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THE MAIN DIRECTIONS FOR PHARMACOLOGICAL CORRECTION (COMBINATIONS OF DRUGS FOR GENERAL ANESTHESIA) OF NEUROLOGICAL AND COGNITIVE DISORDERS IN PATIENTS WITH NEOPLASMS OF THE CENTRAL NERVOUS SYSTEM

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Abstract

Introduction: the problem of neuroprotective or neurodegenerative effects of drugs for general anesthesia is relevant in connection with a large number of cases of postoperative cognitive dysfunction (POCD).

Objectives: the aim of the study was to develop a goal-oriented combination of drugs for general anesthesia, based on a retrospective assessment of the baseline level of neurological and cognitive disorders in adults and children at the stage of preparation for surgery for neoplasms of the central nervous system (sub- and supratentorial neoplasms – SubTNN and SupraTNN), and a prospective evaluation of complications in the postoperative period.

Methods: an experimental prospective multicenter open-label study. Criteria for including patients in the study. Patients over 5 years divided into subgroups of children (5-17 years) and adults (over 18 years), with neoplasms of the CNS, with indications for surgical treatment (operation: total or subtotal neoplasm removal). We examined 303 adult patients and 125 children who underwent surgery for CNS neoplasms of different localization.

Results: a special feature in the initial assessment of the severity of patients with ICP tumor origin is the relationship not only with neurological deficits (GCS 11.0 ± 3.0 points, MMSE 23.0 ± 2.2 points, MRC 3.2 ± 1.1 points), but with multiple organ damage according to the SOFA scale (up to 4-5 systems, with an estimate of 12.0 ± 3.5 points). The constant intraoperative risks associated with ICP syndrome include: a chance of developing hemodynamic instability in adults from 32.1 to 32.7% for SubTNN, in children up to 30% for SubTNN. Characteristics of the dynamics of neurospecific proteins were first isolated depending on the indicators of central and cerebral dynamics in children and adults with neoplasms of the central nervous system. Disturbance of cerebral hemodynamics and the presence of the main pathology (neoplasms of the posterior cranial fossa – PCF) in patients of the SubTNN group caused an increase in the value of the S-100 protein. The mean values were 0.239 ± 0.13 μg/ml, Me = 0.179 (0.171-0.19) in adults and 0.251 ± 0.093, Me = 0.16 (0.12-0.2) in children, which was higher than normal. When assessing the degree of neuroregeneration by the level of the CNTF value, it was revealed that the mean values were significantly increased in the subgroups of adults and children, and amounted to 17.64 ± 7.92 pg/ml, Me = 11.63 (9.37-12.26) in adults, and 12.9 ± 0.71, Me = 11.35 (8.46-12.18) in children. In the SupraTNN group, the elevated levels of the average S-100 protein values up to 0.266 ± 0.043 μg/ml, Me = 0.148 (0.129-0.145) were found in adults, and up to 0.225 ± 0.04 μg/ml, Me = 0.135 (0.092-0.165) in children. The degree of neurodegenerative processes, due to the supratentorial neoplasm, was high in both children and adults. At the same time, mean values of the level of CNTF in this group were significantly higher than in all comparison groups and amounted to 27.09 ± 11.5 pg/ml, Me = 17.76 (14.55-20.7) in adults, and 26.24 ± 5.06 pg/ml, Me = 14.56 (12.04-15.84) in children. Multicomponent modifications of general anesthesia for patients with neoplasms of the central nervous system aimed at correction and

prevention of neuro-cognitive impairment by the influence on the links of the stress system have been developed. To stimulate the stress-limiting (SL) link, benzodiazepines, sodium oxybutyrate are used, barbiturates, inhalation anesthetics are used to stimulate the stress-limiting link and inhibit the stress-activating (SA) link, ketamine is used to stimulate the stress-activating link, clonidine is used for simultaneous stimulation of the stress-activating and stress-limiting link, and fentanyl is used for simultaneous suppression of stress-activating and stress-limiting elements.

Conclusion: The revealed age-specific features of neuro-cognitive deficits in patients with neoplasms of the central nervous system indicate the need for an individual pharmacological approach to the combination of drugs for general anesthesia, with an aim to reduce postoperative deficits.

Key words: pharmacological correction; neurosurgery; neoplasms; anesthesia; intensive therapy; postoperative cognitive dysfunction.

Introduction.

The problem of neuroprotective or neurodegenerative effects of drugs for general anesthesia is a conjunctural topic for most participants in the treatment support process (mainly for insurance companies). While for professionals who are directly involved in treatment, this problem is still unsolvable, so it is often tried to ignore it, under the cover of existing protocols and algorithms of anesthesia. Nevertheless, the problem exists.

So, for example, there are interesting publications that children who have undergone anesthesia are violated ability to learn skills, cognitive functions. Some authors do not agree that the data obtained in animal experiments can be transferred to humans, and they state that there is no neurodegeneration from general anesthetics in children on the basis of magnetic resonance imaging [1]. R.T. Wilder et al. Studied 8548 pupils in the city of Rochester in Minnesota (USA) and found that children who had undergone several anesthesia before the age of four were more likely to register an inability to learn [2]. On the other hand, general anesthetics are used to protect the brain with various injuries of neurons: traumatic, ischemic-hypoxic, toxic. Improvement of protein synthesis, GABA-ergic activity and antioxidant properties of propofol, barbiturates and NMDA antagonists can be the main mechanisms of their neuroprotective action [3, 4]. Thus, in some situations, the positive effect of general anesthetics on the brain, and in others – negative. Methods of preventing the neurotoxic effect of anesthesia have not yet been developed. Most often, for this purpose, preparations of the nootropic group are used, which improve the synthesis of nucleic acids in neurons, mediator exchange.

