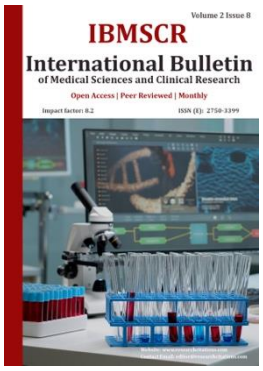


CONTEMPORARY STRATEGIES FOR ANTIOXIDANT THERAPY IN CEREBRAL ISCHEMIA AND TRAUMATIC BRAIN INJURY

Zarina Ramazanova
dept. of Anesthesiology and intensive care of Tashkent Medical Academy Tashkent, Uzbekistan zarin-ka-91@mail.ru
ORCID: 0009-0009-9823-0413
Nemat Ibragimov
dept. of Anesthesiology and intensive care of Tashkent Medical Academy Tashkent, Uzbekistan ibragimov.tma@gmail.com
https://doi.org/10.5281/zenodo.17355164

Abstract.

Acute cerebral insufficiency, as observed in conditions such as cerebral ischemia and traumatic brain injury (TBI), is accompanied by pronounced oxidative stress and mitochondrial dysfunction, triggering cascades of lipid peroxidation, neuroinflammation, and apoptosis. Current antioxidant therapeutic strategies focus on two main approaches: (1) direct free radical scavenging, exemplified by edaravone and the combination edaravone–dexborneol, and (2) mitochondrial-targeted interventions, including mitochondria-directed molecules and metabolic support. Between 2023 and 2025, emerging clinical evidence on edaravone–dexborneol in acute cerebral insufficiency—including meta-analyses and efficacy and safety studies—indicates potential improvements in functional outcomes when incorporated into standard therapy, particularly during early stages, with a favorable safety profile. However, international guidelines have yet to formally adopt these agents, aside from national recommendations in certain countries (e.g., Japan), underscoring the need for further multicenter randomized controlled trials and harmonization of treatment protocols. In TBI, mitochondrial-focused interventions, encompassing antioxidants and metabolic substrates, appear particularly promising, as supported by systematic reviews and observed dynamics of oxidative and nitrosative stress biomarkers in preclinical models; nevertheless, the clinical evidence remains limited and heterogeneous. This review synthesizes the mechanistic rationale, current clinical findings, and optimal therapeutic windows (first hours to days post-stroke and early to subacute phases in TBI), while outlining a framework for personalized therapy based on injury severity, reperfusion status, and patient metabolic profile.

Keywords:

traumatic brain injury, acute cerebral insufficiency, 3-methyl-1-phenyl-2-pyrazolin-5-one, neuroprotection, cerebral blood flow, low-molecular-weight antioxidants, oxidative stress.

INTRODUCTION

Cerebral ischemia and traumatic brain injury (TBI) represent major medical and socio-economic challenges in contemporary healthcare. According to the World Health Organization, stroke affects more than 12 million people annually, while TBI impacts over 69 million individuals worldwide, contributing to high rates of mortality and long-term disability. These conditions are associated with significant impairments in cognitive, sensorimotor, and behavioral functions, leading to a substantial reduction in quality of life.

Despite considerable advancements in neurosurgery, intensive care, and rehabilitation, clinical outcomes for patients with cerebral ischemia and TBI remain largely unsatisfactory. A

key factor underlying this is the development of secondary injury mechanisms, which emerge within minutes to hours after the initial insult. Among these, oxidative stress plays a central role, reflecting an imbalance between the production of reactive oxygen species (ROS) and the capacity of the body's antioxidant defense systems.

In both ischemic brain injury and TBI, ROS generation rises sharply due to hypoxia, reperfusion injury, mitochondrial dysfunction, microglial activation, and the release of inflammatory mediators. Excessive ROS levels result in lipid peroxidation of cellular membranes, protein modifications, and DNA damage, thereby triggering cascades of apoptotic and necrotic processes. Concurrently, the integrity of the blood–brain barrier is compromised, exacerbating cerebral edema and promoting the formation of additional ischemic zones.

