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EVALUATION OF THE INFLUENCE OF COMBINATIONS OF DRUGS FOR GENERAL ANESTHESIA ON CHANGE OF ACTIVITY OF STRESS-LIMITING AND STRESS-REALIZING LINKS ON THE CLINICAL MODEL OF ACUTE STRESS DAMAGE

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Abstract
Introduction: When a person is in a state of anesthesia – sedation, the realization of the stress reaction is carried out through the mesocortical – limbic system, while performing intensive therapy outside sedation – through the amygdala and the hippocampus. In this regard, the response of the stress system under anesthesia and outside it will be different and, consequently, the evaluation of reactions during anesthesia is extremely interesting and necessary for targeted (individual) choice of combinations of drugs for anesthesia, depending on their effect on the links of the stress system. The more interesting is the response of the stress system in the conditions of the existing pathology, which in itself is accompanied by a stressful response.
Objectives: Evaluation of the reaction of the stress system (with the identification of age-specific features), determining the response characteristics of the stress-realizing and stress-limiting links, determining the total response of the stress system, depending on the combination of drugs used for general anesthesia on the clinical model of general surgical acute stress (adults and children).
Methods: Multicentre open clinical trial (2003-2015). This article presents the data of the group without the syndrome of intracranial hypertension (WSICH) – a general surgical group: 78 adults and 87 children. The group without SICH was interesting, as a group of "typical response" to stress in the form of trauma, emotional stress, pain factor. Two types of total intravenous anesthesia were used: standard (SA) – fentanyl, propofol and modified (MA) – fentanyl, propofol, ketamine, sodium oxybate. The markers of activity of the stress system (cortisol, corticotropic releasing factor (CTRF), β-endorphin, serotonin, histamine) were studied, the concentrations of interleukins in the blood serum (IL-4, IL-6, TNFa, IL-lß, IL-2). The study was conducted in the preoperative period and on the 5th-7th day after the operation. Statistical processing of the results was carried out.
Results and discussion: The normal initial reaction of the stress-realizing-link (SR) of the stress system was determined (the normal stress-typical stress response in adults and children) on preoperative (psycho-emotional) and pain (traumatic) stress, which is expressed in: normal level of cortisol (adrenal level); normal level of CTRF (hypothalamic level); increased level of histamine; The normal level of IL1; normal level of IL6; increased IL2; decrease in the level of TNFα. The normal initial reaction of the stress-limiting-link (SL) of the stress system is determined which is expressed in: normal serotonin level in children and increase in 30% of adults (a typical pathophysiological reaction associated with age, which demonstrates the "vulnerability" of the SL link in adults); Reduction of β-endorphin level (a discussion on the need to enhance opioid exposure in order to prevent

inadequate anesthesia); An increase in IL4 mean values. The typical reaction of the SR and SL – stress system links to the surgical intervention (surgical stress) using standard (group SA) and modified (group MA) variants of TIA was revealed. For the SR-link, increased cortisol levels, increased CTRF level, normalization of histamine level, normalization of IL1 indices, a decrease in IL6 level, an increased level of IL2, an increase in the level of TNFα. For the SL-link, serotonin level was decreased (decrease of the SL potential and the need for additional activation via NMDA receptors), increased β-endorphin level (adequacy of opioid stimulation of the SL-link), an increase in IL4 in 75% of adults and 80% of children Need for additional stimulation via GABA receptors).

Conclusions: The "norm of pathology" (or "stress-norm") of the reaction of the SL-link (activation of stress-limitation), which can be estimated as normal when it is identical to the stimulation of the SR-link, for leveling the destabilizing influence of SR-stimulation, that is, Vegetative stabilization is achieved. In contrast to the SR-link, the possibility of combinations of drugs for general anesthesia to the activity of the SL-link receptors was revealed, the "point of application" for drugs was shown, with the prospect of developing techniques (new combinations) that could affect serotonin metabolism in the brain. It is possible to introduce a new concept – stress-limiting anesthesia, which is necessary, due to the received data that "depth of anesthesia" and "adequacy of anesthesia" are not identical concepts. Preparations for general anesthesia affect, first of all, the activity of the SL-link of the stress system and it is due to their combinations based on the initial activity of the stress system that it is possible to achieve adequate stress-limiting anesthesia.

