TO DETERMINE THE OPTIMAL NEUROPROTECTIVE TREATMENT TYPE IN ISOLATED CLOSED HEAD INJURY VICTIMS BY COMPARATIVE COMPARISON OF STANDARD THERAPY AND KALLIDINOGENESIS.

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Summary: Closed head injury is a leading cause of morbidity, mortality, and disability in young and middle-aged adults. The most vulnerable group is comatose patients with severe traumatic brain injury. Kallidinogenase is a kallikrein-kinin system inhibitor that exerts neuroprotective effects on all neurons in the brain, inhibiting apoptosis, inflammation, oxidative stress, and excitotoxicity.

Objective: to optimize the treatment outcomes of patients with isolated CHI using tissue kallikrein (kalgen) in complex therapy.

Materials and methods. The study included 20 patients aged 18 to 70 years with isolated CHI with a Glasgow Coma Scale score of 6 to 11, including 6-7 points - 5 (25%), 8-9 points - 11 (55%), 10-11 points - 4 (20%). All patients were diagnosed with severe cerebral infarction. 13 men (65%) and 7 women (35%).

Research results: at the beginning of treatment, the average values of ICP and M-exopulsogram in group 1 were (27.5±2.5 and 63.5±2.6 mm.s.m.) and in group 2 (26.5±2.6 and 64.3±2.4), indicating an increase in cerebral blood flow. After treatment, the intergroup ICP and M-exopulsogram indices decreased compared to baseline (by (55.6 and 73.7%) and (59.8 and 78.6%), respectively, and the brain edema resolved. In group 1 of patients, the CPP increased by 44.7% compared to the initial result after treatment. In group 2, the increase was more modest, amounting to 45.9%, respectively. Compared with the initial values, at the end of therapy, the INR increased by 11.2% in group 1 and 20.5% in group 2. With parallel development, the IRR in both groups decreased by 26.7 and 30.2% at the end. Fibrinogen and D-dimer in patients receiving Kalgen were initially 500.7±10.1 and 525.7±21.1, and on the 10th day of treatment they decreased by 38 and 61%. In groups 1 and 2, the dynamics of IL-1β after therapy decreased by (51% and 72%), IL-6 (45.9% and 62%) and returned to normal. At the same time, at the end of therapy, C-reactive protein decreased by 51.2 % and 71.8% in groups 1 and 2 , respectively, while IL-10 increased by 42.5% and 51.7%.

Conclusion: Calgen pathogenetically suppresses neuroinflammation in closed craniocerebral trauma and improves hemodynamics and hemostasis in the brain.

Key words: closed head injury, tissue kallikrein (kallidinogenase), intracerebral hypertension, cerebral perfusion pressure, mean arterial pressure, M-echo pulsogram, coagulogram.

Entrance. Closed head injury (CHI) is a result of mechanical trauma. Experts define CHI as a possible combination of injuries to the skull and its contents: brain matter, blood vessels, cerebrospinal fluid spaces, meninges, soft tissues of the head, skull base, and facial bones [20].

According to the Russian Ministry of Health, the average traumatic brain injury incidence in 2000-2018 was 9.1 per 1,000 people per year (9.1%). In the same period, traumatic brain injury took the leading place among all injuries. As of the beginning of 2019, MSD is the leading cause of disability in Russia. The most common victims are men aged 21-45. In Russia, the mortality rate from CHI reaches 4.0 %, while the postoperative mortality rate is 19.0%. This significant difference is explained by the severity of the condition of victims requiring surgery [21]. According to literature sources, the main cause of BMJ in Russia is violent trauma (39.0 %); the second most common is falls from a height (26.0%), approximately (70.0%), in third place is BMJ of unknown etiology (16.0%), less common causes of injury are road traffic accidents (11.0%) and falls from a height (8.0%) [21, 10]. In Uzbekistan, 120,000-130,000 people with BMJ are registered annually, of which 10.0 % die, another 10.0% become disabled. Among the registered cases of traumatic brain injury, 15% are of moderate and severe severity, and are treated mainly by resuscitators and neurosurgeons for a long time, while the remaining 85-90% is treated by therapists for 2-10 days inpatient or outpatient [14]. Due to complex and diverse pathophysiological mechanisms, pathogenetic factors develop at the time of injury and over time, which are divided into primary and secondary stages. In response to primary mechanical damage, an evolutionary pathological inflammatory reaction occurs in brain tissue. The action of the primary traumatic agent initiates biochemical and immunological destructive processes.

