Impact Factor: 5.723

ISSN: 2181-0982
DOI: 10.26739/2181-0982
www.tadqiqot.uz

# JNNR

## JOURNAL OF NEUROLOGY AND NEUROSURGERY RESEARCH

VOLUME 3, ISSUE 5

2022

ISSN 2181-0982

Doi Journal 10.26739/2181-0982

# ЖУРНАЛ НЕВРОЛОГИИ И НЕЙРОХИРУРГИЧЕСКИХ ИССЛЕДОВАНИЙ

ТОМ 3 НОМЕР 5

# JOURNAL OF NEUROLOGY AND NEUROSURGERY RESEARCH

VOLUME 3, ISSUE 5

ТОШКЕНТ-2022

# ЖУРНАЛ НЕВРОЛОГИИ И НЕЙРОХИРУРГИЧЕСКИХ ИССЛЕДОВАНИЙ

Бухарский государственный медицинский институт и tadqiqot.uz





Рецензируемый научно-практический журнал “Журнал неврологии и нейрохирургических исследований”
Публикуется 4 раза в год
№5 (03), 2022
ISSN 2181-0982

**Адрес редакции:**
ООО Tadqiqot город Ташкент, улица Амира Темура пр.1, дом-2.
web: http://www.tadqiqot.uz/;
Email: info@tadqiqot.uz
Тел: (+998-94) 404-0000

Макет и подготовка к печати проводились в редакции журнала.

**Дизайн - оформления:**
Хуршид Мирзахмедов

Журнал зарегистрирован в Управлении печати и информации г. Ташкента Рег. № от 01.07.2020 г.

“Неврологии и нейрохирургических исследований” 5/2022

**Электронная версия журнала на сайтах:**
https://tadqiqot.uz
www.bsmi.uz

MINISTRY OF HEALTH OF THE REPUBLIC OF UZBEKISTAN PUBLIC ASSOCIATION OF NEUROLOGISTS OF UZBEKISTAN

# JOURNAL OF NEUROLOGY AND NEUROSURGICAL RESEARCH

Bukhara State Medical Institute and tadqiqot.uz



Peer-reviewed scientific and practical journal "Journal of Neurology and Neurosurgical Research"
Published 4 times a year
#5 (03), 2022
ISSN 2181-0982

**Editorial address:**
Tadqiqot LLC the city of Tashkent, Amir Temur Street pr.1, House 2.
Web: http://www.tadqiqot.uz/;
Email: info@tadqiqot.uz
Phone: (+998-94) 404-0000

Layout and preparation for printing held in the editorial office of the journal.

**Design – pagemaker:**
Khurshid Mirzakhmedov

Journal is registered at the Office of Press and Information Tashkent city, Reg. No. July 1, 2020

"Neurology and neurosurgical research" 5/2022

**Electronic version of the Journal on sites:**
www.tadqiqot.uz,
www.bsmi.uz

# СОДЕРЖАНИЕ | CONTENT

ISSN: 2181-0982
www.tadqiqot.uz
JOURNAL OF NEUROLOGY AND NEUROSURGERY RESEARCH
ЖУРНАЛ НЕВРОЛОГИИ И НЕЙРОХИРУРГИЧЕСКИХ ИССЛЕДОВАНИЙ

УДК 616.831-005

**Khaydarova Dildora Kadirovna**
**Raupova Nasiba Shokirovna**
Tashkent Medical Academy.
Tashkent State Dental Institute

# NEUROPROTECTIVE TREATMENT IN ACUTE ISCHEMIC STROKE

http://dx.doi.org/10.5281/zenodo.7384678

**ABSTRACT**

The review discusses the role of neuroprotective therapy in the acute period of ischemic stroke in the era of active introduction of reperfusion treatment methods. The main mechanisms of brain damage during ischemia/reperfusion and the leading neuroprotective strategies studied in clinical trials are considered. Neuroprotective approaches aimed at suppressing excitotoxicity, oxidative stress, and neuroinflammation are presented. Current data on the safety and efficacy of uric acid, edaravone, fingolimod, natalizumab, interleukin 1 receptors antagonists, cerebrolysin, and other drugs have been analyzed. Non-drug methods of neuroprotection are characterized, including remote ischemic conditioning, therapeutic hypothermia, and neurostimulation. According to the author's position, the safest and most effective neuroprotective agent in acute ischemic stroke is neuroprotective treatment.

