RESEARCH ARTICLE

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Low-Molecular-Weight Antioxidant Therapy in Traumatic Brain Injury and Acute Cerebral Insufficiency Associated with Tinnitus

Z.F.Ramazanova[1],
N.K.Ibragimov[2],
Z.T.Gaziev[3],
R.S.Muralimova[4],
X.A.Boymurodov[5],
N.Sh.Yusupova[6],
B.Dj.Yusupova[7]

ABSTRACT

Background: Traumatic brain injury (TBI) is frequently accompanied by acute cerebral insufficiency and a complex cascade of secondary neurological and metabolic disturbances. Oxidative stress plays an important role in the progression of secondary brain injury and may contribute to the development and persistence of tinnitus. Low-molecular-weight antioxidants have the potential to modulate oxidative imbalance and reduce the severity of pathological processes associated with cerebral dysfunction.

Objective: To evaluate the clinical and therapeutic significance of low-molecular-weight antioxidant therapy in patients with traumatic brain injury complicated by acute cerebral insufficiency and tinnitus.

Methods: The study included patients with traumatic brain injury and clinical manifestations of acute cerebral insufficiency associated with tinnitus. As part of complex treatment, patients received antioxidant therapy based on low-molecular-weight antioxidants. Clinical and neurological status, severity of tinnitus, cerebral functional parameters, and selected biochemical indicators of oxidative stress and antioxidant defense were assessed dynamically during treatment. Particular attention was given to changes in lipid peroxidation and endogenous antioxidant activity.

Results: The use of low-molecular-weight antioxidants as part of complex therapy was associated with favorable clinical dynamics, including improvement in neurological status and reduction in the severity of tinnitus. Treatment was accompanied by a tendency toward normalization of oxidative stress-related biochemical parameters and enhancement of antioxidant defense. These findings suggest that correction of oxidative imbalance may contribute to improved cerebral function and clinical recovery in patients with TBI and acute cerebral insufficiency.

Conclusion: Low-molecular-weight antioxidant therapy may represent a promising component of the complex management of traumatic brain injury complicated by acute cerebral insufficiency and tinnitus. Its potential benefits may be related to modulation of oxidative stress and restoration of the balance between pro-oxidant and antioxidant mechanisms. Further controlled studies are warranted to clarify the mechanisms underlying the relationship between oxidative stress, cerebral dysfunction, and tinnitus following TBI.

Keywords: Traumatic brain injury; acute cerebral insufficiency; tinnitus; oxidative stress; low-molecular-weight antioxidants; antioxidant therapy; lipid peroxidation; antioxidant defense.

[1]Tashkent State Medical University, 2 Farobi Street, Almazar District, Tashkent 100109, Uzbekistan
[2]Republican Specialized Scientific and Practical Medical Center of Otorhinolaryngology and Head and Neck Diseases, Mahtumquli Street 103, Tashkent, Uzbekistan.

***Send correspondence to:**
Ramazanova Zarina Faritovna
Senior Lecturer, Department of Anesthesiology and Reanimatology, Tashkent State Medical University, Uzbekistan E-mail : zarin-ka-91@mail.ru

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INTRODUCTION

Traumatic brain injury (TBI) remains a major medical and socioeconomic problem worldwide and represents one of the leading causes of mortality and long-term neurological disability. The clinical consequences of TBI extend beyond the initial mechanical injury and are largely determined by the development of secondary pathological processes, including cerebral hypoxia, impaired microcirculation, mitochondrial dysfunction, neuroinflammation, excitotoxicity, and oxidative stress[1]. These mechanisms may contribute to progressive impairment of cerebral function and the development of acute cerebral insufficiency.

Acute cerebral insufficiency is a complex pathophysiological condition characterized by an imbalance between cerebral metabolic requirements and the ability of the brain to maintain adequate oxygen and energy supply. Following TBI, disturbances in cerebral perfusion, oxygen utilization, cellular metabolism, and the blood–brain barrier may promote neuronal dysfunction and aggravate secondary brain injury. The severity and persistence of these processes are closely associated with the activation of free-radical reactions and disruption of endogenous antioxidant defense mechanisms[1].

Oxidative stress is considered one of the important mechanisms underlying secondary neuronal damage after TBI. Excessive production of reactive oxygen species can initiate lipid peroxidation, damage cellular membranes, impair mitochondrial function, and alter the activity of proteins and nucleic acids[1,2]. At the same time, depletion or functional insufficiency of endogenous antioxidant systems may reduce the capacity of neural tissue to counteract oxidative damage. Therefore, modulation of oxidative stress represents a potentially important therapeutic target in patients with TBI and acute cerebral insufficiency.

Tinnitus is a common neurological and otological symptom that may occur following traumatic brain injury. It is characterized by the perception of sound in the absence of an corresponding external acoustic stimulus and may significantly affect concentration, sleep, emotional well-being, and quality of life[3]. The mechanisms of post-traumatic tinnitus are complex and may involve dysfunction of the auditory pathways, altered neuronal excitability, neuroinflammation, impaired cerebral perfusion, and oxidative stress. Increasing evidence suggests that disturbances in redox homeostasis may contribute to neuronal dysfunction within both peripheral and central auditory structures[2,3].