Keywords: pharmacological action, surgical stress, hormones, cytokines, anesthesia.

Introduction

The stress system is a complex regulatory complex that helps coordinate homeostasis under normal conditions and plays a key role in realizing and coordinating all changes in the body that make up an adaptive response to stressors [1]. In general, the stress system receives information from the environment and the body through a variety of sensory systems and blood flow, from the "waking" brain – through the amygdala and the hippocampus and from the "emotional" brain – through the mesocortico-limbic system [2, 3, 4]. Thus, when a person is in the state of anesthesia-narcosis-sedation, the realization of the stress response is carried out through the mesocortical-limbic system, while performing intensive therapy outside sedation through the amygdala and the hippocampus. In this regard, the response of the stress system under anesthesia and outside it will be different and, consequently, the evaluation of reactions during anesthesia is extremely interesting and necessary for targeted (individual) choice of combinations of drugs for anesthesia, depending on their effect on the links of the stress system. The more interesting is the response of the stress system in the conditions of the existing pathology, which in itself is accompanied by a stressful response.

It is enough conditionally to separate neuropeptides, mediators and cytokines according to their role in stress reactions. So, the stress-realizing part of the stress system [2, 5, 6, 7, 8, 9, 10] will include: hypothalamic hormones – corticotropic hormone (corticotropic releasing factor, CTRF), vasopressin, oxytocin, histamine, neuropeptide Y, Adrenal hormones (epinephrine, norepinephrine, dopamine), cortisol, IL 1, IL 2, IL 6 and TNF. In the implementation of the stress response, a special role is played by the "pro-inflammatory" cytokine IL 1b [11, 12, 13], which consists not only in the mediation of inflammation (produced mainly by activated macrophages, enhances the production of IL2, IL6, TNF, CRP, proliferation and B- Lymphocytes, NK cells), and the "inclusion" of the hypothalamic-pituitary system itself with a characteristic hyperthermia reaction and a cascade of stress response (stimulation of production of IL 6, CTRF). Only IL 1b [11] can penetrate through blood-brain barrier (BBB), directly stimulating the hypothalamus. Particular attention should be paid to the involvement of proinflammatory cytokines (IL 1b, TNF, IL2) in the pathogenesis of neurodegeneration, due to the latter's violation of serotonin metabolism in the brain [12, 13]. The level of IL6 is interesting, as a cytokine realizing the stress-realizing link (SR) of the stress system [14, 15, 16] (hypothalamic-pituitary-adrenal system by increasing the level of ACTH and cortisol) and participation in stress-induced suppression of inflammatory reactions, by Inhibition of the formation of TNF and IL 1b. IL2 is one of the cytokines of the "cohort" of stress-realizing [14, 15, 16], the mechanism of action is neurodegenerative – IL2 increases the activity of tryptophan and serotonin-degrading enzyme – indolamine-2,3-dioxygenase. An increase in the activity of this enzyme contributes to a decrease in the level of both tryptophan and serotonin in the brain and this is accompanied by a weakening of serotonergic brain mechanisms. TNF (TNF) – is one of three "classical pro-inflammatory" cytokines [14, 15, 16], stimulating the stress response (stress-realizing link). Enhances the production of IL1, IL6, enhances the reuptake of serotonin [17].