**Keywords:** stroke; neuroprotection; inflamation; ischemic conditioning;

**Хайдарова Дилдора Кадировна**
**Раупова Насиба Шокировна**
Ташкентская медицинская академия.
Ташкентский государственный стоматологический институт

# НЕЙРОПРОТЕКТОРНОЕ ЛЕЧЕНИЕ ПРИ ОСТРОМ ИШЕМИЧЕСКОМ ИНСУЛЬТЕ

**АННОТАЦИЯ**

В обзоре обсуждается роль нейропротекторной терапии в остром периоде ишемического инсульта в эпоху активного внедрения реперфузионных методов лечения. Рассмотрены основные механизмы повреждения головного мозга при ишемии/реперфузии и ведущие нейропротекторные стратегии, изученные в клинических исследованиях. Представлены нейропротекторные подходы, направленные на подавление эксайтотоксичности, окислительного стресса и нейровоспаления. Проанализированы современные данные о безопасности и эффективности препаратов мочевой кислоты, эдаравона, финголимода, натализумаба, антагонистов рецепторов интерлейкина-1, церебролизина и других препаратов. Охарактеризованы немедикаментозные методы нейропротекции, в том числе дистанционное ишемическое кондиционирование, лечебная гипотермия, нейростимуляция. По мнению автора, наиболее безопасным и эффективным нейропротекторным средством при остром ишемическом инсульте является нейропротекторное лечение.

**Ключевые слова**: инсульт; нейропротекция; воспаление; ишемическое кондиционирование;

**Introduction.** Stroke remains a serious health issue that impacts millions of individuals worldwide, representing the second-most common cause of mortality and the third-most common cause of disability. Approximately 60–80% of all strokes are ischemic and result from thrombotic or embolic occlusion of a cerebral artery. The management of acute ischemic stroke has undergone many changes. Regarding recanalization therapies such as thrombolysis and mechanical thrombectomy, the number of patients who may benefifit from them is still low. Therefore, different therapeutic strategies have been developed, targeting the pathophysiological cascade that starts with ischemia and leads to irreversible tissue damage.

The increase in the ageing population has led to the requirement of a substantial therapy that can restrain the mortality and morbidity rate among AIS patients. Till date the only US FDA-approved drug therapy for ischemic stroke is the intravenous (iv.) thrombolysis with tissue plasminogen activator (t-PA); that must be administered within 4.5 hours of the symptom onset. The short window period of the therapeutic intervention limits its usage and only 2–5% of the population gets the benefit of the drug [2]. Moreover, the recently reported clinical trials have raised concerns regarding the utility of other acute treatment options such as the modern endovascular therapy with mechanical thrombectomy and intra-arterial fibrinolysis [3,4]. Therefore, there is a substantial need for the development of an effective and safe therapy that will benefit a large number of ischemic stroke patients

For the last two decades, neuroprotective agents designed to block these cascades (Table 1) have been investigated in animal models of cerebral ischemia. Numerous agents have been found to reduce infarct size in rodent, rabbit, and primate stroke models. However, translation of neuroprotective benefits from the laboratory bench to the emergency room has not been successful. According to a recent review,of 178 controlled clinical trials that were published in the stroke-related literature, more than 100 were related to neuroprotection. Reasons for the failures have led to intense discussion for the last several years. In this review, we will discuss some of the key trials of neuroprotective therapy, potential problems leading to the failures of these trials, and

possible correction of those mistakes, which may form a basis for future trials.

