EFFECTS OF L-LYSINE AESCINAT ON INTRACRANIAL PRESSURE IN CRITICALLY ILL PATIENTS WITH SEVERE TRAUMATIC BRAIN INJURY

S.S. Petrikov, A.A. Solodov, S.A. Badygov, E.D. Mekhia Mekhia, V.V. Krylov

N.V. Sklifosovsky Research Institute for Emergency Medicine of the Moscow Healthcare Department, Moscow, Russian Federation

ABSTRACT	Increased intracranial pressure results in cerebral blood flow decrease and cerebral edema formation. Correction of intracranial hypertension is one of the most important goals of intensive care in patients with severe traumatic brain injury.
OBJECTIVES	To determine the effects of L-lysine aescinat on ICP in patients with severe TBI.
MATERIAL AND METHODS	Twenty patients with TBI and Glasgow coma scale below 9 enrolled in the study. All patients were operated: 6 patients underwent craniotomy and intracranial hematoma removing; 11 — decompressive craniotomy and intracranial hematoma removing. In 3 patients only ICP-sensor was implanted. ICP-monitoring was used in all patients. Ten patients were randomized to L-lysine aescinat treatment (daily dose of 20 ml for 7 days after surgery) (study group), 10 — to standard therapy (control group). We perfomed a comparative analysis of the mean ICP and the incidence of ICH within 7 days after surgery in the study and control groups.
RESULTS	The length of ICP monitoring was 6.4±3.7 days: in the control group — 7.6±4.9 days, in the study group — 5.2±1.4 days. Mean intracranial pressure was less in the study group as compared to patients in the control group. The number of intracranial hypertension episodes was higher in the control group compared with patients who received L-lysine aescinat.
CONCLUSION	L-lysine aescinat treatment in patients with severe traumatic brain injury is accompanied by reduction of mean intracranial pressure and the number of intracranial hypertension episodes.
Keywords:	traumatic brain injury; L-lysine aescinat; brain edema, intracranial pressure, intracranial hypertension.

ATP — adenosine triphosphate
CT — computed tomography
CSF — cerebrospinal fluid
DCT — decompressive trepanation
GCS — Glasgow Coma Scale
ICH — intracranial hypertension
ICP — intracranial pressure
OPT — osteoplastic trepanation
TBI — traumatic brain injury

INTRODUCTION

Treating patients with severe traumatic brain injury (TBI) is an actual problem of modern medicine and has a great social and economic importance. In the Russian Federation, the incidence of TBI is 4-4.5 cases per 1000 population annually [1]. The main contingent of victims are people of working age (20-50 years), and the mortality in severe head injury with the presence of intracranial hematomas, foci of brain contusion ranges from 41 to 85% [1-3]. It should be noted taht TBI is a leading cause of disability. Thus, the number of cases with a permanent incapacity as a result of brain injury reaches 25-30% [2-5].

The main reasons for poor outcomes in patients with severe traumatic brain injury include progressive intracranial hypertension (ICH), accompanied by the development of acute dislocation syndrome, which is expressed in the displacement and compression of the brain stem with subsequent impairment of respiration and circulation [1, 6-8]. Early diagnosis and elimination of ICH are keys to success in the treatment of patients with severe traumatic brain injury. Procedures for normalization of intracranial pressure (ICP) are aimed at increasing the cerebrospinal compliance by creating extra spaces in the cranial cavity. The main course of intensive therapy is reduction of intracranial volumes of blood and cerebrospinal fluid (CSF). Hyperosmolar solutions increasing plasma osmolarity allow for a short time to reduce the liquid content primarily in intact brain regions [9-11]. Effective methods of managing ICH are ventricular CSF drainage and timely decompressive trepanation [12].

