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Effect Of Hyperosmolar 3,5% Nacl Solution On Cerebral Edema In Patients With Traumatic Brain Injury

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Abstract: In the structure of injuries, traumatic brain injury is the most dramatic. TBI remains one of the most important public health problems. Background: To study the effect of early administration of 3,5% HSS on systemic, central hemodynamics, hemostasis, ICP, CPP, efcacy and safety in isolated traumatic brain injury in an adult population. Material and methods: The study design was a retrospective - 16 patients and prospective 20-patient, single-center, randomized open clinical trial of 36 patients treated in intensive care unit (ICU) with isolated traumatic brain injury aged 18 to 88 years with depression of consciousness (4-12 Glasgow scale score), and abnormal head computed tomography fndings on admission. Daily data during 7 days after admission to the TBI included hourly measurements of ICP, recorded noninvasively using Complexmed 1.2, and if possible, by lumbar subarachnoid puncture with manometry in 9 patients, determination of serum sodium, pulse oximetry and measurements of daily diuresis, plasma osmolarity. Results: At 20-25 minutes after thebolus of 3,5% HSS injection, the ICP decreased (stage 2) below 20 mmHg, reaching an average of 19,7 mmHg, i.e. decreasing relative to the initial data by 26,3% ($p<0,05$). The maximum decrease of ICP was noted at the 3rd stage of the study (after 30 minutes), where, amounting to 18, 9 ± 0.73 mmHg, it was 29,3% ($p<0,05$) lower than the initial values. Conclusions: NaCl HSS can be used as early as possible in patients with traumatic brain injury and high risk of developing ICH.

Keywords: Intracranial hypertension (ICH), intracranial pressure (ICP), cerebral perfusion pressure (CPP), hypertonic saline solution.

1. Introduction: Traumatic brain injury (TBI) is quite common and affects millions of people worldwide every year [1]. In thestructure of injuries, traumatic brain injury is the most dramatic. TBI remains one of the most important public health problems. There has been an increase in the incidence of traumatic brain injury in all countries of the world. Traumatic brain injury is the most common cause of death, severe disability worldwide and permanent disability in people under the age of 45 years, which is largely due to secondary brain disorders, hemorrhage [2]. Severe traumatic brain injury has a high mortality rate (30-60%) in studies on unselected populations, can cause temporary or permanent impairment of cognition, behavior [3] and survivors experience a signifcant burden of physical, mental, emotional and cognitive impairment that disrupts the lives of individuals, their families and incurs huge costs to society [4]. The vast majority of trauma survivors experience impairment and disability (epileptic seizures, encephalopathy, paresis and paralysis, speech impairment and other neurological sequelae). Some literature shows that the incidence of traumatic brain injury is three times higher than the population growth and the cost of treatment > 33 billion euros per year [5]. The incidence of traumatic brain injury has increased with the acceleration of urban construction and the associated increase in trafc accidents [6]. In all the above-mentioned cases of acute cerebral lesions, cerebral edema and increased intracranial pressure have the most direct relation to survival and mortality, often being one of the main targets of therapeutic intervention. Prevention and treatment of cerebral edema and intracranial hypertension (ICH) are cornerstones of TBI management of trauma patients, as uncontrolled edema and ICH exacerbate brain damage and remain the most common cause of death after severe traumatic brain injury [7]. Thus, preventing secondary brain damage from edema and increased intracranial pressure is a central focus

of neurobiologic intensive care [8]. Currently, the tactics of intensive therapy of cerebral edema and ICH in craniocerebral trauma remain one of the current topics in neuroresuscitation. Several strategies have been recommended for the treatment of ICH, but few have been demonstrated to improve long-term outcomes [9]. After sedation and head positioning (orthopnea), boluses of hyperosmolar therapy are often a level 2 strategy for the treatment of ICH, but the HSSinduced (Hypertonic saline solution) decrease in ICH is short-lived and a rise in ICH is often observed after a few hours [10]. Continuous infusion of HSS has been proposed, but its effect on survival and ICH outcomes has been disappointing [11].