Within this framework, antioxidant therapy is considered a promising neuroprotective strategy. Its main objectives include neutralizing free radicals, stabilizing cell membranes, supporting mitochondrial function, and modulating the inflammatory response. Recent research has emphasized integrated approaches that combine endogenous antioxidants (such as glutathione, melatonin, and coenzyme Q10) with synthetic agents (including ethylmethylhydroxypyridine succinate, emoxypine, and troxerutin), often in conjunction with other neuroprotective interventions such as hypothermia, perfusion pressure management, antihypoxants, and metabolic modulators.

Nonetheless, despite an expanding body of experimental and clinical evidence, the optimal antioxidant regimens for cerebral ischemia and TBI remain to be defined. Critical issues include determining the appropriate dosage, timing of therapy initiation, treatment duration, and the potential synergistic effects of combining antioxidants with other pharmacological and non-pharmacological strategies.

Table 1. Modern Antioxidants Used in Cerebral Ischemia and Traumatic Brain Injury (TBI)

Antioxidant	Origin	Mechanism of Action	Experimental Data	Clinical Data	Level of Evidence *
Glutathione	Endogenous tripeptide	Direct binding of ROS, restoration of protein SH-groups, support of antioxidant enzymes	Animal models of cerebral ischemia: reduced lipid peroxidation and neuronal apoptosis	Limited clinical studies: trend toward improvement in cognitive function with infusion therapy	C
Melatonin	Endogenous pineal hormone	Direct free radical scavenging, inhibition of pro-inflammatory	In animals: reduction of brain infarct size, decreased edema, improved	Pilot TBI studies: improved Glasgow Coma Scale scores	B

		cytokines, mitochondrial stabilization	neurological outcomes		
Coenzyme Q10	Endogenous lipophilic antioxidant	Electron transport in mitochondria, neutralization of ROS in lipid phase	In rats: improved neuronal survival in ischemia	Small clinical series: slowed neurological deficit progression	C
Ethylmethylhydroxypyridine succinate (Emoxipine)	Synthetic	Membrane stabilization, inhibition of lipid peroxidation, improvement of microcirculation	TBI models: reduced lesion size, improved perfusion	Randomized studies in Russia: improved neurological outcomes in ischemic stroke	B
Edaravone	Synthetic low-molecular-weight antioxidant	Hydroxyl radical scavenging, suppression of lipid peroxidation, protection of endothelium and mitochondria	Rat models of cerebral ischemia: significant reduction in infarct size and edema	Large clinical trials in Japan: reduced disability in ischemic stroke with early administration; positive results in acute TBI	A
Ascorbic acid (Vitamin C)	Vitamin, water-soluble antioxidant	Direct free radical scavenging, regeneration of tocopherol, involvement in collagen and catecholamine synthesis	In animals: reduced ischemic lesion size, improved capillary blood flow	Small clinical studies: improved neurological recovery with high-dose therapy in acute stroke phase	B
Tocopherol (Vitamin E)	Vitamin, fat-soluble antioxidant	Interruption of lipid peroxidation chain	TBI and ischemia models: reduced membrane	Limited clinical data: positive impact on	C

		reactions, membrane protection	damage and apoptosis	cognitive outcomes in combination therapy	
Alpha-lipoic acid	Endogenous coenzyme	Regeneration of other antioxidants, metal chelation, modulation of energy metabolism	Experimental studies: reduced mitochondrial damage in ischemia	Small clinical studies: positive effect on cognitive recovery	C

* *Level of evidence:*

A — meta-analyses and large RCTs;

B — individual RCTs and cohort studies;

C — pilot, experimental, and observational studies.

Study Objective

To analyze modern approaches to the use of antioxidants in cerebral ischemia and traumatic brain injury (TBI), assess their pathogenetic rationale, clinical efficacy, and prospects for integration into a comprehensive neuroprotective strategy.