One of the promising areas of ICH treatment may be direct influence on cerebral edema. The reduction of cerebral edema may reduce the severity of ICH [14]. However, today there are almost no drugs with proven effect on

cerebral edema. In 2003, we published results of a research showing the positive effect of *L*-lysine aescinat in the treatment of patients with severe traumatic brain injury [13]. *L*-lysine aescinat is a water-soluble salt of horse chestnut saponin (aescin), and the amino acid *L*-lysine [13]. In blood, the drug rapidly dissociates into ions lysine and aescin. Aescin reduces the activity of lysosomal hydrolases that prevents decomposition of mucopolysaccharides in the walls of capillaries and connective tissue which surrounds them, and thus normalizes the increased vascular permeability, and has antiexudative, anti-inflammatory and analgesic activity. It is noted that *L*-lysine aescinat may normalize the ATP content in endothelial cells, prevent activation of phospholipase A2, the release of arachidonic acid and dose-dependently inhibit enzymatic and non-enzymatic lipid peroxidation [14, 15]. The use of *L*-lysine aescinat in patients with TBI was associated with improvement of general condition, neurological status, reduction of a perifocal zone around contusion foci, as well as compression and displacement of the ventricular system and midline structures of the brain. [15]

The purpose of research is to evaluate the effect of *L*-lysine aescinat on ICP in patients with severe traumatic brain injury in critical condition.

MATERIAL AND METHODS

We examined 20 patients with severe traumatic brain injury, score 8 according to Glasgow Coma Scale (GCS). At the time of inclusion into the study, 10 patients were in a moderate coma (GCS score 6-8), and 10 patients were in a deep coma (GCS score 4-5). The average age of patients was 39.3±13.6 years, male/female ratio was 18/2.

All the injured were urgently operated on (Table 1). Six patients (30%) underwent osteoplastic trepanation (OPT), intracranial hematomas were removed and a sensor for measuring intracranial pressure was installed. Decompressive trepanation (DCT) was performed in eleven victims (55%) due to dislocation and the cerebral prolapse into the defect of trepanation; we removed intracranial hematomas and also installed sensors measuring intracranial pressure. Three patients (15%) had a sensor already been installed, intracranial hematomas and contusions foci were small and did not require surgery. Three patients were re-operated. In connection with the development of uncontrolled ICH, 2 patients with initially performed OPT underwent DCT, and one victim required DCT on the opposite side in relation to the originally performed DCT (see Table 1).

Table 1

Types of surgical interventions in surveyed patients

Type	All patients *n (%* of total number of patients in each group)	Study group, *n (%* of total number of patients in each group)	Control group, *n (%* of total number of patients in each group)
CPT, removal of intracranial hematoma, installation of ICP sensor	6 (30%)	2 (20%)	4 (40%)
DCT, removal of intracranial hematoma, installation of ICP sensor	11 (55%)	6 (60%)	5 (50%)
Installation of ICP sensor without removal of intracranial hematomas	3 (15%)	2 (20%)	1 (10%)
Repeatedly operated due to refractory intracranial hypertension	3 (15%)	0	3 (30%)

Note: OPT — osteoplastic trepanation, DCT — decompressive trepanation, ICP — intracranial pressure

MONITORING INTRACRANIAL PRESSURE

The intracranial pressure was monitored in all patients.

In 17 patients, we used parenchymal *Codman MicroSensor™ (SNS*, USA). After calibration on the border of the water and air environment the sensor was installed in the frontal or temporal lobe opposite to the main lesions of the brain to a depth of 1.5-2 cm. The proximal tip of the sensor was connected to the ICP monitor *Codman ICP Express (SNS,* USA) and then measuring of ICP was initiated.

In 3 affected, ICP was measured by means of *Air-Pouch Probes,* 3*XL (Spiegelberg,* Germany). For that, a special double-lumen probe with an air pouch on its tip was installed in the anterior horn of the right and/or left lateral ventricle. The measuring tube of the probe was connected to the *Spiegelberg: Brain-Pressure Monitor»* (*Spiegelberg,* Germany), the drainage tube was connected to a system of controlled relief of cerebrospinal fluid (CSF). After that, the monitor filled the pouch with air and the degree of CSF pressure exerted on the pouch walls defined ICP. The correct position of sensors in the cranial cavity was confirmed by the computed tomography (CT).