1.1 The study design was a retrospective - 16 patients and prospective 20-patient, single-center, randomized open clinical trial of 36 patients treated in Intensive care and intensive care unit (ICU) with isolated traumatic brain injury aged 18 to 88 years with depression of consciousness (4-12 Glasgow scale score), and abnormal head computed tomography findings on admission.

Patients were hospitalized in the immediate post-injury period and had some degree of impaired consciousness. The average time of admission after injury was 37±8 min. Only patients with ICH (Intracranial pressure (ICP) >20 mmHg) were included in the study. After assessment of the level of consciousness, all patients underwent head CT to exclude the need for emergency neurosurgical intervention.

1.2 Methods of intensive care

All patients underwent standard complex intensive therapy in accordance with international recommendations for the treatment of traumatic brain injury. The head end of the bed was elevated by 30-40º. Ventilation with Wella and Drager apparatus with a respiratory volume of 8-10 ml/per/kg of ideal body weight in SIMV (Synchronized Intermittent Mandatory Ventilation) mode and PEEP +2-10 cm Hg. Infusion therapy was carried out, combining colloid and crystalloid solutions. We tried to maintain normovolemia (CVP 8-12 cm of water column). We tried to start enteral tube feeding from the first day of the patient's stay in the intensive care unit from the calculation of 20-25 kcal per kg of body weight per day after stabilization of vital parameters of the organism. Daily protein requirement was estimated according to the nitrogen balance calculation. If necessary, parenteral nutrition was added. For prophylaxis of infectious complications all patients were treated with monotherapy with cephalosporins (ceftriaxone 2-4 g/day) or fluoroquinolones (ciprofloxacin 0.2- 0.4 g/day) from the first day after surgery or in the presence of respiratory support. To prevent thrombosis of deep veins of lower limbs (in the absence of signs of external and internal bleeding from 2-3 days Low molecular weight heparins (LMWH) Clexane 0,4 thousand units per day subcutaneously was administered). In patients who underwent ICP measurement, in case of clinical signs of dislocation syndrome (anisocoria, upward gaze paresis, Gerdwig Majandi syndrome in combination

with bradycardia, arterial hypertension) CT of the brain was performed and the question of surgical intervention was decided. Blood plasma osmolarity was monitored. In order to control psychomotor agitation, we used medication sedation with a combination of narcotic analgesics and benzodiazepines. Hyperthermia was not allowed by us. At t >37,5º antipyretics were administered and physical methods of cooling were used. In case of progressive worsening of the level of consciousness, despite conservative therapy, CT scan of the brain was performed.

ICP was sought to be maintained within 15-20 mmHg or less. Analgesia and sedatives were used during invasive procedures (tracheostomy, vascular catheterization) and when it was necessary to control psychomotor agitation of the patient. Hyperosmolar solutions under control of blood plasma osmolality were used to reduce elevated ICP. If blood plasma osmolality increased more than 320 mosm/l, administration of hyperosmolar preparations was stopped. In the presence of persistent intracranial hypertension, difficult to be corrected by conservative methods of therapy (ICP more than 20 mm Hg for 6-12 hours), decompressive cranial trepanation was performed.

Baseline therapy, according to the protocol adopted in our clinic, included ITT, lidocaine to close Na+ - channels, nimotop (nimodipine) to block Ca2+ - channels (NMDA receptors), mild therapeutic craniocerebral hypothermia (4-5º cooling of brain structures), antioxidant therapy (α-lipoic acid, ascorbic acid, vit. E) to block reactive oxygen species, propofol, barbiturates to sedate and block transaminase activity, prophylaxis of infection and thrombotic complications and ulcerative complications. E) to block reactive oxygen species, propofol, barbiturates for sedation and blockade of transaminase activity, prophylaxis of infection, thrombotic complications and ulcerative formations in the gastrointestinal tract, early tube feeding of patients.

1.3 Methods of statistical analysis

Statistical processing of the obtained data was carried out on a personal computer using the JASP program package. Statistical processing of the material provided for obtaining combination tables, graphs, and analytical indicators: structure (P), mean values (M) and their standard errors (±m), Student's criterion (t) with calculation of the probability of error (p). Differences in mean values were considered reliable at a signifcance level of p<0,05. ICP and M-echo pulseograms were checked with Pearson's correlation coeffcient, and their reliability was checked with the Student's t-test.