**Table 1.**

**Families of Neuroprotective Agents and Their Prototype Drugs**

| Proposed Mechanism of Neuroprotection | Drugs | Clinical Trials and Results |
|---|---|---|
| Glutamate receptor antagonists | | |
| NMDA antagonists | Selfotel (CGS19755) | Complete/no benefit |
| | Eliprodil | Halted/no benefit |
| | Aptiganel (Cerestat, CNS1102) | Complete/no benefit |
| | MgSO4 | Ongoing/result pending |
| AMPA antagonist | YM872 | Ongoing/result pending |
| Ion channel modulators | | |
| Calcium channel blockers | Nimodipine | Complete/no benefit |
| | Flunarizine | Complete/no benefit |
| Sodium channel blockers | Fosphenytoin | Complete/no benefit |
| Potassium channel activator | Maxipost (BMS-204352) | Complete/no benefit |
| Anti-inflammatory agents | Enlimomab | Complete/worsening |
| | LeukArrest (Hu23F2G) | Halted/no benefit |
| | rNIF | Halted/no benefit |
| Free radical scavengers | Tirilazad (U70046F) | Complete/no benefit |
| | Citicoline (cytidyl diphosphocholine) | Complete/no benefit |
| | Ebselen | Ongoing/result pending |
| | NXY-059 | Ongoing/result pending |

**Glutamate antagonists**

Some of the most studied neuroprotective agents are glutamate antagonists. Glutamate is the most common excitatory neurotransmitter in the CNS and is released excessively during ischemia. Various postsynaptic neuron receptors are activated by glutamate including NMDA, AMPA, KA, and metabotropic receptors. Activation of most of these receptors is associated with calcium ion (Ca2+) influx with secondary Ca2+-mediated cellular enzymatic activation leading to cell damage and cell death including necrosis and apoptosis

**Anti-inflammatory agents**

Neuroprotection may be achieved by targeting the inflammatory processes and mediators that contribute to the production of brain injury following ischemic stroke. Enlimomab, a murine anti-intracellular adhesion molecule (ICAM)-antibody specific to the human receptor ICAM-1 receptor, was studied in preclinical and clinical trials. By blocking the ICAM-1 receptor, and thus inhibiting neutrophil adhesion and migration through the vascular endothelium, Enlimomab was shown to reduce the damage in stroke models. However, the clinical trial failed; patients who received Enlimomab were harmed relative to placebo controls. Another agent, LeukArrest (Hu23F2G), is a monoclonal antibody that targets the neutrophil CD11/CD18 cell adhesion molecule. A phase III trial of LeukArrest in patients who had anischemic stroke was terminated because the interim results were unfavorable.

**Calcium channel blockers.**

Activation of intracellular destructive enzymes results from abnormal calcium influx during ischemic-triggered cascades, which leads to brain tissue damage. Therefore, calcium channel blockers might potentially have a neuroprotective role. Nimodipine is a dihydropyridine calcium channel blocker; it dilates the intracranial circulation and might be beneficial if it improves the regional blood flow in the margins of the brain infarct. This drug was studied using multiple doses in 1,064 patients treated within 48 h from stroke onset. No overall benefit was found, although a meta-analysis showed a statistically significant effect of one of the doses when the drug was administered within 12 h. Very Early Nimodipine Use in Stroke was another clinical trial that used nimodipine within 6 h after stroke onset.The trial was ended prematurely because of lack of benefit on a futility analysis. Moreover, upon reviewing 47 trials that included 7,665 patients and that used calcium antagonists for stroke therapy, Horn et al.found no benefit of these agents in stroke therapy.

**Serotonin agonists**

Serotonin agonists may serve as neuroprotectants by activating postsynaptic serotonin receptors (5-HT1A) with secondary increase in potassium efflux, inhibition of cell excitability during the ischemic insult, and protection of neurons from glutamate-mediated neuronal death. Repinotan (BAY X3702) is one of these agonists that has a high affinity for serotonin (5-HT1A) receptors. It has been shown to reduce excitotoxic neuronal death and was shown to be an effective neuroprotectant in a rat focal ischemic brain injury. A phase II clinical trial studied Repinotan in 240 patients and showed a better neurologic and functional outcome at 4 weeks and 3 months with a dose of 1.25 mg/day for 3 days when the agent was given within 6 h after stroke onset. A phase IIb trial has been projected to include 680 patients with a window of administration of 4.5 h.