Given the fact that current clinical studies have not clearly demonstrated a worsening of behavioral development, it is possible that more harm can be done if urgent surgical intervention is needed, and timely treatment is delayed due to concerns about the hypothetical effects of anesthesia on subsequent development. However, the best effort to take into account all risks should be welcomed.

Thus, anesthesia itself can not be toxic, but the drugs that we use can have neurotoxicity features. Therefore, it is desirable to clearly separate the desired effects from toxic and clearly determine the desired dose and / or combination of drugs to reduce toxicity. It is also not advisable to extrapolate the results of studies from one drug to the whole group (from isoflurane to sevorane or from nitrous oxide to ketamine, and from one group of patients to another) [5, 6, 7].

In this context, taking into account the initial disturbances in the neurological and cognitive status, with the prediction of complications in the postoperative period, the development of methods for correcting the revealed and predicted disorders is topical.

The development of delirium and cognitive disorders has been studied in a number of works by the authors [8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21]. Disturbances of hemodynamics are the most unpredictable, but the most insidious pathology of the intranarkoznogo period, so it is possible to relate the percentage of postoperative cognitive disorders (POCD), up to the development of strokes. The authors revealed the relationship between the development of postoperative delirium with preoperative neurological status, hemoglobin level, patient age, natriuretic peptide, cerebral oximetry. Based on the results of the study and statistical analysis, it was concluded that it is the level of preoperative cerebral insufficiency that affects the development of postoperative cognitive impairment.

It was revealed [22], that the frequency of postoperative delirium in adults is up to 4.7%, of the independent provoking factors, pre-operative administration of benzodiazepines, thoracic surgeries, abdominal cavity surgery and the duration of the operation were also isolated. It is known that new postoperative cognitive disorders account for up to

0.8% for planned surgery and up to 5.2% for urgent surgery. The risk of postoperative stroke increases in cardiovascular and neuro-vascular surgery, in patients with predisposing risk factors such as a previous stroke, carotid artery stenosis, open oval window, atrial fibrillation, infective endocarditis, diabetes mellitus, kidney failure, and advanced age [23, 24, 25]. In heart operations, POCD varies from 28 to 100%, with extracardiac operations from 7 to 26% [26].

Cognitive disorders in the elderly cause as much controversy as violations in children. However, available data suggest that POCD in elderly patients is diagnosed, as a rule, by local studies, rather than large-scale multicenter. The evaluation is based, as a rule, on subjective data of the patient or members of his family. Nevertheless, after even short surgical or diagnostic manipulations, up to 47% of patients demonstrate a decrease in cognitive function 24 hours after anesthesia, at the time of discharge from 31 to 47% and 3 months after surgery in 10% of patients [27, 28, 29]. However, there was no clear correlation with the type of anesthesia. As risk factors, elderly age, low educational level, duration of anesthesia and complexity of surgical intervention (vascular, orthopedic and heart surgery) were identified.

However, no review discusses POCD after cerebral operations, although this is relevant [30, 31].

Objectives.

The aim of the work was to assess the baseline level of neurological and cognitive disorders in adults and children at the stage of preparation for surgery for neoplasms of the central nervous system (sub- and supratentorial neoplasms) to predict complications in the postoperative period and the development on their basis of goal-oriented variants of anesthesia and intensive therapy. The main direction is pharmacological correction and prevention of cognitive and neurologic disorders in the half-operative period.

Methods.

Organization of basic research – experimental, prospective, multicenter, open-label study. Criteria for including patients in the study. Patients older than 5 years divided into subgroups are children (5-17 years) and adults (over 18 years), with neoplasms of the CNS, with indications for surgical treatment (operation: total or subtotal neoplasm removal). Criteria for exclusion from the study. Failure of surgery, critically ill patient (ASA V-VI).

Patients and study groups. The research in 2003-2009 was conducted in the Donetsk regional clinical territorial association: in the clinic of neurosurgery (the head of the clinic is d.med.n., Prof. Kardash AM), the department of neurosurgery intensive care unit (the head of the department is d.med.n., Prof. Gorodnik GA), department of anesthesiology (head of the department – Ph.D., Associate Professor Smirnova NN), and also in 2009-2015 in "Clinical Rudnichnaya Hospital", Makeevka: in the department anesthesiology and intensive care (head of the department – Ph.D., Associate Professor Kolesnikov AN), neurosurgery (the head of the department Dr. Zhiharev DV). A total of 303 adults and 125 children who were operated on the central nervous system tumors of different localization (Table 1).

Table 1

Nosological forms of CNS involvement with ICP syndrome in the study groups

Characteristic Subgroups		**Subtentorial Tumors (SubTNN)**	**Supratentorial Tumors (SupraTNN)**
Study groups (adults, n = 303)			
amount Patients		135	168
Age, years (M±m)		50.6±8.4	37.8±5.2
Sex (%)	male	42.7	32.3
	Feminine	57.3	67.7
Study groups (children, n = 125)			
amount Patients		59	66
Age, years (M±m)		13.9±4.4	12.9±2.3
Sex (%)	male	42.3	37.8
	Feminine	57.7	62.2

Scales used in the study and description of groups. Patient history and complaints collection, including GCS scores, taking into account the need to assess neurological deficits, the modified Modified Rankin Scale (MRE) was used for adults and children, for the diagnosis of the degree of cognitive impairment, the scale "A Brief Scale of Mental Status

Assessment – MMSE (MiniMental Score Examination)».

Interpretation of MMSE results [32]: the result of the test is obtained by summing the results for each of the items. The maximum in this test can be 30 points, which corresponds to the highest cognitive abilities. For the relative rate, the MMSE score was more than 26 points. An estimate of 21-25 points was taken for moderate cognitive impairment, and less than 20 for severe cognitive impairment.

