

**ANALYSIS OF THE EFFECT OF KALLIDINOGENASE ON THE SEVERITY  
OF ISOLATED CLOSED HEAD INJURY, PROGNOSIS OF DEATH,  
CONSCIOUSNESS, AND BRAIN EDEMA**

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**Summary:** Disability of victims of CTBI is one of the most important factors determining the urgency of the problem of injuries. The consequences of CTBI manifest themselves in the long term and are characterized by morphological and functional changes in the brain and its structures, which determine various clinical manifestations. The consequences of CTBI are "highly soluble sediments" that accumulate over the years, essentially determining the health status of the population and determining the humanitarian, social and economic significance of brain injuries. Kallidinogenase - tissue kallikrein, a component of the kallikrein - kinin system (KKS), has a protective effect against cerebral ischemia.

**Key words:** Traumatic brain injury, tissue kallikrein (kallidinogenase), intra cranial pressure, cerebral perfusion pressure, medial arterial pressure, Glasgow scale, SAPS and APACHE II scales, M echo pulsogram.

**Introduction.** According to studies based on the analysis of epidemiological data and scientific works on CTBI in the world, attention is drawn to the peculiarity of the distribution of these injuries, where the high frequency of CTBI in different regions of the world varies from 95 to 783 cases per 100 thousand people [19]. Unfortunately, in many countries of the world there are episodes of increased incidence of CTBI, which often affect the working-age population, with high mortality and disability in young and middle-aged people. The most common causes of CTBI in the world are falls, accidents, violent acts, sports and work-related injuries (50%), in Russia - accidents, household and occupational injuries [18, 4, 22] and in Belgium - falls [20].

In Uzbekistan, 120,000-130,000 people are registered with CTBI every year, and 10.0% of them die, and another 10.0% become disabled. Of the registered cases of BMJ, 15% are of severe and moderate severity, and are mainly treated by resuscitators and neurosurgeons for a long time, while the remaining 85-90% are treated by therapists for 2-10 days as inpatients or outpatients [17]. The treatment of patients with severe closed traumatic brain injury (CTBI) is an urgent task of modern medicine and is of great social and economic importance [21]. CTBI

causes death in 30–50% of victims under the age of 40, leading to severe disability at a rate of 15–20 per 100,000 per year [28]. Of the 600,000 people who develop CTBI, about 50,000, or about 10%, die [27].

In the pathogenesis of CTBI, primary and secondary mechanisms of brain injury are distinguished. Primary mechanisms include: 1) laceration of brain tissue and focal contusion of the brain. 2) Intracerebral hematoma. 3) diffuse axonal injury. 5) Rupture or contusion of the cerebral vasculature. 6) Damage to cranial nerves.

Intracranial factors include: disruption of the dynamics of cerebrospinal fluid and hemocirculation due to intraventricular and subarachnoid hemorrhages, compression of the brain due to intracranial hematomas; cerebral edema due to venous congestion, hyperthermia and hyperemia. Extracranial injuries include [1]: 1. Arterial hypotension and hypertension. 2. Hypoxia. 3. Hypo- and hypercapnia. 4. Hypo- or hypernatremia. 5. Hyperthermia. 6. Disorders of carbohydrate metabolism. 7. Disseminated intravascular coagulation syndrome.

In TBI, from the standpoint of pathophysiology, several phases of the development of brain damage can be distinguished. Negative outcomes of severe traumatic brain injury are mainly associated with the development of uncontrolled secondary tissue damage and neuroinflammation (systemic inflammatory response syndrome - SIRS). The acute period of injury is characterized by a specific metabolic response that occurs in three phases: hypometabolic (Ebb phase, early shock), catabolic (Flow phase), and anabolic [23, 24]. The early phase of damage, as a rule, occurs in the first 24 hours after injury and is directly related to tissue damage and physiological dysfunction; the intermediate phase occurs in the first days after CTBI and entails the development of neuroinflammation; the late phase is associated primarily with cognitive impairment, seizures, and epileptogenesis and occurs within days to weeks after TBI. The ischemic cascade begins with impaired cerebral blood flow and oxygenation of the brain tissue [11]. It has been experimentally shown that these processes develop more intensively in the brain of older individuals compared to young ones [7]. Due to such a high importance of brain perfusion control for assessing the development of its ischemic damage, the Brain Trauma Foundation recommends the use of monitoring of intracranial pressure (ICP) and cerebral perfusion pressure (CPP) in all patients with severe TBI [2]. However, there is evidence that the control of ICP and CPP does not replace the assessment of true oxygenation of the brain tissue [6].

