Research Article

Effect of hyperosmolar combined solution of mannitol 15% plus 3.5% NaCl solution on cerebral edema in patients with traumatic brain injury

Running title: Effect of combined solution of mannitol 15% plus 3,5% NaCl solution on cerebral edema

Temur Malik Murotov,
Associate Professor, Department of Anesthesiology and Resuscitation of the Tashkent Medical Academy, Tashkent, Republic of Uzbekistan
E-mail:temurmalik_murotov@mail.ru
ORCID: 0009-0003-1204-4342

Abstract:

Background and Aim: Craniocerebral trauma remains one of the most important public health problems and causes elevated intracranial pressure and low cerebral perfusion pressure.

Methods and Materials/Patients: In this work, we used both hyperosmolar solution colloid-mannitol 15% and crystalloid-NaCl 3.5% at the same time. Both have the same mechanism of action creating an osmotic gradient between the blood-brain barrier and brain tissue.

retrospective - 15 patients and prospective - 20 patients, single-center, randomized open clinical study of 35 patients, who were treated in the intensive care unit (ICU) with isolated traumatic brain injury at the age of 18 to 65 years with depression of consciousness (4-12 points on the Glasgow Coma Scale (GCS)), and abnormal computed tomography (CT) data of the head on admission.

Results: The presented data demonstrate the positive effect of mannitol 15% + NaCl 3.5% on ICP and cerebral blood flow. At 20-25 minutes after administration of a bolus of mannitol 15% + NaCl 3.5%, ICP decreased (stage 2) below 20 mmHg, reaching an average of 18.1±0.72 mmHg, decreasing relative to baseline by 33.2%.

Conclusions: combined use of mannitol 15% + NaCl 3.5% in the treatment of intracranial hypertension in patients with isolated craniocerebral 3.5±0.2 ml/kg can be recommended in patients with baseline hypovolemia and hyponatremia.

Keywords: mannitol, hypertonic sodium chloride, intracranial pressure, cerebral perfusion pressure, hyperosmolar therapy, craniocerebral trauma.

1.Introductions. Hyperosmolar agents such as mannitol and hypertonic saline solution (HSS) are pharmacologic options to reduce intracranial pressure (ICP), especially in patients with high-severity craniocerebral trauma (SCT) [1,2,3]. Hypertonic sodium chloride solution [4] and mannitol are used for emergency treatment of acute cerebral edema and other neurologic conditions. High-quality randomized controlled trials comparing these agents are limited. Emerging evidence suggests that HSR may have a stronger effect on ICP and cerebral perfusion pressure (CPP) [5,6,7,8].

In this work, we used both hyperosmolar solution colloid-mannitol 15% and crystalloid-NaCl 3.5% at the same time. Both have the same mechanism of action creating an osmotic gradient between the blood-brain barrier (BBB) and brain tissue.

1.1 The present study aimed to investigate the efficacy, and safety of the combined use of mannitol 15% + NaCl 3.5% in the treatment of intracranial hypertension in patients with isolated head injury aged ≥18 years. All patients in this group had severe isolated craniocerebral trauma caused mainly by motor vehicle accidents (MVA), falls, and sports injuries.

1.2 Study design - retrospective - 15 patients and prospective - 20 patients, single-center, randomized open clinical study of 35 patients, who were treated in the intensive care unit (ICU) with isolated traumatic brain injury at the age of 18 to 65 years with depression of consciousness (4-12 points on the Glasgow Coma Scale (GCS)) and abnormal computed tomography (CT) data of the head on admission.

2. Methods and Materials/Patients:

Patients were hospitalized in the immediate post-injury period and had some degree of impaired consciousness. The mean time of admission after injury was 37±8 min. Only patients with intracranial hypertension (ICH) (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.

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

The exclusion criteria were:

-Need for urgent cranial or extracranial surgery;

-Previous decompressive craniectomy

-Polytrauma

-Oliguric, renal failure.

-Hb level<80 g/L

-Serum osmolarity >320 mosmol/L

-Use of mannitol or HSS in the previous 6 hours

-Pregnancy

-Patients who died within 72 hours of admission to ICU

-Coagulopathies

Baseline data on admission included: age, sex, weight, brain CT scan not necessary for APACHE II severity score calculation, mechanism of injury, pupil reactivity (reactive/non-reactive).

A set of variables were collected for each patient, which included, in addition to the demographic characteristics described, GCS and Glasgow Outcome Scale (GOS), treatment time, blood pressure (BP) monitoring, mean arterial pressure (MAP), heart rate (HR), ICP, CPP, serum osmolarity, sodium level, blood glucose, urine volume, central hemodynamic (CH) parameters (shock index (SI), cardiac index (CI), total peripheral resistance (TPR)), hemostasis (prothrombin time, activated partial thromboplastin time, fibrinogen).