Rankin's modified scale (The Modified Rankin Scale, MRS) [32]: allows to objectify the dynamics of neurological symptoms and functional disorders. The uniqueness of this scale consists in the possibility of using it in both adults and children, as well as in the ability to assess neurological deficits not only after a stroke, but after any cerebral insufficiency.

The Coma Scale Glasgow (The Glasgow Coma Scale, GCS) is a scale for assessing the degree of impairment of consciousness and comedians over 4 years old and adults [32]: Evaluation of cerebral hemodynamics. The parameters of cerebral hemodynamics were studied both in the preoperative and intra- and postoperative periods [33, 34, 35]. In the preoperative period, ICP measurement by a direct method was performed in groups with supra- and subtentorial neoplasms – only in the absence of risk to the life of the patient (wedging). In most cases, the initial data was taken with intraoperative ventriculostomy (in the presence of indications). The postoperative ICP measurement was performed in the neurosurgery intensive care unit / IT department until the moment of transfer to the neurosurgical department. Intraoperatively, fluctuations in ICP at different stages of the operation were noted.

Cerebral perfusion pressure (CPP) was calculated according to the formula [36]: CPP = MAP-ICP, where MAP – mean arterial pressure; ICP – intracranial pressure.

Table 2

Calculated indices of CPP for different age groups [36]**:**

Age	Value of the CPP
Newborn	от25 mm Hg.
2-5 years	45-65 mm Hg.
6-12 years	55-75 mm Hg.
Adults	Not less than 70 mm Hg.

Laboratory methods of research. Studies evaluating the degree of neurodegeneration and neuroreparation (neurospecific proteins).

Protein S-100 (glial) kit is designed to quantify the tumor marker of protein S-100B (S-100A1B + S-100BB) in serum samples by the enzyme immunoassay [37], evaluating the degree of neurodegeneration. This method, Fujirebio S100 EIA, is based on the use of two different types of monoclonal antibodies: biotinylated anti-S-100B, monoclonal antibody S-23 and monoclonal anti-S-100B MAb S-53 antibody conjugated with horseradish peroxidase, specifically recognizing different epitopes The S-100B molecule.

Ciliary neurotrophic factor (neurons and glia) (CNTF) [38], as a factor of neuroregeneration. The Human CNTF Kit Quantikine ELISA Kit is designed to quantify the human ciliary (glial) neurotrophic factor (CNTF) in supernatant samples of cell cultures, serum, plasma by enzyme immunoassay. Measuring range: 8-2000 pg / ml. Analytical sensitivity: 8 pg / ml.

Statistical processing of data. The obtained data were subjected to statistical processing using the program STATISTICA 6.0. The quantitative indices for the normality of the distribution were estimated using the Kolmogorov-Smirnov agreement criterion (with the Lillieforce correction) [39]. The quantitative indicators are presented in the form M ± sd, where M is the arithmetic mean, sd is the standard deviation, the median (Me), minimum and maximum values were also determined. Since the distribution law of the quantitative indicators studied differed from the normal one, the statistical significance of the differences was checked using the Kruskall-Wallis criterion (in the case of multiple independent samples). This criterion is intended to assess differences between three or more samples at the level of a feature and can be considered as a nonparametric analog of the method of dispersion single-factor analysis for unrelated samples. In the case of dependent populations, the Wilcoxon W-test was used [40]. To estimate the difference between groups, a method was used to calculate the frequency of deviation from the norm. For the indicators characterizing the qualitative characteristics, the absolute number and the relative frequency in percent (P%) with the representation error (m) were indicated, and 95% confidence interval (95% CI) of the relative value was also calculated. To test the statistical hypotheses about the differences in relative frequencies, proportions, and ratios in two independent samples, the Pearson $\chi 2$ criterion (with the Yates correction), the 95% CI difference, and the Fisher * φ criterion (the Fisher angular conversion), which is designed to compare two samples On the frequency of occurrence of the effect (sign). Fisher's angular transformation makes it possible to assess the significance of the differences between the shares of two samples in which the effect (feature) is registered [41]. In evaluating the effectiveness of the modified anesthetic method, the absolute risk (absolute difference) difference (AR), relative risk (RR), chances and odds ratio (OR) were calculated [42]**.** In all statistical analysis procedures, the achieved significance level (p) was calculated, with the critical significance level being assumed to be 0.05.

Results.

Patients with subtentorial neoplasms (SubTNN). In this group of patients, cognitive dysfunction (see Table 3-4) of medium degree (MMSE 21-25 points) was revealed in 72 ± 2.9% of adults and 94 ± 2.9% of children. Severe cognitive impairment was inherent in 10.0 ± 1.25% of adults and 5.1 ± 2.9% of children. When assessing the degree of neurological deficits (see Figure 1, Table 3-4) in the group of subtentorial neoplasms, it was revealed that both adult patients and children were characterized by a higher severity on the Rankin scale, mean values for adults were 3.26 ± 0.53, Me = 3.0 (3.0-4.0), for children 2.90 ± 0.71, Me = 3.0 (2.0-3.0). An evaluation of the distribution of changes in age groups showed that 4 points were found in 30.4 ± 4.0% of adults and in 20.3 ± 5.2% of children, 3 points in 65.2 ± 4.1% of adults and in 49 , 2 ± 6.5% of children; and 2 points in 4.4 ± 1.8% of adults and in 30.5 ± 6.0% of children.