Secondary disorders include: excitotoxicity, apoptosis, oxidative stress, mitochondrial disruption, damage to the blood-brain barrier, and neuroinflammation [32]. These processes are exacerbated by the severity of the primary injury [3]. During the first 3 hours after the

development of TBI, the energy deficit is maximal in the ischemic tissue; after 3-6 hours - glutamate excitotoxicity, disturbances of calcium homeostasis and lactic acidosis, fading away by the end of the first day. Long-term effects of ischemia begin to appear at 2-3 hours, reach a maximum after 12-36 hours (oxidative stress and local inflammation) and on days 2-3 (apoptosis), but persist for a long time (for several months), contributing to progression of atherogenesis processes and diffuse damage to brain tissue (encephalopathy) in the post-stroke period [15].

As a therapy that could stop the ongoing damage in the form of glutamate excitotoxicity and cell death, including apoptosis and necrosis, reduce the inflammation cascade, the use of tissue kallikrein is being considered, one of which is kallidinogenase (serine proteinase extracted from human urine) [31].

Kallidinogenase - tissue kallikrein, a component of the kallikrein-kinin system (KKS), has a protective effect against cerebral ischemia. Tissue kallikrein is a serine proteinase (protein) extracted from human urine, which plays an important role in the regulation of local blood flow and vasodilatation, which reduces total vascular resistance, in reducing inflammation and oxidative stress, and in stimulating angiogenesis and neurogenesis [22].

Tissue kallikrein is able to cleave low molecular weight kininogen to release vasoactive kinins, which in turn activate bradykinin B1 and B2 receptors on vascular endothelial cells, promoting the release of nitric oxide (NO) and prostaglandins (PGL2). Additional mechanisms are activated, including restoration of the blood-brain barrier through an increase regulatory T cells, suppression of the death of apoptotic cells [30]. Multiple lines of evidence indicate that KKS is important for the normal functioning of the cardiovascular system and KKS deficiency is associated with cardiovascular and endogenous pathology [14]. Kallidinogenase has a relaxing effect on the arteries and inhibits platelet aggregation, increases the elasticity of red blood cells and the ability to dissociate oxygen. Kallidinogenase, a KKS regulator and a kallikrein producer, exhibits anti-inflammatory, anti-apoptotic, angiogenesis, and neurogenesis effects [14]. Several studies have shown that kallidinogenase improves functional deficiency promotes angiogenesis and improves cerebral blood flow [33, 10, 13]. The main mechanism is upregulation of vascular endothelial growth factor and activation of bradykinin B1 and B2 receptors [8]. In addition, kallidinogenesis has been shown to improve cognition [34].

The above characteristic of human urinary kallidinogenase was the reason for our study.

**Purpose of the study:** To optimize the results of treatment of patients with CTBI by using tissue kallikrein in complex therapy.

**Material and methods.** The study included 20 patients aged 18 to 72 years with an isolated CTBI and depression of the level of consciousness from 4 to 11 points on the Glasgow coma scale, including 1 of 4-5 points - 3 (15%), 6- 8 points - 11 (55%), 9-11 points - 6 (30%). All patients were diagnosed with severe brain contusion. There were 13 men (65%), women - 7 (35%). All patients underwent ICP (invasively - if possible - lumbar punctures with manometry and non-invasively (qualitatively) using a portable diagnostic ultrasound machine (Complexmed, Russia) by M-echo pulsation of the 3rd ventricle of the brain (normal, moderate and pronounced increase in ICP).

The patients were divided into 2 groups, 10 patients received standard therapy. The remaining 10 patients received standard therapy + after stabilization of vital parameters on the 5th day, intravenous excretion of collagenase 0.15 ED IV per 100 ml of saline at a rate of 1.7 ml/hour was started.

One of the fundamental parameters of hemodynamics, providing the proper level of tissue perfusion, is the value of cerebral perfusion pressure (CPP), which was determined by the formula:  $CPP \text{ mm Hg. Art.} = MAP \text{ mm Hg Art (mean arterial pressure)} - ICP \text{ mm Hg. Art. (intracranial pressure)}$ . MAP was determined by the formula:  $MAP = (ADS + 2ADD)/3$ .