When ICP exceeded 20 mmHg and ICH lasted more than 5 minutes, one of the mentioned hyperosmolar solutions was bolus infused through the central venous line at a rate of 5-7 mL/min (120 drops/min), i.e., within the range of 1000-1100 mosm/L. Solution infusion was stopped when the ICP decreased ≤20 mmHg, which was the goal of our therapy.

ICP was measured invasively by lumbar puncture at the level of L3-L4 and noninvasively. In total, out of 35 patients with isolated traumatic brain injury in the absence of CT signs of dislocation syndrome, lumbar puncture with manometry and obligatory filling with auto blood was performed in 8 patients. In the absolute majority and repeatedly, the ICP was measured noninvasively.

These parameters were analyzed at the following stages of the study:

-before the infusion was started;

-after discontinuation of infusion (achieved ICP <20 mmHg);

-30, 60, and 120 minutes after discontinuation of infusion (after ICP <20 mmHg).

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

Ultrasound diagnostics

We used for determination of M-echo pulsation in the third ventricle of the of the brain diagnostic complex of "Complexmed 1.2", which allows echoencephaloscopy, extra and transcranial dopplerography (Fig.1).

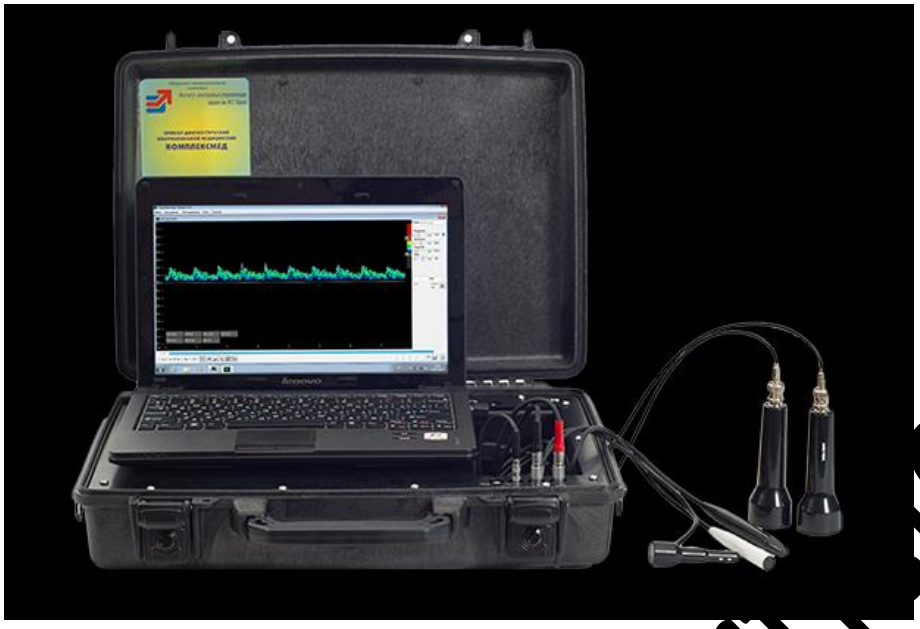

Figure 1. Ultrasound device Complesmed 1.2

Echoencephaloscopy. Essence of the method. The principle of this diagnostic method, also called the M-method, is based on echolocation of the so-called sagittal structures of the brain, which normally occupy a median position in relation to the temporal bones of the skull. From the ultrasound transducer in pulse mode, the echo signal through the bone penetrates the cranial cavity, reaching the contralateral bone plate and reflecting on its way from the interfaces of media with different echo density (tissue-liquid or tissue-bone). Three most typical and repetitive signals are registered. The first signal is the reflection from the bone plate of the skull, where the ultrasound sensor is installed, the so-called initial complex (IC). The second signal is formed due to the reflection of the ultrasound beam from the midbrain structures. These include the interhemispheric gap, the transparent septum, the III ventricle and the epiphysis. The third signal recorded along the path of the ultrasound beam is represented by the inner surface of the temporal bone, opposite to the location of the transmitter. A unique feature of EchoEC is the possibility to register echopulsation of the ventricular system of the brain. When intracranial pressure increases, not only the power of reflected signals changes, but also the amplitude of their pulsation.