In mitochondria, oxidative phosphorylation, increased intracellular Ca+ concentration, release of free O2 $_{radicals}$ and vasoactive substances, arachidonic acid metabolites, activation of complement cascade mechanisms, and lipid peroxidation are disrupted. Accumulation of "excitatory" amino acids, namely glutamate and aspartate, leads to damage to the endothelial membranes of neurons and capillaries in the brain (excitotoxicity). Disturbances in microcirculation and cellular metabolism in the brain contribute to the development of brain tumors [9, 16].

As a result of brain damage, neuronal metabolism is activated, which is accompanied by a decrease in ATP and a violation of the function of the Ca+ pump. As a result, the permeability of cell membranes for Ca+ ions increases and Ca+ is released from intracellular depots, which leads to depolarization of nerve endings and the release of "excitatory" neurotransmitters (glutamate) from them. Glutamate activates postsynaptic complexes, causing the influx of sodium ions into the cell, depolarization, the influx of Ca+ ions through ion channels, and much more. Overload of calcium in the cell leads to the activation of phospholipases, proteases , and nucleases, disruption of phosphorylation, protein synthesis, and expression of the genome, and the lysis of structural proteins of the cell, leading to a violation of the integrity of cell membranes. In MS, neuronal death also occurs as a result of apoptosis processes. Apoptosis can be induced both directly by the direct effects of a traumatic agent on the cellular genome and indirectly by the damaging effects of inflammatory mediators [9, 16].

As a result of the influence of factors, secondary brain damage occurs - a violation of the supply of oxygen and nutrients, the absorption of substances by brain cells and their insufficient utilization. Cells are especially affected in the penumbra zone, which is located mainly near the site of brain damage. Cerebral microcirculation, oxygen supply and neuronal metabolism are disturbed, and brain edema and ischemia develop. Secondary ischemic brain damage occurs in 36-42.6% of patients with moderate cerebral infarction and in 81-86.4% of patients with severe cerebral infarction. The development of secondary brain damage worsens the condition, mental and motor activity of patients with cerebral infarction, and increases the risk of developing adverse consequences in patients. Therefore, the prevention and timely correction of secondary brain damage factors is the most important task in the treatment of patients with severe cerebral infarction [9].

Cerebral perfusion pressure (CPP) is the driving force that supplies blood to the brain tissue and is strictly dependent on the intracranial pressure (ICP) and mean arterial pressure (MAP) according to the formula CPP=MAP-ICP. The formula for determining CPP is: MAP=ADsis+2ADdias/3. Prolonged and excessively low CPP represents an important and preventable cause of secondary brain injury. According to the recommendations of the Brain Trauma Foundation, CPP values are 90-100 mm.sym.ust. to prevent cerebral hypoperfusion. should be in the range [22].

In 45-80% of patients with BMJ, BMI exceeds the accepted limit by 20-22 mm.sym.s. [24, 19]. With intact autoregulation, an increase in mean OAB leads to vasoconstriction, which reduces BMI and increases SPB. There are four main types of edema development after BMJ - vasogenic, cytotoxic, osmotic and Ionic edema [2]. IBD is a major adverse prognostic factor in IBD, resulting from excessive fluid accumulation and serving as an important link in the ischemic cascade [11, 18].

Tissue kallikrein/kallidinogenase (TK) is widely expressed in the kidney, blood vessels, CNS, pancreas, intestine, neutrophils, etc. [8]. TK protein and mRNA are located in endothelial and smooth muscle cells of large, medium and small blood vessels. In addition, immunohistochemical studies show that B2 is distributed in smooth muscle cells and endothelial arterioles in arteries and arterioles [6]. It is widely expressed in various tissues and has been shown to be involved in various pathophysiological processes, such as the suppression of oxidative stress, inflammation, apoptosis and fibrosis [27], and the stimulation of angiogenesis and neurogenesis [25]. Kallidinogenase Clinical and experimental studies have shown that tissue kallikrein, a component of the kallikrein/kinin complex, has a protective effect against cerebral ischemia. Tissue kallikrein is a serine proteinase that plays a crucial role in the regulation of microcirculation, blood pressure, and blood flow [17]. A large body of evidence suggests that KKS is essential for a healthy cardiovascular system, and KKS deficiency is associated with cardiovascular and endogenous pathology [12]. Human urinary kallidinogenase, a regulator of KKS and a kallikrein producer, exhibits anti-inflammatory, apoptotic, angiogenic, and neurogenic effects and has been approved for the treatment of stroke in China [3]. Several studies have shown that kallidinogenase ameliorates functional deficits [31], promotes angiogenesis, and improves cerebral blood flow [13]. Kallidinogenase has been shown to reduce inflammation in cerebral edema. It also supports its important role in preserving and repairing brain damage caused by ischemia and reperfusion, and improving biochemical, physiological, and functional parameters [29].

