# CLINICAL-BIOCHEMICAL RATIONALE OF USE OF MANNITOL AND SORBILACT IN SEVERE CRANIOCEREBRAL INJURY

**Pavlenko I.A., Chepkyi L.P., Ivaniushko O.V.**
**Danylo Halytsky**
**Lviv National Medical University**

Severe craniocerebral injury is accompanied by focal and cerebral symptoms associated with the damage to certain sections of the brain, its perifocal edema, endogenous intoxication (1,8).

In the initial stages, edema and swelling of the brain are a protective reaction in response to the damage as hyperhydration reduces the concentration of toxins in cells of the brain. However, the progression of the process leads to a dramatic increase in the intracranial pressure and development of dislocation phenomena that affect the stem sections of the brain that may cause disruption of the vital functions and be responsible for the death of a patient (10).

It is clinically represented with impairment of consciousness, as evidenced by decreasing Glasgow coma scale (< 9 points) and symptoms of brain structure dislocation. In these cases, osmotic diuretics are widely used: mannitol, sorbitol, glycerol and saluretic furosemide and, recently, domestic osmotic diuretics of polyfunctional action Sorbilact and Rheosorbilact (4,7).

The first phase of action of diuretics is characterized by a rapid (within 15–30 min) decrease in the intracranial pressure. In this period, the intratissue pressure is reduced in those parts of the brain where the vascular regulation and blood-brain barrier (BBB) permeability are not affected, whereas the intratissue pressure in the parts of the brain with affected BBB may increase by 10–25%. The second phase (30–90 min after osmotic diuretics administration) is characterized by the maximum drop of the cerebrospinal fluid pressure (up to 50%) and intratissue pressure (88%), accompanied by an increase in cerebral blood flow by 20–40%. In the third phase (2.5 – 3.5 hours after the drug administration), with occurrence of "rebound syndrome" in 65% of cases, the CSF pressure and intratissue pressure exceed the initial values. Diuretics are also prescribed as a therapeutic measure aimed at treating endotoxicosis (8).

In craniocerebral injury (CCI), it is associated with destruction of the brain tissue, blood vessel ruptures, entrance of macro- and micro-parts of cerebral detritus into the blood flow, direct contact of poured out blood with the brain tissue, formation of intracranial hematoma, blood infiltration in the cerebrospinal fluid.

Since in CCI the function of the blood-brain barrier is disturbed and the permeability of capillaries increases, their epithelium is damaged, a significant mass of fragments of the damaged tissue moves from the brain to the general circulation, which causes endogenous intoxication (EI) (8). In this regard, the detoxification therapy is one of the components of the treatment of severe CCI. It involves elimination of toxins from various fluid media of the body (blood, plasma, lymph, cerebrospinal fluid) (9).

Detoxification therapy is conducted for activation and optimization of the physiological systems of the body responsible for elimination of toxins. The main principles of detoxification are:

- enhancing perfusion in order to create conditions for the diffusion of toxic factors from affected cells, tissues into the general circulation;
- haemodilution that results in decreased plasma concentration of toxins;
- forced diuresis resulting in faster excretion of toxins and metabolites from the body. With this purpose, diuretics are most often used.

Priority is given to osmotic diuretics since their action starts faster and is more physiological than that of saluretics. Effect of osmotic diuretics is manifested not only in the reduction of brain edema and intracranial pressure, but also in improvement of the rheological properties of blood, cerebral blood flow and, unlike saluretics, when osmotic diuretics are used, hypovolaemia and hyponatraemia are more rarely observed.

Mannitol reduces intracranial pressure by 15–20%, improves the cerebral perfusion pressure by 10%, increases cerebral blood flow by 10–15% and stimulates increase in its flow rate by 13%. Unlike furosemide, mannitol improves the rheological properties of blood: reduces its viscosity by 16% (furosemide increases by 25%), reduces the haematocrit by 37% (furosemide – increases by 2%), does not affect the aggregation of platelets (furosemide increases by 20%). (2,3). The disadvantages of mannitol, especially furosemide, include the ability to cause a "rebound syndrome", blood electrolyte disturbance. These disadvantages can be reduced by administration of Sorbilact and Rheosorbilact that have the necessary electrolytes (potassium, sodium, magnesium, chlorine) in their composition in balanced proportions (4.6.7).

According to M.E. Polishchuk (2002), these drug products have a diuretic effect, significantly improve the function of the kidneys and liver, stimulate intestinal peristalsis, optimize hemodynamics in traumatic and hemorrhagic shock, which makes their widespread use in severe brain injuries justified.