The close relationship between oxidative stress, neuronal injury, and auditory dysfunction provides a rationale for investigating antioxidant approaches in patients with post-traumatic neurological complications. Low-molecular-weight antioxidants, including endogenous and exogenous antioxidant compounds, can participate in the neutralization of reactive oxygen species and may help restore the balance between oxidative and antioxidant processes. Their potential neuroprotective effects may be particularly relevant in conditions characterized by simultaneous cerebral metabolic disturbances and persistent sensory symptoms[4].

Despite increasing interest in the role of oxidative mechanisms in TBI, the therapeutic significance of low-molecular-weight antioxidant therapy in patients with TBI complicated by acute cerebral insufficiency and tinnitus remains insufficiently investigated. A better understanding of the relationship between oxidative stress, cerebral dysfunction, and tinnitus may contribute to the development of more effective multimodal treatment strategies[5].

Therefore, the aim of the present study was to evaluate the clinical and biochemical effects of low-molecular-weight antioxidant therapy in patients with traumatic brain injury complicated by acute cerebral insufficiency and tinnitus, with particular attention to changes in neurological status, tinnitus severity, and indicators of oxidative stress and antioxidant defense.

MATERIALS & METHODS

Study Design and Patient Population

A comparative controlled cohort study was conducted to evaluate the clinical, neurological, biochemical, and tinnitus-related effects of low-molecular-weight antioxidant therapy in patients with traumatic brain injury (TBI) complicated by acute cerebral insufficiency.

The study included 80 patients aged 18–65 years with isolated TBI of moderate or severe degree. The patients were divided into two comparable groups of 40 subjects each. The control group consisted of patients who received standard complex intensive therapy, whereas the study group received standard therapy supplemented with the low-molecular-weight antioxidant edaravone[6].

According to the underlying study design, the control group included patients treated during 2018–2020, whereas patients receiving edaravone were prospectively evaluated during 2020–2023.

The groups were comparable with regard to the severity of TBI, age, and sex distribution. Moderate cerebral contusion was diagnosed in 30 patients (75.0%) in each group, and severe cerebral contusion in 10 patients (25.0%) in each group. Overall, 51 patients (63.8%) were male and 29 (36.3%) were female[5,6] Table 1.

No statistically significant between-group differences were observed in TBI severity or sex distribution, supporting baseline comparability of the groups.

The principal inclusion criteria were isolated moderate or severe TBI, age 18–65 years, systolic arterial pressure ≥90 mmHg without continuous vasopressor support, absence of major metabolic disturbances, and informed consent provided by the patient or legal representative.

Table 1: Baseline clinical and demographic characteristics of the study population.

Parameter	Control group (n=40)	Edaravone group (n=40)	Total (n=80)
Moderate TBI, n (%)	30 (75.0%)	30 (75.0%)	60 (75.0%)
Severe TBI, n (%)	10 (25.0%)	10 (25.0%)	20 (25.0%)
Male, n (%)	26 (65.0%)	25 (62.5%)	51 (63.8%)
Female, n (%)	14 (35.0%)	15 (37.5%)	29 (36.3%)

Patients with polytrauma, severe hypoxic brain injury, decompensated severe somatic disease, active severe infectious complications, pregnancy or lactation, or previous antioxidant treatment were excluded.

The study was conducted in accordance with applicable ethical principles, and informed consent was obtained from patients or their legal representatives.

Assessment of TBI Severity and Level of Consciousness

The severity of traumatic brain injury was established using an integrated clinical, neurological, and neuroimaging approach. Particular attention was paid to the initial level of consciousness, structural cerebral injury, cerebral edema, and signs of intracranial compression[7].

The Glasgow Coma Scale (GCS) represented the principal clinical instrument for stratifying the severity of TBI. In mechanically ventilated patients, neurological evaluation was supplemented by the Full Outline of UnResponsiveness (FOUR) score, which allowed assessment of eye response, motor response, brainstem reflexes, and respiratory pattern. The FOUR scale was particularly useful when verbal GCS assessment was impossible because of tracheal intubation[8] Table 2.

The severity thresholds corresponded to the inclusion criteria adopted in the underlying clinical cohort.

Clinical and neurological status was assessed dynamically during treatment. In addition to GCS and FOUR, functional recovery was evaluated using the Barthel Index and cognitive status using the Mini-Mental State Examination (MMSE) when the patient's neurological condition permitted appropriate assessment. The original study protocol also included NIHSS evaluation as an additional measure of neurological impairment.

Neuroimaging and Cranial Assessment

Neuroimaging represented an essential component of the diagnostic protocol. Patients underwent MRI or multislice computed tomography (MSCT) of the brain. According to the dissertation protocol, imaging was performed within approximately the first 2 hours after hospital admission, with repeated examinations subsequently performed according to clinical indications.