All patients received standard, basic and differentiated intensive therapy for TBI, adopted in our clinic, craniocerebral hypothermia, antibacterial, antioxidant therapy, blockers of sodium and calcium channels and NMDA receptors, drugs that improve the rheological properties of blood, sedatives. Infusion therapy was carried out with a combination of colloid and crystalloid preparations. The volume and structure of the infusion was determined on the basis of systemic hemodynamic monitoring data. Enteral tube feeding was started from the first day of the patient's stay in the intensive care unit at the rate of 20-25 kcal per kg of body weight per day. If necessary, parenteral nutrition was added. All patients were artificially ventilated using Wella and Drager devices with a tidal volume of 7-9 ml per kg of ideal body weight in normoventilation mode, PEEP 2-8 cm of water. Art. The head end of the bed was kept elevated by 30°. For the first 2 days, patients received haemostatic therapy; from 3-4 days, low molecular weight heparins were prescribed.

**The studied parameters** (ICP, CPP, MAP, Glasgow, SAPS and APACHE II scales, M-exo pulsogram, length of stay in intensive care) were checked in patients on admission, on days 5 and 10.

### Results and discussion

**Table № 1. Dynamics of the level of consciousness according to the Glasgow scale.**



| Indicator<br>s | Research stages            |         |          |                  |          |          |
|----------------|----------------------------|---------|----------|------------------|----------|----------|
|                | 1-group (standart therapy) |         |          | 2-group (kalgen) |          |          |
|                | outcom<br>e                | 5 day   | 10 day   | outcome          | 5 day    | 10 day   |
| GS             | 6,1±0,6                    | 9,2±0,5 | 13,5±0,5 | 7,1±0,6          | 10,2±0,3 | 14,5±0,5 |

In the presented table, the average values at the time of admission in patients of groups 1 and 2 on the Glasgow scale were  $6.1 \pm 0.6$  and  $7.1 \pm 0.6$ , which corresponds to a loss of consciousness equivalent to a coma of II degree. In the first group of patients on the background of standard therapy on the 5th day, the impairment of consciousness had the form of stupor and coma 1, and on the 10th day the level of consciousness recovered to a state of moderate stupor. Already on the 5th day after the use of Kalgen in complex therapy, the consciousness of patients gradually cleared up both clinically and according to the Glasgow scale. By the end of 10 days, the level of consciousness reached 14.5 points ( $P < 0.05$ ), indicating an almost complete recovery of consciousness.

**Table № 2. Severity and lethality in dynamics.**

| Scale                   |        | SAPS    |        |         | APACHE II |        |         |
|-------------------------|--------|---------|--------|---------|-----------|--------|---------|
| Day                     |        | outcome | 5 day  | 10 day  | outcome   | 5 day  | 10 day  |
| 1-group<br>(st.therapy) | Points | 22±0,8  | 17±0,2 | 9±0,9   | 28±1,1    | 16±0,9 | 10±0,5  |
|                         | let. % | (63%)   | (27%)  | (10,3%) | (56%)     | (25%)  | (10,6%) |
| 2-group<br>(kalgen)     | Points | 21±1,1  | 16±0,8 | 8±0,5   | 28±0,6    | 15±1,0 | 7±0,7   |
|                         | let. % | (61%)   | (25%)  | (8,3%)  | (55%)     | (25%)  | (8%)    |

From the above, it can be seen that in patients of the 1st group who received standard therapy, the severity at the time of admission was 22 and 28 points on the SAPS and APACHE II scales, and mortality was estimated at 63% and 56%, respectively. On the 5th day, the severity was 17 and 16 points, and the mortality was 27 and 25%, in the last 10 days of treatment, the severity was 9 and 10 points, in parallel, the mortality was 10.3 and 10.6%, respectively.

In patients receiving Kalgen of the 2nd group, the average severity on the SAPS and APACHE II scales at the time of admission was 11 and 27, respectively, predicting a 60 and 55% chance of death. On the 5th day in the process of complex therapy with the inclusion of the drug Kalgen in the dynamics there was an improvement in clinical condition and on the indicated scales by almost 30% (8 points). By the end of 10 days, the number of points in

patients decreased to 4.3 and 5.6, respectively, which corresponded to 7 and 9.6% of the possibility of death and indicated the effectiveness of our therapy.

