclusion of the disease risk factors like obesity, endocrine diseases in decompensation stage, and harmful habits such as smoking and alcohol abuse, is required for the higher success of the treatment outcome (Hacke, 2000). The sooner the correct therapy is started, the more chances for a positive result. Besides, to establish whether the disease is ischemic or hemorrhagic is of high importance as it may help to determine the correct treatment tactics.

One of the essential points on the way to recovery is neuroprotective therapy, the main purpose of which is to prevent the development of mechanisms of neuronal death in the ischemic brain tissue. In modern medicine, there is a large number of drugs with neuroprotective properties (Mildronate, Emoxypinum, Citicoline, Dicynone, etc.) However, scientific recommendations with a sufficiently proven effect of these drugs are missing in the available literature sources being considered ineffective from the perspective of evidence-based medicine. Therefore, studying the effectiveness of various neuroprotective drugs are still relevant today due to the lack of evidence-based action.

Certain neuroprotectants have a positive effect on the course and prognosis of various cerebral vascular pathologies. However, their success depends on several factors: the active ingredient, dose, frequency of administration, duration of use, etc. Often, doctors prescribe 2 or 3 neuroprotective drugs, although there is no specific need and no evidence base for this. On the contrary, their irrational intake can lead to the development of polypragmasy with further negative effects on the body. Therefore, the estimation of the neuroprotective therapy efficiency in the complex treatment of cerebrovascular disorders of different genesis remains an important point in world medicine.

Citicoline is a naturally derived endogenous compound. This compound is an intermediate metabolite involved in phosphatidylcholine synthesis processes (Ortega, 2010). The latter is a major component of the cellular membrane. Citicoline is a complex substance composed of cytidine and choline. There is a diphosphate bridge between them that decomposes following the hydrolysis reaction. In this respect, Citicoline has a very high level of bioavailability - approximately 100% when administered orally. The two components of citicoline pass the haematoencephalic barrier. After passing the barrier, citicoline is synthesized in the brain and then extracted from the body via air and urine (Donmez & Outeiro, 2013). Citicoline is characterized by a membranotropic effect, which promotes the repair of membranes in neurons. This happens because of phosphatidylcholine, as well as due to slower

neuronal membrane damage through the decrease in the activity of enzyme phospholipase A2 (Parfenov, 2012). Citicoline also promotes the preservation of not only phospholipids but also sphingomyelin, as well as standardizes the work of the sodium-potassium pump and the functional capacity of such organelles as mitochondria. Increased acetylcholine synthesis contributes to the standardization of cholinergic neurons function (Secades, 2011). The effect of citicoline is associated with its positive influence on the mechanisms that determine cerebral plasticity, as well as on neuro repair processes. That defines its therapeutic effect, which is why citicoline is used to treat various nervous system dysfunctions like dementia, memory loss, depressive disorders, as well as Parkinson's disease (Polito, 2013).

Piracetam's action mechanism is based on changes in metabolic processes, bioenergy metabolic processes occurring in the neuron, and increased protein biosynthesis. The action of piracetam on the use of O_2 and metabolic processes linked to glucose is based on aerobic or anaerobic conditions, which determine the response. Aerobic conditions facilitate the O_2 uptake by one-third under the influence of piracetam, while anaerobic conditions lead to an increase in glycolysis (Flicker & Evans, 2004). The latter is caused by activation of the pentose-phosphate cycle, which leads to the formation of NADPH, which is the main source of energy in brain metabolism. Under anaerobic (or hypoxic) conditions, the ATP synthesis is more intense, and the ATP-cAMP cycle in neuronal cells is more active. Based on the fact that lactate levels do not increase, anaerobic processes do not play the primary role (PASS II, 2001).

A stroke occurs in more than 15 million people annually worldwide, and almost 5 million people subsequently die (Belova, 2016). The incidence of stroke is 100-200 cases per 100 thousand people in different European countries. According to the World Health Organization, the number of stroke patients will increase by 30% by 2025 (Truelsen, 2006). Over the last decade, the WHO has reassessed the development of stroke and its consequences. Thus, there are 16 million primary cases of stroke and 5.7 million deaths due to it worldwide. Acute cerebrovascular disorder ranks 3rd by material costs of treatment and 2nd by causes of death in the United States and Europe.