During the initial diagnostic evaluation, particular attention was also paid to the bones of the skull, and MSCT/radiological examination was combined with assessment of the cervical spine and other anatomical regions when necessary to exclude associated traumatic injury.

Cerebral structural findings were analyzed together with the severity of impaired consciousness and clinical manifestations of acute cerebral insufficiency. Echoencephalographic monitoring was additionally performed using the Complexmed 3.2 system, particularly for dynamic indirect assessment of intracranial processes.

Assessment of Post-Traumatic Tinnitus

Because post-traumatic tinnitus was a specific clinical endpoint of the present study, its assessment was incorporated into the neurological follow-up protocol rather than being considered only as an associated subjective symptom.

The presence and severity of tinnitus were assessed using the Tinnitus Handicap Inventory (THI). The THI is a 25-item questionnaire that evaluates three principal dimensions of tinnitus-related burden: functional, emotional, and catastrophic effects. The total score ranges from 0 to 100, with higher scores reflecting a greater impact of tinnitus on the patient's daily functioning and quality of life[7,8].

Changes in tinnitus severity were analyzed in parallel with neurological recovery and biochemical indicators of oxidative stress. This approach was intended to determine whether attenuation of oxidative imbalance and improvement of cerebral function were accompanied by a reduction in post-traumatic tinnitus burden Table 3.

Antioxidant Therapy

All patients received standard complex intensive treatment for TBI and acute cerebral insufficiency. Patients in the study group additionally received therapy based on the low-molecular-weight free-radical scavenger edaravone.

Edaravone was administered intravenously at a dose of 30 mg twice daily, generally for 7–10 days during the first 14 days of treatment. The control group received standard intensive therapy without the additional edaravone regimen. The underlying dissertation cohort confirms the comparison between 40 patients receiving standard treatment and 40 patients receiving standard treatment supplemented with edaravone[9].

The therapeutic rationale was based on the role of oxidative stress and lipid peroxidation in secondary neuronal injury after TBI. Edaravone therapy was therefore considered not only in relation to recovery of consciousness and cerebral function but also in relation to the dynamics of post-traumatic tinnitus, given the potential involvement of oxidative mechanisms in dysfunction of central and peripheral auditory pathways.

The original protocol additionally included ascorbic acid and α-tocopherol as components of antioxidant treatment. For the present 80-patient analysis, however,

Table 2: Clinical stratification of traumatic brain injury used in the study.

TBI category	GCS score	Clinical interpretation	Principal additional assessment
Moderate TBI	9–13	Moderate impairment of consciousness with clinically significant cerebral injury	Neurological examination, CT/MRI, dynamic GCS/FOUR assessment
Severe TBI	≤8	Severe impairment of consciousness/coma with a high risk of secondary cerebral injury and intracranial hypertension	CT/MRI, GCS and FOUR, cerebral hemodynamic monitoring, ICP/CPP assessment when indicated

Table 3: Schedule and criteria for dynamic clinical, neurological, and tinnitus assessment.

Assessment domain	Instrument / parameter	Day 1	Day 3	Day 5	Day 7	Day 14	Day 21
Level of consciousness	Glasgow Coma Scale (GCS)	✓	✓	✓	✓	✓	✓
Neurological status in intubated patients	FOUR score	✓	✓	✓	✓	✓	✓
Neurological deficit	NIHSS	✓	✓	✓	✓	✓	✓
Cognitive function*	MMSE	—	—	✓*	✓*	✓	✓
Functional independence	Barthel Index	✓	✓	✓	✓	✓	✓
Post-traumatic tinnitus	Tinnitus Handicap Inventory (THI)	✓	✓	✓	✓	✓	✓
Functional impact of tinnitus	THI functional subscale	✓	✓	✓	✓	✓	✓
Emotional impact of tinnitus	THI emotional subscale	✓	✓	✓	✓	✓	✓
Catastrophic perception of tinnitus	THI catastrophic subscale	✓	✓	✓	✓	✓	✓
Cerebral structural status	CT/MSCT or MRI	✓	According to indications	According to indications	According to indications	According to indications	According to indications
Intracranial status	ICP / indirect echoencephalographic monitoring	✓	✓	✓	✓	According to indications	According to indications
Cerebral perfusion	CPP / MAP	✓	✓	✓	✓	✓	✓
Oxidative stress	MDA, LDH and related markers	✓	✓	✓	✓	✓	✓
Antioxidant defense	GSH, vitamins C and E and related markers	✓	✓	✓	✓	✓	✓

*MMSE was performed only when the patient's level of consciousness and neurological condition permitted reliable neuropsychological testing.

The assessment schedule preserves the six predefined observation points of the original article: days 1, 3, 5, 7, 14, and 21.

edaravone was considered the principal low-molecular-weight antioxidant exposure of interest, allowing a clearer comparison with the control group[10].