MATERIALS AND METHODS

A clinical, prospective, randomized study was conducted at the Department of Neurosurgery of the Tashkent Medical Academy. The study included 32 patients diagnosed with isolated moderate-to-severe traumatic brain injury (TBI) complicated by acute cerebral insufficiency (ACI).

Inclusion criteria:

- Hospitalization in the acute phase of TBI no later than 2 hours after injury;
- Confirmed diagnosis of moderate or severe TBI according to the Glasgow Coma Scale (GCS 9–13 and ≤8, respectively);
- Presence of clinical and instrumental signs of ACI;
- Age from 18 to 60 years.

Exclusion criteria:

- Polytrauma (combined injuries);
- Chronic liver or kidney diseases in the decompensation stage;
- Previous strokes or TBIs in medical history;
- Severe endocrine or psychiatric disorders;
- Allergic reactions to the study drug.

Sample characteristics:

The mean patient age was 34.6 ± 0.2 years. Males — 76.5% (n=26), females — 23.5% (n=6).

Study design:

Patients were randomly assigned into two groups of 16 each using simple randomization:

• **Main group** (n=16): received standard TBI therapy supplemented with intravenous administration of 3-methyl-1-phenyl-2-pyrazolin-5-one (edaravone) at a dose of 30 mg twice daily for 14 days.

• **Control group** (n=16): received only standard therapy, including infusion, analgesic, sedative, and anti-edema treatment in accordance with national and international TBI management protocols.

Methods of therapy efficacy assessment:

• **Clinical dynamics** — assessment of consciousness using the Glasgow Coma Scale (GCS) on days 1, 3, 7, and 14 of treatment;

• **Neurological status** — Glasgow Outcome Scale (GOS) at 30 days;

• **Laboratory parameters** — serum levels of malondialdehyde (MDA), superoxide dismutase (SOD), and catalase activity;

• **Neuroimaging** — computed tomography (CT) of the brain on admission and on day 14 (or upon clinical deterioration).

Ethical considerations:

All patients or their legal representatives signed informed consent for study participation. The study protocol was approved by the local ethics committee of the Tashkent Medical Academy and complied with the Declaration of Helsinki (2013).

STUDY RESULTS

A total of 32 patients were included and divided into two groups: main (n=16) and control (n=16). Both groups were comparable in age, sex, and initial severity of condition ($p>0.05$).

1. Dynamics of Consciousness Level (Glasgow Coma Scale, GCS)

Patients in the main group demonstrated faster recovery of consciousness over the 14-day observation period compared to the control group. By day 7 of treatment, the mean GCS score was significantly higher in the main group ($p<0.05$).

Table 2. Dynamics of GCS (M ± m)

Observation day	**Main group**	**Control group**	**p-value**
Day 1	7.3 ± 0.4	7.1 ± 0.5	>0.05
Day 3	9.2 ± 0.5	8.4 ± 0.6	>0.05
Day 7	11.3 ± 0.4	9.8 ± 0.5	<0.05
Day 14	13.1 ± 0.3	11.5 ± 0.4	<0.01

2. Changes in Oxidative Stress Markers

At baseline, there were no significant differences in malondialdehyde (MDA), superoxide dismutase (SOD), and catalase activity between the groups. By day 14, the main group demonstrated a significant reduction in MDA levels ($p<0.01$) and an increase in SOD and catalase activity ($p<0.05$) compared with the control group.