**Table № 3 Dynamics of ICP, MAP, M-echo pulsogram and CPP in the process of complex therapy of CTBI.**

| Indicators                  | Research stages            |               |                |                  |           |            |
|-----------------------------|----------------------------|---------------|----------------|------------------|-----------|------------|
|                             | 1-group (standard therapy) |               |                | 2-group (kalgen) |           |            |
|                             | outcome                    | 5 day         | 10 day         | outcome          | 5 day     | 10 day     |
| <b>P%, M-echo pulsogram</b> | 64,3±2,4                   | 34,4±1,1*     | 16,6±1,3*<br>* | 63,5±2,6         | 30,4±1,1* | 12,6±1,3** |
| <b>ICP, mm Hg</b>           | 27,5±2,5                   | 18,0±1,1<br>* | 12,5±0,5<br>** | 25,5±2,5         | 14,0±1,1* | 10,5±0,5** |
| <b>CPP, mm Hg</b>           | 60,2±6,5                   | 86,4±4,6*     | 91,5±0,7<br>** | 61,0±6,5         | 88,3±4,6* | 92,8±0,6** |
| <b>MAP, mm Hg</b>           | 75,3±3,0                   | 93,3±3,0*     | 98±3,0**       | 76,35±3,0        | 95,3±3,0* | 103±3,0**  |

**Note: reliability relative to the original data \* -  $p < 0.05$ , \*\* -  $p < 0.01$ .**

At the time of admission in the first group of patients and on days 5–10, the values of M-echopulsogram (R.%) and ICP (mm Hg) were  $64.3 \pm 2.4$ ,  $34.4 \pm 1.1$ ,  $16.6 \pm 1.3$  and  $27.5 \pm 2.5$ ,  $18.0 \pm 1.1$ ,  $12.5 \pm 0.5$ . Accordingly, there was a decrease in severe, moderate and normal values of ICP. As well as the second group of patients with the above indicators were  $63.5 \pm 2.6$ ,  $30.4 \pm 1.1$ ,  $12.6 \pm 1.3$  and  $25.5 \pm 2.5$ ,  $14.0 \pm 1.1$ ,  $10.5 \pm 0.5$ . This indicates a decrease in ICP and M-echopulsogram in both groups after 10 days of treatment (by 55.6 and 73.7%) and (by 59.8 and 78.6%), respectively.

In the first group of patients, CPP increased by 39.8 and 44.7% on days 5 and 10 compared with the initial result. In the second group of patients, the increase was 42.4 and 45.9%, respectively. In parallel, CPP in the first and second groups improved to (23.4 and 29.6%) and (25.3 and 33.8%), respectively, compared with the baseline at the stages of treatment.

The average stay of the studied patients in the intensive care unit was  $13.4 \pm 1.2$  days in the first group and  $10.6 \pm 1.1$  days in the second group.

Kallidinogenase promotes angiogenesis and improves cerebral blood flow [9]. Kallidinogenase has been shown to reduce inflammation of cerebral edema, also support its critical role in maintaining and repairing brain damage caused by ischemia and reperfusion, and

improve biochemical, physiological and functional parameters [12]. Many in vivo and in vitro studies have shown that kallidinogenese significantly improves neurological function [26] and reduces infarct size [29]. Treatment with kallidinogenese resulted in a 4.52% reduction in infarct size [16]. The effective frequency of kallidinogenese was approximately 80% in cerebral ischemia [9].

On the general data of the literature, we can say that urinary kallidinogenese (kalgen), acting on the kallikrein-kinin system, improves cerebral hemodynamic, eliminating spasm of cerebral blood vessels, prevents vascular restenosis, promotes postischemic angiogenesis, reduces cerebral edema, improves cerebral perfusion, and also has a neuroprotective effect, contributing to the formation of a neuronal synapse, the protection of nerve cells, the growth of neurons and suppressing their apoptosis.

### Conclusions:

1. Based on the foregoing, it must be assumed that the standard therapy + the drug Kallidinogenase (tissue kallikrein) demonstrated a pronounced effect on the survival of patients and increased the effectiveness of treatment with isolated craniocerebral trauma. In addition, a clear shortening of the length of stay of patients in the intensive care unit was noted.

2. After the application of the Kallidinogenase preparation, a decrease in ICP was noted and, in parallel, an increase in the CPP index, which leads to a decrease in the ischemic zone in the brain.

3. Under the influence of Kallidinogenase, consciousness comes more painfully faster than in a coma.

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