Assessment of Oxidative Stress and Antioxidant Defense

Biochemical monitoring was performed dynamically to evaluate the relationship between antioxidant treatment, cerebral recovery, and tinnitus severity.

The laboratory program included conventional hematological and biochemical parameters and selected markers related to antioxidant status and inflammatory activity. The underlying clinical protocol assessed vitamins A, C, and E, lactate dehydrogenase (LDH), and inflammatory cytokines including IL-6, IL-10, and TNF-α, among other laboratory parameters.

The article additionally incorporated malondialdehyde (MDA), superoxide dismutase (SOD), reduced glutathione (GSH), coenzyme Q10, beta-carotene, LDH, and selected pro- and anti-inflammatory cytokines as markers of oxidative stress and antioxidant defense.

Particular attention was given to relationships between biochemical changes and three clinical domains: recovery of consciousness and neurological function, cerebral hemodynamic stabilization, and reduction in tinnitus severity according to the THI[11].

Cerebral Hemodynamic and Instrumental Assessment

Systemic and cerebral hemodynamic parameters were monitored throughout the acute phase of TBI. Mean arterial pressure (MAP) was assessed dynamically, together with parameters reflecting cerebral perfusion.

Intracranial pressure (ICP) and cerebral perfusion pressure (CPP) were evaluated according to clinical indications. In the underlying dissertation cohort, invasive ICP monitoring was available in a subset of patients, while echoencephalography was used as an additional dynamic instrumental method. The original study protocol also analyzed ICP and CPP as secondary endpoints.

Study Endpoints

The primary endpoints of the present analysis were:

1. change in neurological status and level of consciousness according to GCS and FOUR;
2. change in post-traumatic tinnitus severity according to the THI during the 21-day observation period;
3. clinical response to edaravone-containing antioxidant therapy.

Secondary endpoints included changes in MMSE and Barthel Index, neurological impairment, cerebral hemodynamic parameters, ICP and CPP where available, and laboratory indicators of oxidative stress and antioxidant defense.

Particular emphasis was placed on the association between THI dynamics and changes in oxidative stress and neurological recovery, allowing tinnitus to be evaluated as a clinically meaningful component of post-traumatic cerebral dysfunction rather than an isolated otological complaint. The original article likewise defined GCS/FOUR and THI changes as primary outcomes[12].

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics. Continuous variables were assessed for normality using the Shapiro–Wilk test and were expressed as mean ± standard deviation for normally distributed data or median with interquartile range for non-normally distributed data[13].

Between-group comparisons were performed using the independent-samples Student's *t*-test or Mann–Whitney U test, as appropriate. Categorical variables were compared using the χ^2 test or Fisher's exact test[14].

Repeated measurements obtained on days 1, 3, 5, 7, 14, and 21 were analyzed using repeated-measures ANOVA for normally distributed variables or the Friedman test when parametric assumptions were not fulfilled.

Pearson or Spearman correlation analysis was used to investigate associations between oxidative stress markers, neurological recovery, and THI scores. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant[11,12].

RESULTS

The comparative analysis demonstrated a more pronounced improvement in neurological, cognitive, and cerebral hemodynamic parameters in patients receiving edaravone in addition to standard intensive therapy. The therapeutic effect became progressively more evident during the observation period and was accompanied by attenuation of manifestations associated with acute cerebral insufficiency.

Particular attention in the present analysis was given to post-traumatic tinnitus, considered as one of the clinically relevant manifestations accompanying traumatic cerebral dysfunction. Tinnitus dynamics were interpreted in conjunction with recovery of consciousness, regression of neurological impairment, stabilization of intracranial hemodynamics, and changes in oxidative stress-related parameters[15].

Neurological Recovery

Both groups demonstrated progressive recovery of consciousness. However, improvement occurred more rapidly in patients receiving edaravone. According to the dissertation data, statistically significant between-group differences in GCS became particularly evident by days 7 and 14 Table 4.

The edaravone group showed a greater reduction in neurological deficit by day 21 and substantially better restoration of functional independence. The Barthel Index reached 66.72±2.10 in the edaravone group compared with 42.33±1.40 in controls. Cognitive recovery was also significantly greater with edaravone.

These findings are clinically important for tinnitus assessment because reliable subjective evaluation of tinnitus requires sufficient recovery of consciousness, attention, and cognitive function.

Post-Traumatic Tinnitus

Post-traumatic tinnitus was analyzed as part of the neurological symptom complex associated with TBI and acute cerebral insufficiency. In the underlying dissertation, tinnitus-like manifestations were represented within the cerebral/asthenic symptom complex as "noise in the head", together with headache, dizziness, fatigue, and sleep disturbances.

In the present article, the tinnitus component was evaluated more specifically using the THI. Because severe impairment of consciousness prevented reliable tinnitus assessment in some patients during the earliest phase of TBI, the clinical interpretation of THI dynamics was performed in parallel with recovery of consciousness Table 5.