**Caspase inhibitors**

Cerebrolysin Cerebrolysin is currently approved for the treatment of ischemic and hemorrhagic stroke in 45 countries. The molecule is a porcine brainderived preparation of low molecular weight neuropeptides and free amino acids. The neuroprotective properties of this drug molecule include anti-excitotoxicity, inhibition of free radical formation, microglia activation, and apoptosis. Additionally, it also exhibits neurotrophic action, promotes neuronal sprouting, improves cellular survival and stimulates neurogenesis [21]. Animal studies have shown that this molecule can improve the neurological function and reduce the infarct size, by preventing the free radical formation and counteracting excitotoxicity that can prevent cell death [22–24]. Clinical studies were conducted to study the safety and efficacy of cerebrolysin in AIS patients

Apoptosis has been suggested to be one of the key elements in delayed brain injury after ischemic stroke

One of the important factors in the apoptosis cascade is caspase activation. Caspases are a group of cysteine proteases that cleave various proteins associated with neuronal apoptosis including poly(ADP-ribose) polymerase (PARP), DNA-dependent protein kinase, U1-soluble nuclear RNA polymerase (U1-snRNP), spectrin, lamin A, actin, and protein kinase C. Activation of caspases has been shown in some animal ischemic models, while inhibition of caspase activity reduced infarction size in rodent ischemia stroke models.47,48 Chen et al49 further demonstrated that caspase inhibitor Z-VAD improved the survival of grafted bone marrow cells in rats subjected to unilateral MCA occlusion, and significantly improved their functional outcome. Although evidence in preclinical studies is reasonable, none of the caspase inhibitors has yet been tested in a clinical trial, probably because many of the caspase inhibitors are irreversible and have poor brain penetration.

**Results and discussion.**

Although evidence from preclinical studies has been exciting and many drugs have progressed to multi-center clinical trials, none of the neuroprotective agents has been proven to be clinically beneficial. In this section, potential problems that hindered the translation of preclinical success into clinical practice will be discussed.By learning from our past mistakes, we may be able to have more successful studies in the future.

The discrepancies between preclinical studies and clinical trials may be the cause of some of the problems encountered previously. Below are five suggested discrepancies that may explain some of the disappointing outcomes.

**Discrepancies on the outcome measures.**

In most preclinical studies, efficacy of neuroprotective agents was detected by reduction of histological infarction volume. However, in clinical trials, neuroprotective efficacy is measured by neurological function such as the NIH Stroke Scale and the modified Rankin Scale. Infarction volumes correlate poorly with functional outcome because small lesions in critical locations can produce major functional deficits. Conversely, large lesions in relatively silent areas cause little detectable function loss. While most of animal stroke models used in preclinical neuroprotection studies are MCA occlusion models, patients enrolled into clinical trials often include infarcts of diverse brain regions. Thus, some animal models may be poor predictors of clinical trial results.

Another factor that may play a role in the discrepancies between preclinical and clinical study outcomes is the difference in the composition of brain between rodents and humans. It has been reported that more than 90% of brain tissue in rodents is composed of gray matter, whereas in human, gray matter makes up about 50% of the brain. Even in the most homogeneous population of cortical stroke patients, the damage to white matter in humans will be significantly larger than in rodent models. This is not necessarily important, but is a reason to be cautious in extrapolation of rodent model results to humans, particularly for drugs that have differential effects in white versus gray mater. Various families of neuroprotective agents target different aspects of the neurodegenerative cascade. Thus, used in combination, they may have synergistic effects against ischemic injury. For this reason, the dose of each drug may be reduced to limit the drug toxicity and increase patient tolerability; however, combining two or more drugs in the same study will add to the complexity of trial design.