Table 3

Degree of neurological deficiency, cognitive deficiency and degree of disturbance of cerebral hemodynamics in groups of adult abs./P±m, в % (95% CI)

Groups / coefficient Excesses From the norm	**Scale Rankin (MRS)**	**Level of ICP**	**Level of MAP**	**CPP level**	**SCale MMSE**	
SubTNN	**Before (n=135)**	**Before (n=135)**	**Before (n=135)**	**Before (n=135)**	**Before (n=135)**	
2	6/4.4±1.8 (1.0 – 7.9)	46/34.1±3.9 (21.2 – 36.5)	10/7.4±0.7	-	Backlog / Violation Mental development	4/0.7±0.7 (4.0 – 9.2)
3	88/65.2±4.1 (57.1 – 73.2)	83/61.5±4.3 (44.2 – 61.0)	-	-	Medium Cognitive impairment	97/72±2.9% (46.5 – 80.7)
4	41/30.4±4.0 (22.6 – 38.1)	6/4.4±1.8 (1.0 – 7.9)	-	-	severe cognitive Violations	16/12±3.6 (8.5 – 20.4)
SupraTNN	**Before (n=168)**	**Before (n=168)**	**Before (n=168)**	**Before (n=168)**	**Before (n=168)**	
2	51/30.4±3.5 (23.4 – 37.3)	152/90.5±3.8 (53.9 – 68.7)	22/13.1±3.4	8/4.8±1.6 (1.5 – 8.0)	Backlog / Violation Mental development	8/4.8±1.6 (1.5 – 8.0)
3	117/69.6±3.5 (62.7 – 76.6)	6/3.6±1.4 (0.8 – 6.4)	-	-	Medium Cognitive impairment	129/76.8±3.3 (70.4 – 83.2)
4	0/0.6±0.6 (0.0 – 1.7)		-	-	severe cognitive Violations	31/18.5±3.0 (12.6 – 24.3)

Table 4

Degree of neurological deficiency, cognitive deficiency and degree of disturbance of cerebral hemodynamics in groups of children abs./P±m, в % (95% CI)

Groups / coefficient Excesses From the norm	**Scale Rankin (MRS)**	**Level of ICP**	**Level of MAP**	**CPP level**	**Scale MMSE**	
SubTNN	**Before (n=59)**	**Before (n=59)**	**Before (n=59)**	**Before (n=59)**	**Before (n=59)**	
2	18/30.5±6.0 (18.8 – 42.3)	8/13.5±3.9 (2.5 – 17.9)	2/3.4±2.4 (0.0 – 8.0)	-	Backlog / Violation Mental development	0/1.6±1.6 (0.0 – 4.8)
3	29/49.2±6.5 (36.4 – 61.9)	49/74±6.2 (52.2 – 76.6)	-	-	Medium Cognitive impairment	55/93.2±3.3 (86.8 – 99.6)
4	12/20.3±5.2 (10.1 – 30.6)	2/3.3±2.4 (0.0 – 8.0)	-	-	severe cognitive Violations	4/6.8±3.3 (0.4 – 13.2)
SupraTNN	**Before (n=66)**	**Before (n=66)**	**Before (n=66)**	**Before (n=66)**	**Before (n=66)**	
2	16/24.2±5.3 (13.9 – 34.6)	58/87.9±5.7 (58.6 – 80.8)	3/4.5±2.6 (0.0 – 9.6)	4/6.1±2.9 (0.3 – 11.8)	Backlog / Violation Mental development	3/4.5±2.6 (0.0 – 9.6)
3	43/65.2±5.9 (53.7 – 76.6)	5/7.6±3.3 (1.2 – 14.0)	-	-	Medium Cognitive impairment	58/87.9±4.0 (80.0 – 95.8)
4	7/10.6 – 3.8 (3.2 – 18.0)		-	-	severe cognitive Violations	5/7.6±3.3 (1.2 – 14.0)

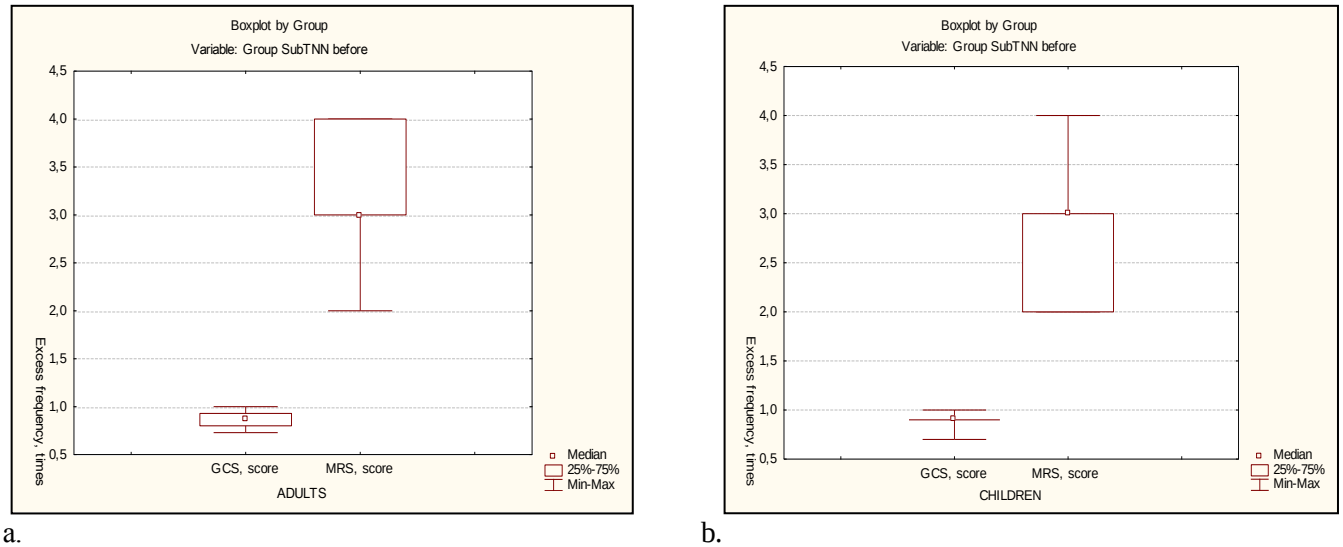
The mean values for the GCS were different, compared to 12.76 ± 1.21, Me = 13.0 (12-14.0) in adults and 13.25 ± 1.36, Me = 14.0 (13.0-15.0) in children. When assessing the distribution according to the GCS, it was found that 41.5 ± 4.2% of adults and 20.3 ± 5.2% of children had 10-11 points; 11-12 points 58.5 ± 4.2% of adults and 69.5 ± 6.0% of children; and only 10.2 ± 2.9% of children had 13-14 points.