To date, neuroprotective drugs provoke numerous debates among scientists. Some authors argue about the necessity of their use during ischemia zone recovery (Shabanov, 2020). Other scientists believe that neuroprotectors do not have a sufficient evidence base and their effectiveness is minimal (Sharayeva, 2018). Over the past 20 years, great importance has been attached to Citicoline as a strong neuroprotective agent. There are also a large number of articles that testify to the useful properties of Piracetam as a nootropic agent in acute ischemic stroke, especially in patients with speech impairment (De Deyn, 1997; Zhang, 2016).

Piracetam is the pioneer of nootropics. Recently, this preparation has received renewed attention, given its role in the therapy of psychosomatic diseases. Piracetam is effective in preventing neurocirculatory dystonia of psychosomatic origin such as bronchial asthma, coronary heart disease (CHD), and arterial hypertension.

Among disadvantages of Piracetam therapy, including those of psychosomatic origin, are its excessive influence on the excitability of the central nervous system, which may manifest itself as increased nervousness of a patient. Therefore, it is advisable to prescribe the intake of this drug in the period before 3 p.m. Noteworthy, such side effect was observed in less than 5% of cases (Al-Kuraishy & Al-Gareeb, 2020).

Clinical trials of Citicoline performed in the United States in the treatment of acute and chronic cerebrovascular disorders demonstrated a slight positive effect of the substance, which may be associated with the time of drug administration (therapeutic window of 1-6 hours from the onset of the first symptoms of stroke), the dose, and the method of administration (Adibhatla & Hatcher, 2002). Other researchers argue that Citicoline is safe to use and can

favorably affect patients with acute ischemic stroke, and most favorable in less severe stroke in elderly patients who have not received recombinant tissue plasminogen activator. None of the neuroprotective agents has been effective in confirmatory clinical trials (Overgaard, 2014). Neuroprotective agents can promote reperfusion at the capillary level in the target tissue area and increase the period for effective recanalization by preserving brain tissue and reducing the hemorrhage rate. However, such an effect is possible only in combination with mechanical thrombectomy. Neuroprotectants have been shown to constrain ischemic damage while the patient is in the acute period of stroke. Therefore, the potential usefulness of neuroprotection as an adjunctive agent before, during, and after mechanical thrombectomy has been emphasized (Babadjouni, 2017).

Recent clinical study by a group of scientists from Japan confirmed that combined treatment with Citicoline and docosahexaenoic acid may have synergic benefits for partial improvement of memory deficits after passing brain ischemia and prevent neuron cell death in the brain (Nakazaki, 2019). A multicenter Italian clinical trial established the effect of Citicoline in elderly people with mild vascular cognitive impairment. It was found that by increasing cell metabolism and activating phospholipid biosynthesis in brain neuronal membranes, Citicoline was quite effective and can be recommended for patients with mild vascular impairment. No adverse effects of the drug were reported in the study (Cotroneo, 2013; Porfiryeva, 2020). There are also numerous scientific articles describing the benefits of Pyracetam as a neuroprotective agent. A group of Chinese researchers from Hangzhou studied the effect of Piracetam on the rehabilitation of speech activity in patients after stroke. Evaluation of speech at the end of the trials did not show a significant improvement in general aphasia but showed a marked improvement in writing. The effect of Piracetam on general language and writing tends to improve for a short period but decreases with time (Zhang, 2016).

A randomized, multicenter, placebo-controlled PASS (Piracetam in Acute Stroke Study) showed no efficacy of Piracetam in acute ischemic stroke when administered within 12 hours from the onset of acute ischemic stroke. However, post-analysis suggested that Piracetam may be useful when administered within 7:00 after onset, especially in patients with moderate to severe stroke (De Deyn, 1997).

However, the Guidelines 2013 by the American Heart Association state that no neuroprotective pharmacological agents have demonstrated clinical efficacy in various clinical trials, and, therefore, are not currently recommended (Jauch, 2013).

