Received: 16 September 2025 / Accepted: 27 January 2026 / Published online: 27 February 2026

DOI 10.34689/SH.2026.28.1.013

UDC 616-005.4

COMPARATIVE EFFICACY OF INTRANASAL AND PARENTERAL ADMINISTRATION OF CITICOLINE IN EXPERIMENTAL CEREBRAL ISCHEMIA IN RODENTS

Altynay Talgatkyzy[1], https://orcid.org/0009-0000-1390-4322

Talgat N. Khaibullin[1], https://orcid.org/0000-0003-1886-0538

Elvira K. Ozhmukhametova[2], https://orcid.org/0000-0001-5963-855X

Dinara Sh. Shagieva[1], https://orcid.org/0009-0009-2278-9624

Asiya A. Yesenbaeva[1], https://orcid.org/0000-0001-7994-8934

Merey M. Askarova[1], https://orcid.org/0009-0002-6936-2010

Meruert R. Masabayeva[1], https://orcid.org/0000-0001-8240-361X

[1] Semey Medical University, Semey, Republic of Kazakhstan;
[2] City Multidisciplinary Hospital No. 2 of the Akimat of Astana, Astana, Republic of Kazakhstan.

Abstract

Background. The limited availability of reperfusion therapies for ischemic stroke highlights the need for effective neuroprotective strategies. Intranasal drug delivery is considered a promising approach for targeting the central nervous system by bypassing the blood-brain barrier.

Materials and Methods. The study was conducted on Wistar rats with experimentally induced ischemic stroke. Brain citicoline concentrations, neurological deficits, behavioral performance, and histomorphological changes were assessed.

Objective of the study. To assess the comparative efficacy of intranasal and intraperitoneal administration of citicoline in a rat model of experimental cerebral

Results. Intranasal administration of citicoline resulted in significantly higher brain drug concentrations, faster recovery of motor and cognitive functions, and less pronounced morphological damage compared with intraperitoneal administration.

Conclusion. The intranasal route of citicoline delivery demonstrates superior bioavailability and neuroprotective efficacy compared with parenteral administration in experimental cerebral ischemia.

Keywords: *ischemic stroke, neuroprotectio, citicolin, intranasal administration, blood-brain barrie, experimental ischemia.*

For citation:

Talgatkyzy A., Khaibullin T.N., Ozhmukhametova E.K., Shagieva D.Sh., Yesenbaeva A.A., Askarova M.M., Masabayeva M.R. Comparative efficacy of intranasal and parenteral administration of citicoline in experimental cerebral ischemia in rodents // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2026. Vol.28 (1), pp. 106-111. *doi 10.34689/SH.2026.28.1.013*

Резюме

СРАВНИТЕЛЬНАЯ ЭФФЕКТИВНОСТЬ ИНТРАНАЗАЛЬНОГО И ПАРЕНТЕРАЛЬНОГО ВВЕДЕНИЯ ЦИТИКОЛИНА ПРИ ЭКСПЕРИМЕНТАЛЬНОЙ ЦЕРЕБРАЛЬНОЙ ИШЕМИИ У ГРЫЗУНОВ

Алтынай Талғатқызы[1], https://orcid.org/0009-0000-1390-4322

Талгат Н. Хайбуллин[1], https://orcid.org/0000-0003-1886-0538

Эльвира К.Ожмухаметова[2], https://orcid.org/0000-0001-5963-855X

Динара Ш. Шагиева[1], https://orcid.org/0009-0009-2278-9624

Асия А. Есенбаева[1], https://orcid.org/0000-0001-7994-8934

Мерей М. Асқарова[1], https://orcid.org/0009-0002-6936-2010

Меруерт Р. Масабаева[1], https://orcid.org/0000-0001-8240-361X

[1] НАО «Медицинский университет Семей», г. Семей, Республика Казахстан;
[2] Городская многопрофильная больница №2 акимата г. Нур-Султан, Республика Казахстан.