Monitoring of ICP was discontinued 2 days after normalization of ICP without ICH therapies.

INTENSIVE THERAPY

All patients underwent standard intensive therapy. The head end of the bed was lifted by 30-40°. Crystalloid and colloid solutions were combined to perform the infusion therapy. We strived to maintain the normal blood volume. In the presence of hemodynamic monitoring system the infusion therapy was arranged on the basis of data obtained during the transpulmonary thermodilution. If necessary, sympathomimetics were administered to sustain adequate cerebral perfusion. We tried to initiate enteral nutrition on the first day of stay in the intensive care unit (20-25 kcal per 1 kg of body weight daily). The daily need for protein was evaluated according to calculation of nitrogen balance. If necessary, parenteral nutrition was added. Mechanical ventilation was carried out in the auxiliary mode with a breathing capacity of 6-8 ml per 1 kg of ideal body weight, the carbon dioxide tension in arterial blood was sustained within 33-40 mmHg.

All the victims underwent the intensive therapy aimed at maintaining the level of ICP less than 20 mmHg. If ICH developed (persistent rise in ICP up to 20 mmHg or more), the CT was performed in the early postoperative period and in the absence of the need to conduct surgery we used a stepwise algorithm for increased ICP management.

Hyperosmolar solutions were administered intravenously (stream infusion of 15% Mannitol solution, 1.5 g/kg/day and "HyperHAES", not more than 250 ml/day). The plasma osmolality was monitored. When the osmolality of blood plasma grew higher than 320 mosm/l, the infusion of hyperosmolar drugs was discontinued. The psychomotor agitation was managed with sedative medications (combination of propofol with narcotic analgesics or α_2-adrenoceptor agonists). Hyperthermia was managed with antipyretics and physical cooling methods. In case of failure or inability to administer hyperosmolar solutions, we used barbiturates and moderate hypothermia. To reach "barbituric" coma, we administered sodium thiopental solution intravenously, 4-6 g/day. Hypothermia was performed using physical methods and devices for cooling a patient. Blood temperature was maintained within 34-36°C.

STUDY DESIGN

The patients were sequentally randomized into two equal groups of 10 affected in each. The patients of the study group *(n*=10) received a solution of *L* -lysine aescinat, 20 ml daily for 7 days after surgery (the study group). The patients of the control group *(n*=10) underwent the standard therapy. Patients of both groups did not differ in the level of consciousness, average age and gender at the time of inclusion into the study (Table 2). ICP values were recorded every 1-2 h. With the development of ICH, its value was additionally recorded. We conducted a comparative analysis of average ICP, incidence of ICH and its severity within 7 days after the surgery.

Table 2

General characteristics of patients examined in the at study entry

Indicators	The study group *(n*=10)	The control group *(n*=10)
LOC: moderate coma (GCS, score 6-8)	6	4
LOC: deep coma (GCS, score 4-5)	4	6
Average age, years	38.5±12.3	40.1±15.5
The ratio of male/female	8/2	10/0

Note: GCS – Glasgow Coma Scale, LOC – level of consciousness

The data is given in the format $M \pm \sigma$ (M — arithmetic mean, σ — standard deviation) for the "normal" distribution and in Median format (25 and 75 percentiles) for the "abnormal" distribution, n — the number of observations in the group.

RESULTS AND DISCUSSION

The duration of monitoring for intracranial pressure in surveyed patients was 6.4±3.7 days. Patients of the control group had a prolonged increase in intracranial pressure (7.6±4.9 days) compared to similar data from the study group (5.2±1.4 days) (Fig. 1).

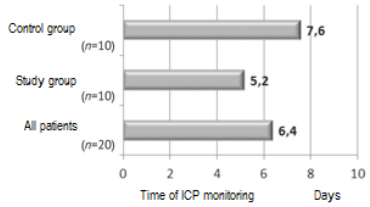

Fig. 1. The duration of monitoring for intracranial pressure in surveyed patients with severe traumatic brain injury *(n* – number of patients in each group)

The number of ICP measurements was comparable between the groups (Fig. 2).

