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THE EFFECT OF HYPERTONIC SALINE SOLUTION (7%) ON INTRACRANIAL PRESSURE AND CEREBRAL PERFUSION PRESSURE IN PATIENTS WITH ISOLATED TRAUMATIC BRAIN INJURY

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***Abstract:** TBI is a complex pathophysiological process that includes primary and secondary brain damage that affects the structure and function of the nervous system. The incidence of TBI is 3 times higher than the population growth and the cost of treatment is more than 33 billion euros per year. Recently, there has been a growing interest in hypertonic saline solutions, which act in the same way, exerting an osmotic effect, increasing the movement of water from the tissues into the circulatory system. The present study was to study the efficacy and safety of using 7% NaCl in the treatment of intracranial hypertension in patients with isolated traumatic brain injury in the adult population. This group consisted of 35 patients with isolated traumatic brain injury at the age of 21-80 years (42.6 ± 13.2 years).*

***Keywords:** Intracranial pressure, cerebral perfusion pressure, traumatic brain injury, hypertonic sodium chloride solution.*

INTRODUCTION

Traumatic brain injury, known as traumatic brain injury (TBI), can cause temporary or permanent impairment of cognition, behavior and is a leading cause of death and disability in people <45 years of age [1,2]. The incidence of TBI is 3 times higher than the population growth and the cost of treatment is more than 33 billion euros per year [3,4].

TBI is a complex pathophysiological process that includes primary and secondary brain damage that affects the structure and function of the nervous system.

Primary trauma includes irreversible brain damage, vascular and diffuse axonal injury [5], while secondary trauma is associated with hypoxia, release of inflammatory mediators, abnormal coagulation fibrinolysis function, and monocyte infiltration [6]. The main characteristics of TBI are cerebral edema, brain damage, progressive increase in intracranial pressure (ICP), as well as tissue ischemia, hypoxia and necrosis. Irreversible brain damage is mainly caused by microcirculatory disorders, increased vascular permeability, and damage to the blood-brain barrier. [7.8].

Both primary and secondary damage can lead to increased ICP. With high ICP, direct damage to brain tissue impairs cerebral blood flow and metabolic regulation, which directly or indirectly triggers a new cascade in which terminal cell membranes depolarize and begin to secrete excitatory neurotransmitters such as glutamate and aspartate. The constant cellular flow of calcium and sodium leads to the catabolic intracellular process of "Autoignition". Calcium flux activates proteases and phospholipase, which leads to an increase in the concentration of free fatty acids and oxygen radicals, which cause further swelling of the brain tissue after the initial damage. Complications resulting from brain injury involve all compensatory mechanisms and further increase ICP, edema and cerebral ischemia. Intracranial hypertension and cerebral hypoperfusion increase the likelihood of secondary ischemic injury. Therefore, the management of patients is aimed at timely and effective treatment of increased ICP and decreased cerebral perfusion pressure (CPP) [9]. Hyperosmolar therapy remains a well-established treatment for increased ICP, with the most commonly used drugs being mannitol and hypertonic saline NaCl [10]. Mannitol is traditionally used as a first-line drug that has both a direct effect on intracranial pressure due to a decrease in blood viscosity and a late osmotic effect. However, this is due to osmotic diuresis, which can lead to hypovolemia and hypotension [11]. Recently, there has been a growing interest in hypertonic saline solutions, which act in the same way, exerting an osmotic effect, increasing the movement of water from tissues into the circulatory system [12]. In addition, with regard to cerebral microcirculation, administration of hyperosmolar saline solutions initially lowers serum viscosity and hematocrit, increasing cerebral perfusion, which leads to reflex narrowing of autoregulatory cerebral arterioles, which decreases blood volume in the brain and intracranial pressure [13]. Finally, hyperosmolar saline solutions enhance the stabilization of brain cell membranes, at the same time as their administration leads to an anti-inflammatory effect. Although the transition to hyperosmolar saline solutions is clearly visible and many different concentrations of NaCl have been used (1.5%, 3%, 7.5%, 15%, 23.4%), the concentration of superiority of each of them has yet to be evaluated [17]. Their comparative characteristics in the literature are very scanty, sometimes contradictory [14].

The aim of this study was to study the efficacy and safety of using 7% NaCl in the treatment of intracranial hypertension in patients with isolated traumatic brain injury in the adult population. This group consisted of 35 patients with isolated traumatic brain injury at the age of 21-80 years (42.6 ± 13.2 years). The injury was associated with an accident (16), a

fall (11), a high-altitude injury (4), a blow to the head (4). In 6 patients, vomiting of gastric contents took place, in 3 of whom an aspiration syndrome was diagnosed, for which they underwent sanitation bronchoscopy with airway lavage.