**Conclusion.**

From the line of evidence it appears that neuroprotective agents have a rather bleak future in the treatment of AIS. Pre-clinical studies have shown that the administration of neuroprotective agents offers significant improvement in the reduction of brain infarct size and improvement in the functional outcomes. For the last two decades, the search for the neuroprotective therapies for acute ischemic stroke has experienced a roller coaster ride. Early success in the preclinical studies may have prematurely pushed numerous agents into clinical trials. Translating bench success to the bedside proof of efficacy and safety has been frustrating. Lack of satisfactory animal models resembling the human disease, and discrepancies between preclinical studies and clinical trials have proven costly. However, we have one important success: rt-PA is approved for acute stroke management in many countries because it is truly effective and safe when administered properly. Much more needs to be done; learning from past failures, we have reasons to believe that at least some of the neuroprotective agents will be proven to be beneficial.

**References**


1. G.A. Donnan, M. Fisher, M. Macleod, et al., Stroke. Lancet Lond Engl. 371 (9624) (2008) 1612–1623
2. S.D. Reed, S.C. Cramer, D.K. Blough, et al., Treatment with tissue plasminogen activator and inpatient mortality rates for patients with ischemic stroke treated in community hospitals, Stroke 32 (8) (2001) 1832–1840.
3. J.L. Saver, R. Jahan, E.I. Levy, et al., Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial, Lancet Lond Engl. 380 (9849) (2012) 1241–1249.
4. R.G. Nogueira, H.L. Lutsep, R. Gupta, et al., Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial, Lancet Lond Engl. 380 (9849) (2012) 1231–1240.
5. J. Minnerup, B.A. Sutherland, A.M. Buchan, et al., Neuroprotection for stroke: current status and future perspectives, Int J Mol Sci 13 (9) (2012) 11753–11772.
6. A.R. Green, Pharmacological approaches to acute ischaemic stroke: reperfusion certainly, neuroprotection possibly, Br J Pharmacol 153 (Suppl.1) (2008) S325–338.
7. Review Manager (RevMan) [Computer program]. Version 5.3, The Nordic Cochrane Centre. The Cochrane Collaboration, Copenhagen, 2014. [8] N. Garrido-Mesa, A. Zarzuelo, J. Gálvez, Minocycline: far beyond an antibiotic, Br J Pharmacol 169 (May (2)) (2013) 337–352.
8. Д.К. Хайдарова, А.У. Самадов. Совершенствование нейропротекторной терапии при остром ишемическом инсульте. Журнал "Медицина и инновации. №3. 2021. С. 92-98.
9. Khodjieva D. T. Review clinical assessment of the manifestations of social disadaptation in patients with cerebral stroke. Journal of Critical Reviews. 2020. P 203-204
10. JurayevA.M., Khalimov R.J. New methods for surgical treatment of Perthes Disease in children. International Journal of Psychosocial Rehabilitation, Vol 24, Issue 02, 2020. P.301-307
11. R. Dj.Khalimov, A.M.Djurayev, Kh.R. Rakhmatullayev Rehabilitation Program For Children Withperthes Disease. Turkish Journal of Physiotherapy and Rehabilitation. 32(3).2021. P.18403 – 18406
12. AM Dzhuraev, RD Khalimov Our experience in the surgical treatment of Perthes disease in children. Postgraduate Physician 2012. N1.3 Том 50.P. 377-383.
13. N. Matsukawa, T. Yasuhara, K. Hara, et al., Therapeutic targets and limits of minocycline neuroprotection in experimental ischemic stroke, BMC Neurosci 10 (2009) 126.
14. H.F. Elewa, H. Hilali, D.C. Hess, et al., Minocycline for short-term neuroprotection, Pharmacotherapy 26 (4) (2006) 515–521.
15. Khaydarova Dildora Kadirovna, Samadov Alibek Uktamovich. Pharmacodynamic Properties Of Some Non-Neuroprotective Drugs Widely Used In The Treatment Of Ischemic Stroke. Turkish Journal of Physiotherapy and Rehabilitation. 2021
16. Akramova D., Rakhimbaeva G., Vakhabova N. &Akramova., N.(2017). Stroke incidence and association with risk factorsin women in Uzbekistan //CEREBROVASCULAR DISEASES. – T. 43.

