

TO A PRACTICING PHYSICIAN

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*V.I. Chernii, R.I. Cherniavskii, A.N. Kolesnikov, G.I. Yermilov, G.A. Gorodnik***PROGNOSTICATION OF OUTCOMES AND PECULIARITIES OF NEUROPROTECTIVE THERAPY IN PATIENTS WHO SUFFERED CRITICAL STATE AND REANIMATION***M.Gorky Donetsk National Medical University, Ukraine*

Abstract. Topicality of the problem of integral approach to intensive therapy of patients who suffered critical states during the post-reanimation period is caused by the socioeconomic importance and is related to high lethality, incapacitation and mass character of such pathology. The issues of outcome prognostication, the search of process irreversibility criteria and the brain death diagnostics are of special significance. The choice of intensive therapy tactics depends to a great extent on the localization of pathological process, on the level and degree of the brain injury. Moreover, intensive therapy must be complex, and the character of pathogenesis of different types of encephalopathy must be taken into account. The research was conducted on the base of the regional reanimation centre DOKTMO in the city of Donetsk and the department of intensive therapy of CTH in the town of Antratsit, in patients with acute cerebral insufficiency, conditioned by critical states of different etiology. Acute cerebral insufficiency was the result of the strangulated asphyxia (suicide), carbon oxide poisoning of different degrees of severity (domestic and industrial), severe craniocerebral injury. Among patients there were 48 women and 140 men at the age from 16 to 74. In the research, we have developed and applied an integrative estimative complex of the state of patients with acute cerebral insufficiency of different genesis. This complex included estimation of DIC-syndrome parameters and omega-potential change, estimation of the common state of patients by GCS score, and estimation of the brain edema-swelling pronouncement, according to the data of impedancemetry. Favourable and unfavourable integrative symptom complex was obtained for every type of acute cerebral insufficiency. A conclusion has been drawn that in spite of different pathophysiological events in the development of acute cerebral insufficiency, mechanisms of the brain death will be shown in a universal integrative symptom complex. The variants of intensive therapy with their correction, according to the indexes of integrative symptom complex and the kind of ACI have been developed for patients with acute cerebral insufficiency of different etiology.

Keywords: acute cerebral insufficiency, diagnostics, prognostication, intensive therapy.

Topicality of the problem of integral approach to intensive therapy in patients who suffered critical states in the post-reanimation period is due to the socio-economic importance and is associated with high lethality, disability and mass character of such a pathology. In neuroreanimatology and neuroanesthesiology, there came about the era of conceptualism and recommendations, based on the data of critical states estimation, which have replaced eclectics and empirics, reigning throughout centuries. A specific aspect of the problem is the development and compulsory use of standards. The American Association

of Neurosurgeons has issued the first recommendations based solely on the data from evidentiary medicine "Guidelines for the Management of Severe Head Injury", 1996 [18]. However, in their systematic review I. Roberts et al. [21], using the standard procedures of meta-analysis, came to a conclusion that the data allowing to make final conclusions as to the efficacy and safety of this or that treatment method were obviously insufficient. In the randomized studies by various authors a conclusion was made that unless the new randomized studies are carried out, the treatment of patients must be based on the general principles of emergency therapy, making it possible to prevent the development of hypoxia and shock, especially dangerous in critical states [6, 8, 19].

Of special significance now are the issues of outcomes prognostication, search of the process irreversibility criteria, the brain death diagnostics.

The "gold standard" in neuroreanimatology is the use of the computer and magnetic resonance imaging to diagnose acute cerebral insufficiency [1–3, 5, 7, 9, 20]. However, the above techniques may, only with certain degree of error, help to diagnose the affected area, whereas the issue of investigating into the condition of the central nervous system (CNS) remains open, as a rule.

A great number of experimental and clinical studies are dedicated to the CNS function in the post-reanimation period [9, 15, 16]. It was found that during the post-reanimation the postponed post-hypoxic encephalopathy may develop, when the commenced CNS functional recovery may be interrupted and ended with a patient's death [9, 11].

The choice of intensive therapy tactics depends largely on the pathologic process localization, on the level and degree of the cerebral lesion. At that, an intensive therapy must be complex and must be conducted with regard for the peculiarities inherent in the pathogenesis of different kinds of encephalopathy.

Specific problem in the therapy of acute cerebral insufficiency in recent times is the therapy of endothelial dysfunction of the cerebral vessels, which the disordered microcirculation in these vessels is associated with. Thus, the increasing from year to year number of patients who suffered critical states,

Table 1. Patients distribution into groups and disease outcome

Critical states	Number of patients				
	survived		deceased		
	absolute	%	absolute	%	
Strangulated asphyxia	33	94.3	2	5.7	35
Carbon oxide poisoning	85	87.5	10	10.5	95
Severe craniocerebral injury	39	67.2	19	32.8	58
Total	157	87.2	31	16.5	188

a great social-economic significance of the problem and lack of sufficiently clear recommendations on diagnostics and conceptual intensive therapy of the above states, conditions the problem immediacy.

Objective of the research is to improve the quality of intensive therapy in the post-reanimation period in patients who suffered variously originated critical states (strangulated asphyxia, carbon oxide poisoning, severe craniocerebral injury), via developing new integral methods of diagnostics, revealing the diagnostic and prognostic regularities, developing the directions of neuroprotective therapy for this category of patients.

Materials and methods

The research was carried out on the base of the regional reanimation centre DOKTMO in the city of Donetsk and the department of intensive therapy of CTH in the town of Antratsit, in patients with acute cerebral insufficiency, conditioned by the critical states of different etiology (strangulated asphyxia [suicide], variously severe carbon oxide poisoning [domestic and industrial]), severe craniocerebral injury. Among 188 patients there were 48 women and 140 men, aged from 16 to 74 years.

Distribution of patients into groups and the disease outcome are presented in Table 1.

To analyze the dynamics of the course and to evaluate the character of acute cerebral deficiency, investigations were performed in periods I (1–3 days) and II (5–7 days).

All the patients were given dynamical neurologic examination where, in order to determine the degree of the cerebral insufficiency severity, the Glasgow coma scale (GCS) score was used.

To determine the degree of the cerebral insufficiency severity and to prognosticate the outcomes, we used dynamical observation by the method of omegametry. To register omega-potential from the head surface, we used apparatus for evaluating the human functional condition “Omega-4”, by PA “Krasnodar ZIP” (Fig.1).