This study aims to update the comparison of the therapeutic effects of Citicoline and Piracetam in combination with standard intensive therapy on brain cells of patients with acute ischemic stroke. These drugs are used not as the main treatment, but as an additional neuroprotective therapy.

The purpose of the work is to evaluate the effectiveness of Citicoline and Piracetam in combination with standard intensive therapy in patients with acute ischemic stroke.

The task of this study was to find out the evidence for the use of neuroprotective agents in cerebrovascular disease; to conduct a comparative analysis of Citicoline and Piracetam preparations; to identify the consequences and general effectiveness of treatment in improving the blood supply to the brain.

MATERIALS AND METHODS

Materials

The study used and analyzed medical histories and records of patients with acute cerebrovascular disease in hospitals of major cities in Russia and Ukraine.

For this purpose, the effect of neuroprotective drugs in patients with cerebrovascular disease was analyzed and compared, namely, the effect and benefits of prescribing Citicoline and Piracetam have

been studied.

The study enrolled a total of 1120 case histories of patients with acute cerebral circulation disorder (acute ischemic stroke) confirmed through computer tomography data between December 2019 and June 2020 in different hospitals in 8 cities of post-Soviet countries (4 cities in Russia and Ukraine). In 35 case histories, patients received drugs from other pharmacological groups as neuroprotective therapy, and, thus, were excluded from the study. Hence, the study involved a total of 1,085 patients. All patients were treated in the neurological departments of different hospitals in Russian and Ukrainian cities.

The authors declare that the work is written with due consideration of ethical standards. The study was conducted in accordance with the ethical principles approved by the Ethics Committee of Ukrainian Engineering and Pedagogical Academy (Protocol № 3 of 15.02.2021).

Methods

The study included 2 groups of patients: Group 1 received Citicoline as an additional neuroprotective therapy, and Group 2 received Piracetam. The dose of Citicolin was 1.0 g per 200 ml of physiological solution, and that of Piracetam – 4.5 g per 200 ml of physiological solution. Both drugs were administered intravenously by drop infusion, with subsequent reduction of the dose until the drug was completely withdrawn.

The first group of patients who received Citicoline as neuroprotective therapy included 680 patients (62.7%). The second group consisted of patients who received Piracetam and included 405 patients (37.3%).

The majority of the patients analyzed (65.9% or 715 persons) were women, and the rest of 370 patients (34.1%) were men. The average age of the patients was 57 years (42 to 74 years) (Table 1).

Table 1. Basic information about patients

Total number of case histories - 1,085	
City	Number of case histories analyzed
Moscow (Russia)	450 (41.47%)
Saint Petersburg (Russia)	211 (19.51%)
Kyiv (Ukraine)	122 (11.2%)
Kharkiv (Ukraine)	75 (6.9%)
Novosibirsk (Russia)	71 (6.54%)
Odessa (Ukraine)	60 (5.53%)
Yekaterinburg (Russia)	57 (5.25%)
Lviv (Ukraine)	39 (3.6%)
Gender	
Women	715 (65.9%)
Men	370 (34.1%)
Age	
Up to 45 years old	165 (15.3%)
45-55 years old	380 (35%)
55-65 years old	452 (41.6%)
Older than 65	88 (8.1%)

Study Design

Recent literature data were processed by meta-analysis.

The main criteria for evaluating the effectiveness of treatment with neuroprotective drugs included:

Degree of cerebral vasoconstriction;

Severity of the clinical disease course;

Risk of neurological complications.

The level of psychosomatic disorders (level of the anxiety-depressive syndrome) in patients from both groups at the beginning of the study and after its completion was calculated using the Hamilton scale (HDRS). The work was conducted with the patients' consent (written agreement on non-disclosure of information, observance of moral and ethical norms). This study included 44 patients, 23 from the Piracetam group and 21 from the Citicoline group. All patients were conscious. The daily dose of Piracetam and Citicoline corresponded to the minimum recommended dose for pronounced effects on the normalization of the central nervous system.