Methodology: the patient lies on the back, without a pillow, with the right hand freely and at the same time with some support on the parieto-parietal region of the patient, turning the patient's head to the left or right, we perform echolocation and measurement of echodistances, while with the free left hand we carry out the necessary movements of the echodistance meter. To determine Ps - M-echo pulsation amplitude in percent after lubrication of the frontal and temporal parts of the head with contact gel, a standard transducer was placed 3-4 cm upward from the external auditory canal and 1-2 cm anterior to it, due to a particularly powerful, constant and easily detectable M-echo complex at this location.

A P (pulsation amplitude) of about 15-25% is considered normal for the M-echo complex. As a rule, it is considered that echo pulsation within 25-50% corresponds to moderate, and above 60-70% - pronounced intracranial hypertension We present the characteristics of echopulsation in increasing hypertension syndrome according to the "Manual" for the operation of "Complexmed".

ECHO Phenomena	Moderate hypertension	Severe hypertension-hydrocephalus syndrome	Edema, swelling of the brain	Brain death.
Pulsation amplitude	30-60%	70-90%	Less than 10%	-
Pulsation pattern and relationship to physiological functions	The pulseogram is synchronous with the rhythm of the heartbeat	Either a pulseogram or undulation for asymmetric hydrocephalus.	Sluggish, synchronized with respiratory movements	
Pulsation direction	More often single-phase	Single or two-phase (50/50)	Often antiphasic	-

The above data indicate that M-echo pulsation of the III ventricle of the brain, obtained by using the device "Complexmed 1.2", gives the possibility of non-invasive qualitative determination of ICP and ICH indicators (moderate, pronounced hypertension).

We made an attempt in our studies to translate the resulting qualitative expressions of M-echo pulsation into numerical values.

Figure 2. Non-invasive method for determining ICP

To assess the effectiveness of hyperosmolar solutions and mannitol in the treatment of traumatic brain injury, careful monitoring of ICP is necessary.

Invasive methods of its monitoring (drainage of brain ventricles, using sensors in the epi- or subdural space) are accurate, but are the prerogative of large neurosurgical centers. A simpler invasive method of determining ICP - intrathecal lumbar puncture with monomanometry of liquor pressure - is not always feasible in severe traumatic brain injury (wedging syndrome) and cannot serve as a method of monitoring ICP and ICH. Generally accepted methods for non-invasive determination of ICP do not currently exist or are in clinical trials.

The essence of our study was as follows. 113 patients operated under spinal anesthesia with traumatic and degenerative changes in hip and knee joints (41), with traumatic brain injury (brain contusion without displacement of brain structures (28)), suspected meningitis (17), coma (27) underwent lumbar puncture with monomanometry of liquor tensions for therapeutic and diagnostic purposes. All these patients were not included in this study. In parallel, these same patients

underwent qualitative noninvasive determination of ICP using M-echo pulsation of the III ventricle of the brain, comparing them with the data of lumbar puncture.

The studies performed showed with a high degree of representativeness that echopulsation between 25-50% "moderate ICH" corresponds to invasively obtained data between 20-24 mmHg, and ICP ≥25 mmHg is clearly within the range of "severe ICH"-60-80%.

Echopulsation in the range of 15-25% corresponded to the data of lumbar puncture with monometry in wide ranges - from 4 to 19 mmHg. The obtained comparative data allowed us to use the method of echopulsation for the purpose of ICH monitoring during its treatment with hyperosmolar solutions. ICP values exceeding 29 mmHg correspond to >70% with asynchronous echopulsation of undulatory type.

In the studied patients with normal values of IAP, we determined the correlation coefficient of IAP, data obtained by noninvasive and invasive method (lumbar puncture) according to the formula proposed by us.

$$ICP=\frac{P}{k}$$, where

P-pulsogram in %, k=1.388 correction coefficient at normal pulsogram (percentage data of M - echo).

Thus, with M - echo pulsagram equal to 16.2% on average, we divide this value by the coefficient 1.388 and obtain the values of 11.7 mmHg obtained by lumbar puncture.

Next, we determined the correction index for moderate ICH using the same formula and obtained a correction coefficient equal to k=1.677 for moderate ICH.

Thus, with M - echopulsagram equal to 37.2% on average, we divide this value by a coefficient of 1.677 and obtain values of 22.2 mm.Hg obtained by lumbar puncture.

In the same way, we calculated the correction coefficient for pronounced ICH, and it amounted to k=2.339.

Thus, with M - echopulseogram equal to 64.3 on average, we divide this value by the coefficient of 2.339 and get the value of 27.5 mm.Hg obtained by lumbar puncture.