The importance of determining the intragroup distribution by severity is evidenced precisely by this group of patients. So, clinically, children with a score of 4 on the Rankin scale and 10-11 points in the GCS, despite their small number (20%), were extremely difficult for an anesthesiologist, compared to even a similar group of adults (up to 40%).

The revealed regularity was confirmed in the evaluation of cerebral hemodynamics (see Table 3-4). The incidence of ICP in adults was significantly higher than in children, the mean values were 50.6 ± 12.1, Me = 50.0 (38.6-62.7) in adults and 44.9 ± 8.7, Me = 44.0 (36.1-53.4) in children. Intra-group distribution of ICP change was characterized by a large spread of ICP indices. In terms of the severity of ICP, excess of up to 3.1-4.0 norms was found in 4.4 ± 0.7% of adults and 5.3 ± 0.7% of children, exceeding to 2.6-3.0 norms – in 8.9 ± 1.4% of adults and 18.6 ± 3.6% of children; the excess to 2.1-2.5 rates – in 52.6 ± 2.2% of adults and 64.4 ± 4.2% of children; up to 1,0-2,0 norms in 28,9 ± 3,5% of adults and 10,1 ± 1,5% of children. Thus, 83% of children and 61.5% of adults had high and extremely high rates of ICP.

The initial severity of patients in this group also characterized the average values of MAP (see Table 3-4), which tend to be hypodynamic in the blood circulation. In adults, the MAP was 103.8 ± 13.2, Me = 100 (90.6-117), in children 71.25 ± 7.5, Me = 70.0 (63.7-78.8). An evaluation of the intra-group distribution of MAP variation showed that a decrease in MAP to 0.3-0.5 norms was observed in 62.2 ± 9.5% of adults and 33.9 ± 4.6% of children, a decrease to 0.7-0.8 Norms were found in 25.9 ± 3.7% of adults and 45.7 ± 7.5% of children. An increase to 1.2-1.5 rates in 5.9 ± 0.7% of adults and 3.4 ± 1.9% of children.

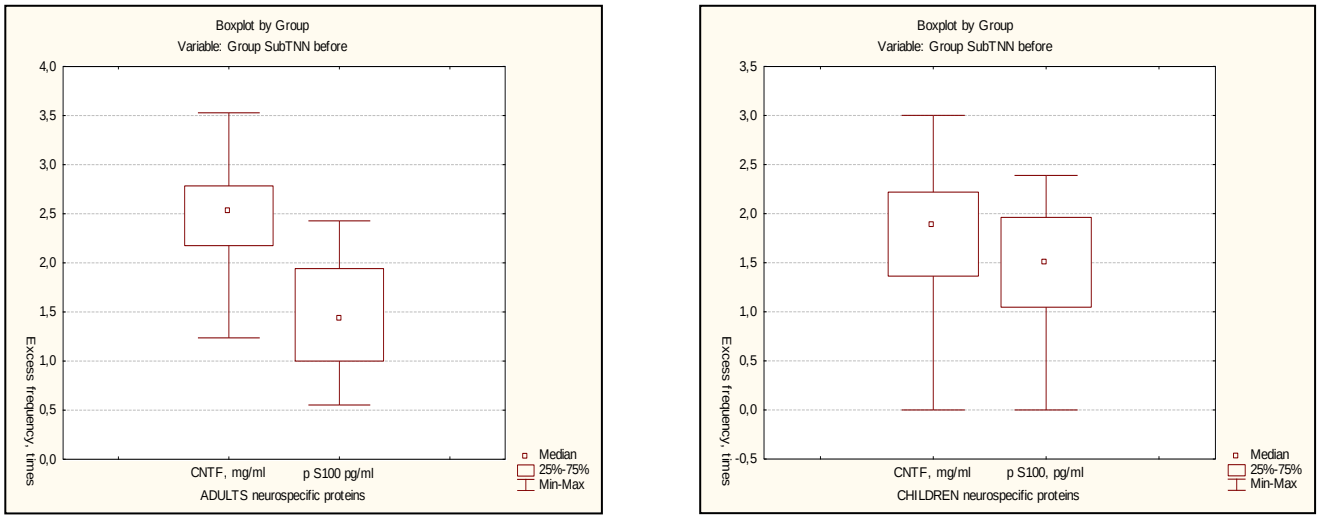
The received data, expectedly, were reflected in the indicators of the CPP (see Table 3-4). Mean values for adults were 53.7 ± 9.2, Me = 54.0 (52-54.5) and 46.36 ± 6.7, Me = 40.0 (40.1-53.1) in children, which significantly differed from the norm and between themselves. Evaluation of the intra-group change in the CPP showed no statistical difference between the dynamics of changes in age groups. Thus, a decrease in the CPP to 0.3-0.5 norms was found in 50.4 ± 8.5% of adults and 54.2 ± 5.7% of children. Subnormal (up to 0.7-0.8 norms) in 45.9 ± 3.3% of adults and 40.7 ± 7.9% of children.



a. b.