The analysis of maximum values of ICP per day did not reveal any significant differences between the groups (Fig. 3, Table 3). However, maximum values of ICP were higher in patients of the control group almost over the entire course of the study .

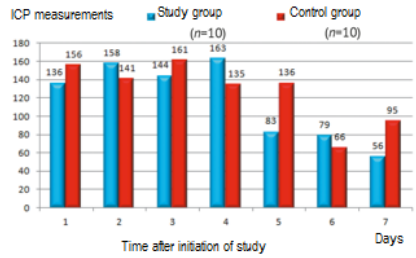

Fig. 2. The number of measurements of intracranial pressure per day in the examined patients with severe traumatic brain injury *(n* – number of patients in each group). Note: ICP – intracranial pressure

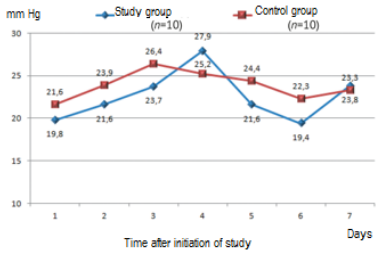

Fig. 3. The maximum intracranial pressure (mean values) in the examined patients with severe traumatic brain injury in the study group and the control group *(n* – number of patients in each group)

Table 3

The minimum and maximum intracranial pressure per day in surveyed patients

Groups	Twenty-four hours after surgery						
	1	2	3	4	5	6	7
	Max ICP (mmHg)						
Study group	19.8±5.0	21.6±6.9	23.7±8.6	27.9±16.8	21.6±10.3	19.4±6.1	23.8±18.0
Control group	21.6±2.4	23.9±2.3	26.4±9.3	25.2±5.6	24.4±5.4	22.3±8.3	23.3±15.0

Note: ICP – intracranial pressure

The average ICP in the group, who received *L*-lysine aescinat was lower throughout the study than the average ICP in the control group of patients (Fig. 4, Tab. 4). The maximum difference between the average ICP in comparison with its value in patients who received *L*-lysine aescinat was observed starting on day 4 of the study. The mean ICP in the control group compared to values in the study group was higher by 3.4±5.9 mmHg on day 4, by 4.3±5.6 mmHg on day 5, by 3.1±6.4 mmHg on day 6, and by 2.0±7.6 mmHg on day 7(see Table 4). Our findings confirm the results of studies of L.A. Dzyak et al. (2010) [14]. The authors observed a decrease in the average daily intracranial pressure in patients with severe head injury who used *L*-lysine aescinat starting on day 2 of the study. According to these researchers, the average daily fall of ICP in the study group was significant on day 5,6 and 7 compared to baseline values.

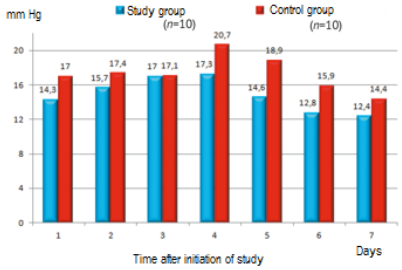

Fig. 4. Average daily intracranial pressure in patients with severe traumatic brain injury in the study and control group *(n* – number of patients in a group)

The number of ICH episodes was also significantly lower in patients treated with *L*-lysine aescinat than in the control group (Fig. 5). In patients of the study group, the maximum number of episodes of increased intracranial pressure up to 20 mmHg or more was observed on day 2 and 4 after the surgery and was 3 (1; 5) per day (see Table 4). Starting from day 5 day there was a trend to reduction in reported cases of increased intracranial pressure. Alternatively, there was a tendency to the development of ICH over the entire period of observation in the control group. The largest number of episodes of ICH was observed on day 4 after the operation and was 8 (1.5; 16) per day. Varying frequency and severity of ICH may indirectly affect the incidence of deaths in surveyed patients. The mortality rate in the study group was 40%, while in the control group it was 70%.