Summarizing the above described, we came to the conclusion that it is possible to use M-echo pulsogram of portable ultrasound device (Complesmed 1.2) for non-invasive monitoring of ICH in trauma victims with traumatic brain injury in the process of complex therapy and to evaluate the effectiveness of the latter.

The correction indices calculated by us at normal values of ICH (k=1,388), moderate ICH(k=1,677) and pronounced ICP (k=2,339) obtained using Complexmed 1.2 when comparing them with the data of lumbar puncture correlate with Pearson correlation coefficients.

A patent for the invention "Method for non-invasive assessment of intracranial pressure in patients with brain injury" (№. IAP 06573) was obtained. This method was developed for effective treatment of diseases by preventing brain swelling through non-invasive assessment of intracranial pressure in patients with brain injury

2.1 General care of patients in ICU (stage I of treatment). We followed the recommendations of the Fond Brian Foundation (2016). All patients were sedated by continuous IV administration of propofol and opiates and were on artificial ventilation (AVL). Patients were placed in a semi-reclined position (with the head end of the bed elevated 30-40º), in the absence of contraindications to this. Secondary brain damage was prevented by therapeutic craniocerebral hypothermia (CCH), by covering the head and carotid vessels with cold elements with subsequent measurement of t0 in the external auditory canal, maintaining body temperature between 36-37ºC, ensuring normoglycemia, avoiding hypoxemia.

Basic therapy, according to the protocol adopted in our clinic, included infusion and transfusion therapy (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, thrombotic complications and ulcerative complications and ulcerative formations in the gastrointestinal tract, early tube feeding of patients.

Intracranial hypertension was evaluated as susceptible (i.e., responsive to therapy, including osmotherapy, with ICP returning to <20 mmHg) or refractory (stable ICP>20-25 mmHg), requiring surgical decompression.

Neurological status was assessed clinically using the Glasgow scale, and the severity of the patient's condition and outcome were assessed using APACHE II.

35 patients were included in this study conducted over 5 years (2018-2022) in the Departments of Neurosurgery and Anesthesiology and Critical Care Medicine of TMA. All patients in this group received a mannitol infusion of 15% mannitol + NaCl 3.5% to reduce ICH. In this study, we investigated the effect of a combined solution of mannitol 15% + NaCl 3.5% on individual episodes of intracranial hypertension, as well as on the time and duration of reduction of ICH peaks, the dose of these solutions reducing ICH <20 mmHg.

Pre-hospital physiologic parameters were recorded, including post-resuscitation GCS, pupillary response to light, Hb, Ht, and blood glucose levels. Daily data during 7 days after admission to the ICU included hourly measurements of ICP recorded noninvasively using Complexmed 1.2, and if possible by lumbar intrathecal puncture with manometry in 8 patients, serum sodium studies, pulse oximetry and measurement of daily diuresis, plasma osmolarity. Important aspects of the care of trauma patients included neurosurgical operations performed when necessary (clot evacuation, decompression craniotomy), mannitol 15% + NaCl 3.5% osmotherapy, and ventilatory support. Outcome data included ICU and in-hospital mortality, length of stay in ICU, dose of combined mannitol 15% + NaCl 3.5% solution, and time required to reduce ICP <20 mmHg.

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

2.2 Methods of intensive therapy

All patients received standard complex intensive therapy by international recommendations for the treatment of traumatic brain injury. The head end of the bed was raised by 30-40º. Ventilation by Wella and Drager apparatus with the respiratory volume of 8-10 ml per kg of ideal body weight in SIMV (Synchronized Intermittent Mandatory Ventilation) mode and PEEP (positive end-expiratory pressure) +2-10 cm of water column. Infusion therapy was carried out, combining colloid and crystalloid solutions. We tried to maintain normovolemia (central venous pressure (CVP) 8-12 cm of water column). Enteral tube feeding was tried to start 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 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. To prevent 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 the lower extremities (in the absence of signs of external and internal bleeding, low-molecular-weight heparin (LMWH), clexane 0.4 thousand units per day subcutaneously was administered from 2-3 days). In patients who underwent ICP measurement, in case of clinical signs of dislocation syndrome (anisocoria, upward gaze paresis, Gerdwig-Majandi syndrome combined with bradycardia, arterial hypertension) CT of the brain was performed and the question of surgical intervention was decided. Blood plasma osmolarity was monitored. 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, a 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 the psychomotor agitation of the patient. Hyperosmolar solutions under the 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.

2.3 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 significance level of $p<0.05$.

ICP and M-echo pulseograms were checked with Pearson's correlation coefficient, and their reliability was checked with the Student's t-test.