During the study, the Glasgow Coma Scale was used to assess the condition of patients with ischemic stroke after hospitalization. All patients were recommended to be continuously monitored by a neurologist after stroke treatment.

According to the Glasgow Coma Scale criteria, all patients were divided into three groups. The first group consisted of patients with a stun (12-13 points), amounting to 580 (53.45%). The second group included patients with soporus (9-11 points), amounting to 400 people (36.88%). The third group consisted of patients in a coma (3-8 points), amounting to 105 people (9.67%).

Statistical analysis

Statistical methods of calculation were applied for the data processing. The Microsoft Excel 2016 (USA, MicrosoftCorp) was used as a database. The data were further processed using Statistica v. 7.0 software (StatSoft Inc., USA). Student's t-test was used to compare data between samples (groups of patients) after testing for normality of distribution. Mean values and standard error of the mean were calculated as well. Differences were significant at $p \leq 0.05$.

RESULTS AND DISCUSSION

Analyzing the symptomatology of the disease, the following results were obtained: sudden weakness in the arm, leg, and half of the face (which is unilateral). Severe headache, dizziness, and movement coordination disorders were noted in all 1085 patients (100%) who were included in the study. Of these, speech problems (speaking, writing, and comprehension disorders) were observed in 226 patients (20.8%), and a sudden deterioration or absence of vision was noted in 54 patients (4.9%). Loss of consciousness was recorded in 105 patients (9.67%), of whom only four patients survived. Pain in the remaining 101 patients was fatal.

Of all 1085 patients (100%), 984 patients (90.7%) had positive dynamics of general psychoneurological symptoms against the background of the above therapy ($p \leq 0.05$ with the start of therapy). The condition of 101 (9.3%) patients worsened, which was caused by the severity of the disease and resulted in a lethal outcome in the long-term period due to complications of the underlying disease.

The first (main) group included 680 patients with sudden weakness in the arm, leg, and half of the face, severe headache, dizziness, and impaired movement coordination ($p \geq 0.05$ with the start of therapy). Of these, 130 patients had speech problems and 22 patients had impaired eyesight. Only 9 patients had speech impairment, 5 of whom were found to be fatal.

The second group included 405 patients with sudden weakness in the arm, leg, and half of the face,

severe headache, dizziness, and impaired movement coordination. Of these, 96 patients had speech problems, and 32 patients were with impaired eyesight. There were 96 comatose patients, and unfortunately, none of them survived, which was attributed to severe complications in the long-term period of the disease ($p \geq 0.05$ with the start of therapy).

Among the 680 patients (100%) who received Citicoline as a neuroprotective therapy, 625 (91.9%) patients showed improvement in general condition already after three days ($p \leq 0.01$ with the start of therapy). In 50 patients (7.3%), the improvement occurred on the 4th day (Figure 1) ($p \leq 0.05$ with the start of therapy). Another five patients (0.8%) died of pulmonary embolism as a complication of the underlying disease on day 3 from the start of the therapy. Analyzing 405 patients (100%) that received Piracetam, the results were disappointing. The regression of neurological symptoms occurred on day 4 in 59 patients (14.6%), day 5 in 195 patients (48.2%), and day 6 in 55 patients (13.4%) (Figure 2) (all possible outcomes at $p \geq 0.05$ with the start of therapy). The lethal outcome was observed in 96 patients (23.8%), of whom 56 patients died of pulmonary embolism and another 40 died of myocardial infarction (all possible outcomes at $p \geq 0.05$ with the start of therapy).

In Group 1, the regression of neurological symptoms was noted at 3±1 days compared to the control group, in which the recovery time was slightly longer (5±1 days, $p \leq 0.05$).