Введение.Ограниченная доступность реперфузионной терапии при ишемическом инсульте определяет необходимость разработки эффективных нейропротективных стратегий. Интраназальный путь введения лекарственных средств рассматривается как перспективный способ доставки препаратов в центральную нервную систему с обходом гематоэнцефалического барьера.

Цель исследования: Оценить сравнительную эффективность интраназального и интраперитонеального введения цитиколина в модели экспериментальной ишемии головного мозга у крыс.

Материалы и методы. Эксперимент выполнен на крысах линии Wistar с моделированием ишемического инсульта. Оценивали концентрацию цитиколина в ткани мозга, неврологический дефицит, поведенческие реакции и морфологические изменения.

Результаты. Интраназальное введение цитиколина обеспечивало достоверно более высокую концентрацию препарата в мозге, более быстрое восстановление двигательных и когнитивных функций и менее выраженные морфологические повреждения по сравнению с интраперитонеальным введением.

Заключение. Интраназальный путь доставки цитиколина превосходит парентеральный по биодоступности и нейропротективной эффективности при экспериментальной ишемии мозга.

Ключевые слова: *ишемический инсульт, нейропротекция, цитиколин, интраназальное введение, гематоэнцефалический барьер, экспериментальная ишемия*.

Для цитирования:

Талғатқызы А., Хайбуллин Т.Н., Ожмухаметова Э.К., Шагиева Д.Ш., Есенбаева А.А., Асқарова М.М., Масабаева М.Р. Сравнительная эффективность интраназального и парентерального введения цитиколина при экспериментальной церебральной ишемии у грызунов // Наука и Здравоохранение. 2026. Vol.28 (1), С. 106-111. *doi 10.34689/SH.2026.28.1.013*

Түйіндеме

КЕМІРГІШТЕРДЕГІ ЭКСПЕРИМЕНТТІК ЦЕРЕБРАЛДЫ ИШЕМИЯ ЖАҒДАЙЫНДА ЦИТИКОЛИНДІ ИНТРАНАЗАЛЬДЫ ЖӘНЕ ПАРЕНТЕРАЛЬДЫ ЕНГІЗУДІҢ САЛЫСТЫРМАЛЫ ТИІМДІЛІГІ

Алтынай Талғатқызы[1], https://orcid.org/0009-0000-1390-4322

Талгат Н. Хайбуллин[1], https://orcid.org/0000-0003-1886-0538

Эльвира К.Ожмухаметова[2], https://orcid.org/0000-0001-5963-855X

Динара Ш. Шагиева[1], https://orcid.org/0009-0009-2278-9624

Асия А. Есенбаева[1], https://orcid.org/0000-0001-7994-8934

Мерей М. Асқарова[1], https://orcid.org/0009-0002-6936-2010

Меруерт Р. Масабаева[1], https://orcid.org/0000-0001-8240-361X

[1] "Семей медицина университеті" КЕАҚ, Семей қ., Қазақстан Республикасы;

[2] Астана қаласы әкімдігінің №2 қалалық көпсалалы ауруханасы, Астана қ., Қазақстан Республикасы.

Кіріспе. Ишемиялық инсульт кезінде реперфузиялық терапияның қолжетімділігінің шектеулі болуы тиімді нейропротективті стратегияларды әзірлеу қажеттілігін айқындайды. Дәрілік заттарды интраназальды енгізу гематоэнцефалиялық бөгетті айналып өтіп, препараттарды орталық жүйке жүйесіне жеткізудің перспективалы тәсілі ретінде қарастырылады.

Зерттеудің мақсаты: Кеміргіштердің инсульттің эксперименттік моделінде цитиколинді интроназальді және интроперитонеальді енгізудің салыстырмалы тиімділігін бағалау.