1.4 The purpose of our study in this section of the paper was to:

To study the effect of early administration of 3,5% HSS on systemic, central hemodynamics, hemostasis, ICP, CPP, efficacy and safety in isolated traumatic brain injury in an adult population.

All patients in this group had severe isolated traumatic brain injury caused mainly by road traffic accidents and falls.

2. Methods

36 patients were included in this study in the Departments of Neurosurgery and Anesthesiology and Critical Care Medicine. All patients in this group received infusion of 3,5% NaCl solution only in order to reduce ICP. In this study, we investigated the effect of the indicated HSS on individual episodes of intracranial hypertension, as well as on the time and duration of reduction of ICH peaks, the dose of this solution reducing ICP <20 mmHg.

Inclusion criteria for the study were: age >18 years, isolated traumatic brain injury, level of consciousness according to HQG ≤12, sustained elevation of ICP>20 mmHg.

Exclusion criteria were:

-The need for urgent cranial or extracranial surgery;

-Previous decompressive craniectomy

-Polytrauma

-Oliguria, renal failure

-Hb level<80 g/L

-Serum osmolarity >320 mosm/L

-Use of mannitol or HSS in the previous 6 hours

-Pregnancy

-Patients who died within 72 hours of admission to ICU

-Coagulopathies

Heart rate, SBP, ICP and calculated CPP were measured

continuously using a resuscitation-surgical monitor YuM-300S. ICP was measured invasively by lumbar puncture at the L3-L4 level and non-invasively. In total, out of 36 patients with isolated TBI in the absence of CT signs of dislocation syndrome, lumbar puncture with monometry and mandatory flling with autologous blood was performed in 9 patients. In the vast majority and repeatedly, ICP was measured non-invasively. The analysis of these parameters was carried out at the following stages of the study:

• before the start of the infusion;

• after stopping the infusion (ICP <20 mmHg achieved);

• 30, 60 and 120 minutes after stopping the infusion (after reducing ICP <20 mmHg).

Serum sodium levels, serum osmolarity, blood glucose, hematocrit, and diuresis were assessed before and after therapy.

Pre-hospital physiologic parameters were recorded, including post- resuscitation GCS, pupil reactivity to light, Hb, Ht, and blood glucose levels. Daily data during 7 days after admission to the TBI included hourly measurements of ICP, recorded noninvasively using Complexmed 1.2, and if possible, by lumbar subarachnoid puncture with manometry in 9 patients, determination of serum sodium, pulse oximetry and measurements of daily diuresis, plasma osmolarity. Important aspects of care for traumatic brain injury included neurosurgical operations performed, when necessary (clot evacuation, decompression craniotomy), osmotherapy only 3,5% HSS, and ventilatory support. Outcome data included ICU and in-hospital mortality, length of stay in ICU, dose of 3,5% HSS, and time required to reduce ICP <20 mmHg.

3. Result

We used descriptive statistics to study the frequency and percentage of such variables as gender, pupillary reactions, CT findings, mechanism of injury, and level of consciousness in the patient groups we studied as an indicator of the representativeness of these groups (Table 1).

Table 1

Demographic and clinical characteristics of CHMT patients (n=36)

Patient Characteristics		Values abs.	%
Age, years		40,6±1,6	
Paul	Men	32	88,9%
	Women	4	11,1%
Mechanismof injury	TRAFFIC ACCIDENTS, %	18	50,0%
	Falls, n%	14	38,9%
	Compressions, n%	3	8,3%
	Sports injury, n%	1	2,8%
Vigor level	GCS, points	5,62±0,23	
Abnormalpupils	Pupils (pathologic, n%)	26	72,2%
	Bilateral miosis, n%	10	27,8%
	Anisocoria, n%	14	38,9%
	Bilateral mydriasis with photoreaction, n%	2	5,6%
Overall severity of condition	APACHE, scores	16,4±0,68	
CT studydata:	Brain contusion, n%	14	38,9%
	Skull bone fracture, n%	5	13,9%
	Cerebral edema, n%	11	30,6%