Omega-potential was registered in prone position, for functional load we used the windbag hyperventilation (10 aspirations). The device's technical characteristics: voltage range – from -50 to +100 mV, frequency bandwidth: from 0 to 0.5 Hz, with total and additional error in the interval from ± 4.1 to ± 10.0 mV – no more than 3%; in the interval from ± 10 to ± 100 mV – 2%. Omega-grams were recorded and analyzed on PC, working in WINDOWS – 95, with assistance of an additional program “OMEGA” monitor. As sensors, the fluid diffusion silver-chloride electrodes “Rhythm” were used. One of them was positioned in the middle of the forehead and another – on the wrist thenar. The procedure was as follows: omega-potential was registered discretely with an interval of 10 s before its value was stabilized or during 10 minutes. On the 10th minute the functional load was performed:

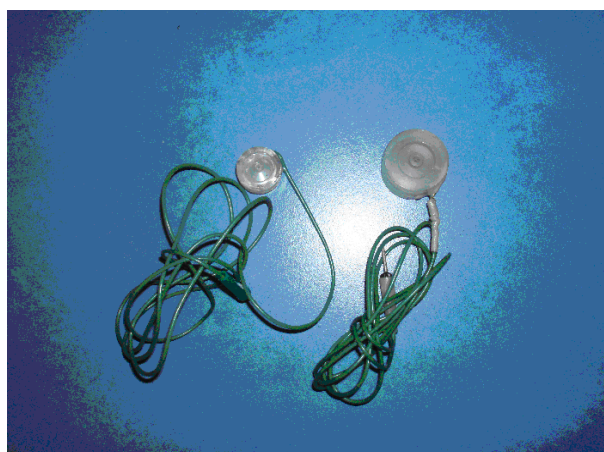


Fig. 1. Device “Omega-4” for registration of omega-potential and fluid diffusion silver chloride electrodes “Rhythm” for the said device

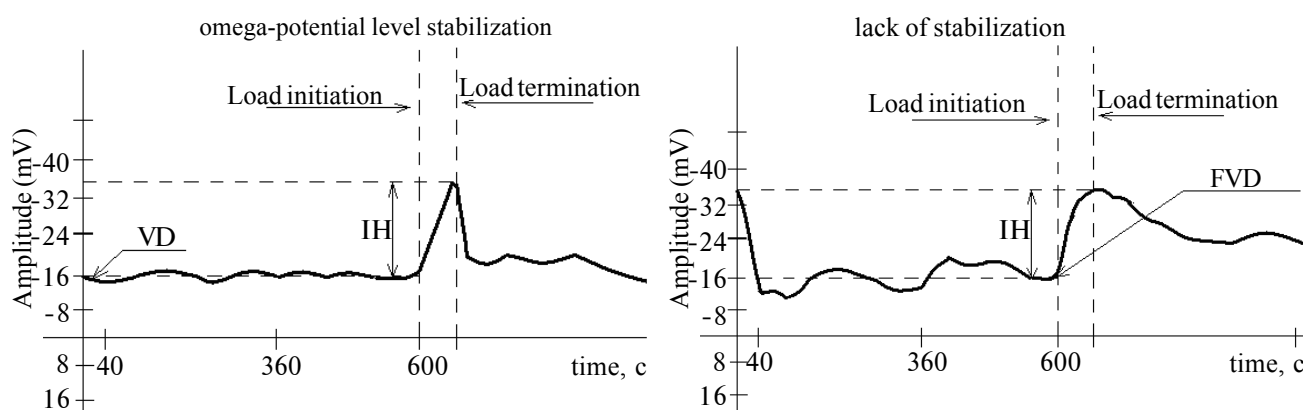


Fig. 2. Examples of omegagram estimation

hypoxic test, pain test or Ashner test, depending on patient condition. As per the abbreviation used in the program to analyze omegagrams, the following indices were quantitatively assayed and analyzed: VF (mV) – level of omega-potential after entering plateau (for omegagrams with stabilization); FVD (mV) – a point that divides initial omega-potential and omega-potential after functional load (for omegagrams without stabilization of omega-potential level); IN (mV) – change of omega-potential level after functional load.

When studying the control group the availability of the two types of omegagrams was identified (Fig.2): type 1-omegagram with omega-potential level stabilization (stabilization was the reduction of its fluctuations within the limits of 2 mV); type 2 – omegagram without stabilization (omega-potential does not stabilize and does not have a tendency to stabilization during 10 minutes).

Taking into account a slight level of difference in the results between indices VF (-14.7 ± 5.4 mV) and FVD (-13.4 ± 6.2 mV), which were obtained when studying the control group – we did not note them further on, when analyzing the types of omegagrams.

For early diagnostics of the cerebral edema and dynamic control over this process, the cerebral impedancemetry was used. The cerebral electrical conductivity was measured with the aid of a four-channel rheograph 4RG-1M with generator frequency – 10 kHz. Standard round electrodes for rheoencephalography with diameter of 2 cm were applied in fronto-mastoidal lead from both sides. The skin was treated with alcohol solution. On the electrode surface contacting the skin, the gauze wad moistened with 5% sodium chloride solution was applied. The electrodes were fixed with rubber belts. The rheograph cross-piece was balanced, and then the value of cerebral impedance was determined.

The study of hemostatic system included 15 hemostasiologic parameters, characterizing the state of: procoagulant chain: – activated recalcification time (ART), prothrombin index (PTI as per Quick, activated partial thromboplastin time (APTT, thrombin

time (TT), fibrinogen amount as per Rudman; vascular-thrombocytic link: – amount of platelets, degree of platelet aggregation, hemorrhage duration as per Duke; anticoagulant link: – activity of antithrombin III (AT III); fibrinolytic link: – amount of plasminogen, fibrinolysis XIIa – dependent and induced, antiplasmin activity, amount of soluble fibrin-monomeric complexes (SFMC). The data obtained were processed by the method of variation statistics, using Student's test. The control group was composed of 20 practically healthy people.

Results and discussion

The choice of the groups of patients groups for the research is explained by the fact that they were united by a common pathogenesis of an acute cerebral insufficiency, including the basic pathogenetic factors in the development of encephalopathy: anoxia, hypoxia, ischemia, hypoperfusion, endogenous and exogenous toxemia, metabolic disorders, etc.

Looking at the basic pathogenic factors in the occurrence of each of the critical states under study, one can isolate the principal pathogenic link in the development of this or that encephalopathy.

While analyzing the circumstances where the strangulated asphyxia happened it may be concluded that in the overwhelming majority of observations the tracheal compression took place with the development of hypoxia, and, at that, there was no complete circulatory arrest in the sufferers, but an ineffective circulation. Thus, in the preserved arterial blood flow (via the vertebral arteries and partially via carotids) the venous outflow was impaired abruptly. Due to the increased hydrostatic gradient, between the cerebral vessels and cerebral tissue an effective filtration pressure grew up, cerebral edema developed rapidly and the intracranial pressure elevated.

The major pathogenic factors, causing encephalopathy in the carbon oxide poisoning, are toxemia and hypoxemia, leading to the development of hematic and cytotoxic hypoxias. Dyscirculatory

disorders develop secondarily and lead to the circulatory hypoxia. An important factor is the secondary intoxication associated with the development of position syndrome.

The cerebral ischemia pathogenesis in craniocerebral injury (CCI) is complex and includes the links directly associated with impairment of the vital functions, cerebral circulation, liquor dynamics, neurohumoral shifts, changes in the nervous tissue metabolism against the background of the development of hypoxia, acidosis and cerebral edema. Pathogenesis of CCI sequels is based on the posttraumatic and posthypoxic states, leading to the development of violations in metabolic processes in the cerebral tissues, and before all, in the cerebral cortex, limbic-reticular complex, whose pathology, along with the focal disorders, determines the nucleus of the traumatic encephalopathy picture.

Our task was to isolate the main triggering pathogenic factors, causing the development of encephalopathy, conditioned by critical states and reanimation. From our viewpoint, there are three such factors: anoxia (hypoxia), dyscirculation (ischemia) and toxemia.