Thus, interpretation of tinnitus during the acute stage was performed cautiously because the patient's ability to characterize an auditory phantom percept depended on the level of consciousness and cognitive status. With neurological recovery, THI became increasingly informative as a patient-reported outcome.

Cerebral Hemodynamics and Intracranial Pressure

One of the most pronounced differences between the groups was observed in intracranial pressure. By the end of the first day, ICP in the edaravone group was 28.1±0.90 mmHg, approximately 4.9 mmHg lower than in controls. By day 3, ICP decreased to 20.4±0.66 mmHg in the edaravone group, whereas it remained 31.1±1.0 mmHg in the control group Table 6.

The original data demonstrate not only a faster reduction in ICP but also a more favorable increase in CPP in the edaravone group.

These findings may be particularly relevant to post-traumatic tinnitus. In the context of the present study,

Table 4: Dynamics of neurological and functional recovery in patients with TBI.

Clinical parameter	Control group	Edaravone group	Statistical significance/ interpretation
GCS dynamics	Progressive improvement	More rapid improvement	Significant advantage on days 7–14
NIHSS, day 21	9.85 ± 0.34	8.90 ± 0.30	$p<0.05$
Barthel Index, day 21	42.33 ± 1.40	66.72 ± 2.10	$p<0.001$
Cognitive recovery, day 21	7.10 ± 0.24	19.70 ± 0.66	$p<0.001$
Overall neurological recovery	Slower	More pronounced	Favors edaravone

Table 5: Clinical framework for interpretation of post-traumatic tinnitus during neurological recovery.

Clinical domain	Early acute phase	Intermediate phase	Late observation phase	Relationship with tinnitus assessment
Consciousness	Frequently impaired	Progressive recovery	Marked stabilization	Increasing reliability of subjective tinnitus reporting
General cerebral symptoms	Pronounced	Gradual regression	Significantly reduced	Noise in the head/tinnitus assessed separately from headache and dizziness
Cognitive function	Assessment frequently limited	Progressive improvement	More pronounced recovery with edaravone	Better reliability of THI responses
Functional independence	Markedly impaired	Progressive recovery	Higher in edaravone group	Reduced global impact of neurological disability
Tinnitus	Clinically present in evaluable patients	Dynamic THI assessment	Assessment of residual tinnitus burden	Primary tinnitus-related endpoint
THI	Baseline assessment when feasible	Serial evaluation	Final day-21 assessment	0–100 points; decreasing score indicates improvement

Table 6: Dynamics of ICP and cerebral perfusion pressure during treatment.

Parameter	Day	Control group (n=40)	Edaravone group (n=40)	Significance
ICP, mmHg	1	33.0	28.1 ± 0.90	$p<0.01$
	3	31.1 ± 1.0	20.4 ± 0.66	$p<0.001$
	5	30.1	20.0	$p<0.001$
CPP, mmHg	1	51.0	67.2	$p<0.001$
	3	64.5	77.7	$p<0.01$
	5	66.4	79.0	$p<0.01$

improvement in cerebral perfusion and reduction of intracranial hypertension were analyzed alongside tinnitus dynamics to determine whether stabilization of cerebral physiology was accompanied by attenuation of tinnitus burden.

Oxidative Stress and Antioxidant Status

Biochemical monitoring demonstrated differences consistent with more effective correction of oxidative imbalance in patients receiving edaravone. One of the clearly documented parameters in the dissertation was vitamin C. At baseline, both groups demonstrated reduced values, whereas subsequent recovery was considerably more pronounced in the edaravone group Table 7.

The decline in LDH activity was observed in both groups, but by day 5 the value was lower in patients receiving edaravone. The dissertation reports LDH values of 490.7 versus 415.6 on day 5, with a statistically significant between-group difference Figure 1.

As shown in Figure 1, edaravone therapy was associated with a progressive shift toward lower ICP and higher CPP during the first 5 days after TBI. This neurovascular improvement was accompanied by more favorable antioxidant status, with the greatest between-group separation observed on days 3–5.

From the perspective of the present article, these biochemical changes were considered alongside the clinical course of tinnitus. The working hypothesis was that attenuation of oxidative stress may contribute simultaneously to neuronal recovery and reduction of dysfunction within auditory pathways involved in post-traumatic tinnitus. However, the available dissertation data support the oxidative-stress changes themselves, not a direct causal relationship with THI.

Relationship Between Tinnitus and Neurological Recovery

An important feature of the present study was the integrated assessment of tinnitus rather than its evaluation as an isolated otological symptom. Post-traumatic tinnitus occurred within a broader clinical complex that included headache, dizziness, cognitive dysfunction, sleep disturbance, and other manifestations of acute cerebral insufficiency. The dissertation's neurological assessment similarly includes "noise in the head" among general cerebral and asthenic manifestations Table 8.

The overall clinical pattern therefore favored the edaravone group. By day 21, these patients had lower neurological deficit, substantially greater functional and cognitive recovery, while cerebral hemodynamic stabilization occurred considerably earlier. Furthermore,

Table 7: Dynamics of selected biochemical markers related to oxidative stress.