The above features of human urinary callidinogenase motivated our study on isolated CHI.

Research objective: to optimize the treatment outcomes of patients with isolated CKD by using tissue kallikrein (kalgen) in complex therapy.

Materials and methods. The study included 20 patients aged 18 to 70 years with isolated CHI with a Glasgow Coma Scale score of 6 to 11, including: 4-5 points 5 (25%), 6-8 points 11 (55%), 9-11 points 4 (20%). All patients were diagnosed with severe cerebral infarction. 13 men (65%) and 7 women (35%). BMIB was performed using the invasive lumbar puncture method, monometry (6 patients) and non-invasive portable ultrasound diagnostic device (Kompleksmed, Russia) according to the instructions of an ophthalmologist (M-exo pulsation of the 3rd ventricle of the brain, (repeatedly for all). Taking into account intensive therapy, the patients were conditionally divided into 2 groups, 10 patients in group 1 received standard therapy only for CHI. The remaining 10 patients were given standard therapy plus 0.15 IU of callidinogenase. The Kalgen preparation was administered intravenously with 100 ml of physiological solution at a rate of 1.6 ml/h on the 3rd-4th day after the stabilization of vital signs.

According to the protocol adopted in our clinic, standard therapy was: lidocaine (10 mg/kg/day) for blocking Na+ channels, nimotope (nimodipine) for inhibiting $Ca2^{+}$ channels (NMDA receptors), mild therapeutic craniocerebral hypothermia (cooling the brain structure to 4-5º), antioxidant therapy (glutathione, ederavon, mixedol, ascorbic acid, vitamin E), for blocking reactive oxygen species (propofol, barbiturates), hemostatic therapy (tranexan, etamsylate) was performed for the first 3 days to calm and block transaminase activity, and if there was no risk of bleeding, anticoagulant therapy (low molecular) was performed at 0.1/kg/day. To prevent infection and prevent gastrointestinal ulcers, patients were given drugs that improve hemorheology and early enteral feeding. Infusion therapy (30-40 ml/kg/day on day 1, 20-30 ml/kg/day on day 2, and 15-20 ml/kg/day on the remaining days) was carried out in the form of colloid and crystalloid solutions. Nootropic therapy (piracetam, citicoline) was used to improve cerebral circulation. All patients were artificially ventilated using AVENTA, Mindray, and Drager devices from the first day of their stay in the intensive care unit. Tidal volume was 7-9 ml/kg, PEEP was 2-8 mbar, and Fio2 was 30-40%. From the first day of their stay in the intensive care unit, patients were started on nasogastric tube feeding at the rate of 20-25 kkal/kg per day of body weight. Patients were fed parenterally at 20-25 kcal/kg if enteral feeding was not possible.

Parameters studied: During the study, the following parameters were dynamically studied in patients: hemodynamic indicators in the brain (ICP, CPP, MAP, M-exo pulsogram), inflammatory indicators (interleukins 1, 6, 10 and C-reactive protein), coagulogram analysis (APTT, INR, PTI, D-dimer, fibrinogen).

Study design: A prospective, single-center, randomized, open clinical trial was conducted in the intensive care units No. 1 and No. 2 of the TMA.

Research results:

Table No. 1. Monitoring of hemodynamic parameters in the brain .

Indicators	M-exo pulsegram (P %)	ICP (mm/Hg)	CPP (mm/Hg)	MAP (mm/Hg)
Traditional therapy n=10				
Before treatment	64.3±2.4	27.5±2.5	6 0.2±6.5	77.3±3.1
After treatment	16.6±1.3**	12.5±0.5* *	91.5±0.7 **	107.3±2,6 **
Kalgen (0.15 PNA) n=1 0				
Before treatment	63.5 ±2.6	26.5±2.6	61.2±5.2	75.6±2.1
After treatment	12.7±1.5**	10.5±0.9* *	91.5±0.5 **	110,3±2,4 **

Note: reliability compared to baseline **–p<0.01.