Prescription and timely performance of neuroprotection in the global post-hypoxic cerebral lesion is associated with a number of problems:

- there exists the proven similarity of pathologic cerebral damages in acute CCI and cerebral ischemia, but there also exist some objective distinctions that complicate arriving at a single tactics;

- there exists the notion of a therapeutic window, common to any critical state, but any action within its limits is fairly troublesome from the viewpoint of neuroprotection – in the developed countries the percentage of actions within the limits of therapeutic window accounts for 12–18%, whereas in Ukraine a real such action is practically impossible;

- there exist the notions of the primary and secondary neuroprotection [7, 15, 21], which are, in our opinion, fairly vague and make sense rather from the neurophysiologic and scientific side, than from the practical side.

To our opinion, an implicit moment to be reflected in neuroprotection is the strategy of extra – and intracerebral impact. With that, in terms of conducting the primary neuroprotection it is necessary, first of all, to use “Safar ABC”, to recover adequate oxygenation (ALV, AR), to support cardiac function, to perform adequate perfusion of both cerebral and bodily tissues (reperfusion), i.e. to do everything, whose lack makes cerebral functioning impossible at all. Yet, the prescription of medicinal products, possessing neuroprotective, metabolic, trophic, antihypoxant or antioxidant properties, must be based, in our opinion, not on the “per-minute or per-hour administration”, specified by the definition of primary

or secondary neuroprotection, but on the data of clinical, neurologic state of patient. More simply, it is necessary to divide drugs administration into the periods; when patient is in coma (estimation by Glasgow coma scale (GCS) score: 4–8 points), – primary neuroprotection or emergency therapy, and when he/she emerges from coma (GCS score – over 8 points), the so-called secondary neuroprotection or restorative therapy.

The choice of intensive therapy tactics depends largely on the pathologic process localization, the level and degree of the cerebral lesion.

Treatment must be comprehensive and must be conducted with regard for the specificities of various kind of encephalopathy.

All the remedial measures are rather conveniently divided into 2 groups [11, 13]:

- first group – extracerebral measures, i.e. those exerting effect on the CNS indirectly;

- second group – measures exerting direct effect on the CNS (intracerebral).

The conventionality of such a division is because a number of pharmaceutical effects are not strictly specific to the brain, but exerts effect on the whole body.

Our research [10-14] showed that the intracerebral measures should be taken with a permanent control of the CNS functional state and the body humoral status, using a stage-by-stage approach as follows: to create the brain protective inhibition and reduce its energy demands; to recover functions of the cellular and vascular membranes; to recover circulation in the brain vessels and the brain tissue perfusion; to prevent and treat the brain edema-swelling; to recover the brain aerobic energy exchange; to oxygenate the nervous tissue, to drain decay products from the brain, to provide active methods of detoxication; to recover the brain circulation and metabolism.

However, all drugs and therapeutic measures must be taken selectively, proceeding from the kind of encephalopathy, state of the brain structures, neuroreflectory and vegetative mechanisms of its regulation, and crucially – from the period of disease.

In our research, we developed and used an integrative complex to estimate the state of patients with variously originated acute cerebral insufficiency. The above complex included analysis of DIC-syndrome parameters, changes of omega-potential, general condition of patients by GCS score and severity of the brain edema-swelling by the data of impedancemetry.

While estimating the data obtained in the dynamics of the postreanimation period in patients with strangulated asphyxia, one may isolate the following diagnostic and prognostic moments: all patients examined at DOKTMO and CTH, were admitted in the state of coma I-II, whose depth by GCS score was 5.0 ± 0.97 and 7.1 ± 0.91 , respectively.

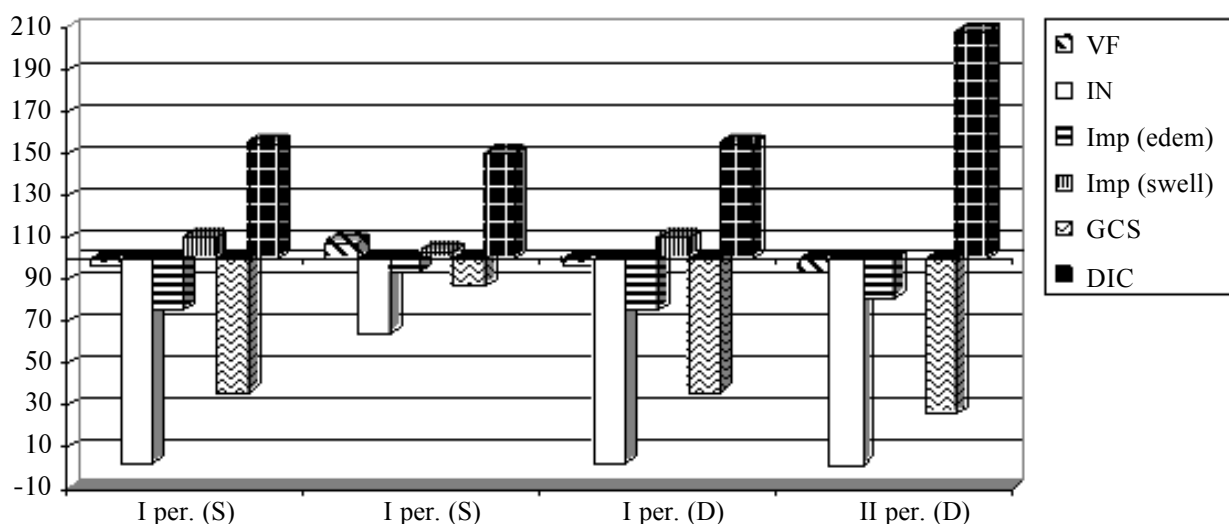


Fig. 3. Integrative estimative complex in patients with strangulated asphyxia

The functional studies showed that omega-potential level (UF) after entering the plateau either decreased or had the tendency to decrease. With that, an essential change (over 80%) of omega-potential in response to the functional load (IN) was noted. These changes are inextricably connected with impedance changes. The level of omega-potential after entering the plateau (UF) in period I is in strong inverse correlation dependence ($r = -0.74$) on the growing impedance indices. Correlative analysis also gives evidence of the availability of a weak negative correlative connection between GCS indices and increased impedance in period 1 of the study. Similar correlation dependencies remained in period 2 of the study as well.

In period 1 of the study (Fig. 3) patients with strangulated asphyxia demonstrated: decreased baseline potential on omegagram (VF), which characterized an insufficient condition of neuro-reflectory and vegetative mechanisms to regulate the respiratory cardiovascular systems, supplying oxygen to the tissues. After the functional load, an abrupt disorganization of the vegetative mechanisms was noted, being evident as a fast decrease of the tension index (IN) in response to the functional load. During impedancemetry, we diagnosed the brain-swelling with edema prevalence. At that, the brain rheology abnormality correlated with DIC-syndrome degree.