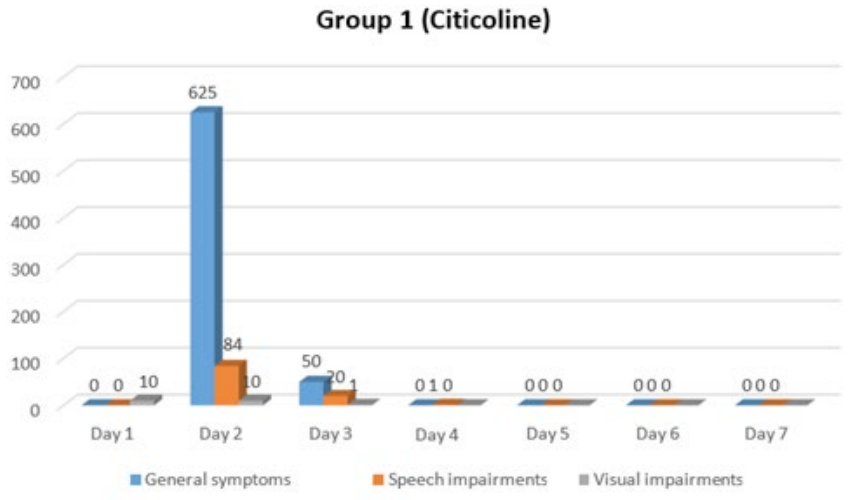

Figure 1. Improvement indices in the condition of patients depending on the use of Citicoline (number of patients)

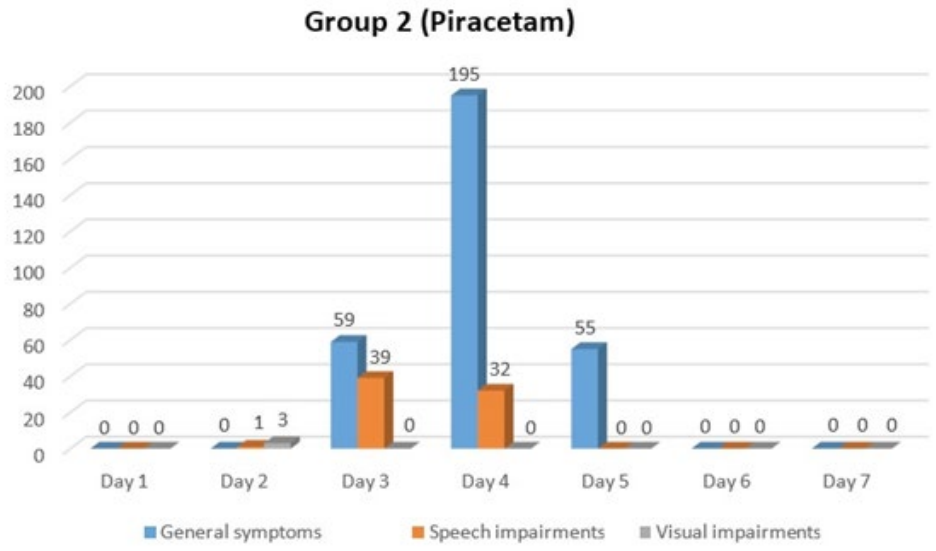

Figure 2. Improvement indices in the condition of patients depending on the use of Piracetam (number of patients)

Of all the patients analyzed, speech impairments were observed in 130 patients from the group that received Citicoline and 96 patients from the control group (Piracetam) ($p \leq 0.05$). As a result of the treatment, 105 patients in the main group, and 72 patients in the control group improved their speech ability ($p \leq 0.05$). Full recovery of the speech reactions was observed in 112 patients of the group, in which Citicoline was prescribed as neuroprotective therapy and in 76 patients of the Piracetam group during the long-term observation period (1.5–2 months) ($p \leq 0.05$). It is worth noting that patients in the first group improved speech after 2±1 days, and the second group – after 3±1 days ($p \geq 0.05$).