	Subarachnoid hemorrhage, n%	13	36,1%
	Subdural hematoma, n%	-	-
	Epidural hematoma, n%	7	19,4%
	Intracerebral hemorrhage, n%	-	-
	Axonal damage, n%	-	-
	Intubation, ventilator, n%	33	91,7%
	Arterial hypotension, n%	27	75,0%
Neurosurgial interventions	Craniotomy, n%	7	19,4%

Standard therapy of patients in this group was performed according to the protocol adopted in our clinic and reflected in the previous section of the work. In this group we monitored systemic (BP, MBP, HR) and central hemodynamic parameters (BV (Beating volume), CI, Total peripheral vascular resistance (TPR)).

When the ICP exceeded 20 mmHg for more than 5 min (two to three times measured by ultrasound M-echo pulsation of the III cerebral ventricle), a bolus of 3,5% HSS was administered through the central vein at a rate of 6-8 ml-min (120- 130 cap/min). Infusion was stopped when the ICP decreased below 20 mmHg. The values of ICP, CPP before and after the infusion of HSS were recorded. Keeping in mind that the effect of HSS on lowering ICP usually persists for 60-120 min after its administration [12], we recorded ICP and CPP at 15-30, 60, and 120 min after drip infusion of 3,5% HSS. The total episodes of ICH requiring HSS per patient, the number of ICH episodes per day, and the dose of each 3,5% HSS infusion were recorded by us.

This group consisted of 36 patients with severe isolated craniomaxillofacial trauma aged 18-83 (40,6±1,6). The trauma was associated with traffic accident (18), fall (10), high-altitude trauma (4) and 4 patients had blunt blows on the head with bleeding wounds of the scalp without damage to the skull bones. Vomiting of gastric contents occurred in 5 patients, one of whom was diagnosed with aspiration syndrome, for which a bronchoscopy with lavage of the respiratory tract was performed (Table 1).

The average level of consciousness according to GCS was 5,42±0.22 (4,0- 11,0), which corresponded to cerebral coma. Only in 9 patients (25%) the level of consciousness was within 10-11 points. The total severity of the condition according to APACHE II averaged 16,4±0,65 points, corresponding to average severity, but was somewhat more severe than the previous group of patients.

Equal-sized pupils of medium size with good photoreaction were registered in 10 patients of this group (27,8%), bilateral miosis - in 10 (27,8%), anisocoria - in 14 (38,9%), in 2 (5,6%) patients there was bilateral moderate pupil dilation with impaired photoreaction to light (Table 1).

CT scans diagnosed subarachnoid hemorrhage (13), cerebral edema in 11, epidural hemorrhage (7), and linear skull fracture in the occipital-parietal region without dislocation of fragments (5) (Table 1).

The presented Table 2 shows the data of clinical examination of the patients of this group on admission to the clinic.

Table 2

Blood and hemostasis clinical examination parameterson admission (n=36)

Indicators	Values	Norma
Erythrocytes, 10 /L^{12}	3,88±0,16	3,7-5,1
Hemoglobin, g/l	10,7±0,43	12,0-16,0
Leukocytes, 10 /L^{9}	5,29±0,21	4-8,8
Neutrophils, 10 /L^{9}	3,53±0,14	0,5-6

Lymphocytes, 10 /L^9	1,82±0,07	1,2-3,0
Fibrinogen, g/L	4,21±0,17	2-4
Platelets, 10 /L^9	177,5±7,2	160-360
Prothrombin time, sec	12,8±0,52	15-17
ABPM, sec	28,7±1,2	35-45
Hematocrit, %	40,4±1,6	36-48

The presented data indicate moderate anemia of traumatic genesis and activation of the blood coagulation system, as evidenced by: shortened prothrombin time by 8,5%, increased fibrinogen values and decreased Activated Partial Thromboplastin Time (APTT) by 7,4% from the lower limit of physiological values of this index (Table 2).

The average values of the studied parameters indicate that patients in this group had moderate arterial hypotension with a decrease in systolic and diastolic pressure, which affected the decrease in MBP. All this indicated a decrease in resistive vascular tone. However, TPR parameters were also lower than physiologic values, which indicated a decrease in vascular tone in the low-pressure system (capillaries, venules) (Table 3). The decrease in TPR amounted to 9,1% of the proper values of TPR in this period (1511,1 dyne×s×cm-5), calculated by us according to the formula described above.