With regard for the data obtained, this contingent of patients, along with the methods of intra- and extracerebral impact, routinely used by us, needed, before all, intensive therapy directed to the improvement of oxygen supply to the tissues and organs. This principle was met via taking 3 measures:

- ALV with PEEP (before levelling VF and IN indices);
 - improvement of rheology and perfusion (Reosorbilact 5–7 ml/kg, HES drugs – 2–2.5 ml/kg, pentoxifylline);
 - brain edema-swelling therapy: mannitol, furosemide.
- Also important is:

- improvement of the venous outflow from the cranial cavity and endotheliotropic therapy (L-lysine escinat – 10.0 ml per 100.0 ml of normal saline, 2 times a day, sodium etamsylate 4.0 ml, 3 times a day);

- therapy/prophylaxis of DIC-syndrome – freshly frozen plasma (FFP), 1–2 doses, pentoxifylline, 5.0–10.0 ml;

- decrease in PL intensity and kallikrein-kinin system: Tiatrizolin 2.5% solution, 4.0 ml, i/v, Contrykal 30000-100000 IU per day, i/v;

- reduction of the brain energy requirements (antihypoxic drugs), especially in patients with GCS score less than 4 points and seizures (diazepam 0.1–0.2 mg/kg, propofol 1–2 mg/kg/h, sodium oxybate 70–100 mg/kg, stadol 0.01 mg/kg);

- primary neuroprotection: Nimodipine was administered via a probe, 30–60 mg 3–4 times a day.

In period 2 of the study (Fig. 3) the survived patients with strangulated asphyxia had the following integrative estimate, considered by us to be prognostically favourable: the level of the baseline omegagram-potential (VF) grew to the norm (or had a tendency to grow), the values of the tension index in response to the functional load (IN) improved significantly, impedancemetry indices improved, characterizing residual effects of the brain edema, this being clinically manifested by the increased GCS score.

Patients examined in the second period were, as a rule, conscious (GCS score: over 8 points), on unassisted breathing, and needed the following therapeutic complex: continuation of anti-edematous and endothelio-tropic therapy (Reosorbilact 3–5 ml/kg; L-lysine escinat 5.0–10.0 ml per 100.0 ml of normal saline, 2 times a day, sodium etamsylate 4.0 ml, 3 times a day); secondary neuroprotection: Thiocetam was administered intravenously, by drop infusion, in an average dose of 0.2–0.3 ml/kg per 150 ml of normal saline, during an hour, for 7 days. The baseline thiocetam dose accounted for 25–30 ml/day.

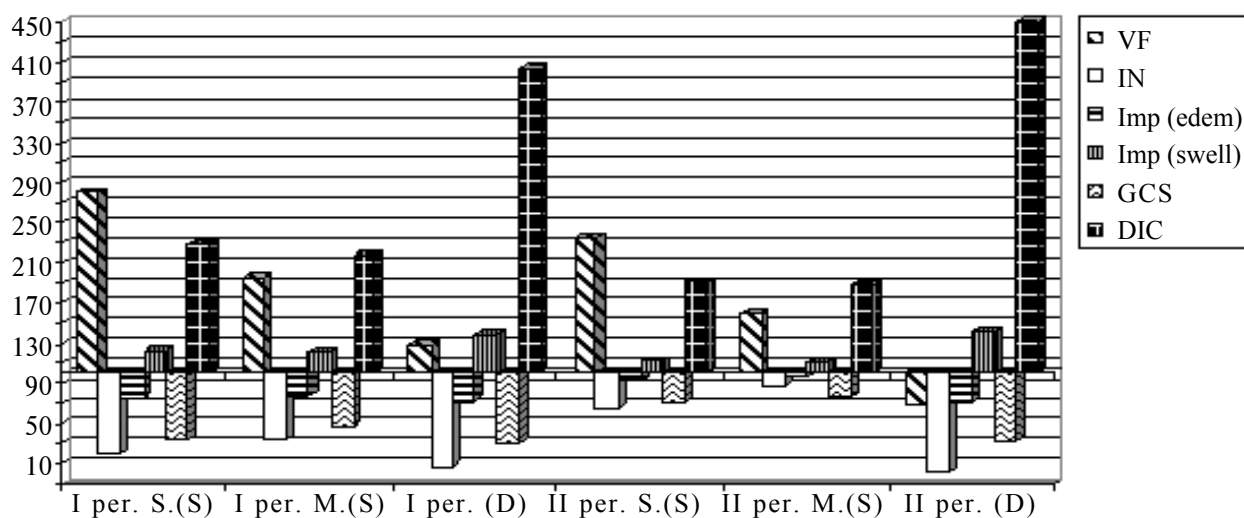


Fig. 4. Integrative estimative complex in patients with carbon oxide poisoning

Neurotrophic therapy: recovery of an adequate cerebral perfusion – Nimodipine (30 mg 3–4 times a day, orally) in combination with actovegin (16–30 mg/kg, i/v, by drop infusion). Simultaneous use of nimodipine and actovegin leads to more effective recovery of anoxically depolarized bone hemostasis via activating the processes as follows: recovery of the nervous tissue energy failure by means of increasing metabolism of high-energy phosphate compounds (ATF), activation of oxidative phosphorylation enzymes (pyruvate – and succinate dehydrogenase, cytochrom-C-oxidase), improvement of acid phosphatase activity and cellular lysosomal activity, increase of potassium (K^+) ions inflow into the cell, activation of potassium-dependent enzymes (catalases, saccharases, glycosidases), acceleration of the decay of anaerobic glycolysis products (lactate and beta-hydroxybutyrate); ceraxon (citicoline) intravenously, by drop infusion, in a dose of 4–20 mg/kg/day; cerebrolysin, intravenously in a dose of 10–60 ml/day.

In the deceased patients, both in the first and second period of the study an unfavourable integrative symptom complex was revealed in the form of dramatic drop in the level of IN omega-potential, increased brain edema-swelling according to the data of impedancemetry, with prevailing swelling that was clinically manifested in a deep coma and low GCS score, with the signs of pronounced DIC-syndrome.

When estimating the data obtained in dynamics in the course of postreanimation period in patients with carbon oxide poisoning one may single out the following diagnostic and prognostic moments. Negative moderate correlative relationship ($r = -0.61$) is seen between the indices of omega-potential level (VF) and the change of omega-potential level after the functional load (IN). An analogous dependence is established between GCS score change and omega-potential (VF) ($r = -0.51$). Resolution of the brain edema, accompanied by the increase of impedance to the control figures, is in a strong correlative relationship

with the change in omega-potential level after the functional load.

When analyzing the data of omegametry it is necessary to state that omega-potential mirrors the cerebral dysfunction and the degree of its severity. So, the higher is VF, the severer is the degree of ACI: in coma 2 it is higher than in coma 1. But when coma 2 transforms into coma 3, the neurohumoral mechanisms of the CNS function regulation are disordered, and a failure of compensation occurs. The level of omega-potential (VF) decreases by 20% to that below the control level. The brain swelling processes lead to the cerebral blood flow reduction and formation of irreversible changes in the brain. In this period (VF) drops dramatically, impedance grows up to 150 ohm and IN does not absolutely respond to the functional load.

A strong reverse correlative relationship ($r = -0.88$) was revealed between omega-potential (VF) in period 1 and the change of omega-potential level after the functional load IN. It was found that the severer is the carbon oxide poisoning, the lesser is the change of omega-potential level after the functional load and the higher is VF index. Analogously looking is the interrelationship between omega-potential and the change of impedance. Noted is a strong correlative relationship when impedance grows up ($r = 0.74$) and moderate reverse correlative relationship when it drops ($r = -0.63$). This goes to prove that both the increase of fluid in the brain, i.e. the increased brain blood content and its edema, and the brain blood flow reduction and swelling development brings VF index to a higher level in coma 2–3. And the deeper is the level of conscious impairment by GCS score, the higher is VF ($r = -0.92$).