Материалдар мен әдістер. Зерттеу ишемиялық инсульт моделі жасалған Wistar тұқымындағы егеуқұйрықтарда жүргізілді. Ми тініндегі цитиколин концентрациясы, неврологиялық тапшылық, мінез-құлықтық реакциялар және морфологиялық өзгерістер бағаланды.

Нәтижелер. Цитиколинді интраназальды енгізу интраперитонеальды енгізумен салыстырғанда препараттың ми тініндегі концентрациясының едәуір жоғары болуын, қозғалыс және когнитивтік функциялардың жылдамырақ қалпына келуін, сондай-ақ морфологиялық зақымданулардың аз айқындалуын қамтамасыз етті.

Қорытынды. Цитиколинді интраназальды жеткізу жолы эксперименттік ми ишемиясы жағдайында биожетімділігі және нейропротективтік тиімділігі бойынша парентеральды енгізуден басым екендігін көрсетті.

Түйін сөздер*: ишемиялық инсульт; нейропротекция; цитиколин; интраназальды енгізу; гематоэнцефалиялық бөгет; эксперименттік ишемия.*

Дәйексөз үшін:

Талғатқызы А., Хайбуллин Т.Н., Ожмухаметова Э.К., Шагиева Д.Ш., Есенбаева А.А., Асқарова М.М., Масабаева М.Р. Кеміргіштердегі эксперименттік церебралды ишемия жағдайында цитиколинді интраназальды және парентеральды енгізудің салыстырмалы тиімділігі // Ғылым және Денсаулық сақтау. 2026. Vol.28 (1), Б. 106-111. *doi 10.34689/SH.2026.28.1.013*

Introduction

Acute cerebrovascular accident (stroke) remains one of the leading causes of morbidity and mortality worldwide, placing a significant burden on healthcare systems and society as a whole. In 2021, over 11.9 million new cases and 7.3 million deaths were recorded globally, reflecting the

immense global burden of the disease [8]. Among patients who have suffered an ischemic stroke, the prevalence of cognitive impairment reaches approximately 66–70% within the first 6–12 months post-stroke. The combination of motor and cognitive deficits significantly worsens functional status, increases the risk of loss of self-care, and complicates rehabilitation, leading to prolonged disability and reduced quality of life [4].

Despite advances in reperfusion therapy (thrombolysis and mechanical thrombectomy), these methods are only available to a small proportion of patients due to a narrow therapeutic window and contraindications, highlighting the ongoing need for additional treatment strategies aimed at neuronal protection and recovery [7].

Pharmacological neuroprotection is aimed at modulating key pathogenic mechanisms of ischemic injury (excitotoxicity, oxidative stress, inflammation, and apoptosis) and is considered a promising complement to reperfusion methods [7]. One of the major factors limiting the effectiveness of many neuroprotective agents is the blood-brain barrier (BBB), which prevents therapeutic agents from reaching brain tissue [13]. In this regard, the intranasal route of drug delivery has attracted attention as a way to bypass the BBB by delivering active molecules directly from the nasal cavity to the central nervous system via olfactory and trigeminal neural pathways. This approach has shown increased bioavailability and potential therapeutic efficacy in models of neurodegenerative and ischemic conditions [13].

Modern preclinical studies indicate that intranasal delivery of neuroprotective agents in ischemic stroke promotes neurogenesis and enhances functional recovery compared to traditional administration routes [11].

The intranasal route significantly increases the bioavailability of therapeutic molecules in brain tissue compared to traditional systemic delivery, as the drug can reach neuronal structures without having to cross the dense endothelial layer of the BBB [11]. This delivery method has already demonstrated promising results in preclinical studies of ischemic stroke and other neurological disorders: intranasally delivered molecules and carriers (e.g., nanoparticles, stem cell products, neurotrophic factors) help increase drug concentration in the brain, stimulate neurogenesis, and restore damaged neuronal structures, leading to improved functional and behavioral outcomes in stroke models [17].