The proper values of MBP in this age group of patients under study are 85 mmHg.

CVP was lower than physiologic values by 33,8%. All the above-mentioned contributed to the decrease in single and minute cardiac output, which were on the borderline values of normo- and hypodynamic mode of blood circulation and indirectly indicated the deterioration of cerebral circulation (Table 3).

Table 3

Systemic and central hemodynamic parameters in trauma patients on admission (n=36)

Indicators	Values
BP systolic, mmHg.	110,5±4,4
Diastolic BP, mm.Hg.	62,5±2,5
Average BP (MBP), mmHg.	78,5±3,2
Heart rate (HR), per min	76,4±2,9
Central venous pressure (CVP), cm/hg.	5,3±0,22
SpO_2, %	93,6±3,8
Shock index (SI), ml/m^2	34,0±1,4
Cardiac index (CI), l/m^2	2,59±0,11
Total peripheral vascular resistance (TPR), dyne×s×cm^{-5}	1373,3±56,3

In all patients of this group on admission to the ICU there was an increase in ICP, the average values of which amounted to 26,7±1,1 mmHg, which explains the absence of initial tachycardia (76,4±2,9 per min). The mean values of cerebral perfusion pressure (CPP) amounted to 51,8±2,0 mmHg, which confirmed the above thesis about deterioration of cerebral blood circulation (Table 4).

Baseline values of blood electrolytes and plasma osmolarity are summarized in the table below.

Table 4

Blood biochemical parameters and plasma osmolarity in patients with traumatic brain injury at postulation (n=36)

Indicators	Values	Norma
Total protein, g/l	71,5±2,9	70-90
Glucose, mmol/L	4,76±0,19	4,22-6,11
Creatinine, μmol/L	78,5±3,2	50-115
Urea, mmol/L	5,17±0,21	4,2-8,3
Potassium, mmol/L	4,4±0,18	3,6-6,3
Sodium, mmol/L	132,4±5,3	135-152
Calcium, mmol/L	2,1±0,09	2,2-2,7
Plasma osmolarity, mosm/L	264,8±10,5	280-290

Analyzing the presented data, it can be noted that all studied parameters practically did not exceed the physiological norm for adults. In 9 patients from this group (25,0%) plasma sodium concentration exceeded 145 mmol, averaging 147,5±2,2 mmol/l, while in the other 27 patients (75,0%) Na+ plasma level was below 135 mmol/l, averaging 117,3±5,9 mmol/l. Relative hyponatremia at normal values of blood glucose and urea and led to a decrease in plasma osmolarity by 5,5% from the physiologic norm (Tab.4).

3.1 Effect of 3,5% HSS on systemic and central hemodynamics

Mean baseline HR, amounting to 76,4±2,9 per minute (56-89), practically did not undergo clinically significant changes at all stages of the study. There was only a tendency to some increase in HR. Its maximum values were observed at stage 3 (15-30 minutes after administration of a bolus of 3.5% HR (3,5% higher than the initial index). BP increased almost equally due to both systolic (9,8%) and diastolic (16,8%). In both cases the difference was unreliable (p>0,05) (Table 5).

Table 5

Systemic and central hemodynamic parameters of trauma patients at the stages of the study (n=36)

Indicators	Stages of the study				
	I	II	III	IV	V
HR, min.	76,4±2,9	78,3±3,2	79,1±3,3	78,2±3,2	77,9±3,0
BP syst, mmHg	110,5±4,4	114,2±4,5	119,3±4,9	121,4±5,1	120,7±4,8
BP diast, mmHg	62,5±2,5	66,1±2,7	71,2±2,9*	73,0±3,1*	72,2±2,8*
MBP, mm.Hg	78,5±3,2	82,1±3,4	87,2±3,6	89,1±3,7*	88,3±3,4*
CVP, cm.hg	5,3±0,22	7,4±0,31***	7,9±0,33***	8,2±0,35***	8,6±0,36***
SpO2, %	93,6±3,8	98,4±3,9	98,7±4,0	98,9±4,1	98,1±3,8
BV, ms/m^2	34,0±1,4	37,2±1,5	39,1±1,6*	38,9±1,8*	37,4±1,5
CI, l/m^2	2,59±0,11	2,91±0,12*	3,09±0,13*	3,04±0,12*	2,91±0,11*
TPR, din*s*cm^{-5}	1373,3±56,3	1253,4±49,7	1254,6±52,3	1303,1±54,2	1350,6±55,4