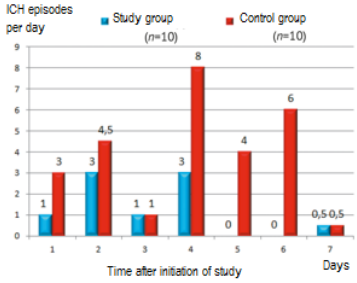

Fig. 5. The number of episodes of increased intracranial pressure up to 20 mmHg or more per day in patients with severe traumatic brain injury in the study group and the control group *(n* – number of patients in each group)

Table 4

Average ICP per day and the number of episodes of increased intracranial pressure up to 20 mmHg or more per day in examined patients with severe traumatic brain injury

Groups	Average ICP per day (M±σ) after operation (days)							Episodes of increased intracranial pressure up to 20 mmHg or more per day (Median — 25; 75 percentiles) after operation (days)						
	1	2	3	4	5	6	7	1	2	3	4	5	6	7
All patients	15.8±5.0 *n*=292	16.5±5.1 *n*=299	17.0±6.7 *n*=305	18.9±8.3 *n*=298	17.2±6.1 *n*=218	14.2±5.6 *n*=145	13.6±8.0 *n*=151	1 (0; 8)	4 (2; 5)	1 (0; 5)	4 (1; 8)	4 (0; 8)	0 (0; 2)	1 (0; 2)
Study group	14.3±5.9 *n*=136	15.7±5.4 *n*=158	17.0±6.5 *n*=144	17.3±9.5 *n*=163	14.6±5.9 *n*=83	1.8±4.5 *n*=79	12.4±8.6 *n*=56	1 (1; 5)	3 (0; 5)	1 (1; 2)	3 (1; 5)	0 (0; 5)	0 (0; 0)	0,5 (0; 1.8)
Control group	17.0±3.8 *n*=156	17.4±4.6 *n*=141	17.1±6.9 *n*=161	20.7±5.9 *n*=135	18.9±5.6 *n*=136	15.9±6.4 *n*=66	14.4±7.6 *n*=95	3 (0; 8)	4,5 (3.5;9.3)	1 (0; 16)	8 (1.5; 16)	4 (1.8; 11)	6 (0; 13.3)	0,5 (0; 5.5)

Note: n — number of observations; ICP — intracranial pressure; TBI — traumatic brain injury

In 5 patients of the control group, we noted the development of uncontrolled ICH, which required the use of hypothermia and "barbituric" coma. In the study group, hypothermia and barbiturates were used in 2 patients. In 3 patients of the control group, the development of refractory ICH required re-operation (decompressive trepanation). There were no repeated surgeries required among patients of the study group. Thus, the conservative treatment in the course of *L*-lysine aescinat effectively managed episodes of increased intracranial pressure without decompressive trepanation.

The lower severity and incidence of ICH episodes in the study group may have been due to the positive effects of *L*-lysine aescinat on cerebral edema.

CONCLUSION

The use of *L*-lysine aescinat in patients with severe traumatic brain injury tends to decrease the intracranial pressure and the number of intracranial hypertension episodes. A possible explanation for the positive effect of the drug on ICP may be a decrease in the severity of cerebral edema.

FINDINGS

1. The duration of monitoring for intracranial pressure in surveyed patients was 6.4±3.7 days.

2. The average intracranial pressure in the study group, who received a solution *L*-lysine aescinat was lower throughout the study compared to the average intracranial pressure in the control group of patients.

3. In patients who received *L*-lysine aescinat, we noted fewer intracranial hypertension episodes as compared to the control group.

4. The conservative treatment of intracranial hypertension in the course of therapy with *L*-lysine aescinat effectively managed episodes of increased intracranial pressure without decompressive trepanation and improved treatment outcomes.

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For correspondence:
Aleksandr Anatolyevich Solodov,
Cand. Med. Sci., Head of the Resuscitation and Intensive Care Unit for Neurosurgical Patients,
N.V. Sklifosovsky Research Institute for Emergency Medicine of the Moscow Healthcare Department
E-MAIL: DOCSOL@MAIL.RU