As a result of acute impairment of cerebral circulation, unilateral decrease or absence of eyesight was observed in 54 patients. After primary ophthalmological examination, all patients were diagnosed with the ocular ischemic syndrome. All patients were evenly divided into two groups, 22 patients from the Citicoline group and 32 from the Piracetam group (Piracetam). Treatment showed improvement of visual function in 21 patients from the group, where Citicoline was administered as neuroprotective therapy. At that, the regression of visual symptoms was noted in 10 patients on the first day, 10 patients felt the improvement on the second day, and one patient – on the third day after the disease had begun. Quite different results were obtained in patients of the second group. Improvement of visual functions by 10% was noticed only in 3 patients on the second day from the start of the disease. This progress was explained by the mild general state of the patients and a rather high visual acuity (10-20%) compared to other patients where the acuity of vision was in the range from improper color perception to 10% of impairment. Also, the improvement of the visual function of the patients from the first group during the first days was insignificant (progress of 20±5% from the initial one, $p \leq 0.05$). Analysis of distant eye consequences of the cerebrovascular disorder showed complete recovery of vision in 5 patients of Citicoline group 1.5–2 months after the loss of vision. Eight more patients had a 40±5% increase of visual function during the same period ($p \leq 0.05$), and in

another eight patients, visual progress remained at the level of 20±5%. In the group where Piracetam was used in the long-term period, full recovery of vision was not observed in any patient ($p \geq 0.05$). In three patients, the improvement was noted at 20±5% of the initial level. In the follow-up period, all 54 patients were excluded from observation.

The duration of hospital stay depending on the prescription of neuroprotective therapy has been analyzed. In the group of patients, to whom Citicoline was prescribed, the average hospitalization period lasted 7±2 days, while in the control group, this figure was slightly longer, amounting to 9±2 days ($p \leq 0.05$).

The use of Piracetam, on the other hand, produced a more pronounced psychosomatic effect in terms of decreasing the level of anxiety and depression. No pronounced changes were observed in patients treated for up to seven days, whereas patients who used Piracetam for more than seven days showed a 24% reduction in the level of anxiety and depression ($p \leq 0.05$) compared to the group of patients who took Citicoline.

No such effects were observed for Citicoline, which may be because Piracetam is the first of the nootropics with a complex effect, including the prevention of psychosomatic diseases, a protective effect, and normalization of the central nervous system.

The study found that the administration of Citicoline was more justified compared to Piracetam. After analyzing research works and articles by other scientists, both differences and convergence in results were found.

A recent study of Piracetam use in acute ischemic stroke indicated that the revised data did not provide conclusive evidence for the effect of using this drug in acute cerebrovascular accidents (Ricci, 2006).

Another study on the pharmacological treatment of aphasia after stroke with Piracetam, Piribedil (Pronoran), Bromocriptine, and Dextran 40 (Reopolyglucinum) in patients with acute cerebral circulation disorder did not reveal evidence that patients were more likely to experience improvement in speech performance at the end of the study after Piracetam treatment. Patients who received Piracetam as a neuroprotective therapy had slightly fewer adverse events, including death than those who received placebo. Such data raise some concerns that there may be an increased risk of death from Piracetam intake (Greener, 2001). The data in these two studies are consistent with the results of this work.

The study on neuroprotective properties of Citicoline found that this drug is non-toxic, which is confirmed by numerous preclinical data. Neuroprotective effect of Citicoline on the brain is based on the assumption that after injection or ingestion, this substance is sequentially hydrolyzed and dephosphorylated into cytidine and choline. These two metabolites then separately enter the brain tissue and are used to re-synthesize citicoline, which provides intracellular neuroprotection by supporting cellular phospholipid biosynthesis (Grieb, 2014).

Some data indicate the ability of Citicoline to normalize the patterns of neurotransmitter release. Under the conditions of cerebral hypoxia at ischemia, noradrenalin release may decrease, whereas dopamine release may increase. In several animal models, Citicoline has been shown to inhibit impaired neurotransmitter release in hypoxic states. Besides, administration of Citicoline to rats that were kept in a chronic hypoxic state decreased behavioral impairment and increased survival time. Additional studies have shown that Citicoline can increase vasodilation in animals with cerebral microcirculatory trauma, significantly increasing cerebral blood flow (Weiss, 1995).

The efficacy of Citicoline was also evaluated in a study that included 92 patients with chronic cerebrovascular disease. In this placebo-controlled study, 46 patients were randomized to each group. Patients received Citicoline (1000 mg/day intravenously) or placebo for two treatment cycles for four weeks, each with one week between cycles. The patient's response was assessed with several psychometric tests, measuring memory, behavior, attention, and emotional control. The results of the study showed that Citicoline significantly improved attention by reducing the number of incorrect reactions to nonverbal stimuli. Also, the continuous and progressive improvement was noted with Citicoline treatment on memory tests and assessments of emotion and behavior (Piccoli, 1994; Ignateva, 2020).