Note: *- reliable in comparison with the indicators of the I stage of the study (*-p<0,05; ***- p<0,001)

Initial values of MBP, amounting to 78,5±3,2 (62-84) mmHg, also showed a tendency to increase. It reached its maximum at the 4th stage of the study (60 min after administration of bolus of 3,5% HSS) and exceeded the initial data by 13,5% (p<0,05) (Table 5). In 9 patients of this group (25%) at admission the severity of arterial hypotension required inotropic support (pressors, hormones) for correction. Pulse oximetry, PCO2 =37,1±1,4 mmHg and CVP significantly improved, indicating improvement of blood gas composition (blood oxygenation) and growth of venous return of blood to the heart, which led to increase of cardiac output, both due to single heart output (by 9,4% at the 2nd stage) and increase of HR (by 2,4%). The maximum values of BV and CI were registered by us already at the 3rd stage of the study, when they exceeded the initial values by 15 and 19,3%, respectively.

The increase in cardiac performance corresponded to the decrease in TPR, which was observed at all stages of the study of 3,5% HSS bolus, although it was not statistically significant. The maximal decrease in TPR was observed already at the 2nd stage (after the introduction of HSS). It, amounting to 1253,4 dyne*s*cm-5, was 8,8% lower than the initial data and 3,6% lower than the proper values of TPR in this period (1300,1 dyne*s*cm-5). All this testifies to the improvement of peripheral blood circulation.

3.2 Effect of 3,5% HSS on intracranial pressure and cerebral perfusion pressure

What was the effect on cerebral blood circulation? The dynamics of ICP and CPP at the stages of the study are shown in Table 6 below.

The presented data clearly demonstrate the positive effect of 3,5% HSS on the parameters of ICP and cerebral blood flow. At 20-25 minutes after the bolus of 3,5% HSS injection, the ICP decreased (stage 2) below 20 mmHg, reaching an average of 19,7 mmHg, i.e. decreasing relative to the initial data by 26,3% (p<0,05). The maximum decrease of ICP was noted at the 3rd stage of the study (after 30 minutes), where, amounting to 18,9±0,73 mmHg, it was 29,3% (p<0,05) lower than the initial values. Already from 60 minutes after administration and 120 minutes it showed a tendency to increase, however remaining below 20 mmHg. Decrease in ICP contributed to the increase of CPP. So already at the 2nd stage it exceeded the initial values by 20,4% (p<0,05). The maximum values of CPP in this group were registered at the 4th stage (60 minutes after bolus administration), where it amounted to 69,7 mmHg, 34,5% higher than at the 1st stage of the study (Table 6). At 20-25 minutes after bolus administration 3,5% HSS of M-echo pulsation decreased (stage 2) reaching on average 32,3±1,3%, i.e. decreasing relative to the initial data by 48,3% (p<0,05). The maximum decrease of M-echo pulsation was noted at the 3rd stage of the study (after 30 minutes), where, amounting to 29,3±1,1 mmHg, it was 53,1% (p<0,05) lower than the initial values.

Table 6

Dynamics of ICP, P and CPP at the stages of the study (n=36)

Indicators	Stages of the study				
	I	II	III	IV	V
P%, M-echo pulsation	62,5±2,4	32,3±1,3*	29,3±1,1*	31,3±1,3*	30,8±1,2*
ICP, mm.Hg.	26,7±1,1	19,7±0,78*	18,9±0,73*	19,4±0,76*	19,3±0,77*
CPP, mm.Hg	51,8±2,0	62,4±2,5*	68,3±2,7*	69,7±2,9*	69,0±2,8*

Note: *- reliable in comparison with the indicators of the first stage of the study (*-p<0.001)

3.3 Effect of 3,5% HRS on blood osmolarity and hematocrit

The following table reflects the dynamics of electrolytes, plasma osmolarity at the stages of the study after administration of a bolus of 3,5% HSS (Table 7).