The level of cortisol is interesting as the level of the resultant effect of stress-realizing mechanisms [7, 9, 10] on the one hand (adrenal level), and as the most important hormone affecting immune responses that inhibits most aspects of the immune response, including proliferation of lymphocytes, production Immunoglobulins, cytokines and inflammatory mediators and cellular toxicity, including the production of inflammatory leukotrienes. Corticotropic hormone (CTRF), one of the most interesting stress-realizing hormones (neurotransmitters) [12], responsible for the actual triggering of the central link of the stress system (hypothalamic level), is stimulated by IL 6, after activation of the last IL1. Histamine is produced in a number of organs and tissues [6, 7, 8, 9, 14], it is a broad-spectrum biologically active substance widely distributed in the CNS synapses of the parasympathetic nervous system, so in our opinion it can be used to assess the adequacy of the parasympathetic Systems for the determination of sympathetic-parasympathetic equilibrium in the work of a stress-realizing system (as a serotonin antagonist in terms of activation of NMDA receptors and development of neurodegeneration) [14, 17].

The stress-limiting part is [2, 5, 6, 7, 8, 9, 10] opioid peptides (enkephalins, endorphins, β-endorphins); GABA (GABA); Serotonin; IL 4, NO; Substance P; Acetylcholine; Hormones of the posterior hypothalamus; Hormones of the adrenal glands (A, NA, GCS, DOFA). In this case, serotonin and IL4, can be attributed to mediators (neuro-immune-endocrine), and β-endorphin [6] already to the effector part. The stress-limiting system as a system of "tight control" from the destructive effects of stress is protected by evolutionary mechanisms, many of which have not yet been studied (activated mainly by the gamma-aminobutyric acid system (GABA), opioid peptides) [15, 16, 18], but The changes revealed in it are the most dangerous for the body and therefore are most interesting from the point of view of the impact on them (including the drugs for anesthesia), because the brain's response to cytokines and neurotransmitters can be both beneficial and destructive. IL4 is a "classic" anti-inflammatory cytokine, which, according to its mechanism of action in the neuroendocrine system, is stress-limiting by suppressing production of IL-1, TNF, IL 6 [5, 12, 14, 19].

One of the most promising ways of solving the problems of inadequacy of anesthesia in anesthetics may be the study of the involvement of neuroregulatory stress-limiting systems of the brain in the implementation of compensatory and sanogenetic processes under the influence of drugs for anesthesia and without them. And also in the formation of optimal for the brain and organism of the patient level of neurovegetative stabilization during surgical intervention [3, 4, 5, 6, 7, 8, 9].

Objectives

The purpose of the study was to evaluate the reaction of the stress system (with the identification of age-related features), to determine the characteristics of the response of the stress-realizing and stress-limiting elements, to determine the total response of the stress system, depending on the combination of drugs used for general anesthesia on the clinical model of the general surgical Acute stressful effects (adults and children).

Methods

Multicentre open clinical trial. The research in 2003-2009. Was conducted in the Donetsk Regional Clinical Territorial Association: in the Neurosurgery Clinic, Neuroreanimation Unit and Anesthesiology Department, in 2009-2015. In "Clinical Rudnichnaya Hospital": in the departments of anesthesiology and intensive care, neurosurgery. In this article, the data of the group without the syndrome of intracranial hypertension (WSICH) – a general surgical group: 78 adults and 87 children (Table 1).

Table 1

Separation of patients by subgroup (anesthetic components) in study groups

Characteristic of subgroups		**Study groups (adults, n = 78)**	
		I	
The type of anesthesia*		I.1	I.2
Amount of patients		31	47
Age, years (M±m)		52,2±3,3	51,7±2,6
Sex (%)	male	52,4	32,7
	female	48,6	67,3
Characteristic of subgroups		Study groups (children, n = 87)	
Amount of patients		24	63
Age, years (M±m)		12,1±4,3	11,7±3,7
Sex (%)	male	44,4	49,7
	female	55,6	50,3

Note: * – (1 – standard anesthesia, 2 – modified anesthesia)

The group without ICH was interesting, as a group of "typical response" to stress in the form of trauma, emotional stress, pain factor. This group includes patients who underwent primary surgical treatment of splinter wounds after a mine explosion injury, tangential bullet wounds, reposition of the facial skeleton, surgical treatment of diseases of the spine, etc.

The group with standard anesthesia (SA) was initial in the study (2003-2006), the patients of the group with modified anesthesia (MA) were included in the study as the regularities were revealed, so the group was recruited from 2006 to 2015. In two clinical institutions.