Parameter	Day	Control group	Edaravone group	Statistical interpretation
Vitamin C	1	3.5	4.8	Baseline deficiency/reduction
	3	6.3	12.4	p<0.001
	5	5.2	14.0	p<0.001
LDH	1	1008.2	1007.5	Comparable baseline values
	3	690.7	652.5	More pronounced decline with edaravone
	5	490.7	415.6	p<0.01

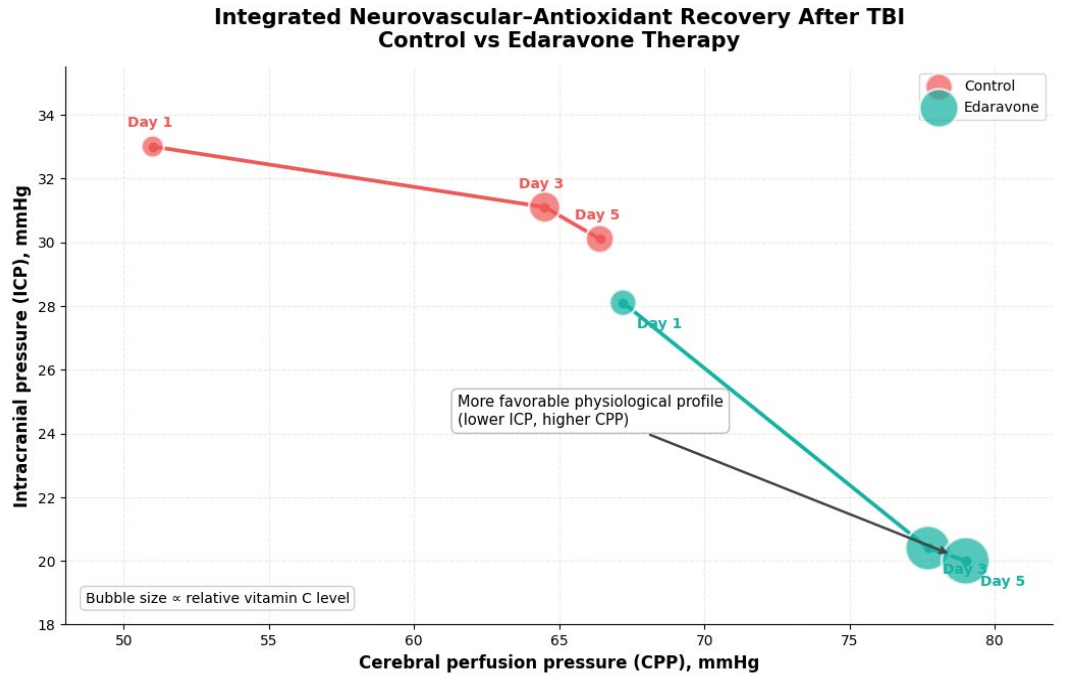

Figure. Joint trajectory of ICP and CPP during the first 5 days after traumatic brain injury. Bubble size reflects the relative vitamin C level at the same time point. The edaravone group moves toward lower ICP and higher CPP, accompanied by higher vitamin C values. Numeric THI values were not available in the source dataset and are therefore not plotted.

Figure 1: Results of Patient 1's six-frequency method.

Table 8: Integrated clinical outcomes relevant to post-traumatic tinnitus.

Outcome	Control group	Edaravone group	Clinical interpretation
NIHSS, day 21	9.85 ± 0.34	8.90 ± 0.30	Lower residual neurological deficit with edaravone
Barthel Index, day 21	42.33 ± 1.40	66.72 ± 2.10	Better functional recovery
Cognitive recovery, day 21	7.10 ± 0.24	19.70 ± 0.66	Markedly greater cognitive recovery
ICP, day 3, mmHg	31.1 ± 1.0	20.4 ± 0.66	Faster control of intracranial hypertension
CPP, day 3, mmHg	64.5	77.7	More favorable cerebral perfusion
Vitamin C, day 5	5.2	14.0	Better preservation/restoration of antioxidant status
Hospital stay, days	22.8 ± 0.9	18.6 ± 0.8	4.2-day reduction; p<0.05
Post-traumatic tinnitus	THI monitored dynamically	THI monitored dynamically	Numeric THI values require source dataset

the mean hospital stay was reduced from 22.8±0.9 to 18.6±0.8 days (p<0.05).

Overall Results

Taken together, the results demonstrate that incorporation of edaravone into the complex treatment of moderate-to-severe TBI was associated with accelerated neurological and cognitive recovery, more effective reduction of intracranial hypertension, improvement of cerebral perfusion, and favorable changes in parameters associated with oxidative stress[17].

For the tinnitus-focused component of the study, the principal clinical concept was the parallel evaluation of THI with neurological and biochemical recovery. This approach allowed post-traumatic tinnitus to be considered as part of the broader spectrum of cerebral dysfunction after TBI rather than solely as an isolated auditory complaint.