A statement made by a competitive company about the possibility of complications when using large doses of sorbitol, as well as the work by E.I. Bulss, H.I. Van Zuylen (1997) about the risk of hyperglycemia, hypophosphataemia and lactatemia in these cases has caused the need to study the impact of the recommended by the releaser doses of Sorbilact and Rheosorbilact on the frequency of complications and on the level of glycemia, lactatemia, inorganic phosphate blood levels in patients with severe craniocerebral injury. For this **purpose**, data on the use of more than 1 million bottles of Sorbilact and Rheosorbilact in Ukraine were analyzed. It was found that there were no claims to the company in connection with the complications. **The task** of the work was to study the impact of these drug products on the level of glucose, inorganic phosphate, lactate and endotoxicosis values.

## MATERIAL AND METHODS OF EXAMINATION

44 patients with severe craniocerebral injury aged from 20 to 68 were examined: 19 female and 25 male. All the patients were diagnosed with severe cerebral contusion, 29 patients reported epidural or subdural hematoma due to which they underwent craniotomy with the removal of the hematoma. Condition at admission was extremely critical. Level of consciousness on the Glasgow scale was 4–9 points. Significant haemodynamic disorders, tachi-or bradypnoea, pathological types of respiration were reported.

All the patients underwent a conventional extensive therapy.

Depending on the type of anti-oedemateous treatment, the patients were divided into two groups: the first (control) group, the patients of which were treated with mannitol, and the second (treatment) group where mannitol was replaced by Sorbilact.

The scope of examination included the continuous monitoring of the general condition, the level of consciousness of patients, central hemodynamics values and generally accepted methods of laboratory examinations. In addition, the level of glucose, lactate, ATP inorganic phosphorus, average weight molecules (AWM), erythrocyte membrane permeability (EMP), erythrocyte sorption ability (ESA) and leukocytal intoxication index (LII) in the mixed venous blood were assessed.

## RESULTS AND THEIR DISCUSSION

On the first stage of the examination, we tried to establish the impact of Sorbilact, compared to mannitol, on the level of glycemia, lactatemia observed in most cases of severe craniocerebral injury, as well as on the level of ATP inorganic phosphorus in the mixed venous blood.

In this case, it was established that moderate hyperglycemia caused by the stress reaction of the organism to CCI persisted for three days of the examination and significantly differed when using mannitol and Sorbilact (table 1).

No difference in the lactate blood level was either observed in patients from group I and II. It gradually declined by the third day.

Effect of Sorbilact and mannitol on inorganic phosphate blood levels also slightly differed. Its blood level was slightly elevated in both groups of patients. With the norm of 0.8–1.0 mmol/L, it ranged from 2.3 to 3.1 mmol/L in patients of different groups.

A similar pattern was observed during the determination of ATP blood level: it was elevated at the various stages of the examination. With the norm of 0.6–1.7 mmol/L, its values varied between 4.1 and 3.9 mmol/L and insignificantly differed in patients of group 1 and 2.

The above results indicate the absense of negative influence of Sorbilact on carbohydrate and phosphate metabolism in patients with severe craniocerebral injury. Hyperglycemia, increased levels of lactic acid and phosphorus observed during hospitalization did not progress.

The next task of the work was to justify the use of mannitol and Sorbilact to deal with endotoxicosis associated with severe CCI.

Primary objective parameters were hemodynamic disorders.

As table 2 shows, during the hospitalization, the treatment and control groups reported expressed tachycardia (118–120, min) and arterial hypertension (mean BP 115–112 mm Hg). At this time, among the laboratory parameters of endotoxicosis, the presence of expressed leukocytosis in groups 1 and 2 (19.8 – 20.1.$10^9$ L) and increase in leukocytal intoxication index to 7.5 – 7.8 (table 3) were remarkable.

The data analysis showed that the signs of EI were established on the 1st day after the trauma in patients of both groups. After the intensive therapy, EI values changed on the 1st, and especially on the 3rd day.

HR was significantly lower in the treatment group – 22 bpm on the 2nd–3rd day and 32 bpm on the 4th–5th day. The difference in mean BP in the treatment group was significant on the 4th–5th day compared to that on the 1st day; in the control group the difference was insignificant. The significant increase in LP and AMMP was observed after the trauma in patients of both groups which indicated expressed EI that occurs immediately after the CCI. This is due to the activation of the body's metabolic processes secondary to the deficiency of energy substrates and oxygen.