Thus, due to the possibility of direct “nose-to-brain” transport, higher bioavailability, minimal systemic effects, and non-invasiveness, the intranasal route is a promising and potentially more effective method of delivering neuroprotective agents in acute and chronic brain injuries, including stroke, compared to classical parenteral routes [11].

Citicoline (cytidine-5-diphosphocholine, CDP-choline) is an endogenous compound that, when administered as a drug, participates in the synthesis of cell membrane phospholipids and the stabilization of neuronal membrane structures, which is important in protecting cells from ischemic damage [12]. Current data demonstrate that citicoline in cerebral ischemia modulates key pathogenic processes, including suppression of NF-κB activation and reduction of neuronal apoptosis. It also improves membrane stability and energy metabolism, contributing to reduced neuronal death and better functional outcomes in ischemic injury models [2].

Modern pharmacokinetic studies show that after administration, citicoline is rapidly metabolized into cytidine and choline, which efficiently penetrate the brain and are involved in the biosynthesis of neuronal membrane phospholipids and cholinergic neurotransmitters, thereby supporting membrane integrity, synaptic transmission, and neuronal function under ischemic conditions [10]. Clinical studies and meta-analyses indicate that citicoline may be an effective adjunct to standard therapy for ischemic stroke, improving neurological outcomes and daily functioning in some patients, although results vary depending on dosage and timing of administration [19]. Literature data show that citicoline exerts pleiotropic neuroprotective and neuroregenerative effects, including stimulation of membrane phospholipid synthesis, inhibition of phospholipase A2 activation, and reduction of free radical formation. It also modulates microglial responses and reduces neuroinflammation, which collectively promotes neuronal protection and regeneration after ischemic brain injury [2].

In light of the above, intranasal delivery of citicoline is attracting attention as a potentially more effective route of drug transport into the CNS, capable of enhancing its therapeutic efficacy in ischemic stroke. However, direct comparisons between traditional and intranasal administration routes in experimental models of ischemia are lacking, making it necessary to conduct studies aimed at comparing them in terms of key pharmacokinetic, neurological, behavioral, and morphological parameters.

Objective of the study

To assess the comparative efficacy of intranasal and intraperitoneal administration of citicoline in a rat model of experimental cerebral ischemia.

Materials and Methods

Study design: Experimental

Experimental animals. The study was conducted on 20 sexually mature Wistar rats (weighing 180–250 g), meeting age and weight criteria appropriate for modeling ischemic brain injury. The selection of experimental animals was based on the fact that Wistar rats represent a validated model of ischemic stroke with high reproducibility in preclinical studies. The animals were housed under standard vivarium conditions with controlled microclimate parameters (temperature: 22 ± 2 °C, relative humidity: 50–60%, light/dark cycle: 12:12 h) and had free access to food and water. All procedures were performed in strict accordance with ethical standards established by EU Directive 2010/63/EU and the European Convention ETS No.123. The present study was approved by the Local Ethics Committee of the NAO ‘Semey Medical University’ (Protocol No. 2 dated October 28, 2020). The experimental part of the study was carried out at the vivarium and the Central Research Laboratory of NAO ‘SMU’ in 2023.

After randomization, the rats were divided into four equal groups of 5 animals each (n = 5), totaling 20 animals:

1. Control group (ischemia without therapy);
2. Intraperitoneal administration of citicoline;
3. Intranasal administration of citicoline in a Pluronic F127-based formulation;

4. Placebo group (0.9% NaCl solution).

Modeling of ischemic stroke. Acute cerebral ischemia was induced using a combined method that simulates the pathogenesis of human stroke and ensures high reproducibility of neurological symptoms. The method consisted of the following stages:

1. *Pharmacological induction of thrombosis* – vitamin K (menadione) was administered intravenously in a dose sufficient to activate the blood coagulation cascade. This led to the formation of multiple emboli in small cerebral vessels and microarterioles.