3. Results.

When the ICP exceeded 20 mmHg for more than 5 min (two to three times measured by ultrasound (US) M-echo pulsation of the cerebral III ventricle), bolus mannitol 15% + NaCl 3.5% was administered via the central vein at a rate of 6-8 mL/min (120-130 cap/min). The infusion was stopped when the ICP dropped below 20 mmHg. We recorded the values of ICP, and CPP before and after infusion of mannitol 15% + NaCl 3.5%. We recorded ICP and CPP 15, 30, 60, and 120 min after drip infusion of combined mannitol 15% + NaCl 3.5% solution. The total episodes of ICH requiring administration of hyperosmolar solutions per patient, the number of ICH episodes per day, and the dose of each infusion of mannitol 15% + NaCl 3.5% were recorded by us.

The age of patients in this group ranged from 20-82 years (41.5±1.7). The trauma was associated with road traffic accidents (19/54,3%), falls (12/34,3%) compression (2/5,7%), and two (5,7%) patients had sports trauma with a bleeding wound in the frontal-temporal part of the head without damage to the skull bones. Vomiting of gastric contents occurred in 16 patients, in three of them aspiration syndrome was diagnosed, for which sanitation bronchoscopy with lavage of airways was performed (Table 1).

Table 1

Demographic and clinical characteristics of patients (n=35)

Patient Characteristics		Values	
		абс.	%
Age, years		41,5±16,2	
Paul	Men	33	94,3%
	Women	2	5,7%
Mechanism of injury	Traffic accidents, %	19	54,3%
	Falls, n%	12	34,3%
	Compressions, n%	2	5,7%
	Sports injury, n%	2	5,7%
Vigor level	GCS, points	5,81±0,23	
Abnormal pupils	Pupils (pathologic, n%)	30	85,7%
	Bilateral miosis, n %	11	31,4%
	Anisocoria, n %	15	42,9%
	Bilateral mydriasis with photoreaction, n %	4	11,4%
CT scan data	CT data (pathologic, n %)	35	100%
	Brain contusion, n %	24	68,6%
	Skull bone fracture, n %	4	11,4%
	Brain edema, n %	10	28,6%
	Subarachnoid hemorrhage, n %	12	34,3%
	Subdural hematoma, n %	3	8,6%
	Epidural hematoma, n %	3	8,6%
	Intracerebral hemorrhage, n %	1	2,9%
	Axonal damage, n %	1	2,9%
	Intubation, ventilator, n %	30	85,7%
	Arterial hypotension, n %	8	22,9%
Overall severity of condition	APACHE II, scores	15,4±0,61	
Neurosurgical interventions	Craniotomy, n %	5	14,3%

Consciousness disorder according to GCS averaged 5.81±0.23 (4.0-11.0). The total severity of the condition according to APACHE II averaged 15.4±0.61 points.

Equal-sized pupils of medium size with good photoreaction were registered in 5 patients of this group, bilateral miosis - in 11 patients, anisocoria - in 15 patients, and 4 patients had bilateral mydriasis with photoreaction.

CT scan diagnosed: subarachnoid hemorrhage (12/34.3%), cerebral edema in 10 (28.6%), epidural hemorrhage (3/8.6%), linear skull fracture in the occipital-parietal region without fragment separation (4/11.4%), subdural hematoma (3/8.6%), epidural hematoma (3/8.6%)

(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

Indicators of clinical examination of blood and hemostasis on admission (n=35)

Indicators	Values	Norma
Erythrocytes,, 10^{12}/l	3,75±0,15	3,7-5,1
Hemoglobin, g/l	10,6±0,43	12,0-16,0
White blood cells, 10^9/l	5,31±0,22	4-8,8
Neutrophils,10^9 /l	3,51±0,14	0,5-6
Lymphocytes, 10^9/l	1,85±0,08	1,2-3,0
Fibrinogen, g/l	4,19±0,17	2-4
Platelets, 10^9/l	177,3±7,3	160-360
Prothrombin time, sec	12,8±0,52	15-17
APTT, sec	28,8±1,2	35-45
Hematocrit, %	40,8±1,7	36-48

The presented data testify to moderate anemia of traumatic genesis and activity of the blood coagulation system, as evidenced by: shortened prothrombin time by 8.6%, increased values of fibrinogen and decreased kephalin-kaolin time, activated partial thromboplastin time (APTT) by 7.1% from the lower limit of physiological values of this index (Table 2).