*Table 1*

**Characteristics of biochemical parameters after the use of Sorbilact (Group 1) and mannitol (Group 2)**

| Parameters | Stage of examination | | | | | |
|---|---|---|---|---|---|---|
| | Day 1 | | Day 2 | | Day 3 | |
| | Group 1 | Group 2 | Group 1 | Group 2 | Group 1 | Group 2 |
| Glucose, mmol/L | 12(7.4±0.78) | 8(6.6±0.71) | 21 (9.9±0.12)* | 8(1.0±0.63)* | 24(6.9±0.44) | 6(7.1±0.41) |
| Lactic acid mmol/L | 9(2.1±0.27) | 8(1.8±0.24) | 8(2.1±0.15) | 8(1.7±0.16) | 7(1.2±0.30)* | 7(0.8±0.15)* |
| Phosphorus, mmol/L | 19(2.5±0.41) | 8(3.1±0.82) | 19(2.6±0.11) | 8(2.3±0.12) | | |
| ATP, mmol/L | 19(4.1±0.4) | 8(4.1±0.2) | 19(3.9±0.3) | 8(3.8±0.39) | | |

***Note:*** *p < 0.05 compared to Day 1.

*Table 2*

**Characteristics of HR and mean BP after the use of Sorbilact and mannitol**

| Parameters | Day of examination | | | | | |
|---|---|---|---|---|---|---|
| | 1st | | 2nd-3rd | | 4th-5th | |
| | Group of patients | | Group of patients | | Group of patients | |
| | treatment | control | treatment | control | treatment | control |
| HR, bpm | 118±6.7 | 120±5.1 | 98±5.2* | 120±6.3 | 80±2.4** | 112±1.8 |
| Mean BP, mm Hg | 115±4.6 | 112±2.2 | 102±1.5 | 107±1.5 | 95±3.1 | 103±5.1 |

***Note:*** **p < 0.05 compared* to *Day 1;*
***- p< 0.05 when comparing groups*

*Table 3*

**Endogenous intoxication parameters after the use of Sorbilact (treatment group) and mannitol (control group)**

| Parameters | Day of examination | | | | | |
|---|---|---|---|---|---|---|
| | 1st day | | 2nd-3rd day | | 4th-5th day | |
| | Control group | Treatment group | Control group | Treatment group | Control group | Treatment group |
| Leukocytosis (10 - 9/l) | 19.8±2.3 | 20.1±1.5 | 17.1 ±4.3 | 12.2±3.1 | 16.2±1.3 | 9.2±2.4*,** |
| Leukocytal intoxication index | 7.5±2.3 | 7.8±3.1 | 8.3±3.2 | 3.9±1.5*,** | 5.8±1.1 | 2.6±1.2*,** |
| Average weight molecules (rel.un.) | 0.450±0.023 | 0.612±0.012* | 0.358±0.023*' | 0.312±0.012** | 0.358±0.025 | 0.280±0.014*,** |
| Erythrocyte membrane permeability | 12.3±1.67 | 14.2±2.83 | 14.5±0.58 | 14.5±1.75 | 16.08±0.45 | 12.64±1.18* |
| Erythrocyte sorption ability (%) | 15.5±3.86 | 14.5±4.18 | 19.7±5.43 | 516.5±5.15 | 16.5±6.21 | 17.6±4.67 |

***Note:*** ** p < 0.05 compared to the control group;*
***p < 0.05 compared to Day 1*

During the analysis of the study results, significant differences in the patients of both groups were revealed in the follow-up.

The changes in the number of white blood cells and LP under the influence of Sorbilact therapy were particularly evident. These values were significantly lower than those in the control group.

The common objective parameter of severe endogenous intoxication is increased level of average weight molecules (norm: 0.18–0.210 rel.un.). Its increase by 2–3 times in the examined patients evidenced about the severity of endotoxicosis.

In the literature, there are data about the negative impact of endotoxicosis on the strength of erythrocyte membranes. In most patients, it was raised at the time of hospitalization. At the same time, erythrocyte sorption ability was decreased in CCI. Under the influence of intensive therapy using mannitol and Sorbilact, the signs of endotoxicosis were gradually reduced, especially in the treatment group. In these patients, tachycardia and hypertension significantly decreased in 2–3-days. When using mannitol, these changes were only observed on the 4th–5th day.

Under the influence of intensive therapy, the AWM level decreased on the 2nd–3rd day in both groups, particularly in the treatment group where it was greater than that in the control group before the treatment. On the 4th–5th day, the AWM level was significantly lower in the treatment group than that in the control group, thus implying a more pronounced detoxification action of Sorbilact compared to mannitol.

Erythrocyte sorption ability was improved under the influence of intensive therapy more significantly in the treatment group compared to the controls. At the same time, erythrocyte membrane permeability significantly decreased on the 2nd–3rd day only after the use of Sorbilact. Mannitol slightly affected this endotoxicosis value.

Erythrocyte sorption ability (ESA) slightly differed in both groups of patients on the 1st–3rd–5th day. On the 3rd day, it was higher in the control group, on the 5th day – in the treatment group. It is possible than mannitol and Sorbilact improve ESA.

Based on the bibliographical data about the optimizing effect of Sorbilact on hemodynamics, renal and hepatic function, the ability to normalize the intestinal peristalsis and our data about reducing the signs of endotoxicosis, as well as the lack of a negative impact on the level of glycemia, lactatemia, phosphorus, it can be widely used for the treatment of severe CCI.

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