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EVALUATION OF THE EFFECTIVENESS OF URINARY KALLIDINOGENASE (TISSUE KALLIKRIEN) IN THE COMPLEX THERAPY OF PATIENTS WITH ISOLATED CLOSED TRAUMATIC BRAIN INJURY

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Abstract:

Closed traumatic brain injury is quite common and affects millions of people worldwide every year. In the structure of injuries, the most dramatic is traumatic brain injury. In the European Union, up to 1.5 million people are hospitalized, 57,000 die every year due to TBI and three-quarters of them are young people. Kallidinogenase - tissue kallikrein, a component of the kallikrein - kinin system (KKS), has a protective effect against cerebral ischemia.

Keywords: TBI, tissue kallikrein (kallidinogenase), ICP, CPP, MAP, Glasgow, SAPS and APACHE II scales, M echo pulsogram.

INTRODUCTION. Traumatic brain injury remains an urgent problem due to the prevalence and severe consequences, the annual increase in the proportion of the consequences of concussion and mild to severe brain contusions. Disorders that occur after traumatic brain injuries acquire a protracted course with long-term disability among people of the youngest and working age. Mostly males aged 20-50 years (71.7%) are subject to injuries, which determine its social significance. Most of the accidents are 42.1% and work-related injuries 38% [1]. Brain injuries are accompanied by a long and severe course of a traumatic disease [2]. Over the past 10–15 years, the world has seen an increase in natural disasters, man-made disasters, road traffic accidents (RTA), terrorism and military conflicts, accompanied by traumatic injuries, especially to the brain. In particular, injuries to the skull and brain account for more than 1/3 of all injuries [3, 4], increasing annually by an average of 2% [5, 6]. According to the Ministry of Health of the Russian Federation, TBI ranks first in the structure of neurosurgical pathology, 36-40% - in the structure of traumatic injuries [9]. According to the Research Institute of Emergency Medicine. N.V. Sklifosovsky, the number of patients with CTBI in Moscow hospitalized in neurosurgical departments is 10,000–13,000 per year. In general, the incidence of CTBI in Moscow is 1.2–1.4 cases per 1000 people per year [7]. 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 [8].

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 [14, 15]. 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 TBI 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 [10]. It has been experimentally shown that these processes develop more intensively in the brain of older individuals compared to young ones [11]. 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 [12]. However, there is evidence that the control of ICP and CPP does not replace the assessment of true oxygenation of the brain tissue [13].

Secondary disorders include: excitotoxicity, apoptosis, oxidative stress, mitochondrial disruption, damage to the blood-brain barrier, and neuroinflammation [16]. These processes are exacerbated by the severity of the primary injury [17]. During the first 3 hours after the development of TBI,

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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 [18].

There is no specific therapy with isolated CTBI that would reduce the inflammatory cascade, prevent coagulation disorders, and inhibit apoptosis, which is the most important trigger of isolated PTBI, so far does not exist [19].

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) [29].

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 [20].

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 opoptotic cells [21]. 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 [22]. 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 [23]. Several studies have shown that kallidinogenase improves functional deficiency promotes angiogenesis and improves cerebral blood flow [24-26]. The main mechanism is upregulation of vascular endothelial growth factor and activation of bradykinin B1 and B2 receptors [27]. In addition, kallidinogenesis has been shown to improve cognition [28].

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 closed craniocerebral injury 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 mm Hg. Art. = SBP mmHg Art. – ICP mm Hg. Art. (MAP - mean arterial 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

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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.

Indicators	Research stages					
	1-group (standart therapy)			2-group (kalgen)		
	outcome	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±0.6 and 7.1±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 (st.therapy)	Points %	22 (63%)	17 (27%)	9 (10,3%)	28 (56%)	16 (25%)	10 (10,6%)
2-group (kalgen)	Points %	21 (61%)	16 (25%)	8 (8,3%)	28 (55%)	15 (25%)	7 (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.

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

Indicators	Research stages					
	1-group (standart therapy)					
	outcome	5 day	10 day	outcome	5 day	10 day
P%, M-echo pulsogram	64,3±2,4	34,4±1,1*	16,6±1,3**	63,5±2,6	30,4±1,1*	12,6±1,3 **
ICP, mm Hg	27,5±2,5	18,0±1,1 *	12,5±0,5 **	25,5±2,5	14,0±1,1 *	10,5±0,5 **
CPP, mm Hg	60,2±6,5	86,4±4,6 *	91,5±0,7 **	61,0±6,5	88,3±4,6 *	92,8±0,6 **
MAP, mm Hg	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 ± 2.4, 34.4 ± 1.1, 16.6 ± 1.3 and 27.5 ± 2.5 18.0 ± 1.1, 12.5 ± 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±2.6, 30.4±1.1, 12.6±1.3 and 25.5±2.5, 14.0±1.1, 10, 5±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, SBP 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±1.2 days in the first group and 10.6±1.1 days in the second group.