2. *Hypoxic exposure* – immediately after vitamin K injection, the animals were placed in a sealed chamber with reduced oxygen content (10–12%) for 90 minutes. The combination of hypoxia and embolic factors resulted in stable, multifocal ischemic damage accompanied by neurological deficits and morphological changes typical of human ischemic stroke.

3. *Recovery phase* – after hypoxia, the animals were transferred to individual cages with temperature and respiratory monitoring.

This model provides strong clinical and pathological resemblance to human stroke, including motor, cognitive, and morphological alterations.

Drug formulations and administration routes

- Intraperitoneal citicoline was administered as a standard solution (125 mg/mL) with daily injections.
- Intranasal citicoline was delivered as a gel-forming solution based on Pluronic F127 (20%) containing 3 mg/mL of the active substance. The gel was prepared at 5 °C and instilled into the nasal passages in volumes of 0.03–0.05 mL daily for 30 days.

Methods of Evaluating Therapeutic Efficacy

1. *Neurological status* – assessed using the Bederson scale (0–5 points), evaluating paresis, motor impairments, and asymmetry.

2. *Behavioral tests* – including the Tolman maze to assess cognitive activity, orientation, and anxiety.

3. *Histomorphological analysis of the brain* – hematoxylin and eosin staining, assessment of demyelination, neuronal edema, and infiltration.

4. *Pharmacokinetics* – determination of citicoline concentration in the brain using HPLC on days 3, 7, and 14.

Statistical analysis was performed using standard methods of variation statistics. Given the small sample size (n = 5 per group) and the experimental nature of the study, quantitative data were presented as the median and interquartile range Me(Q1–Q3). The Kruskal–Wallis nonparametric test was used for intergroup comparisons. Differences were considered statistically significant at $p < 0.05$.

Results

Analysis of citicoline concentrations in brain tissue revealed differences between routes of administration. In the intraperitoneal group, the median brain concentration of citicoline was 2.99 µg/mL. In the group receiving intranasal citicoline in a Pluronic F127-based gel, the median concentration reached 7.756 µg/mL (Figure 1). The differences between groups were statistically significant ($p = 0.001$).

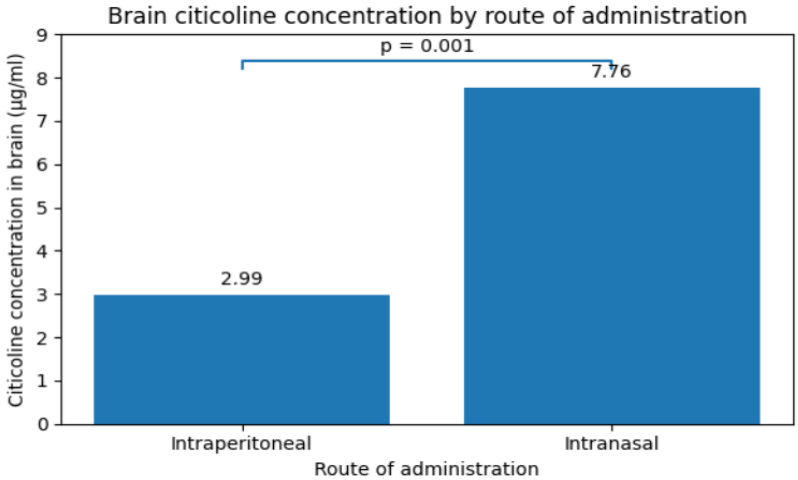

Figure 1. Brain citicoline concentration by route of administration

Neurological deficit assessment using the Bederson scale revealed differences in the severity and dynamics of recovery among the study groups. In the intraperitoneal group, the median neurological deficit score was 2.5 points. By day 7, 70% of animals still exhibited signs of hemiparesis or hemiplegia, and spontaneous motor activity recovered slowly. In the intranasal group, the median Bederson score was 2.3 points. Motor impairment began to decrease as early as days 3–5, with observable restoration of movement symmetry.