Analogous correlative relationships remain in period 2 of study.

In period 1 of the study, the survived patients (Fig.4) of both DOKTMO and CTH groups demonstrated the following integrative symptom complex: a drastic elevation of the baseline level of

omega-potential (VF), statistically significant difference in the dependency on the degree of CO poisoning severity (direct correlative dependence).

These changes may be associated with the vasodilatory shifts, caused by a toxic action of CO on the cerebral vessels, as well as with a dramatic stress-induced impact on the neurohumoral complex, this being characteristic only of the given type of acute cerebral insufficiency. In response to the functional load a statistically significant decrease of the tension index (IN) is noted, having no statistically significant difference, depending on the degree of the poisoning severity. Clinical characteristics of these omegagram changes is estimation of the degree of consciousness impairment by GCS score, the degree of the brain edema-swelling – by the data of impedancemetry. With that, for a given type of ACI indicative is the tendency to the brain swelling prevalence, this being significantly proved by a direct correlative dependence on the degree of the poisoning severity.

When estimating changes in the group of the deceased patients in period 1 (Fig.4) attention is drawn, before all, by the evidence of DIC-syndrome as a possible predictor of irreversible changes in the brain tissues. The bodily response to the functional load is inadequate, this being manifested by the decrease of the tension (IN) index, which points to a complete incoordinateness of response to the stress-induced situation. Clinically unfavourable integrative symptom complex manifested itself by the low GCS score and pronounced cerebral edema-swelling.

The major alternative approaches to the treatment of patients from this group were:

- Recovery of normal oxygen level in tissues: if possible, HBO session or normobaric oxygenation in the form of oxygen insufflation via the nasal catheters or ALV (with regard for the recent publications [4, 24] regarding the lack of HBO direct therapeutic effect in treating acute poisonings, including those in CO poisonings – we did not emphasized this method of intensive therapy);

- among the first choice drugs – recovery of the aerobic energy exchange: cytochrom-C is administered i/m in a dose of 0.5–0.8 mg/kg/day, Cyto-Mack is administered intravenously in a dose of 0.25–0.5 mg/kg/day;

- direct antihypoxants: Actovegin: up to 30 mg/g/day;

- recovery of the cerebral metabolism and microcirculation: Thiocetam: 5.0 ml/kg, by drop infusion
- therapy of the brain edema-swelling: L-lysine escinat: 0.25–0.3 mg/kg, Reosorbilact: 5–6 ml/kg, mannitol: 1 g/kg;

- for patients with convulsive activity – antihypoxants, reducing the brain energy needs (benzodiazepines – seduxen, midazolam: 10 mg 3–4 times a day);

- therapy and prophylaxis of DIC-syndrome: FFP, contrykal, pentoxifylline;

- avoided was the use of cerebral vasodilators in view of the present dilation of the brain blood vessels.

In the second period of the study, in the group of survived patients there was revealed a favourable integrative symptom complex in the form of decreasing the baseline level of omega-potential (VF) as an index of adequate antihypoxant and vasotropic therapy with significant improvement of the norm-seeking functional load (IN) index. These indices were in a direct correlative dependence on the degree of CO poisoning severity and characterized the recovery of concomitant adequate reaction of the vegetative nervous system to the stress-induced impact. Clinical data of a change were confirmed by a significant improvement of GCS score (8–9 points), however, as a consequence of the suffered vasodilation, there remained to exist the signs of the brain edema-swelling, with swelling in predominance, and DIC-syndrome events.

By reference to the data obtained in the integrative estimative complex, the patents in the second period needed the following:

- recovery of microcirculation in the brain blood vessels, the blood tissue perfusion, correction of impairments in the system for regulating the blood aggregation state: trental (pentoxifylline, pentilline, agaperine) in a dose of 2–3 mg/kg/day;

- recovery of the brain aerobic energy exchange – drugs of neuromediatory, neuroreceptory and neurotrophic action: actovegin – 30 mg/day, ceraxon – 4 mg/kg (citicoline), cerebrolysine – 10 ml/day, cytochrome-C – 0.5 mg/kg or Cyto-Mack – 0.25 mg/kg;

- nootropics and GABA-ergic substances (thiocetam, 5-10 ml/day);

- antiedematous and endotheliotropic therapy (L-lysine escinat – 5.0 ml per 100.0 ml of normal saline, 3 times a day, sodium etamsylate – 4.0 ml 3 times a day).

In the group of the deceased patients in the second period (Fig. 4) of the study an unfavourable symptom complex was revealed, which was characterized, first of all, by the growing degree of PIC-syndrome distinct manifestation as a precursor of unfavourable outcome against the background of a drastic drop in the omegagram indices both in the baseline (VF) and after the load (IN), this being characteristic of a sheer exhaustion and disintegration of the vegetative nervous system. Clinically, this symptom complex was characterized by deterioration of GCS score indices in the form of coma deepening against the background of significant increase of the brain edema-swelling (according to the data of impedancemetry).

While estimating the regularities, revealed in patients with severe craniocerebral injuries, it may be said that in this group of patients a baseline response of omega-potential before entering the plateau (VF) strongly correlated with inadequate bodily response to physical load (IN) ($r = -0.88$) and significantly characterized low GCS score ($r = -0.92$). Also revealed

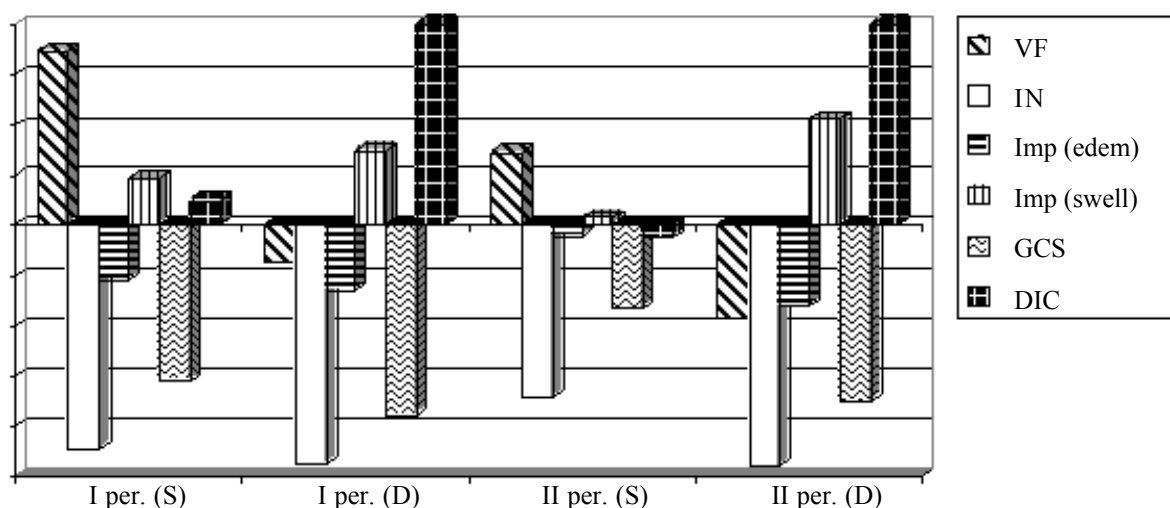


Fig. 5. Integrative estimative complex in patients with severe craniocerebral injury

was a moderate correlative dependence of these indices on the degree of the brain edema-swelling, according to the data of impedancemetry ($r = -0.63$; $r = 0.73$). The changes revealed in period 1, correlated with a high and medium degree of validity, with disorganized omegagram response to the functional load (IN) in period 2 ($r = -0.73$).