Study design. A retrospective study was conducted with the study of case histories and resuscitation cards of 35 patients with isolated traumatic brain injury who were admitted from January 2014 to December 2019 to the intensive care unit of TMA clinics. Inclusion criteria were: age over 18 years, isolated severe traumatic brain injury (Glasgow Coma Scale <8), primary closed traumatic brain injury, the ability to monitor intracranial pressure, the value of intracranial pressure> 20 mm Hg. The exclusion criteria were: patients with GCS 3 after initial resuscitation and fixed dilated pupils without photoreaction, patients who died within 24-48 hours after admission to the clinic, patients requiring neurosurgical treatment [18]. Our study was approved by an ethics committee.

Standard therapy. During the study period, patients with severe traumatic brain injury received standard supportive care in accordance with established guidelines [19]. All patients were given an elevated position of the head up to 20-30° (orthopedic), sedation was provided with benzodeazepines, and analgesia with opiates, mechanical ventilation in order to achieve $PaCO_2$ from 30 to 35 mm Hg. and PaO_2> 100 mm Hg. Maintained normothermia by physical and pharmacological means. Therapeutic brain hypothermia has not been used. Inotropic support was set to maintain a central perfusion pressure> 60 mm Hg. If intracranial pressure remained elevated (> 20 mm Hg) for more than 5 minutes, despite the above therapy, 7% hypertonic saline was administered intravenously.

Osmotherapy was used according to specified institutional guidelines in cases where standard protocol therapy was not successful in reducing intracranial pressure <20 mm Hg.

Contraindications to hypertonic saline were plasma Na> 155 mmol/L and no central venous access.

7% hypertonic saline solution was injected bolus initially at the rate of 5 ml/kg/hour (maximum dose 5 ml/kg body weight) until the intracranial pressure dropped below 20 mm Hg. Thereafter, 7% hypertonic saline was repeated each time the intracranial pressure increased again or reached 20 mm Hg. and was kept at higher numbers for 15 minutes. Dose of 7% hypertonic saline solution 5 ml/kg body weight up to a maximum of 100 ml (equal to sodium load of 2 mmol/kg).

Demographic (age, gender, mechanism of injury) and clinical data (GCS scores, pupil size and response, level of consciousness, intracranial pressure monitoring data, the total number of episodes of increased intracranial pressure requiring the administration of hypertonic saline solution, a daily dose of 7% NaCl solution, average response of intracranial pressure, daily peak of Na in blood serum, creatinine, glucose, chlorides, blood osmolarity). The dynamics of GCS scores was monitored during therapy. These data were analyzed daily for the presence of adverse events associated with hypertonic saline therapy, including severe hypernatremia, central demyelinolysis, subarachnoid hemorrhage, pulmonary failure, pulmonary edema [15,16].

Laboratory data included serum sodium before and after administration of hypertonic saline. The values of intracranial pressure and central perfusion pressure were recorded before and after administration of hypertonic saline solution. Baseline values were calculated as the average of measurements during the last hour before starting the HS infusion. The effect of HS on decreasing ICP usually persists for 60–120 minutes after administration [20]. Thus, the ICP and CPP variables were averaged 15, 30, 60 and 120 minutes after each HS

infusion. General episodes of ICH requiring HS per patient, average episodes per patient per treatment day, and the dose of each infusion of HS were documented in the medical history.

Road accidents were the leading cause of injuries followed by falls. Imaging studies on admission (CT) revealed a contusion of the brain and a linear fracture of the skull in most of the study group, while diffuse cerebral edema was found in more than half of the patients.

The demographic and clinical characteristics of the victims of this group are shown in the table below.