Behavioral analysis using the Tolman maze test showed intergroup differences. Animals receiving intraperitoneal citicoline exhibited signs of anxiety, disorientation, and poor task performance.

In contrast, animals in the intranasal group maintained behavioral performance: they successfully navigated the maze, demonstrated exploratory activity, and showed reduced anxiety levels.

Histomorphological analysis also revealed differences in the severity of ischemic changes between the groups.

In the intraperitoneal group, pronounced ischemic alterations were noted, including multifocal lesions, demyelination, edema, and cellular infiltration, persisting up to day 14. In the intranasal group, limited focal changes were observed, with minimal demyelination and infiltration, showing signs of regression by day 14.

Comparison of pharmacokinetic, neurological, behavioral, and morphological parameters revealed notable differences between the intranasal and intraperitoneal routes of citicoline administration (Table 1).

Intranasal administration was associated with higher drug concentration in brain tissue, earlier reduction of neurological deficits, preserved behavioral responses, and less pronounced morphological damage compared to intraperitoneal administration.

Table 1.

Comparative efficacy of intranasal and intraperitoneal citicoline administration in experimental cerebral ischemia.

Parameter	Intranasal	Intraperitoneal
Brain concentration (Me)	7.756 μg/ml	2.99 μg/ml
p-value	0.001	–
Onset of functional recovery	3-5 days	5-7 days
Neurological deficit (Bederson)	2.3	2.5
Behavioral performance	Preserved	Impaired
Morphological changes	Focal, reversible	Multifocal, persistent

Discussion

The results of this study demonstrated that intranasal administration of citicoline significantly outperforms intraperitoneal administration in terms of brain concentration, neurological function, behavioral activity, and the extent of morphological damage. These findings are consistent with recent reviews emphasizing that intranasal drug delivery allows bypassing the blood-brain barrier and provides more effective delivery of neuroprotective agents to the brain than traditional systemic administration routes [11].

The intranasal route facilitates rapid and direct transport of therapeutic agents to the central nervous system via olfactory and trigeminal neural pathways, bypassing the blood-brain barrier. This substantially increases their bioavailability and targeting precision in the treatment of cerebrovascular and other central nervous system disorders, including in preclinical models of ischemia [15]. Our data showing more pronounced improvements in behavioral responses with intranasal administration are consistent with observations that intranasally delivered therapeutic systems can reduce neurological deficits and accelerate the recovery of sensorimotor and cognitive functions after stroke [18].

In clinical practice, the effectiveness of citicoline remains controversial: some studies have shown limited impact on global stroke outcomes, highlighting the need for optimization of treatment regimens and delivery methods [16]. It is important to note that intranasal delivery methods for active compounds, including citicoline and other neuroprotectants, are being actively explored as promising alternatives to enhance therapeutic efficacy by bypassing the blood-brain barrier and increasing drug concentration directly in post-ischemic brain tissue [15].

Increased brain concentration of citicoline correlates with improved neurological outcomes, partially supported by experiments involving its delivery into the extracellular space of the brain, where significant reductions in infarct volume were observed [18]. Contemporary preclinical research demonstrates that intranasal delivery of nanoparticles and other nanotechnology-based carriers promotes angiogenesis and neurogenesis, improves neuroplasticity, supports white matter repair, and leads to enhanced neurological and behavioral outcomes in models of ischemic stroke. These findings are consistent with our results regarding improved behavioral activity following intranasal citicoline administration [14].

Strategies for intranasal therapy in stroke models also include the delivery of genetically targeted agents that migrate to ischemic regions and enhance neural plasticity and recovery post-injury [5]. Our findings on enhanced behavioral recovery with intranasal administration align with studies showing that intranasally delivered therapeutics can reduce neurological deficits and speed up the restoration of sensorimotor and cognitive functions after stroke [5].