In period 1 of the study, the survived patients with severe craniocerebral injuries (SCCI) (Fig. 5) revealed the following integrative symptom complex, where the polymorphy of the brain tissue lesion in an injury was reflected on the peculiarities of omegagram reaction: first of all, a high baseline response (VF) was noted with reliably minuscule baseline bodily response (IN) to physical load, this being characteristic of a complete disorganization of the body neurohumoral regulation, despite the increased readiness to stress. This disorganization was clinically characterized by a “mosaic” vessel dilation-spasm syndrome (according to the data from morphologic research), this being manifested by a pronounced brain edema-swelling, according to the data of impedancemetry. Also, this category of patients was clinically characterized by a low GCS score, as compared to other categories of sufferers.

Principal distinction of a favourable symptom complex for patients having SCCI were unpronounced DIC-syndrome events.

In period 1 of studying the deceased (Fig.5) patients with SCCI, the following unfavorable integrative symptom complex was noted: as compared to those survived they revealed a negative, decreased baseline omegagram response (VF), characterized by the lack of adequate bodily response to the stress situation. The indices of functional load (IN) were also dramatically decreased, this being evidence of the lack of compensatory and neurohumoral bodily capacities. According to the data of impedancemetry, the processes of the brain edema-swelling were pronounced, with predominant swelling, this being

unfavourable sign in terms of prognostication. Clinically, these patients were in a deep coma (2–3) with exceptionally low GCS score values. With that, the indices of DIC-syndrome manifestation statistically differed and exceeded both the control data and the data from the group of the survived patients. In view of this, a conclusion was made about the prevailing impairments in hemostatic system in SCCI as a predictor of patient death, and as a factor responsible for the lack of stabilizing bodily resources in the sufferers.

Considering the data of an integrative symptom complex, we have developed for patients with SCCI the priorities and algorithms of intensive therapy, as follows:

- keeping in mind the severity of patient state in period 1 of the study (acute hypoxia associated with disordered central breathing regulation, comatose state) ALV was indicated as a moderate hyperventilation, cervical spine stabilization, elevated by 15–30 degrees upper body position (to improve the venous drainage);
- since most patients of this category had the tendency to convulsions and uneconomical metabolism (the brain hypermetabolism), confirmed by the results of omegagram in the form of a high baseline functional readiness of neuroregulatory systems (VF) with simultaneous impossibility to ensure this by an adequate response (low IN), and it was this state that, in our opinion, was the cause of convulsions, then, in view of this, they were given analgosedation (creation of the brain protective inhibition, decrease of the brain energy needs and protection against the secondary hypoxia), neurovegetative stabilization, arrest of psychomotor agitation: midazolam, i/v, by drop infusion, in a dose of 0.03–0.2 mg/kg/h, seduxen, i/v, by drop infusion, in a dose of 0.8–1.2 mg/kg/day, sodium oxybutyrate, i/v, by drop infusion, in a dose of 40–120 mg/day, sodium thiopental, i/v, by drop infusion, in a dose of 4–12 mg/kg/day (thiopental daily dose must not exceed 1g), morphine, i/v, by drop infusion, around-the-clock, in a dose of 0.01–0.016 mg/kg/day during 2–5 days;

- inhibition of glutamate cascade: intravenous administration of 2% magnesium sulfate, 3–6 ml/kg/day;

- recovery of the concentration gradient of the brain potassium ions and recovery of hemostasis of agitating amine acids, elimination of cerebral vasospasm: in the beginning of therapy course, during 2 hours, 1 g of nimotop (5 ml of nifedipine infusion solution) was administered per hour (approximately 15 µg/kg); with good tolerance of the drug (lack of pressure drop) the dose was increased in 2 hours to 2 mg of nimotop (10ml of nifedipine infusion solution) per hour (approximately 30 µg/kg/h); for patients weighing largely less than 70 kg or those with labile blood pressure, an initial dose must amount to 0.5 mg of nimotop (2.5 ml of nifedipine infusion solution) per hour;

- according to the data of impedancemetry, patients of this group had pronounced brain edema-swelling events, wherefore the measures of preventing and treating the brain edema and swelling may be designated as those of the first priority: reosorbilact 5 ml/kg, L-lysine escinat 10.0 ml twice a day; lasix is to be administered intravenously in a dose of 0.3–1.4 mg/kg/day, (the use of saluretics may be combined with sorbit injection into the gastric probe in a dose of 1 g/kg/day); 10% albumin solution is to be administered intravenously, by drop infusion, in a dose of 3–6 ml/kg/day;

- functional recovery of the cellular and vascular membranes: L-lysine escinat was used within the first period, 10ml/twice a day, intravenously, via the venous catheter;

- decrease in the activity of kallikrein-kinin system: aprotinin (trasyolol) was administered intravenously, by drop infusion, in a dose of 500,000 IU/day;

- decrease in the intensity of lipid peroxidation: tiotriazoloni, up to 300 mg/day, i/v, by drop infusion; alpha-lipoic acid (berlitioni) was administered i/v, by drop infusion, in a dose of 300–600mg/day;

- cerebral blood flow recovery: trental or pentoxifylline was administered intravenously, by drop infusion, in a dose of 2–3 mg/kg/day (upon availability of the intracranial hematomas the drugs administration started from the 2nd day); infusion therapy to support moderate cerebral hyperperfusion: Reosorbilact 5–7 ml/kg, Sorbilact 2–3 ml/kg, HES 1.5–3.0 ml/kg, Gelofusine;

- recovery of the brain aerobic energy exchange, elimination of the nervous tissue energy deficit: actovegin was administered by drop infusion, in a dose of 8–16 mg/kg/day, if necessary, the dose was increased to 40–80 mg/kg/day;

- recovery of the neurotransmitter exchange, neurophic and neurotransmitter therapy: ceraxon (citicoline), i/v or i/m, 500-1000 mg twice a day, depending on the state severity, maximal daily dose in the parenteral prescription amounted to 2000 mg, orally – 600 mg; intravenous cerebrolysin in a dose of 50 ml/day;

- recovery of the nervous cells metabolism: thiocetam in a moderate and deep stupefaction was used in a baseline dose of 25–30 ml/day, in sopor – 15–20 ml/day, in coma – 5–10 ml/day.

In the second period of the study the group of the survived patients with SCCI (Fig.5) revealed a favourable integrative symptom complex in the form of moderately decreased as compared to the baseline value, but increased as compared to the norm, omegagram potential (VF) before entering the plateau (as an effect of the correct analgo-sedation with preservation of the regulatory systems activity to response to stress, but with the hyperactivity correction). In keeping with the baseline severity of patients' condition, there remained to exist an insufficient, weak response of the bodily integrative systems to the functional load (IN), exceeding, however, the values obtained in period I of the study. Principally favourable prognostic sign of this integrative complex was the decrease in the brain edema-swelling events, according to the data of impedancemetry (significant tending to norm). Clinically, these changes were proved by GSC score improvement and emergence of patients from coma into the level of stupefaction or sopor. The decreased intensity of DIC-syndrome gave evidence of the therapy efficacy and was a favourable diagnostic moment.