DISCUSSION

The present study demonstrates that the incorporation of the low-molecular-weight free-radical scavenger edaravone into the complex intensive treatment of patients with moderate-to-severe traumatic brain injury (TBI) was associated with more favorable neurological, cerebral hemodynamic, cognitive, and metabolic recovery

compared with standard therapy alone. Particular attention in the present analysis was given to post-traumatic tinnitus as a clinically relevant manifestation accompanying acute cerebral dysfunction[18].

The principal finding was that edaravone therapy was associated with a faster stabilization of intracranial and cerebral perfusion parameters. By the end of the first day, intracranial pressure (ICP) in the edaravone group was 28.1±0.90 mmHg, compared with approximately 33.0 mmHg in the control group. By day 3, the difference became considerably more pronounced: ICP decreased to 20.4±0.66 mmHg in the edaravone group, whereas it remained at 31.1±1.0 mmHg in controls ($p<0.001$) [17,18].

This reduction in ICP was accompanied by improvement in cerebral perfusion pressure (CPP). The integrated trajectory presented in Figure 1 illustrates that patients receiving edaravone progressively shifted toward a physiological profile characterized by lower ICP and higher CPP. Such simultaneous changes may be clinically important because secondary cerebral injury after TBI is closely related to impaired cerebral perfusion, intracranial hypertension, metabolic dysfunction, and oxidative imbalance.

Another important finding was the more pronounced neurological and functional recovery observed in the edaravone group. Although both groups demonstrated progressive improvement, recovery occurred more rapidly in patients receiving edaravone, with particularly evident differences in consciousness during the later observation period.

By day 21, the favorable neurological course was accompanied by substantially greater functional and cognitive recovery. The cognitive recovery index reached 19.7±0.66 in the edaravone group compared with 7.1±0.24 in the control group ($p<0.001$). These findings suggest that the therapeutic effect was not restricted to early stabilization of cerebral physiology but was also associated with subsequent restoration of higher neurological functions.

Oxidative Stress and the Potential Role of Edaravone

The observed clinical effects should be interpreted in the context of oxidative stress, which represented one of the central pathophysiological targets of the present study. Traumatic cerebral injury initiates a cascade of secondary processes involving oxidative imbalance, lipid peroxidation, inflammatory activation, mitochondrial dysfunction, and subsequent neuronal damage[19].

Edaravone, as a low-molecular-weight antioxidant, was incorporated into the therapeutic protocol to reduce free-radical-mediated cellular injury. The biochemical findings obtained in the present cohort were consistent with more effective stabilization of antioxidant defense in the edaravone group.

In particular, vitamin C levels demonstrated substantially different trajectories. By days 3 and 5, values in the edaravone group reached 12.4 and 14.0, respectively, compared with 6.3 and 5.2 in controls ($p<0.001$).

The combination of biochemical and clinical findings is noteworthy. Improvement in antioxidant-related parameters occurred in parallel with reduction of ICP, improvement of cerebral perfusion, and more pronounced neurological and cognitive recovery. The dissertation itself identifies a stable relationship between improvement in oxidative-stress markers and favorable neurological dynamics[18,19].

However, these associations should not be interpreted as definitive proof of a direct causal relationship. The present study demonstrates a clinically relevant parallel between antioxidant stabilization and neurological improvement but does not establish the precise molecular pathway responsible for each clinical outcome.

Post-Traumatic Tinnitus and Neurological Recovery

A distinctive feature of the present article is the emphasis on post-traumatic tinnitus. Tinnitus following TBI should not necessarily be considered an isolated otological phenomenon. In patients with acute cerebral insufficiency, auditory complaints may occur within a broader neurological and neuropsychological symptom complex involving headache, dizziness, sleep disturbances, impaired attention, cognitive dysfunction, and emotional symptoms.

This interpretation is consistent with the underlying clinical dataset, in which “noise in the head” was included together with headache, dizziness, fatigue, and sleep disturbances among cerebral and asthenic manifestations.

The present study therefore incorporated the Tinnitus Handicap Inventory (THI) to provide a more tinnitus-specific framework for clinical evaluation. This is particularly important because the subjective burden of tinnitus cannot be adequately characterized by general neurological scales alone[15,16].

Interpretation of tinnitus during the earliest phase of moderate-to-severe TBI remains challenging. Patients with markedly impaired consciousness, tracheal intubation, cognitive dysfunction, or severe neurological deficits may be unable to provide reliable information regarding tinnitus characteristics. Consequently, tinnitus assessment becomes progressively more informative as consciousness and cognitive function recover.

The more rapid neurological and cognitive recovery observed in the edaravone group may therefore have two implications. First, it enables earlier and more reliable characterization of tinnitus. Second, the parallel improvement in cerebral perfusion and antioxidant status raises the hypothesis that reduction of secondary cerebral injury may also influence the severity or persistence of post-traumatic auditory symptoms.