After admission to intensive care, the average ICP and M-exopulsogram values in patients before treatment were (27.5±2.5 and 63.5±2.6 mm.Hg) in group 1 and (26.5±2.6 and 64.3±2.4) in group 2, which indicates the fact of increased cerebral blood flow. Importantly, after 10 days of treatment, the above indicators in both groups decreased compared to baseline (by 55.6 and 73.7%, respectively) and (by 59.8 and 78.6%) and brain edema resolved.

the control group of patients, CPP increased by 39.8 and 44.7% after treatment compared to the initial result. In the main group of patients, the increase was more modest and amounted to 42.4 and 45.9%, respectively. In parallel, during the treatment of MAP in groups 1 and 2, the SBP improved by (23.4 and 29.6%) and (25.3 and 33.8%) compared to the initial level, respectively. The maximum increase in SBP was observed at the end of therapy and was 98±3.0 and 103±2.4 in groups 1 and 2. Thus, in the group receiving Kalgen, a positive shift in cerebral hemodynamics was observed, which led to an increase in blood circulation in the ischemic focus and penumbra zones.

Table No. 2. Coagulogram dynamics of indicators .

Indicators	APTT	INR	Fibrinogen mg%	D-dimer ng/ml	PTI, %
Traditional therapy n=10					
Before treatment	30.8 ±1,1	0.88 ±0.1	525.7±1 01	530.7±22, 8	123.0± 3,7
After treatment	36.0±1. 7*	0.98 ±0.11*	400.9 ±8,3 *	398.5±9,7 *	90.5±0. 9*
K algen (0.15 PNA) n=1 0					

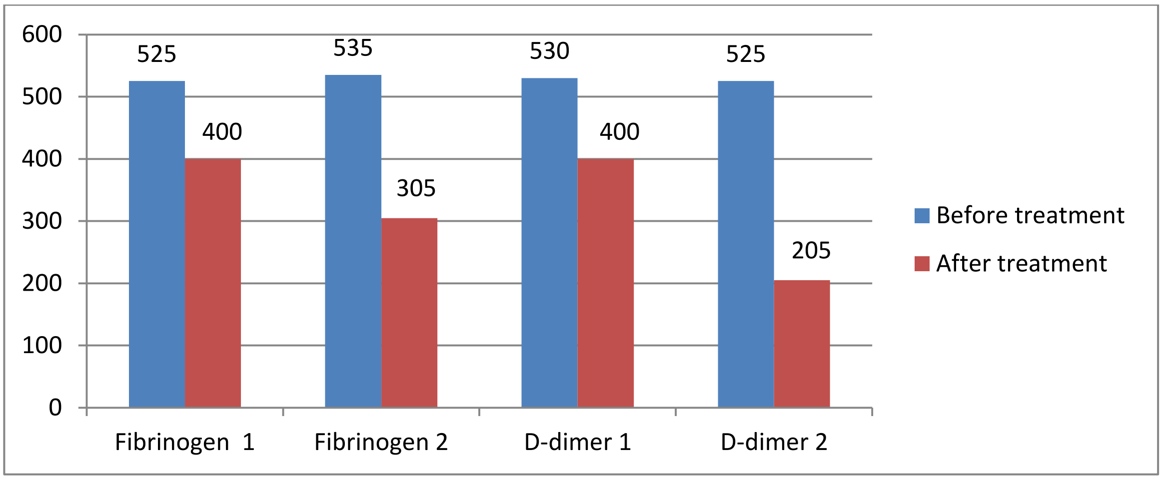
Before treatment	28.8±1.3	0.90±0.1	500.7±10.1	525.7±21.1	122.0 ±2.8
After treatment	39.0±1.7*	1.09±0.11 *	305.9 ±6,3**	205.5±10.2**	85.5±1.2*

Note: reliability relative to baseline: *–p<01, **–p<01.

The reliability of hemostasis system analyses is that at the beginning of the study, APTT was 30.8±1.3 and 28.8±1.3 in groups 1 and 2. Over time, changes of 17.1% and 35.3% were detected in groups 1 and 2 over the 10th day after therapy. Compared with the initial values, at the end of therapy, INR increased by 11.2 % in group 1 and 2 by 20.5% . With parallel development, PTI decreased by 26.7 and 30.2% in both groups after treatment. PTI figures showed a stage I risk of thrombosis and normalized at the end of the study.