The average values of the studied parameters indicate that in patients of this group at admission there was moderate arterial hypotension with a decrease in systolic and diastolic pressure, which affected the decrease in MAP. All this indicated a decrease in the tone of resistive vessels. However, TPR values were also lower than physiologic values, indicating a decrease in tone in the low-pressure system (capillaries, venules). The decrease in TPR amounted to 9.2% of the proper values of TPR during this period (1511.1 dyne×s×cm^{-5}) (Table 3).

Proper values of MAP in this age group of the studied patients amounted to 85 mmHg.

CVP was lower than physiologic values by 36.25%. All these factors contributed to the decrease of single and minute cardiac output, which were at the borderline values of normo- and hypodynamic mode of blood circulation and indicated deterioration of cerebral circulation (Table 3).

Table 3

Systemic and central hemodynamic parameters in patients of this group on admission (n=35)

Indicators	Values
BP systolic, mm.Hg.	103,8±4,3
Diastolic BP, mm.Hg.	61,7±2,4
Mean BP (MBP), mm.Hg.	77,7±3,1
Heart rate (HR), per min	76,3±2,9
Central venous pressure (CVP), cm.vg.	5,1±0,20
SpO_2, %	93,5±3,7
Shock index (SI), ml/m2	33,5±1,3
Cardiac index (CI), l/m2	2,51±0,10
Total peripheral vascular resistance (TPR), dyne×s×cm^{-5}	1372,2±54,6

In all patients of this group on admission to the ICU an increase in ICP was registered, the average values of which amounted to 27.1±1.1 mmHg. Average values of cerebral perfusion pressure (CPP) amounted to 50.6±1.9 mmHg, which confirmed the deterioration of cerebral blood circulation (Table 6).

Initial values of blood electrolytes and plasma osmolarity are shown in Table4.

Analyzing the presented data, it can be noted that all the studied parameters practically did not exceed the physiological norm for adults. However, it is immediately striking that in this group of patients with insignificant hyponatremia (according to the mean values) there is a large difference in the mean square deviation in the variation series, which made us study Na+ concentration in patients in more detail. Thus, in 7 patients from this group the plasma sodium concentration exceeded 145 mmol and averaged 149,3±4,5 mmol/l, while in 28 patients the Na+ level in plasma was below 135 mmol/l, averaging 129,5±7,2 mmol/l. Relative hyponatremia with normal blood glucose and urea values resulted in a 4.0% decrease in plasma osmolarity from the physiologic norm (Table 4).

Table 4

Blood biochemical parameters and plasma osmolarity in patients during fasting (n=35)

Indicators	Values	Norm
Total protein, g/l	72,1±2,8	70-90
Glucose, mmol/L	4,75±0,19	4,22-6,11
Creatinine, μmol/L	79,2±3,3	53-113
Urea, mmol/L	5,08±0,21	2,2-8,3
Potassium, mmol/L	4,2±0,16	3,6-6,3
Sodium, mmol/L	134,4±5,2	135-152
Calcium, mmol/L	2,3±0,09	2,2-2,7
Plasma osmolarity, mosm/L	268,8±10,7	280-290

3.1 Effect of combined solution of Mannitol 15% + NaCl 3.5% on systemic and central hemodynamics

Mean baseline HR, amounting to 76.3±2.9 per minute (60-88), practically did not undergo clinically significant changes during the study stages. There was a tendency to HR increase (Table 5).

Table 5

Systemic and central hemodynamic parameters in patients at the stages of the study (n=35)

Indicators	Stages of the study				
	I	II	III	IV	V
HR, min	76,3±2,9	77,2±3,1	77,8±3,3	77,5±3,2	76,4±3,0
BP syst, mmHg	109,8±4,3	115,8±4,8	121,6±5,1	121,2±4,9	120,8±4,7
BP diast, mmHg	61,7±2,4	67,2±2,7	72,4±2,9*	74,7±3,1**	73,5±2,8**
MAP, mm.Hg	77,7±3,1	83,4±3,4	88,8±3,6*	90,2±3,8*	89,3±3,7*
CVP, cm.hg	5,1±0,20	7,5±0,31***	8,1±0,33***	8,5±0,35***	9,2±0,38***
SpO_2, %	93,5±3,7	98,3±4,0	98,8±4,1	98,9±4,2	98,5±3,9
ShI, ms/m^2	33,5±1,3	40,2±1,7**	42,8±1,8***	41,4±1,6**	39,2±1,6*
HI, l/m^2	2,51±0,10	2,95±0,12*	3,38±0,14***	3,42±0,13***	3,41±0,14***
TPR dyne×s×cm^{-5}	1372,2±54,6	1256,5±50,6	1167,6±47,3*	1174,7±46,7*	1163,9±46,4*

Note: *- reliable in comparison with the indicators of the I stage of the study (*-p<0.05; **-

p<0.01; ***-p<0.001)

Its maximum values were observed at stage 3 (15-30 minutes after administration of a bolus of mannitol 15% + NaCl 3.5%). BP increased almost due to both systolic (10.7%) and more pronounced increase in diastolic (21.0%) components (Table 5).