Tab. № 1. Demographic and clinical characteristics of patients in the group (n = 35)

№	Patient characteristics	The values
1	Age, years	42,6±13,2 (21-80 лет)
2	Sex, m / f	17/18
3	Traffic accident injury mechanism, n%	16 (45,7)
4	Falls, n%	15 (42,8)
5	Pupils (pathological, n%)	26 (74,2)
6	Bilateral miosis, n%	13 (37,1)
7	Anisocoria, n%	11 (31,4)
8	Bilateral mydriasis with photoreaction, n%	2 (5,7)
9	CT data (pathology, n%)	104 (297,1%)
10	Brain contusion, n%	23 (65,7)
11	Fracture of the skull bones, n%	19 (54,2)
12	Cerebral edema, n%	20 (57,1)
13	Subarachnoid hemorrhage, n%	11 (31,4)
14	Subdural hematoma, n%	9 (25,7)
15	Epidural hematoma, n%	7 (20,0)
16	Intracerebral hemorrhage, n%	8 (22,8)
17	Axonal damage, n%	7 (20,0)
18	Intubation, mechanical ventilation, n%	29 (82,8)
19	Arterial hypotension, n%	25 (71,4%)
20	GCS, points	5,01±0,36 (4-11)
21	APACHE II, points	18,3±2,7
22	Craniotomy, n%	6 (17,1%)

The indicators of the clinical study of blood and hemostasis in patients of this group indicated moderate anemia of traumatic genesis and activation of the blood coagulation system.

Tab. №2. Indicators of Ht, systemic and central hemodynamics in patients of the group at admission (n=35)

Indicators	The values
BP systolic, mm Hg	94,6±4,7
BP diastolic, mm Hg	64,1±2,9
Average blood pressure (MAP), mm Hg	74,2±3,8
Heart rate (HR), in min	72,2±4,3
Central venous pressure (CVP), cm H_2O	4,9±0,4
Impact index (II), ml/m^2	29,7±3,9

Cardiac index (SI), l/m^2	2,14±0,08
Pulse oximetry (SpO_2),%	89,9±2,7
Total peripheral vascular resistance (TPVR), $dyn \times s \times cm^{-5}/m^2$	1541,8±139,9
Hematocrit,%	37,0±3,9

The indices of systemic and central hemodynamics upon admission of the victims of this group to the clinic showed moderate arterial hypotension with a decrease in both systolic (17%) and diastolic (19.9%) values from their proper values, which affected a decrease in mean arterial pressure by 7.7%.

The TPVR indicators, having averaged 1370.0±137.5 $dyn.s*cm^{-5}$ upon admission, turned out to be 9.3% lower than their due values (1511,1 $dyn.s*cm^{-5}$, calculated by the formula:

Predicted TPVR = SBP*80/MVH actual

The proper SBP values in the studied age group are 85-90 mm Hg.

CVP was 32.5% lower than physiological values. All of the above contributed to a decrease in the one-time and minute productivity of the heart, which were at the borderline values of the normal and hypodynamic circulation. All of the above indicated a deterioration in cerebral circulation. In all patients of this group, upon admission to the ICU, an increase in ICP was registered, the mean values of which were 27.6±2.1 mm Hg. which explained the initial relative bradycardia (76.2±6.9 bpm). The mean CPP values were 50.9±4.7 mm Hg, which confirmed the above thesis about the deterioration of cerebral circulation.

The baseline values of blood electrolytes and plasma osmolarity are presented in the table below.

Table 3. Biochemical parameters of blood and plasma osmolarity in patients of the group upon admission (n = 35)

Index	**Value**
Total protein, g / l	71,4±5,2
Glucose, mmol / l	5,76±0,64
Creatinine, μmol / L	79,1±4,5
Urea, mmol / l	5,0±0,9
Potassium, mmol / l	4,3±0,6
Sodium, mmol / l	133,6±5,0
Calcium, mmol / l	2,2±0,1
Plasma osmolarity, mOsm / l	268,5±8,8

Analyzing the data presented, it can be noted that all the studied parameters in patients of this group did not go beyond the physiological values. However, it is immediately striking that with insignificant hyponatremia (by mean values), there is a large range of indices of standard deviation (m), which made us study in more detail the concentration of Na^+ in patients. In 11 patients of this group (31.4%), the plasma Na^+ concentration exceeded 145 mmol/L, averaging 147.1±4.1, while in the remaining 24 patients (68.5%) the plasma Na^+ level was below 135 mmol/L, averaging 120.1±6.0 mmol/L. Relative hyponatremia in the prevailing part of the patients of this group at normal blood glucose and urea levels led to a decrease in the initial plasma osmolarity by 6.7% of the physiological norm.