Anesthesia Scheme in the Standard Anesthesia Group (SA). The patients of the CA group underwent standard total intravenous anesthesia (TIA). Introductory anesthesia was carried out with propofol 1% – 1.5-4.5 mg / kg, fentanyl 0.005% – 5-7 μg / kg. The basis of anesthesia included propofol 1% (1.5-2.5 mg / kg / h) in combination with fentanyl (5-7 μg / kg / h). The drugs were injected with a perfusor, if necessary, the rate of administration changed. The main goal was the performance of BIS 40-45. The ventilation was performed in the normoventilation mode (up to 5-7 ml / kg, pETCO2 38-42, FiO2 40%).

Scheme of the multicomponent modification of TIA (MA). Patients of the general surgical group (WSICH) were characterized as a group forming the concept of "stress-norm" or "norm-pathology" (explanation in the text, section "results and discussion").

Adult patients. Considering the normal activity of the SR-link, benzodiazepines were added to the premedication schedule (sibazone 0.5% 0.2-0.5 mg / kg). An additional anesthetic regimen included ketamine 0.5% to 0.5-1.0 mg / kg, propofol 1% 1.5-2.5 mg / kg, fentanyl 0.005% 1.5-2.5 µg / Kg (up to 5 µg / kg). The basis of anesthesia included: continuous administration of propofol 1% – 1.5-2.5 µg / kg / h, fentanyl 0.005% – 3-5 µg / kg / h, ketamine 0.5% – 0.05 mg / kg / Hour (with the restriction of the total dose to 125 mg). The target is BIS 40-45.

Children's contingent of patients. Priority was the additional activation of the SL-link. In the premedication scheme included benzodiazepines (sibazone 0.5% 0.2-0.5 mg / kg). In the introductory anesthesia scheme, sodium oxybate was intravenously administered 20% to 5-10 mg / kg, propofol 1% 1.5-2.5 mg / kg, fentanyl 0.005% 1.5-2.5 µg / kg (up to 5 Mkg / kg). The basis of anesthesia included: continuous administration of propofol 1% 1.5-2.5 µg / kg / h, fentanyl 0.005% – 1-3 µg / kg / h, sodium oxybate 5-10 mg / kg / h. The target is BIS 40-45.

Laboratory methods of research. In this study, blood sampling was carried out in two stages: at the stage of preparing the patient for surgical intervention – with the placement of a venous catheter and at 5-7 days after surgery, taking into account the features of the immune system's biomechanisms with the development of the maximum immune response, which is not required Less than 5 days. Blood sampling, for immuno-biochemical analyzes characterizing the work of the stress system (cortisol, corticotropic releasing factor, β-endorphin) was performed in the morning hours (6.00-7.00), according to the circadian rhythm.

Given pleiotropic effects of cytokines, their activity was taken into account both for assessing the performance of the immune system and for assessing the activity of the stress system. Interleukin concentrations in the blood serum were determined on ELISA test systems-IL-4, IL-6, TNFa, IL-lß, IL-2 (manufactured by OOO Protein Contour, St. Petersburg, by solid-phase ELISA method).

Stress-realizing (SR) link of the stress system: the level of cortisol was studied by an enzyme immunoassay (a set of reagents of the firm "AlcorBio" (Russia, St. Petersburg)), in the laboratory of the Department of Microbiology of DonNMU. M. Gorky; The level of corticotropic releasing factor (KTPF, KRG) was studied by the methods of MKA and ELISA, in accordance with the standard protocol of analysis, which is attached to the reagent kit (IBL ACTH ELISA kit); The level of histamine was determined in the urine (the device for determining – Spectrofluooroometer, JASCO, FP-770, Japan), a biochemical method in the laboratory DDC Doktmo.