Fig.6 presents the dynamics of changes in the integrative symptom complex indices in the survived patient, by the days of intensive therapy. The most indicative were days 2-3 of the disease, when a dramatic shift in the indices being studied happened in the form of VF rise in omegagram, this, in our opinion, showing the integrity of the fast-response structures. From the clinical viewpoint, within this time there happen no abrupt shifts in GCS score, that is why particularly, the omegagram indices may become a prognostic sign in determining the tendency of the disease outcome and a change in the scope of the therapy being given, towards better stimulation in positive data or reduction –

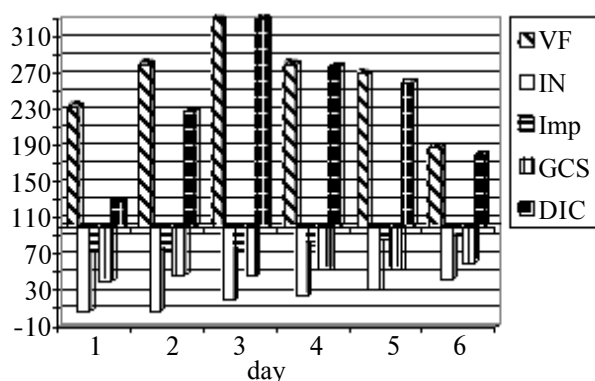


Fig. 6. Change of integrative symptom complex parameters in survived patient (K., 41 years) with diagnosis: CCCI, severe brain contusion, subdural hematoma

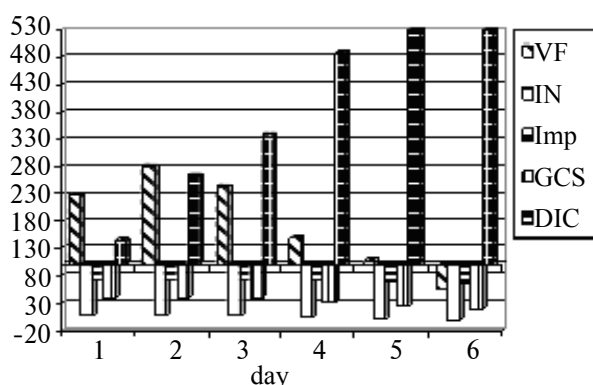


Fig. 7. Change of integrative symptom complex parameters in deceased patient (N., 40 years) with diagnosis: CCCI, severe brain contusion, subdural hematoma

in case of unfavorable symptom complex. At that, up to the 5th day a significant improvement was noted in the indices of the bodily response to load (IN), which fact may serve as a trigger for prescribing an active stimulating and neotrophic therapy, with discontinuation of analgo-sedation, while cutting the anti-edematous therapy (according to the data of impedancemetry).

Proceeding from the data obtained by us, indicated to patients with favorable SCCI integrative symptom complex is the following intensive therapy:

- reduction of analgo-sedation;
- reduction of anti-edematous therapy;
- syndromic therapy (antibacterial and fluid therapy, continuation or reduction of the planned therapy);
- continuation of neurotrophic therapy: nimodipine (30 mg, 3–4 times a day, orally) in combination with actovegin, 16–30 mg/kg, i/v, by drop infusion, ceraxon (citicoline) is administered intravenously, by drop infusion, in a dose of 4–20 mg/kg/day, cerebrolisin is administered intravenously in a dose of 10–60 ml/day;

– recovery of function of the cellular and vascular membranes: L-lysine escinat (5th – 7th day since injury) was administered intravenously, 5ml, twice a day;

– recovery of metabolism of the nervous cells and stimulating therapy: neuromidin – cholinomimetic, being by its a reversible cholinesterase inhibitor and direct stimulator of excitement conduction in the nervous fibres and synaptic transfer to the neuromuscular endings, this being determined by the blockade of potassium channels in the excited membranes; neuromidine possesses nootropic, mnemotropic, psycho-stimulating, anti-asthenic and anti-depressive action, its initial dose amounts to 5–20 mg/day, then it grows with account of the rug tolerance until the state improvement signs appear (more frequently – up to 20–100 mg); samax was administered in dose of 0.05 mg/kg, 3 times a day intranasally (2–3 drops of 0.1% solution into each nasal passage), treatment course – 2–3 weeks; thiocetam (tiotriazoloni, included in thiocetam composition, eliminates the side effect of pyracetam in the form of lactic acid acidosis, therefore it may be prescribed in the acutest and acute

period, unlike pure pyracetam) in a baseline dose of 25–30 ml/day.

In the second period of the study, in the group of the deceased patients with SCCI (Fig.5) there was revealed an unfavourable symptom complex in the form of an abrupt decrease of a baseline response (VF), both as compared to the baseline data and comparing to the control omegagram index before entering the plateau, which, in our opinion, said that the body lacked the possibility to counteract the stress factor and suffered the entire exhaustion of its anti-stress reserve. This thesis was confirmed by deterioration of omegagram index of response to physical load (IN), which characterized a complete disintegration of the brain vegetative coordinating structures. Characteristic unfavourable sign (as in the previous groups) was an abrupt increase of the brain edema-swelling events, with prevalent swelling (according to the data of impedancemetry). Clinically, these changes were characterized by coma deepening and GCS score drop. Classically unfavourable prognostic moment (as in the first period of the study) in the deceased patients was DIC-syndrome pronouncement.

Fig.7 presents the dynamics of changes in the integrative complex indices in the deceased patient, by the days of intensive therapy. With that, as in the survived patient (Fig.6), critical was the 3rd day of the disease, but in the deceased patient, on the 3rd day, a regression of omegagram baseline response was noted (instead of a complete coming to norm, seen in the survived patient on the 5th day of the disease), which, together with deteriorating indices of response to the functional load (IN), appeared to be an unfavourable prognostic sign. Also, an unfavourable sign was the enhancement of the brain edema-swelling events, with prevalent swelling, instead of regression, seen in the survived patient. In keeping with the existed impairments, the deepening of coma in this patient was revealed clinically.

In such a way, a preliminary conclusion may be made that, despite various pathophysiological moments and the development of acute cerebral insufficiency, the mechanisms of forming irreversible changes in the brain tissue will be manifested by a universal integrative symptom complex (this being confirmed by the data of morphologic research [17] carried out by us earlier). Therefore the scales of integrative estimation, developed by us, differ in the universality of estimating an unfavourable outcome of a disease/therapy.

Thus, in a comparative study of the data from our integrative estimating complex in the deceased patients with acute cerebral insufficiency in the first group, the following peculiarities were revealed: in patients with strangulated asphyxia a tendency was observed towards the decrease of omegagram baseline potential (VF), an abrupt significant drop of the tension index in response to functional load (IN), the brain edema-swelling with prevalent swelling. With that, an impairment of the brain

rheology correlated with DIC-syndrome degree.

Patients with severe and moderate carbon oxide poisoning revealed dramatic elevation of baseline omega-potential (VF), statistically significantly correlated with CO-poisoning severity, significant drop of tension index without statistical distinctions, depending on the poisoning severity degree, clinics of the brain edema-swelling with prevalent swelling (direct correlative dependence on the poisoning severity degree).