Effect of hypertonic saline solution on ICP and CPP

In this group of patients, we recorded a total of 157 episodes of intracranial hypertension, which forced the administration of 7% HS, on average 4.5 (3-7) episodes per patient and 1.9 (1.6-2.2) episodes per patient on the day of HS treatment. The average interval between standard therapy and the initiation of HS infusion was 4.5±0.7 hours in this group (3-7). The 7% HS dose was adjusted for each episode, starting at 5 ml/kg/hr and ending with a bolus of HS when the ICP level became <20 mm Hg. For the group as a whole, this dose was 1.9 ± 0.4 ml/kg (1.5-3.1). The route of administration of the HS is important. We have chosen the bolus administration of HS, because it rapidly reduces ICP, improving cerebral hemodynamics. After repeated doses for several hours, HS causes a decrease in brain hyperhydration and a further decrease in ICP. Continuous infusion is associated with hypernatremia and hyperosmolarity, which progressively cause brain dehydration, decreasing ICP [21].

Hypertonic saline (7% NaCl) resulted in a significant decrease in ICP and an increase in CPP 30, 60, and 120 minutes after infusion.

Dynamics of ICP, CPP and sodium concentration in plasma at the research stages are shown in the table (n=35).

Table 4. Effect of 7% HS solution on SBP, ICP, CPP and plasma Na^+ (episodes - 157)

Indicators	**Research stages**			
	Before infusion	After 30 minutes	After 60 minutes	After 120 minutes
ICP, mm Hg	27,6±2,1	17,4±2,7*	18,7±3,1*	19,1±2,9*
CPP, mm Hg	50,9±6,7	57,7±4,2*	60,6±3,7*	61,2±4,0*
Plasma Na^+ level, mmol/l	136,6±10,1	144,7±8,3*	142,0±7,4*	143,4±5,5*
Plasma osmolarity, mOsm/l	268,5±8,8	289,4±5,1*	284,6±4,9*	287,7±3,9*
SBP, mm Hg	76,5±4,9	77,1±3,2	79,3±4,0	80,3±4,4

Note: p <0.05. reliability is given relative to stage I.

In most episodes (146), 7% NaCl solution was able to reduce ICP and increase CPP. In 11 episodes of ICH, they turned out to be very refractory, and in 5 of them it was stopped by a combination of 7% HS with mannitol (0.5 g/kg) and fentanyl (4-6 ml IV). In 6 patients, craniotomy was performed, the lowest ICP values were determined 60 min after the end of the infusion, averaging 18.7±3.1, i.e. 32.3% below the original data.

The content of Na + in the blood serum after the infusion of HS increased by 5.9%. its maximum average values were noted by us 30 minutes after the infusion of the HS (144.7±8.3). We registered hypernatremia exceeding 144 mmol/L in 2 patients of this group (157.6 mmol/L and 161.2 mmol/L). These two patients had acute renal failure with an increase in nitrogenous waste. ARF was stopped in them without renal replacement therapy. No patient had pulmonary edema or thrombosis.

The average number of days of ICP monitoring in this group was 5.3±0.2. The time spent by patients in the ICU averaged 9.7±0.8 days, and in the clinic - 17.2±1.4 days.

Mortality in this group of patients was 17.1%. Most (82.9%) patients survived. It should be noted that 6 patients who died had a more severe form of TBI with abnormal pupils and lower GCS scores on admission (4-6).

Discussion

The present study clearly demonstrates that a 7% bolus infusion of HS is effective in reducing ICP and increasing CPP in patients with severe isolated TBI.

The effectiveness of HS remains at least 120 minutes after infusion. Several studies have examined the effect of different concentrations (from 1.5% to 23.4%) of HS in the treatment of ICH and have demonstrated their advantage in controlling ICP [10,22,23]. One study reported fewer ICH episodes per day in patients receiving 7.5% HS than in those receiving mannitol [24].

Our results, in accordance with the above studies, demonstrated that 7% of the HS allows good control of ICH, quickly (after 15-20 minutes) reduce ICP by 29.8% ($p < 0.05$) relative to the initial values, which lasted at least 120 minutes and indirectly affected the decrease in the volume of post-infusion, by almost 27% from the initial value of pre-infusion. Our results regarding the effect of 7% HS on ICP are consistent with those of Dimitrios R et al, 2017, who studied the effectiveness of 7.5% HS in children with severe TBI. In clinical trials comparing the effects of equimolar doses of 7.2%, 7.45%, 7.5%, 15% HS, all have been shown to be effective in lowering ICP 30, 60, 120 minutes after infusion [25,26,27,28]. And we must agree with their opinion that before the tuning time there is no data demonstrating a clear advantage of one of the HS over the other. This issue is still controversial [29].

As for sodium, by the 30th minute of the study after the introduction of 7% HS, its level in the blood increased by 5.9%. ($p < 0.05$) and stayed at these figures for at least 120 minutes. It is known that the effect of HS is enhanced with increasing plasma sodium concentration. But this is fraught with possible side effects, especially due to induced hypernatremia. On the other hand, with long-term use of HS, renal compensatory mechanisms lead to an increase in sodium excretion in the urine, and, therefore, prevent an excessive increase in blood sodium levels.