Hence, most of the processed materials confirm the results of this study and indicate a clear advantage of Citicoline over Piracetam applied to patients with an acute cerebrovascular accident, namely ischemic stroke. Patients who received Citicoline had faster regression of neurological symptoms, improvement of speech functions, and a significantly shorter period of inpatient treatment. In addition, the study obtained a positive effect of Citicoline as a neuroprotector in the improvement of visual symptoms by restoring the circulation of the optic nerve.

The results of this study did not identify any benefits of Piracetam, despite the large number of scientific articles stating the opposite. In the author's opinion, an improvement of general neurological symptoms in patients of the second group was noted due to basic therapy with anticoagulants, antiaggregants, and vasoactive drugs. As for the improvement of visual function, the use of Piracetam in a neuroprotective therapy was not justified. A slight improvement in visual acuity in 3 patients was associated with a mild course of the underlying disease.

Considering a large number of studies on the useful properties of Piracetam in patients with ischemic stroke with speech impairment and the data of this study allow stating that compared to other neuroprotective agents, Piracetam did not show any advantages. On the contrary, the recovery time of speech reactions was somewhat longer in the second group of patients. Consequently, the effectiveness of Piracetam for speech disorders is also not proven.

Therefore, the results of this study allow concluding that there are no proven neuroprotective properties of Piracetam.

CONCLUSIONS

The results of this study provided convincing evidence of the advantage of Citicoline over Piracetam. Nearly 92% of patients (625 people) indicated that their overall well-being had improved significantly by the third day. Citicoline was applied to all patients in the form of a neuroprotective agent. The effect of applying piracetam was noted later. Thus, in 405 patients, it manifested only on the 4th-5th day. Therefore, the use of citicoline also results in shorter hospitalization times. Furthermore, for citicoline, improvement in visual function was observed in 26 patients treated with citicoline. Similarly, in the piracetam group, this was reported in only three patients. This indicates the greater potential of citicoline as a complex action drug compared with piracetam, which has a limited effect at least on improving visual function.

Based on the evaluation of medical histories and medical records of patients from Russia and Ukraine, suffering from acute cerebrovascular accident, a neuroprotective therapy was prescribed. The first group of patients received Citicoline, and the second group – Piracetam. The analysis of literature and scientific works on the topic allowed stating the best effect for faster recovery after a stroke in Citicoline.

Citicolin is a new compound with a very broad spectrum of benefits for conditions associated with symptoms of neurological dysfunction. It works on several levels to support nervous health and optimal cognitive function. Citicoline has cholinergic and dopaminergic functions and supports the synthesis and incorporation of phospholipids into cell membranes and enhances antioxidant mechanisms in the body while suppressing the damaging effects of free radicals on nervous tissue. Citicoline should be considered a comprehensive therapeutic agent for maintaining brain health. Therefore, referring to these studies, Citicoline can be safely recommended as a neuroprotective therapy for patients with acute ischemic stroke.

As for Piracetam, the study did not identify any advantages of this drug over Citicoline in the treatment of the acute cerebrovascular disorder, and, thus, no evidence-based neuroprotective properties of Piracetam can be stated.

The use of Piracetam is justified in the prevention of psychosomatic disorders as this drug significantly reduces the frequency of anxiety-depressive syndrome by 24% ($p \leq 0.05$) starting from a period of more than seven days of the therapy.

CONFLICT OF INTEREST

All the authors of this article declared no conflict of interest.

AUTHOR CONTRIBUTION STATEMENT

Iryna Sokolova, Serafima Tazina and Oksana Zakharova contributed equally to the experimentation. Iryna Sokolova wrote and edited the article. Serafima Tazina designed and conducted the experiment. Oksana Zakharova studied scientific literature about the topic. All authors read and approved the final manuscript.

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