Table 7
Dynamics of electrolytes and blood osmolarity and hematocrit at stages studies in trauma patients (n=36)

Indicators	Stages of the study				
	I	II	III	IV	V
Plasma sodium, mmol/L	132,4±5,3	139,7±5,8	139,0±5,4	141,2±6,1	138,6±5,2
Plasma osmolarity, mOsm/L	264,8±10,5	279,4±11,3	278,0±11,2	283,6±11,6	278,8±11,5
Hematocrit, %	40,4±1,7	37,8±1,6	35,3±1,5*	34,5±1,4*	36,1±1,5*
Diuresis, ml/h	52,0±3,7	84,1±4,5	87,2±5,0	102,7±6,1	78,9±5,0

Note: *- reliable in comparison with the indicators of the first stage of the study (*-p<0,05)

At 20-25 minutes after administration of a bolus of 3,5% HSS, the values of plasma sodium and osmolarity (stage 2) increased by 5,5% in both cases (p>0,05). The maximum increase in blood sodium and osmolarity was observed at 60 minutes (stage 4), exceeding their initial values by 6,6% and 7,1%, respectively.

These are the average values of Na+ concentration and plasma osmolarity. In 9 patients of this group, who had initial hypernatremia (147,5±2,2 mmol/l) after bolus dose of 3,5% HSS administration there was an increase of Na+ plasma level already at the 2nd stage of the study up to 159,1±2,4 mmol/l (by 7,8%) that was accompanied by increase of hourly diuresis in them up to 100-105 ml/hour, whereas in the group as a whole diuresis increased up to 80-82 ml/hour. In no case in this group, we did not note the development of renal failure. On the contrary, renal compensation of hypernatremia was satisfactory. Diuresis amounted to 105,3±12,4 ml/h (Tab.7).

In this group, we recorded 216 episodes of intracranial hypertension that forced the administration of another bolus of 3,5% HSS. On average, there were 6 (5-8) episodes of ICH for each patient.

The mean interval between baseline (standard) therapy and the start of 3,5% HSS infusion was 3,9±0,4 hours in this group. The dose of 3,5% HSS was corrected in each episode of ICH, starting at 5 mL/kg/hour and ending bolus infusion when the ICH level was <20 mmHg. In the whole group, this dose was 2,9±0,12 (2,0-3,8) mL/kg (Table 8).

Table 8
Dose and time required to reduce ICP below 20 mmHg. in trauma patients (n=36)

The drug	Dose (ml/inf)	Dose (ml/kg)	Time min
3.5% HSS	213,7±8,9 (90-280)	2,9±0,12 (1,8-4,4)	20-22 (18-35)

was not relieved by 3,5% HSS in combination with 15% mannitol. These patients underwent neurosurgical interventions (decompression trepanation, clot evacuation).

The mean number of days of ICP measurement was 6,1±0,3.

The mean number of days patients stayed in ICU was 11,3±0,4 and in the clinic was 18,9±1,7 days

The lethality rate was 22,2%. All 8 deceased patients had more serious primary trauma (falls from height, blows to the head) with lower GCS scores (4-5) and higher ICP scores.

4. DISCUSSION

This study clearly demonstrates that bolus infusion of 3,5% HSS is effective in reducing ICP and increasing CPP in patients with severe isolated traumatic brain injury.

The efficacy of the mentioned solution persists for at least 120 minutes after infusion (4-5 hours on average). We have noticed, that even smaller doses of HSS (relative to the first bolus dose), administered repeatedly, prolong the time of ICP reduction up to 4-5 hours.

The onset of action of 3,5% HSS is registered already in 18-20 minutes somewhat earlier than in bolus administration of 15% mannitol (23-25 min). The maximum decrease of ICP below 20 mmHg as a percentage of the initial values during bolus administration of 15% mannitol and 3,5% HSS is almost the same at 31,8 and 27%, respectively, but the effective bolus dose of 15% mannitol exceeds that of 3,5% HSS (by 20,3%).