Initial values of MAP, amounting to 77.7±3.1 (65-88) mm.Hg, also showed a tendency to increase. It reached its maximum at the 4th stage of the study (60 min after administration of mannitol 15% + NaCl 3.5% bolus) and exceeded the initial data by 16.1% (p<0.05).

In 8 patients of this group (22.8%) on admission, the severity of arterial hypotension required inotropic support (pressors, hormones) for correction. The indices of pulse oximetry and CVP significantly improved, indicating the improvement of blood gas composition (its oxygenation) and the growth of venous blood return to the heart, which led to the increase of cardiac output, both due to single heart output (by 5.1% at stage 2) and increase of HR (by 1.2%). The maximum values of ShI and HI were registered by us already at stages 3 and 4 of the study, respectively, when they exceeded the initial values by 27.7% and 36.2%, respectively (Table 5).

The increase in cardiac performance was promoted by the decrease in TPR, which was traced at all stages of the study bolus mannitol 15% + NaCl 3.5%, although it was not statistically significant. The maximum decrease in TPR was observed already at the 2nd stage (after HS administration). It, amounting to 1256.3 dyne×s×cm^{-5}, was 8.5% lower than the initial data and 3.4% lower than the proper values of TPR in this period (1300.1 dyne×s×cm^{-5}). All this indicated improvement of peripheral blood circulation (Table 5).

3.2 Effect of combined Mannitol 15% + NaCl 3.5% solution on intracranial pressure and cerebral perfusion pressure

The dynamics of M-echo pulsation, ICP and CPP data during the study stages are summarized in the following Table 6.

Table 6

Dynamics of P%, ICP and CPP at the stages of the study (n=35)

Indicators	Stages of the study				
	I	II	III	IV	V
P %, M-echopulseogramme	62,5±6,4	29,1±4,4*	25,3±4,7*	29,2±4,9*	29,4±4,4*
ICP, mm.Hg.	27,1±1,6	18,1±1,5*	17,2±2,2*	18,4±1,8*	18,6±1,4*
CPP, mm.Hg	50,6±7,4	65,3±4,8*	71,6±3,5*	71,8±3,0*	70,7±2,8*

Note: *- p<0.05 relative to the I stage of the study

The presented data demonstrate the positive effect of mannitol 15% + NaCl 3.5% on ICP and cerebral blood flow. At 20-25 minutes after administration of a bolus of mannitol 15% + NaCl 3.5%, ICP decreased (stage 2) below 20 mmHg, reaching an average of 18.1±0.72 mmHg, decreasing relative to baseline by 33.2% ($p<0.05$). The maximum decrease in ICP was noted at the 3rd stage of the study (after 30 minutes), where, amounting to 17.2±0.68 mmHg, it was 36.5% ($p<0.05$) lower than baseline values. Already from 60 minutes after injection and up to 120 minutes it showed a tendency to increase, however remaining below 20 mmHg. Decrease in ICP contributed to the increase in CPP. So already at the 2nd stage it exceeded the initial values by 29.0% ($p<0.05$). The maximum values of CPP in this group were registered at stage 4 (60 minutes after bolus administration), where it amounted to 71.8 mmHg, 41.9% higher than at stage 1 of the study (Table 6).

3.3 Effect of Mannitol 15% + NaCl 3.5% combined solution 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 Mannitol 15% + NaCl 3.5% (Table 7).

Table 7

Dynamics of electrolytes and blood osmolarity and hematocrit at the stages of the in trauma patients (n=35)

Indicators	Stages of the study				
	I	II	III	IV	V
Plasma sodium, mmol/L	134,4±5,4	141,1±5,8	142,4±5,9	139,6±5,7	139,2±5,6
Plasma osmolarity, mOsm/L	268,8±10,7	282,6±11,3	284,8±11,6	280,2±10,8	278,4±10,6
Hematocrit, %	40,8±1,7	37,3±1,5	35,2±1,4*	34,6±1,3*	35,9±1,4*

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 mannitol 15% + NaCl 3.5%, the values of sodium and plasma osmolarity (stage 2) increased by 4.9% and 5.1%, respectively ($p>0.05$). The maximum increase in blood sodium and osmolarity was noted at 30 minutes (stage 3), exceeding their initial values by 5.9% in both cases.