Kallidinogenesis promotes angiogenesis and improves cerebral blood flow [30]. 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 [31]. Many in vivo and in vitro studies have shown that kallidinogenesis significantly improves neurological function [33] and reduces infarct size [34]. Treatment with kallidinogenesis resulted in a 4.52% reduction in infarct size [35]. The effective frequency of kallidinogenesis was approximately 80% in cerebral ischemia [30].

On the general data of the literature, we can say that urinary kallidinogenesis (kalgen), acting on the kallikrein-kinin system, improves cerebral hemodynamics, 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.

REFERENCES:

1. Vasiliev D, Charkova Z. Combination of respiratory patterns of ventilation support modes for correction of central perfusion pressure in patients with isolated severe traumatic brain injury in the acute period. Wschodnioeuropejskie Czasopismo Naukowe (East European Scientific Journal) #9(61), 2020.

World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
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ISSN: 2749-3644

2. E.A. Lebedeva, E.G. Markaryan, S.A. Belyaevskij, G.A. Sasian, A.S. Sogikyan, S.A. Doroshenko, E.V. Yartsev, M.T. Klochkova, M.L. Skoblo banisteria traumatic brain injury are catecholamines Bulletin of Intensive Care named after A.I. Saltanov, 2018, No. 1.
3. Firsov S.A. Pathogenetic bases of medical care in combined craniocerebral and skeletal injury associated with alcohol intoxication: author. dis. Dr. med. Sciences. Arkhangelsk, 2015. 35 p.
4. Korolev V.M. Epidemiological aspects of combined trauma // Far Eastern Medical Journal. 2011. No. 3. P. 124–128.
5. Kuznetsov S.A. Scientific rationale for optimizing the provision of inpatient care to patients with traumatic brain injury (according to the data of the Astrakhan region): Ph.D. dis. cand. honey. Sciences. Voronezh, 2014. 23 p.
6. G. Akhanov, Y. Uteyliev, E. Dyusembekov, A.N. Nurbakyt, T. Popova clinical and epidemiological aspects of an isolated craniocerebral trauma (review) vestnik kaz NMU №-3 2018.
7. Talypov A.E. Surgical treatment of severe traumatic brain injury: Dr. med. Sciences diss. Abstract. Moscow; 2015. Access mode: http://www.neurosklif.ru/Text/Thesises/88.pdf [Accessed October 22, 2019] (in Russian).
8. Petrikov S.S., Solodov A.A., Badygov S.A., Mejia Mejia E.D., Krylov V.V. Influence of L-lysine aescinate on intracranial pressure in critically ill patients with severe traumatic brain injury // Zhurnal im. N.V. Sklifosovsky Emergency medical care. – 2016. No. 2. P. 31–36.
9. Butrov AV, Torosyan BD, Cheboksarov DV, Makhmutova GR. Therapeutic hypothermia in treatment of different cerebral injuries. Alexander Saltanov Intensive Care Herald. 2019; 2:75–81.
10. Leung L.Y., Wei G., Shear D.A., Tortella F.C. The acute effects of hemorrhagic shock on cerebral blood flow, brain tissue oxygen tension, and spreading depolarization following penetrating ballistic-like brain injury // J. Neurotrauma. — 2013. — 30. — 1288-1298.
11. Hawkins B.E., Cowart J.C., Parsley M.A. et al. Effects of trauma, hemorrhage and resuscitation in aged rats // Brain Res. — 2013. — 1496. — 28-35.
12. Bratton S.L., Chestnut R.M., Ghajar J. Et al. Guidelines for the management of severe traumatic brain injury. IX. Cerebral perfusion thresholds // J. Neurotrauma. — 2007. — 24. — S59-S64.
13. Eriksson E.A., Barletta J.F., Figueroa B.E. et al. Cerebral perfusion pressure and intracranial pressure are not surrogates for brain tissue oxygenation in traumatic brain injury // Clin. Neurophysiol. — 2012. — 123. — 1255-1260.
14. Shestopalov A.E., Leyderman I.N., Sviridov S.V. Metabolic response of the organism to stress. In: Khubutiya M.Sh., Popova T.S., Saltanov A.I., eds. *Parenteral and enteral nutrition*. Moscow: GEOTAR-Media Publ., 2014. Ch.8: 142–160. (In Russian).
15. Shakotko A.P., Marutyan Z.G., Kinishemova A.Y., et al. Safety of mixed artificial nutrition in patients with severe multisystem craniocerebral trauma. *Sklifosovsky Journal of Emergency Medical Care.* 2017; 6(3): 257–262. DOI: 10.23934/2223-9022-2017-6-2-257-262 (In Russian)
16. Yilmaz C, Karali K, Fodelianaki G, Gravanis A, Chavakis T, Charalampopoulos I, et al. Neurosteroids as regulators of neuroinflammation. *Front Neuroendocrinol.* 2019; 55: 100788. doi: 10.1016/j.yfrne.2019.100788.
17. Belyaevsky1 A. D, Lebedeva1 Ye. A, Belousova M. Ye Cytokines, Oxidative Stress and Antioxidant Defense in Isolated and Concomitant Brain Injury General resuscitation 5 (6) p 36-39.
18. V.I. Mamchur, S.N. Dronov, V.I. Zhilyuk, Cerebroprotection: Possibilities of Medical Protection of the Ischemic Brain Dnepropetrovsk State Medical Academy https://rpht.com.ua/ru/archive/2008/3%288%29.
19. Raghupathi R., Graham D.I., McIntosh T.K. Apoptosis after traumatic brain injury // J. Neurotrauma. 2000. 17. 927-938.
20. Regoli D and Gobeil F. Critical insights into the beneficial and protective actions of the kallikrein-kinin system/ Vascul Pharmacol 2015; 64: 1-10.
21. Whalley ET, Figueroa CD, Gera L, Bhoola, KD. Discovery and therapeutic potential of kinin receptor antagonists.*Expert Opin Drug Discov.*(2012) **7**:1129–48.doi: 10.1517/17460441.2012.729038.