Evidence confirms that citicoline possesses both neuroprotective and anti-inflammatory properties, demonstrating the ability to improve neurological functions, reduce disability, and positively influence the recovery of cognitive abilities and daily activities in patients with ischemic stroke. However, optimal treatment regimens and patient subgroups remain subjects of ongoing research [1]. Our experimental results also align with reports suggesting that citicoline helps normalize metabolic disturbances and improve biochemical markers of ischemia, reflected in enhanced motor activity and reduced neurological impairments. Authors also note that integrating intranasal delivery with nanotechnology could further enhance neuroprotective efficacy by improving drug stability, controlling its release, and increasing accumulation in ischemic regions [6].

Considering the presented literature, our results support the concept that the route of drug administration is a critical factor for the effectiveness of neuroprotective therapy. The intranasal pathway provides direct access to the central nervous system via olfactory and trigeminal routes, bypassing the blood-brain barrier and increasing therapeutic agent concentrations in the brain. This makes it a promising approach for accelerating recovery following ischemic stroke compared to systemic administration [3].

Current trends in intranasal nano- and microemulsion drug delivery research indicate strong interest in such platforms for CNS drug targeting, while also emphasizing the need for further translational studies—including assessments of efficacy, safety, and standardization—before these innovative approaches can be adopted in clinical practice [9].

Conclusion

The conducted experimental study demonstrated that the route of citicoline administration significantly influences its pharmacokinetic and therapeutic properties in ischemic stroke. Intranasal administration provided higher bioavailability, accelerated drug penetration into brain tissue, and more pronounced neuroprotective effects compared to intraperitoneal administration. This was accompanied by reduced neurological deficits, improved behavioral outcomes, and less severe morphological damage.

The obtained data support the potential of intranasal citicoline administration as a more effective alternative to systemic therapy in cases of acute cerebral ischemia and justify the need for further clinical investigations.

Conflict of Interest: *The authors declare no conflicts of interest.*

Author Contributions: *All authors contributed equally to the preparation of this material.*

Publication Information*: This material has not previously been submitted for publication elsewhere and is not under consideration by other publishers.*

Funding*:This study was not funded.*

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Contact information:

Altynay Talgatkyzy - NCJSC «Semey Medical University», e-mail: talgatkyzyaltynay@gmail.com, https://orcid.org/0009-0000-1390-43226.

Talgat N. Khaibullin- Professor, DSc (Medicine), NCJSC «Semey Medical University», e-mail: talgat.khajbullin@smu.edu.kz, https://orcid.org/0000-0003-1886-05386.

Elvira K. Ozhmukhametova - MD, PhD, Chief Clinical Pharmacologist of the Ministry of Health of the Republic of Kazakhstan, Head of the Department of Clinical Pharmacology and Pharmacy, City Multidisciplinary Hospital No. 2 of the Akimat of Astana, Astana, e-mail: elvira.sybambaeva@gmail.ru, https://orcid.org/0000-0001-5963-855X.

Dinara Sh. Shagieva - PhD, Assistant of the Nursing department at NCJSC «Semey Medical University», e-mail: dinara.shagiyeva@smu.edu.kz, https://orcid.org/0009-0009-2278-9624

Assiya. A Yessenbayeva -PhD, Assistant of the Nursing department at NCJSC «Semey Medical University», e-mail: assiya.yessenbayeva@smu.edu.kz, https://orcid.org/0000-0001-6195-2142.

Merey M. Askarova - master degree, Assistant of the Nursing department at NCJSC «Semey Medical University», e-mail: merei.sagadiyeva@smu.edu.kz**,** https://orcid.org/0009-0002-6936-2010.

Corresponding author:

Meruert R. Massabayeva – Center of Research Laboratory of NC JSC “Semey Medical University”, Semey city, Republic of Kazakhstan, https://orcid.org/0000-0001-8240-361X

Postal address: Republic of Kazakhstan, 071400, Semey city, 103 Abay Kunanbayev str.

E-mail: meruyert.massabayeva@smu.edu.kz

Mobile phone number: +77007770230