In the first group of patients, fibrinogen and D-dimer were registered at baseline at 525.7±10.1 and 530.7±21.1, respectively, and showed an improvement of 23.87 and 25.43% after treatment. Fibrinogen and D-dimer in patients receiving Kalgen were initially 500.7±10.1 and 525.7±21.1, respectively, and decreased by 38 and 61% at the end of treatment. This leads to a reduction in the risk of complications with occlusive-obturation blocks in the vessels of vital organs, and this can be seen in the following graphical section of the intergroup difference.

Graph 1. Graph of fibrinogen and D-dimer values.



As can be seen from the diagram above, in patients receiving standard therapy, fibrinogen and D-dimer levels fell to the upper limit of normal, while under the influence of the Kalgen drug, a significant decrease in fibrinogen and D-dimer levels was observed in the main group compared to group 1.

Table No. 3. Dynamics of inflammatory biomarkers.

Indicators	**IL - 1b** pg/ml	**IL - 6** pg/ml	**IL -1 0** pg/ml	**CRO** mg/l
Traditional therapy n=10				
Before treatment	13 ±1 , 5	15 ±1, 8	21 ±3, 1	17 ±0 .7
After treatment	6 ±1 , 3**	8 ±1 , 2**	31 ±2 , 3**	8 ±0 , 9**
K algen (0.15 PNA) n=1 0				
Before treatment	15 ±1 , 1	14 ±1, 8	22 ±3.7	19 ±0 .7
After treatment	4 ±0 .7 **	5 ±1 , 2**	35 ±2 , 4**	5 ±0 , 9**

Note: reliability compared to baseline **–p<0.01.

In patients in the standard therapy group, the levels of interleukin-1b and 6 were 13±1.5 and 15±1.8, which corresponded to the pathological state. After therapy, the dynamics of IL-1b decreased by 51%, and IL-6 by 45.9%. Before Kalgen therapy, the levels of interleukin-1b and 6 were 2-3 times higher than normal. After therapy, the levels of IL-1b and IL-6 decreased by 72% and 62%, respectively, returning to normal. At the same time, at the end of therapy, C-reactive protein decreased by 51.2% and 71.8% in groups 1 and 2, and IL-10 increased by 42.5% and 51.7%. The blocking of neuroinflammation by inflammatory cytokines, standard therapy, and collagen effect, and the increase in anti-inflammatory cytokines clearly indicate that it has a protective role for brain cells.

The average statistical time of the treatment cycle in the intensive care unit of the studied patients in the first group was 12± 0.9 days. In the second group, it was 10.3±1.1 days.

DISCUSSION. Pharmacological data have shown that kallidinogenase improves collateral circulation, cerebral blood flow, angiogenesis , and cerebral perfusion [4] . Kallidinogenase may be a crucial mechanism in the reorganization of brain structures in the treatment of acute cerebral infarction and protects against cerebral reperfusion injury [5]. Kinin and B2 are among the most potent activators of vascular endothelium, acting on endothelial cells to induce the release of numerous signaling molecules into smooth muscle, inhibit platelet aggregation, and promote fibrinolysis [1]. Kallidinogenase directly binds to protease-activated receptors, which leads to cell migration and proliferation of creatine [7]. Treatment with the gene transfer of the kallidinogenase KLK1 resulted in a decrease in brain macrophage/microglial infiltration [28]. Inhibition of pro-inflammatory Toll-like receptors (TLRs) and nuclear factor (NF) kB and activation of the pro-inflammatory nuclear respiratory factor (Nrf) pathway also likely contribute to the neuroprotective effect [30]. Kallidinogenase reduces the expression of pro-inflammatory cytokines (IL-6, IL-1, and TNFα), chemokines, adhesion molecules, and complement proteins [26], and a parallel increase in IL-10 has a neuroprotective effect [23].

Conclusions:

1. With standard therapy, kallidinogenase reduces cerebral hypertension - brain edema in patients with isolated CHI, leading to an increase in SPB. This is the basis for improving blood circulation in the brain tissues.

2. Kallidinogenase positively changes the coagulogram system of patients with isolated CHI, suppressing hypercoagulation. As a result, the risk of thromboembolic complications in patients is significantly reduced.

3. Kallidinogenase stops the neuroinflammatory and apathetic processes in the brain of patients with isolated CHI, reduces edema, and has a neuroprotective effect by stimulating neuroangiogenesis.

4. The Complexomed M-exopulsogram recording device is a non-invasive method for measuring brain edema and plays an important role in preventing dislocation syndrome that occurs with invasive methods.

5. Kallidinogenase reduced the time spent in intensive care.

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