Patients with severe craniocerebral injury (SCCI) showed a high baseline response (VF) with significantly low bodily response to physical load. This disorganization was clinically manifested in the "mosaic" vessel dilation-spasm syndrome (according to morphology data), this being manifested in the pronounced brain edema-swelling, according to the data of impedancemetry, low GCS score.

In the second period of the study, in the survived patients with strangulated asphyxia the level of baseline omegagram-potential (VF) grew up to normal value (or even exceeded this value), the tension index values significantly improved in response to the functional load (IN), impedancemetry indices improved, characterizing the brain edema-swelling residual events, this being clinically manifested in GCS score increase.

In the survived patients with severe and moderate carbon oxide poisoning there were seen the decreased baseline omega-potential (VF) with improved index of functional load (IN). Clinical data of the change were confirmed by significant GCS score improvement, however, the signs brain edema-swelling with prevalent swelling remained to exist together with residual DIC-syndrome events.

The survived patients with severe craniocerebral injury revealed a moderate, as compared to baseline, but still a growth, as compared to norm, of omegagram-potential before entering the plateau (VF), retained insufficient (weak) response of the bodily integrative systems to the functional load (IN), which, however, was significantly more pronounced as compared to period 1 of the study. Principally favourable prognostic index of this symptom complex was the reduction of the brain edema-swelling events, according to the data of impedancemetry (significant drive of indices for norm). Clinically, these changes were confirmed by the increase of GCS score and emergence of patients from coma to the level of stupefaction or sopor.

The deceased patients with acute cerebral insufficiency (ACI) of different etiology revealed a universal unfavourable integrative symptom complex: decreased baseline omegagram response (VF), characterizing the baseline extreme severity of patients, with the lack of reserve bodily capabilities to respond to the stress reaction, with an abrupt decrease at

the study steps, both as compared to the baseline data and to control, of omegagram indices of reacting to physical load (IN), this being evidence of the lack of compensatory and neuroregulatory bodily capabilities, according to the data of impedancemetry – pronounced processes of the brain edema-swelling, with prevalent swelling. Clinically, these patients were in the state of the deepest coma with extremely low GCS score. A predictor of patients' death in all groups was the growth of DIC-syndrome degree.

For patients with acute cerebral insufficiency of different etiology, some different variants of intensive therapy have been developed, depending on the indices of integrative estimative complex and kind of ACI.

V.I. Cherniy, R.I. Cheniavskiy, A.N. Kolesnikov,
G.I. Yermilov, G.A. Gorodnik

Prognostication of Outcome and Peculiarities of Neuroprotection Therapy at the Patients Suffered the Critical State and Reanimation

Topicality of the problem of integral approach to intensive therapy of the patients suffered the critical states during the post-reanimational period is caused by socioeconomic importance and related to high lethality and mass character of such a pathology. The questions of outcome prognostication, search of the process irreversibility criteria, brain death diagnostics are of special significance. The choice of the intensive therapy tactics to a great extent depends on localization of pathological process, on the level and degree of brain injury. Moreover the intensive therapy must be complex and the character of pathogenesis of different types of encephalopathy is to be taken into account. The research was conducted on the base of a regional reanimation center DOKTMO in Donetsk city and the department of intensive therapy of CTH in the town of Anthracite in the patients with the acute cerebral insufficiency conditioned by the critical states of a different etiology. The acute cerebral insufficiency was the result of asphyxia strangulatia (suicide), carbon monoxide poisoning of a different degrees of severity (domestic and industrial), heavy cranial-cerebral trauma. Among the patients there were 48 women and 140 men at the age from 16 to 74. In the research we have developed and applied an integrative estimation complex of the state of the patients with acute cerebral insufficiency of different genesis. This complex included the estimation of parameters of DIC-syndrome and change of omega-potential, the estimation of the common state of patients on GCS and the estimation of edema-swelling explicitness of cerebrum according to the data of impedansometri. Favourable and unfavourable integrative symptomocomplex was obtained for every type of acute cerebral insufficiency. A conclusion has been drawn that inspite of different pathophysiologic points in the development of acute cerebral insufficiency, the mechanisms of brain death will be shown in universal integrative symptomocomplex. The variants of intensive

therapy with their correction according to the indexes of integrative symptomocomplex and the ACI kind have been developed for patients with acute cerebral insufficiency of a different etiology. (Neuroscience: Theor. Clin. Asp. – 2007. – Vol.3, № 1–2. – P.47–58.)

Keywords: acute cerebral insufficiency, diagnostics, prognostication, intensive therapy

В.І. Черній, Р.І. Чернявський, А.М. Колесніков,
Г.І. Ермілов, Г.А. Городнік

Прогнозування результатів і особливості нейропротекторної терапії у пацієнтів, що перенесли критичний стан та реанімацію

Актуальність проблеми інтегрального підходу до проведення інтенсивної терапії у пацієнтів, які перенесли критичні стани в постреанімаційному періоді, обумовлена соціально-економічною значущістю і пов'язана з високою летальністю, інвалідизацією і масовістю подібної патології. Особливого значення набувають питання прогнозування результатів лікування, пошук критеріїв безповоротності процесу, діагностика смерті мозку. Вибір тактики інтенсивної терапії багато в чому залежить від локалізації патологічного процесу, від рівня і ступеня ураження мозку. При цьому інтенсивна терапія повинна бути комплексною і проводитися з урахуванням особливостей патогенезу різних видів енцефалопатій. Дослідження проводилося на базі обласного реанімаційного центру, відділення нейрореанімації ДОКТМО (м. Донецьк) і відділення інтенсивної терапії ЦМЛ м. Антрацит, де знаходилися на лікуванні пацієнти з гострою церебральною недостатністю, обумовленою критичними станами різної етіології. Гостра церебральна недостатність була слідством странгуляційної асфіксії (суїцид), отруєння чадним газом різного ступеня тяжкості (побутового і виробничого), тяжкої черепно-мозкової травми. Серед пацієнтів було 48 жінок і 140 чоловіків у віці від 16 до 74 років. У проведеному нами дослідженні був розроблений і застосований інтеграційний оцінювальний комплекс стану пацієнтів з гострою церебральною недостатністю різного генеза. Даний комплекс включав оцінку загального стану пацієнтів за шкалою ком Глазго, параметрів ДВЗ-синдрому, зміни омега-потенціалу, оцінку вираженості набряку-набухання головного мозку за даними імпедансометрії. Для кожного виду гострої церебральної недостатності був одержаний сприятливий і несприятливий інтегративний оцінний симптомокомплекс. Був зроблений висновок про те, що незважаючи на різні патофізіологічні моменти в розвитку гострої церебральної недостатності, механізми смерті мозку виявлятимуться у вигляді універсальних інтеграційних симптомокомплексів. Для пацієнтів з гострою церебральною недостатністю різної етіології розроблені варіанти інтенсивної терапії, та її корекції залежно від показників інтеграційного оцінного комплексу і виду ГЦН. (Нейронауки: теор. клін. асп. – 2007. – Т. 3, № 1–2. – С.47–58.).

Ключові слова: гостра церебральна недостатність, діагностика, прогнозування, інтенсивна терапія

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