World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
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ISSN: 2749-3644

22. T Michel A.K Rick Pols John . John J.W. Filip M. Batt and Todd A.V . Tkanevoy kalliykrien cheloveka pri lesheniy ostrovo ishiymisheskovo insulta.her Adv Neural Disord 2019. Vol 12: 1-15 DOI:10.1177/1756286418821918.
23. Chao J, Chao L. Experimental Therapy with Tissue Kallikrein against Cerebral Ischemia. Front Biosci. 2006;11:1323-7.
24. Zhang C, Tao W, Liu M, Wang D. Efficacy and Safety of Human Urinary Kallidinogenase Injection for Acute Ischemic Stroke: A Systematic Review. J Evid Based Med. 2012;5:31-9.
25. Li C, Zha OG, He QY, Wu YZ, Wang TS, Teng JF. Study on the Clinical Efficacy of Human Urinary Kalllikrein in the Treatment of Acute Cerebral Infarction According to Toast Classification. Pak J Pharm Sci. 2015;28:1505-10.
26. Miao J, Deng F, Zhang Y, Xie HY, Feng JC. Exogenous Human Urinary Kallidinogenase Increases Cerebral Blood Flow in Patients with Acute Ischemic Stroke.Neurosci (Riyadh). 2016;21:126-30.
27. Han L, Li J, Chen Y, Zhang M, Qian L, Chen Y, et al. Human Urinary Kallidinogenase Promotes Angiogenesis and Cerebral Perfusion in Experimental Stroke. PLoS One. 2015;10:e0134543.
28. Zhao L, Zhao Y, Wan Q, Zhang H. Urinary Kallidinogenase for the Treatment of Cerebral Arterial Stenosis. Drug Des Devel Ther. 2015;9:5595-600.
29. Wu, D., Lyu, Y., Zhong, P., Liu, F., & Liu, X. (2017).Human urinary kallidinogenase promotes good recovery in ischemic stroke patients with level 3 hypertension. *Brain and Behavior*, *7*(8), e00752. https://doi.org/10.1002/brb3.752.
30. Li C, Zha OG, He QY, Wu YZ, Wang TS, Teng JF. Study on the Clinical Efficacy of Human Urinary Kalllikrein in the Treatment of Acute Cerebral Infarction According to Toast Classification. Pak J Pharm Sci. 2015;28:1505-10.
31. Miao J, Deng F, Zhang Y, Xie HY, Feng JC. Exogenous Human Urinary Kallidinogenase Increases Cerebral Blood Flow in Patients with Acute Ischemic Stroke. Neurosci (Riyadh). 2016;21:126.
32. Lu R-Y, Luo D-F, Xiao S-H, et al. Kallikrein gene transfer induces angiogenesis and further improves regional cerebral blood flow in the early period after cerebral ischemia/reperfusion in rats. CNS Neurosci Ther 2012; 18: 395–399.
33. Si-Qia Chen, Mao D-Y, Wei D-C, He W-Z. Human urinary kallindinogenase therapy for acute ischemic stroke according to Chinese ischemic stroke subclassification: Clinical efficacy and risk factors. Brain Behav. 2020;10:e01461. https://doi.org/10.1002/brb3.146.
34. 78. Wei Z, Lyu Y, Yang X, Chen X, Zhong P and Wu D (2018) Therapeutic Values of Human Urinary Kallidinogenase on Cerebrovascular Diseases. Front. Neurol. 9:403. doi: 10.3389/fneur.2018.00403.
35. Ning Zhang, Fanxia Meng, Wangxiao Bao, Xiaoxia Li, Fangping He, Anli Wang, Ziqi Xu Efficacy of human urinary kallidinogenase in ischemic stroke in animal models: a meta-analysis Int J Clin Exp Med 2019;12(7):8670-8677 www.ijcem.com.