These are the average values of Na+ concentration and plasma osmolarity. In 7 patients of this group, who had initial hypernatremia (149,3±4,5 mmol/l) after administration of bolus dose of mannitol 15% + NaCl 3,5% there was an increase of plasma Na+ level already at the 2nd stage

of the study up to 157,2±2,3 mmol/l (by 5.3%) (Tab.7). Osmodiuretic effect of mannitol was accompanied by increase of hourly diuresis in them up to 110-120 ml/hour, whereas in the group as a whole diuresis increased up to 92-95 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 100.2±10.8 ml/h.

In this group we recorded 195 episodes of intracranial hypertension, which forced the administration of another bolus of mannitol 15% + NaCl 3.5%. On average, there were 5 (4-7) episodes of ICH per patient.

The mean interval between baseline (standard) therapy and the start of mannitol 15% + NaCl 3.5% infusion was 4.4±0.5 hours in this group. The dose of mannitol 15% + NaCl 3.5% was adjusted in each episode of ICH, starting at 5 mL/kg/hour and ending bolus infusion at ICP <20 mmHg. This dose was 3.5±0.2 mL/kg for the whole group (Table 8).

Table 8

Dose and time required to reduce ICP below 20 mmHg.

in trauma patients (n=30)

The drug	Dose (ml)	Dose (ml/kg)	Time min
Mannitol 15% + NaCl 3.5%	260,9±10,6	3,5±0,14	25,0±0,97

In 5 patients of this group rather refractory ICH was noted, which was not relieved by 3.5% HSS in combination with 15% mannitol. These patients underwent neurosurgical interventions (decompression trepanation, clot evacuation).

The average number of days of ICP measurement in this group amounted to 5.4±0.2.

The average number of days of patients' stay in ICU in this group amounted to 10.8±0.6, and in the clinic - 18.4±1.9 days.

The lethality in this group amounted to 17.1%. 4 deceased patients in this group had more serious primary trauma (falls from a height, blows to the head) with lower GCS scores (4-5) and higher ISP indices. In one patient in this group, the fatal outcome was associated with acute myocardial infarction (AMI). Another patient had abscessed pneumonia and sepsis.

4. Discussion: The combination of Mannitol + 3.5% NaCl leads to significant and sustained improvement in systemic and cerebral blood flow. In the group, 284.8±11.6 mOsm/L with a slight decrease due to natriuresis under the effect of mannitol. But both drugs complemented each other, maintaining increased plasma osmolarity, which led to the movement of fluid from the cells and interstitial space into the vascular bed. The results show that the group of patients showed the most marked decrease in hematocrit due to hemodilution and optimal increase in CVP to maintain

adequate hemodynamics.

According to Asma A et al [9] who received combined therapy with mannitol and 3% sodium chloride had the lowest mortality rate, which may indicate more effective methods of treatment of increased intracranial pressure. In our study, the rate of ICP reduction was most significant in stage 2 18.1±0.72 mmHg. The combination of mannitol 15% + NaCl 3.5% rapidly reduced the ICP, and the duration of the decrease was maintained even by 120 minutes, amounting to 18.6±0.76 mm.Hg. The lethality in this group was 17.1%.

Sujita W et al [10] demonstrated mannitol plus hypertonic saline did not increase the risk of renal dysfunction. In our study we did not observe cases of ricochet syndrome and/or acute renal failure in patients in the group.

Thus, the use of combined solution of mannitol 15% + NaCl 3.5% was manifested by a more prolonged decrease in ICP, persistent increase in MAP and CPP. These data show that combined hyperosmolar solutions of mannitol 15% + NaCl 3.5% can be used in clinical practice.

5. CONCLUSIONS.

1. Bolus infusion of a combined solution of 15% mannitol and 3.5% NaCl HSS at a rate of 3.5±0.2 ml/kg body weight leads to a rapid (20-45 minutes) and prolonged (>120 minutes) decrease in ICH (by 36.5% of baseline) and a significant (21.8%) increase in CPP.

2. Combined use of mannitol 15% + NaCl 3.5% in the treatment of intracranial hypertension in patients with isolated craniocerebral [illegible] 3.5±0.2 ml/kg can be recommended in patients with baseline hypovolemia and hyponatremia.

Ethical Considerations Compliance with ethical guidelines: The present study was approved by the medical ethics committee (№. 1/12-1486.) and informed consent was obtained from the relatives of all patients.
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Conflict of interest
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