Fig. 1. Abnormal mean values of GCS and MRS in adults and children in the SubTNN group (where 1 – values of normal indicators)

The indices of the changes in the levels of neurospecific proteins are shown in Fig.2. Disturbance of cerebral hemodynamics and the presence of the main pathology (neoplasms of PCF) in patients of this group caused (see Fig. 2) an increase in the value of protein S-100. The mean values were 0.239 ± 0.13, Me = 0.179 (0.171-0.19) in adults and 0.251 ± 0.093, Me = 0.16 (0.12-0.2) in children, which significantly exceeded the norm. The degree of excess of the normal indices of the S100 protein in this group was most pronounced by exceeding to 2 norms in 92.5 ± 3.8% of adults and 88.8 ± 6.8% of children.



a. b.

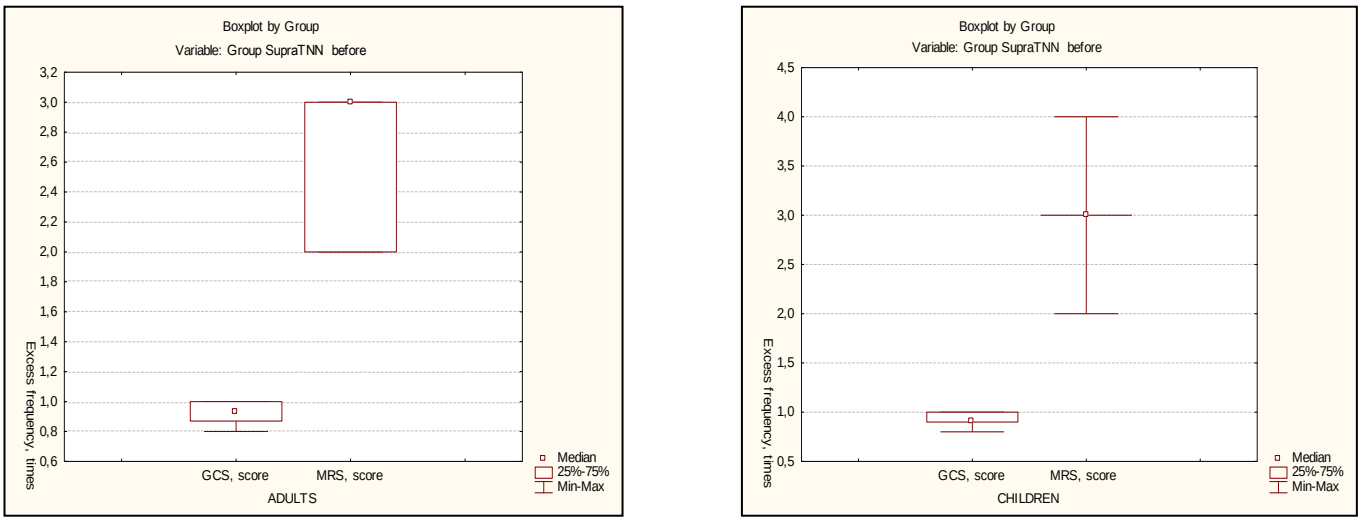
Fig. 2. The deviation from the norm of the mean values of the indices of neurospecific proteins in adults and children in the SubTNN group (where 1 – values of normal indices)

When assessing the degree of neuroregeneration by the level of the CNTF value, it was revealed that the mean values were significantly increased in both subgroups and were 17.64 ± 7.92, Me = 11.63 (9.37-12.26) in adults and 12.9 ± 0.71, Me = 11.35 (8.46-12.18) in children. Exceeding up to 4-7 norms was found in 22.5 ± 7.8% of adults and 38.2 ± 5.2% of children, an increase to 1-3 norms in 76.5 ± 8.2% of adults and 48.9 ± 1,9% of children.

Thus, the high level of ICP, the desire for hypodynamia in the indices of central hemodynamics, and the disturbed CPP dictated the need to observe a "delicate balance" relative to the balance of the neuroregenerative and neurodegenerative processes of the central nervous system.

Patients with supratentorial neoplasms (SupraTNN). Cognitive dysfunction (see Table 3-4) of moderate degree (MMSE 21-25 points) was diagnosed in 77 ± 5.5% of adults and 89 ± 2.5% of children.

Evaluation of the neurological deficit (Figure 3, see t.3-4) on the Rankin scale characterized this group as severe. The mean indices did not differ from the group of SubTNN and amounted to 2.7 ± 0.46 points, Me = 3.0 (2.0-3.0) in adults and 2.86 ± 0.58 points, Me = 3.0 (3.0-3.0) in children. However, the distribution by severity among the patients of the study groups showed that only 10.6 ± 3.8% of children had 4 points on the Rankin scale, 3 points had 69.5 ± 3.5% of adults and 65.2 ± 5.9% children; 2 points 50.4 ± 3.5% of adults and 24.2 ± 5.3% of children.



a. b.

Fig. 3. Abnormal mean values of GCS and MRS in adults and children in the group of SupraTNN (where 1 – values of normal indicators)

The average data from the GCS indicated that in adults this score was 14.05 ± 0.92 points, Me = 14.0 (13.0-15.0), in children – 14.21 ± 0.81 points, Me = 14.0 (14.0-15.0). Intra-group distribution was: 13-14 GCS points in 39.9 ± 3.8% of adults and 40.9 ± 6.1% of children; 11-12 points in 55.4 ± 9.8% of adults and 54.5 ± 6.1% of children and depending on the volume of neoplasm up to 4.8 ± 1.6% of adults and 4.5 ± 2.4 children had disorders of consciousness at the level of sopor (10-11 points of the GCS).

The average values of the ICP level (see tables 3-4) were 28.3 ± 6.6 mm Hg., Me = 28.0 in adults and 35.6 ± 7.1 mm Hg., Me = 35 (28.5-42.7) in children. The severity of ICP, also significantly different from the groups SubTNN. So an increase in ICP to 2.6-3.0 norms was diagnosed only in 3.5 ± 1.2% of adults and 7.5 ± 1.2% of children, an increase in ICP to 1.6-2.0 in 61 , 3 ± 6.4% of adults and 69.7 ± 5.8% of children, and an increase to 1.2-1.5 rates in 29.2 ± 2.1% of adults and 18.2 ± 2.1% of children .