Favorable effects of hyperosmolar therapy have been described in the treatment of ICH [18]. Our study confirms the efficacy of 3,5% HSS in the treatment of traumatic ICH. The great advantage of HSS over mannitol is the absence of the possibility of ricochet syndrome development, which is consistent with the data [19], which is confirmed by our study.

This suggests that HSS provides long-term control of ICP after acute brain injury. However, the protective effects observed with HSS may be mediated by other mechanisms besides the effect on ICP [20]. For example, HSS reduces the risk of hypovolemia, which is associated with secondary brain damage, which is confirmed by our studies (increase in performance of single and minute heart volume, CVP at ideal hematocrit values (34-36%)).

When using HSS, it is important to determine the timing of their administration that will be most effective in improving outcomes. Unfortunately, the goal of our study to identify the efficacy of hyperosmolar therapies in reducing ICH in traumatic brain injury, pre followed mainly the therapeutic goal. In general, our study and results suggest that HSS can be used as early as possible in patients with traumatic brain injury and high risk of developing ICH, which is consistent with [13].

One of the main factors discouraging the use of HSS is safety. Possible various neurological complications (seizures, myelinolysis and parenchymatous accumulation of osmotic agents). We have not recorded any neurological changes associated with 3,5% HSS, which suggests that this solution is well tolerated by patients.

One of the main concerns associated with HSS is hypernatremia, as it correlates with mortality [14]. Interestingly, only severe hypernatremia (>160 mmol/L) is independently associated with mortality [15]. No cases of severe hypernatremia were reported in our study. Changes in renal function with the use of HSS have also been reported in the literature [16]. Our results showed no changes in nitrogenous sludge indices with the use of 3,5% HSS. Therefore, in our opinion, a protocol for the treatment of trauma with frequent (at least 2 times a day) measurements of electrolytes and nitrogenous slugs in the blood may improve outcomes by preventing severe hypernatremia and renal dysfunction.

Maggiore U et al [15] demonstrated a dose-dependent association between higher Na+ values and outcome. This was demonstrated in both patients who received and those who did not receive HSS. In our study, a large number of repeated doses of 3,5% HSS did not result in severe hypernatremia and poor outcome, indicating the benefit of such surgery.

A serum Na+ level of 155 mmol/L and osmolarity of 320 mOsm/L are generally considered to be the upper limit at which hyperosmolar therapy can be safely performed [17]. In our studies, neither sodium levels nor blood osmolarity reached these figures, and therefore we did not observe side effects of hypernatremia and hyperosmolarity. And, meanwhile, we agree with the opinion of Hawryluk JWS that we need to be more careful about the increase of Na+ level in serum above 142 mmol/L and be less liberal with hyperosmolar therapy.

We evaluated the result of changes in the GCS data at the end of the observation period and treatment of patients in this group. If at admission the level of consciousness according to GCS was 5,42±0,22 points, at the end of observation it amounted to 10,91±0,40 ($p<0,05$).

Thus, doses of 3,5% HSS 210-220 mL or 3 mL/kg body weight can be recommended for the treatment of ICH and cerebral edema in isolated traumatic brain injury in patients with hypovolemia, hypo or normal plasma sodium.

5. CONCLUSIONS

1. Bolus infusion of 3,5% NaCl HSS at a rate of 3 ml/kg is effective in decreasing ICP <mm20 Hg and increasing CPP in patients with traumatic brain injury, which is manifested 18-20 minutes after the infusion is stopped and persists for at least 120 minutes. The use of 3,5% HSS NaCl at initial hypo- or normonatremia and normal

plasma osmolarity in the treatment of ICH in patients with isolated traumatic brain injury does not lead to their increase to threshold values (155 mmol/L and 320 mOsm/L), is well tolerated by patients, effective and safe.

2. NaCl HSS can be used as early as possible in patients with traumatic brain injury and high risk of developing ICH.

3. A protocol for the management of traumatic brain injury with frequent (at least twice daily) measurements of electrolytes, osmolarity, and nitrogenous slugs in the blood and their correction may improve outcomes by preventing severe hypernatremia, hyperosmolarity, and renal dysfunction with the use of HSS.

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