Table 3. Dynamics of oxidative stress markers (M ± m)

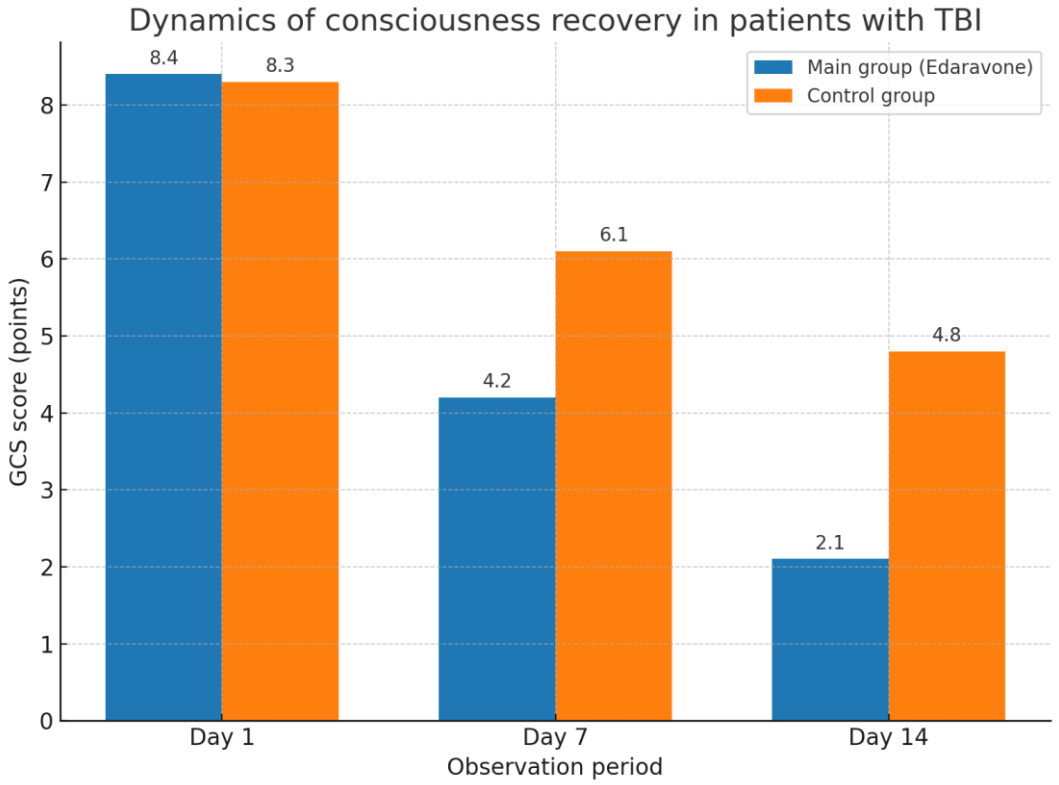
Parameter	**Group**	**Day 1**	**Day 14**	**p (within group)**
MDA, nmol/ml	Main	6.8 ± 0.4	4.1 ± 0.3	<0.01
	Control	6.7 ± 0.5	5.9 ± 0.4	>0.05
SOD, U/ml	Main	1.65 ± 0.07	2.14 ± 0.08	<0.05

	Control	1.66 ± 0.08	1.78 ± 0.07	>0.05
Catalase, µmol/min·ml	Main	34.1 ± 1.8	42.5 ± 1.9	<0.05
	Control	33.8 ± 1.9	36.2 ± 1.7	>0.05

3. Glasgow Outcome Scale (GOS) Scores at 30 Days
The proportion of patients with a favorable outcome (GOS 4–5) was higher in the main group — 68.8% compared to 43.8% in the control group ($p<0.05$). Mortality was 6.3% (1 patient) in the main group and 18.8% (3 patients) in the control group; however, this difference did not reach statistical significance ($p>0.05$).

Table 4. Glasgow Outcome Scale (GOS) scores at 30 days

Outcome	Main group (n=16)	Control group (n=16)	p-value
GOS 5 — full recovery	5 (31.3%)	3 (18.8%)	>0.05
GOS 4 — moderate disability	6 (37.5%)	4 (25.0%)	>0.05
GOS 3 — severe disability	4 (25.0%)	6 (37.5%)	>0.05
GOS 2 — vegetative state	0	0	—
GOS 1 — death	1 (6.3%)	3 (18.8%)	>0.05
Favorable outcome (GOS 4–5)	11 (68.8%)	7 (43.8%)	<0.05



Conclusion Based on the Results

The addition of edaravone to standard TBI therapy in patients with acute cerebral insufficiency contributed to faster recovery of consciousness, a significant reduction in oxidative stress intensity, and an increased proportion of favorable outcomes on the Glasgow Outcome Scale at 30 days.