Relatively recent recommendations from the Brain Injury Foundation have shown that there is insufficient evidence to recommend HS solutions greater than 3% based on studies comparing 1.7% and 3% HS in bolus doses of 6.5 to 10 ml / kg (equals 66 -1027 mOsm / kg) [30]. In this respect, our research does not run counter to the recommendations of the foundation, since included an adjustable dose of 7% HS, the administration was stopped immediately after a decrease in ICP less than 20 mm Hg. We did not use any standard dose, and therefore the HS volume and osmolarity were relatively low (1.5-2.5 ml / kg and 7.2-7.3 mOsm / kg, respectively). As a result, although the peak increase in sodium concentration, which reached by 30 minutes was 5.9% higher than the baseline values, we did not record any side effects.

Infusion of 7% HS led to an increase in plasma osmolarity, which acquired physiological values relative to the initial relative hypoosmolarity. An increase in plasma osmolarity was noted already 30 minutes after stopping the administration of HS, reaching a peak after 60 minutes, when its increase relative to the initial values was 11.3% ($p < 0.05$). At these digits, the plasma osmolarity was kept for at least 120 minutes. All of the above had an effect on the CPP index, which statistically significantly increased relative to its baseline values, reached the highest values by 120 minutes, exceeding them by 20.2% ($p < 0.05$).

However, an excessive increase in sodium level and plasma osmolarity leads to volume overload, which in a congested cardiovascular system can lead to heart failure, pulmonary edema, or can cause hyperchloremic metabolic acidosis and impaired hemostasis [31,32]. Therefore, it is quite natural that the study of hypertonic solutions in patients with impaired heart function should be carried out with careful monitoring of the heart. Diuresis in this group averaged 94.2±10.3 ml/h.

We evaluated the result of changes in GCS data at the end of the observation period in this group of patients. If at admission the level of consciousness according to GCS was 5.91±0.97 points, then at the end of the study it was 7.83±0.36 points ($p < 0.05$). We did not make a detailed analysis of the results in this regard, since this was beyond the scope of this study.

Table 5 shows the dose and time required to reduce ICP below 20 mm Hg. in patients of this group.

Drug	Dose (ml / inf)	Dose (ml / kg)	Time, min
7% HS	141.4±4.7 (60-270)	1.9 (1.4-3.5)	15-20 (12-30)

Patients in this group received a higher osmotic load.

Having set ourselves the above goal, we aimed to investigate the direct effects of an osmotic solution in one basic dose, and, therefore, we did not analyze the late effects of osmotic agents, the effects of repeated infusion

The results of this controlled trial will provide an opportunity to help choose between the studied options for hyperosmolar therapy for isolated TBI.

A dose of 1.9 ml/kg body weight of 7% HS can be recommended for the treatment of ICH in isolated TBI in patients with hypovolemic hyponatremia and renal failure before treatment.

Further research will be needed to analyze late effects, effects of repeated infusions, and long-term neurological outcome.

Conclusion

Our studies have shown that infusion of 7% HS was associated with optimal control of ICP, which contributed to a decrease in post-infusion load by 27.4% of the initial pre-infusion. Since the effect of HS is enhanced by increasing serum sodium concentration, its use is associated with possible side effects, especially due to induced hypernatremia [15, 33]. It has been shown that with long-term use of HS, renal compensatory mechanisms lead to an increase in Na + excretion in the urine and, therefore, prevent excessive increases in the level of sodium in the blood [34]. Recent recommendations from the Brain Injury Foundation indicated that there was insufficient evidence to recommend solutions with HS greater than 3% [30]. Our study included an adjustable dose of 7% HS, which was stopped with a decrease in ICP less than 20 mm Hg. and, therefore, the volume of HS was relatively low (on average 3 ml/kg, which corresponded to 7.2 mOsm / kg). We indicated that 2 patients (?) Had significant hypernatremia after a moderate dose of 7% NaCl, indicating a possible failure of their autoregulation. In accordance with other researchers, we did not record other significant (except for 2 cases of permanently recurrent ARF) side effects associated with HS [35,36]. However, it should be noted that successful ICP control does not guarantee a good

neurological outcome and survival [37, 38]. Since the control of ICP cannot influence the primary traumatic injury, which can in itself lead to irreversible cerebral injury.

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