Nevertheless, this hypothesis requires cautious interpretation. The available dissertation dataset does not contain serial quantitative THI values sufficient to

demonstrate that edaravone directly reduces tinnitus. Therefore, the current findings support an association between global neurological recovery and the clinical evolution of post-traumatic tinnitus rather than establishing a tinnitus-specific pharmacological effect of edaravone.

This distinction is important for the scientific interpretation of the study and provides a rationale for future prospective investigations specifically designed to evaluate THI dynamics together with audiological and neurophysiological measures.

Clinical Significance

The findings have potential clinical relevance for the management of patients with moderate-to-severe TBI. The therapeutic benefits associated with edaravone were multidimensional and included earlier control of intracranial hypertension, improvement in cerebral perfusion, more favorable antioxidant status, and accelerated neurological and cognitive recovery.

The clinical effect was also reflected in hospitalization duration. Patients receiving edaravone had a mean hospital stay of 18.6±0.8 days compared with 22.8±0.9 days in the control group, corresponding to a reduction of approximately 4.2 hospital days ($p<0.05$) [20].

From a practical perspective, these findings suggest that edaravone-containing antioxidant therapy may be considered as an adjunctive component of multimodal intensive treatment rather than as an isolated intervention. Its potential value appears to be related to simultaneous modulation of several processes involved in secondary cerebral injury.

The tinnitus component additionally emphasizes the importance of incorporating patient-reported auditory symptoms into neurological follow-up after TBI. Persistent tinnitus may remain clinically relevant even after stabilization of life-threatening neurological abnormalities and therefore deserves targeted assessment during rehabilitation and follow-up[19,20].

Study Limitations

Several limitations should be considered when interpreting the present findings. First, the sample size was relatively limited, with 80 patients divided into two groups of 40 subjects. Larger multicenter studies are required to confirm the reproducibility and external validity of the observed effects.

Second, the study was not a randomized placebo-controlled clinical trial, which limits the ability to establish a definitive causal relationship between edaravone administration and the observed clinical improvements.

Third, invasive ICP monitoring was not available for every patient, and some cerebral hemodynamic assessments therefore relied on clinically indicated instrumental monitoring.

Most importantly for the tinnitus component of the article, the underlying dissertation dataset did not include a complete longitudinal series of quantitative THI measurements. Consequently, the present study cannot conclusively demonstrate a direct tinnitus-reducing effect of edaravone. Future studies should incorporate standardized serial THI measurements together with pure-tone audiometry, speech audiometry, psychoacoustic tinnitus characterization, and, where feasible, auditory evoked potentials.

Finally, longer follow-up beyond the acute 21-day period would be necessary to determine whether early neurological and antioxidant improvements translate into sustained reductions in chronic post-traumatic tinnitus and long-term neurological disability.

CONCLUSION

In patients with moderate-to-severe traumatic brain injury complicated by acute cerebral insufficiency, the addition of edaravone to standard intensive therapy was associated with more favorable neurological and cerebral hemodynamic recovery.

Edaravone therapy was accompanied by a more rapid reduction in intracranial pressure and improvement in cerebral perfusion pressure, together with favorable changes in antioxidant-related parameters. These physiological improvements occurred in parallel with accelerated recovery of consciousness, neurological function, functional independence, and cognitive performance.

By day 3, ICP decreased to 20.4±0.66 mmHg in the edaravone group compared with 31.1±1.0 mmHg in controls ($p<0.001$), while by day 21 the cognitive recovery index was 19.7±0.66 versus 7.1±0.24, respectively ($p<0.001$). The treatment strategy was additionally associated with a 4.2-day reduction in mean hospital stay.

Post-traumatic tinnitus should be considered within the broader spectrum of neurological and neuropsychological consequences of TBI. The parallel improvement in cerebral physiology, antioxidant status, and neurological function provides a rationale for further investigation of antioxidant therapy in patients with post-traumatic tinnitus. However, based on the available data, a direct tinnitus-specific therapeutic effect of edaravone cannot yet be established.

Overall, the findings support further prospective investigation of edaravone as an adjunctive neuroprotective strategy in moderate-to-severe TBI, with standardized tinnitus-specific outcomes incorporated into future study protocols.

Practical Implications

The results suggest that edaravone may be considered as an adjunct to standard intensive therapy in appropriately selected patients with moderate-to-severe TBI, with treatment effectiveness evaluated using an integrated combination of neurological, cerebral hemodynamic, cognitive, and biochemical parameters.

In patients reporting tinnitus after recovery of sufficient consciousness and communication ability, standardized assessment using the THI should be incorporated into neurological follow-up. Persistent or clinically significant tinnitus should prompt dedicated audiological assessment rather than being attributed solely to general post-traumatic symptoms.

For future clinical research, simultaneous monitoring of THI + GCS/FOUR + cognitive function + ICP/CPP + oxidative-stress biomarkers may provide a more comprehensive model for determining whether improvement of secondary cerebral injury is associated with genuine reduction in post-traumatic tinnitus burden.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest. All authors assume equal responsibility for the content of the submitted material.

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