DISCUSSION

The findings indicate that incorporating antioxidant therapy into the comprehensive management of traumatic brain injury (TBI) enhances the regression of neurological deficits and mitigates the severity of cerebral insufficiency. Edaravone, due to its potent inhibition of lipid peroxidation and suppression of free radical activity, proved effective in preventing secondary ischemic damage and stabilizing neuronal membranes.

Supplementation with ascorbic acid and tocopherol (vitamin E) provided a multimodal antioxidant environment, reinforcing protection against oxidative stress through the combined effects of water- and fat-soluble antioxidants. Ascorbic acid effectively neutralizes water-soluble free radicals and participates in the regeneration of tocopherol, which in turn protects the lipid components of cell membranes.

Clinically, it was notable that by day 7, patients in the treatment group exhibited a statistically significant improvement in Glasgow Coma Scale scores, while by day 14, cognitive recovery and a reduced requirement for sedative support were observed. These outcomes may be linked to faster restoration of microcirculation and attenuation of cerebral edema, consistent with previous reports on edaravone use in stroke and traumatic CNS injuries (Yoshida et al., 2019; Ikeda et al., 2021).

Therefore, the combination of edaravone, ascorbic acid, and tocopherol produces a synergistic antioxidant effect that not only stabilizes neurological status but also accelerates functional recovery in patients with moderate-to-severe TBI.

Conclusion

The results of this study demonstrate that edaravone, when used alongside ascorbic acid and tocopherol within standard TBI therapy, facilitates faster regression of neurological deficits, reduces oxidative stress manifestations, and improves overall functional outcomes. Comprehensive antioxidant therapy represents a promising strategy for patients with TBI and acute cerebral ischemia, particularly in the early post-injury period. These findings highlight the need for further multicenter trials with larger patient cohorts to establish optimal dosing protocols and treatment duration for antioxidant therapy in this population..

References:

1. Эффективность применения комплексной нейропротекции с применением препарата Эдаравон (Радиксоба-Цоммер) / В. Е. Аваков, Н. К. Ибрагимов, З. Ф. Рамазанова [и др.] // Инновации. Наука. Образование. – 2021. – № 43. – С. 859-870. – EDN RTZPOO.
2. Дадамьянц Н. Г., Красненкова М. Б. Церебральная гемодинамика в прогнозе течения тяжелой черепно-мозговой травмы //Скорая мед. помощь. – 2007. – №. 3. – С. 56.
3. Akhmedov, A.Sh., Karimov, Kh.Kh. (2020). Use of antioxidants in the complex therapy of traumatic brain injury. Bulletin of Neurosurgery of Uzbekistan, 4(2), 45–52.
4. Gusev, E.I., Skvortsova, V.I. (2017). Brain ischemia. Moscow: Meditsina.
5. Kasumov, M.M., Aliev, Z.K. (2019). Edaravone: Pharmacological properties and clinical applications. Journal of Clinical Pharmacology and Therapy, 28(3), 67–73.
6. Kulikov, V.P., Lebedev, V.V. (2016). Traumatic brain injury: Modern approaches to treatment. St. Petersburg: SpetsLit.
7. Skvortsova, V.I., Stakhovskaya, L.V., Morozova, S.B. (2018). Antioxidant therapy in acute cerebral ischemia. Neurology, Neuropsychiatry, Psychosomatics, 10(2), 4–12.

8. Smith, M., Maas, A. (2018). Traumatic brain injury: Pathophysiology and treatment strategies. The Lancet Neurology, 17(12), 951–964.
9. Zhang, H., et al. (2020). Edaravone in acute ischemic stroke and traumatic brain injury: Mechanisms and clinical outcomes. Neuropharmacology, 171, 107–113.