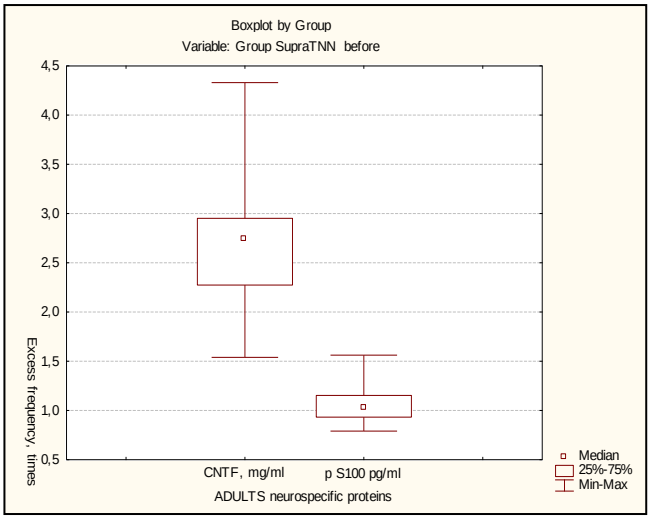
The mean values of MAP (see Tables 3-4) tended to hyperdynamia (apparently compensatory) and significantly exceeded the indices in the previous study groups, and amounted to: adults – 113.4 ± 18.7 mm Hg., Me = 110.0 (94.7-132) mm Hg.. Children – 78.35 ± 5.38 mm Hg., Me = 78 (73-83.7) mm Hg.. Nevertheless, when assessing the group distribution, it was found that 3.6 ± 2.2% of adults and 7.6 ± 3.4% of children had a tendency to reduce MAP to 0.3-0.5 norms, and 19,05 ± 9,3% of adults and 30,3 ± 6,5% of children decrease to 0,7-0,8 norms. Compensatory increase in MAP to 1.2-1.5 norms was observed in 11.9 ± 3.4% of adults and only in 4.5 ± 1.2% of children. The main mass (64.3 ± 4.4% of adults and 57.6 ± 8.6% of children) was normal MAP.

The absence of a pronounced (acute, decompensated) hydrocephalic syndrome, explained the normal values of the CPP (see Tables 3-4). The mean values were as follows: adults 85.3 ± 5.1 mm Hg., Me = 85.0 (73-85) mm Hg.. children 52.3 ± 5.2 mm Hg., Me = 36.0 (50.5-57.7). Normal values of CPP were revealed in 51.8 ± 11.9% of adults and 42.4 ± 9.7% of children. Subnormal (decrease to 0.7-0.8 norms) in 43.5 ± 12.2% of adults and 51.5 ± 5.9% of children.

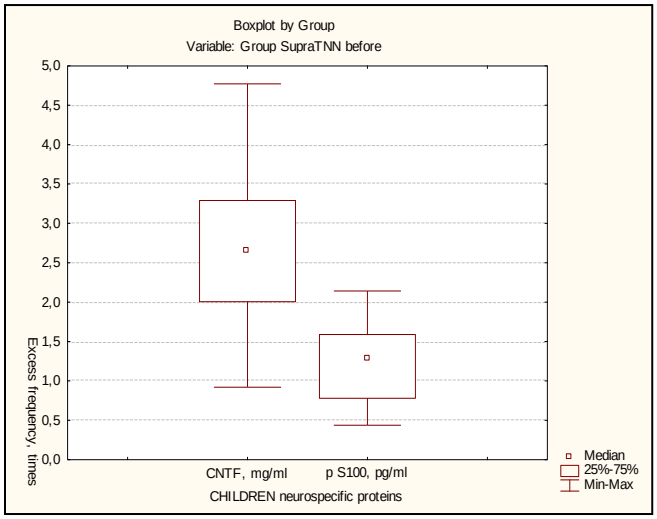
The indices of the changes in the levels of neurospecific proteins are shown in Fig.4.

The existing CNS neoplasm in this group was manifested by an elevated level of average values of the S-100 protein to 0.266 ± 0.043 μg / ml, Me = 0.148 (0.129-0.145) in adults and up to 0.225 ± 0.04 μg / ml, Me = 0.135 (0.092- 0.165) in children. The degree of neurodegenerative processes, due to the supratentorial neoplasm, was high in both children and adults. Exceeding the level of protein S-100 to 1-2 norms was diagnosed in 76.3 ± 5.2% of adults and 92.5 ± 3.8% of children.

The mean values of the level of CNTF in this group were significantly higher than in all comparison groups and amounted to 27.09 ± 11.5 pg / ml, Me = 17.76 (14.55-20.7) in adults and 26, 24 ± 5.06 pg / ml, Me = 14.56 (12.04-15.84) in children. At the same time, an increase in the level of CNTF to 4-7 norms was revealed in 67.4 ± 7.2% of adult patients and 74.3 ± 5.2% of children, an increase to 1-3 in 32.6 ± 8.7 % Of adults and in 16.9 ± 7.7% of children.



a.



b.

Fig. 4. Deviation from the norm of the average values of the indices of neurospecific proteins in adults and children in the group SupraTNN (where 1 – values of normal indicators)

Apparently, if the degree of neurodegeneration depends on the activity (prevalence) of the tumor process, neuroregeneration is based on the degree of manifestation of ICP and the preservation of

autoregulation of the cerebral blood flow.

For patients in this group, preservation of autoregulation of cerebral circulation and maintenance of stable indices of central hemodynamics were of priority for maintaining a positive trend towards the progression of neuroreparative processes. The risk group for "disrupting" compensation was up to 30% of children with unstable hemodynamics.