17. M.V. Padma Srivastava, A. Bhasin, R. Bhatia, A. Garg, S. Gaikwad, K. Prasad, et al., Efficacy of minocycline in acute ischemic stroke: a single-blinded, placebo-controlled trial, Neurol India 60 (1) (2012) 23–28.
18. Akramova D., Rakhimbayeva G., Akramova N. The frequency or vascular parkinsonism in early and< bold> late</bold> stages of Stroke //CEREBROVASCULAR DISEASES. – ALLSCHWILERSTRASSE 10, CH-4009 BASEL, SWITZERLAND : KARGER, 2018. – T. 45. – C. 199-199.
19. Khaydarov N. K. Khodjieva D. T., Khaydarova D. K. New Technologies in Treatment of Patients in the Acute Period of Stroke. American Journal of Medicine and Medical Sciences. P.393-396. 2020.
20. ] Akramova D., Rakhimbayeva G., Narzikulova M. Clinical research-lipid spectrum of blood serum at ischemic stroke against the methabolic syndrome //CEREBROVASCULAR DISEASES. – ALLSCHWILERSTRASSE 10, CH-4009 BASEL, SWITZERLAND : KARGER, 2018. – T. 45. – C. 376-376.
21. M.R. Amiri-Nikpour, S. Nazarbaghi, M. Hamdi-Holasou, et al., An open-label evaluator-blinded clinical study of minocycline neuroprotection in ischemic stroke: gender-dependent effect, Acta Neurol Scand. 131 (1) (2015) 45–50.
22. E. Kohler, D.A. Prentice, T.R. Bates, et al., Intravenous minocycline in acute stroke: a randomized, controlled pilot study and meta-analysis, Stroke. 44 (9) (2013) 2493–2499.
23. Akramova D., Gazieva S. The role of the inconsistency of connective tissue in the development of pathological deformations of cerebral vessels in patients with primary headaches //CEREBROVASCULAR DISEASES. – ALLSCHWILERSTRASSE 10, CH-4009 BASEL, SWITZERLAND : KARGER, 2018. – T. 45. – C. 485-485.
24. Kadirovna, K. D., Kadirovich, X. N., & Tadjiyevna, K. D. (2022). Clinical basis for the development of neuroprotective therapy in acute ischemic stroke. International Journal of Health Sciences, 6(S1), 4177–4183. https://doi.org/10.53730/ijhs.v6nS1.5819
25. Akramova D., Rakhimbaeva G. Role of cerebral perfusion in development of vascular parkinsonism //CEREBROVASCULAR DISEASES. – ALLSCHWILERSTRASSE 10, CH-4009 BASEL, SWITZERLAND : KARGER, 2017. – T. 43.
26. Khaydarova Dildora Kadirovna, Samadov Alibek Uktamovich. Optimization of neuroprotective therapy for ischemic stroke in the acute period. Журнал неврологии и нейрохирургических исследований. №3. 2020 С. 13-15.

ISSN 2181-0982

Doi Journal 10.26739/2181-0982

# ЖУРНАЛ НЕВРОЛОГИИ И НЕЙРОХИРУРГИЧЕСКИХ ИССЛЕДОВАНИЙ

ТОМ 3 НОМЕР 5

# JOURNAL OF NEUROLOGY AND NEUROSURGERY RESEARCH

VOLUME 3, ISSUE 5

**Editorial staff of the journals of www.tadqiqot.uz**
Tadqiqot LLC the city of Tashkent,
Amir Temur Street pr.1, House 2.
Web: http://www.tadqiqot.uz/; Email: info@tadqiqot.uz
Phone: (+998-94) 404-0000

**Контакт редакций журналов. www.tadqiqot.uz**
ООО Tadqiqot город Ташкент,
улица Амира Темура пр.1, дом-2.
Web: http://www.tadqiqot.uz/; Email: info@tadqiqot.uz
Тел: (+998-94) 404-0000