In view of the revealed changes, the neuro-cognitive status (GCS, MMSE, MRS), goal-oriented variants of multicomponent anesthesia (Table 5) were developed, including additional components of premedication, introductory and basic anesthesia, taking into account the effects on the links of the stress system with the aim of reducing Postoperative neuro-cognitive disorders. To stimulate the selective stress-limiting (SL) link, it is possible to use benzodiazepines, sodium oxybutyrate, barbiturates, inhalation anesthetics can be used to stimulate the SL-link and inhibit the stress-activating (SA) link, to use the ketamine, simultaneous stimulation of SA- and SL-links – use clonidine and for simultaneous inhibition of SA- and SL-units – fentanyl.

Table 5

The main directions of the multicomponent modification anesthesia in patients with neoplasms of the central nervous system

Group	The necessary impact and effectiveness of the application of MM
SubTNN adults	It is necessary to strengthen activation of the SA-link, maximum stimulation of the SL-link. Basis anesthesia (total intravenous anesthesia as an "anesthetic of choice"): fentanyl 0.005% -1-1.5 μg / kg / h, ketamine 0.5% 0.05-1.0 mg / kg / h (with reduction Of the total dose to 125 mg), sodium oxybutyrate 20-50 mg / kg / h, clonidine 0.01% 0.5-1.5 μg / kg / h.
SubTNN children	It is necessary to strengthen activation of the SA-link, maximum stimulation of the SL-link. Basis anesthesia (total intravenous anesthesia as an "anesthetic of choice") fentanyl 0.005% - 1.0 mcg / kg / h, ketamine 0.5% - 0.05-1.0 mg / kg / h (with total dose reduction up to 125 mg), sodium oxybutyrate 20-50 mg / kg / h, propofol 1% - 1-1.5 mg / kg / h.
SupraTNN adults	It is necessary to increase the activity of the SL-link (sodium oxybutyrate 10-20 μ / kg / hour (or benzodiazepines 0.5 mg / kg (0.02 mg / kg / h), clonidine 0.5-1.5 μg / kg / h , Fentanyl 1-1.5 μg / kg / h).
SupraTNN children	

In view of the revealed changes in the parameters of the central (SBP) and cerebral (CPP) hemodynamics, modifications of pre- and intraoperative intensive therapy were performed (Table 6).

Table 6

The main directions of intensive modification therapy in patients with neoplasms of the central nervous system

Group	The necessary impact and effectiveness of the application of MM
SubTNN adults	"Method of early detection of pathological reactions of the brainstem during removal of tumors of the posterior cranial fossa in children" (Pat. 46955): the basis of the declared model was the detection of "episodes of tachyarrhythmia" with fluctuations of BIS (from 30 to 60) during removal of the tumor of the PCF. In case of detection of ischemia of the trunk, the tactics of surgical intervention changed with the subsequent introduction of clonidine (0.5-1.5 μg / kg) ("Method of correction of pathological reactions of the brainstem when removing tumors of the posterior cranial fossa in children" - Pat. 47739). Chance of postoperative cerebral ischemia development in adults is 62.8%, in children - 30.0%.
SubTNN children	
SupraTNN adults	Stabilization of the parameters of the cardiovascular system at the level of moderate hyperdynamics, the need for antibiotic therapy; Method of correction of increased intracranial pressure. Chance of postoperative cerebral ischemia development in adults at 14.3%, in children - 12.4%.
SupraTNN children	

Conclusion.

1. Initial detection of neurological and cognitive deficits in patients allows predicting the development of neuro-cognitive dysfunction in the postoperative period. In this case, the basis of therapeutic perioperative effects are mild to moderate disorders, for which a reversible process is possible. Neurological (MRS 4 points) and cognitive (MMSE less than 20 points) of severe severity are irreversible and constitute permanent risks of postoperative complications.

2. For patients with subtentorial neoplasms, a high level of ICP, a decrease in the parameters of central hemodynamics and an impaired CPP dictates the need to observe the "delicate balance" of the balance of neuroregenerative and neurodegenerative processes of the central nervous system.

3. For patients of the group with supratentorial neoplasms, preservation of autoregulation of cerebral circulation and maintenance of stable indices of central hemodynamics in order to maintain a positive trend towards the progression of neuro-reparative processes is a priority. The group of risk for "failure" of compensation is up to 30% of children with unstable hemodynamics.

4. Multi-component modifications of general anesthesia for patients with CNS neoplasms (not excluding baseline analgesic component) have been developed. To stimulate the stress-limiting link – benzodiazepines, sodium oxybutyrate are used, barbiturates, inhalation anesthetics are used to stimulate the stress-limiting link and inhibit the stress-activating link, ketamine is used to stimulate the stress-activating link, simultaneous stimulation of the stress-activating and stress-limiting link – use clonidine and for simultaneous suppression of stress-activating and stress-limiting elements – fentanyl.

5. The goal-oriented strategy of anesthesia and intensive care will solve the problem of improving the quality of anesthesia in patients with neoplasms of the central nervous system by reducing the chances of developing intra- and postoperative complications.

6. The OR of development of postoperative ischemic brain disorders (reduction of CPP) are: in adults from 13 to 62.8% for all nosological groups, in children from 5 to 30%.

7. The use of modified methods of anesthesia and intensive care will reduce the risk of cerebral ischemia (lower CPP in the postoperative period): in adults 40.2 times for SubTNN and 3.0 times for SupraTNN. In children 6.6 times for SubTNN.

8. In the postoperative period, the developed methods of anesthesia and IT will have advantages in influencing the indicators of systemic and cerebral hemodynamics and will allow to achieve a reduction in the risk of development of cognitive dysfunction of average degree in 1.1-3.8 times in adults and in 1.4-3.9 in children, will reduce the degree of neurological deficits (according to the MRS scale): in adults and children.

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