Stress-limiting (SL) link of the stress-system unit: the level of β-endorphin was studied by the methods of MKA and ELISA, according to the standard protocol of analysis that goes in the kit of reagents with commercial sets of Bachem Peninsula Laboratories, Inc.; The level of serotonin was determined in urine (the device for determination – Spectrofluooroometer, JASCO, FP-770, Japan), biochemical method in the laboratory DDC Doktmo.

Statistical processing of data. The obtained data were subjected to statistical processing using the program STATISTICA 6.0. An estimation of the quantitative indices for the normality of the distribution was carried out using the Kolmogorov-Smirnov agreement criterion (with the Lillieforce correction) [20]. 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 [21]. 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 estimate the significance of the differences between the fractions of two samples in which the effect (feature) is registered [22]. In all statistical analysis procedures, the achieved significance level (p) was calculated, while the critical level of significance was assumed to be 0.05 [23].

Results and discussion

Comparative data of the initial change of mediators responsible for realization of a stress response (SR-link).

The level of *IL 1b* (Fig. 1) in both children and adults was within the age limit, the mean values were: 5.43 (4.4) Me = 4.1 (2.9-6.2) in adults And 5.2 (4.24) Me = 3.6 (2.7-4.7) in children. Within the age range was 74.4 ± 4.9% of adults and 75.9 ± 4.6% of children; The excess to 1.2-2.0 norms was detected in 10.3 ± 3.4% of adults and 10.3 ± 3.3% of children; The excess to 2.1-4.0 norms in 21.8 ± 4.7% of adults and 13.8 ± 6.2% of children. Its increase in 25% of both adults and children can be considered a normal typical response to a stressful situation.

The mean values *of IL 6* (Fig. 1) in this group were within the normal range and were 4.2 (2.13) Me 3.8 (2.2-6.0) in adults and 4.25 (2.15) Me 3,8 (2,2-6,0) in children. In assessing the distribution, features were revealed. So within the limits of the age norm, the indices were in 75.6 ± 4.9% of adults and 55.2 ± 5.3% of children, in 17.2 ± 4.0% of adults and 29.9 ± 4.9% of children there was an increase To 1.6-3.0 norms (which corresponded to an increase in the level of IL 1b, due to mediated stimulation). It was interesting to reduce this indicator to 0.8-0.9 norms in 10.3 ± 3.3% of children, and to 0.5-0.7 norms in 4.6 ± 2.2% of adults and 4.6 ± 2.2% of children. This fact spoke of a possible defect in the response of the sympathoadrenal response in 15% of children, with violation of CA activation.

The mean values of *IL2* (Fig. 1) were 0.33 (0.12) Me = 0.33 (0.25-0.37) and children 0.32 (0.13) Me = 0.33 (0.23-0.37), which significantly exceeded the norm in both adults and children. Normal indicators were detected only in 10.3 ± 3.4% of adults. In 46.2 ± 5.6% of adults and 5.7 ± 2.5% of children, the IL2 level exceeded 4.1-6.5 norms, in 10.3 ± 3.4% of adults and 49.4 ± 5.4 % Of children exceeded 2.6-4.0 norms and in 33.3 ± 5.3% of adults and 44.8 ± 5.3% of children there was an excess of up to 2.5 norms. The increase in IL2 levels can be attributed to the typical reaction of the body to a stressful situation, requiring the activation of immune defense systems. Short-term reaction, perhaps, is the key to the absence of adverse reactions on the part of organs and systems, and the central nervous system, which, probably, for an acute stress response just does not need a "soothing" serotonin action.

The mean indices of *TNF* (Fig. 1) were: 3.44 (0.61) Me = 1.25 (0.74-2.22) in adults and 2.19 (1.18) Me = 1.5 (0,74-2.22) and did not differ significantly from age-related indicators, although they tended to increase. The most interesting was the evaluation of the intra-group distribution of this indicator, characterizing the entire heterogeneity of the response to stress. So, within the norm, the TNF (TNF) indicator was diagnosed only in 30.8 ± 5.2% of adults and 16.1 ± 3.9% of children. Exceeding more than 10 norms was revealed in 5.1 ± 2.5% of adults and 4.6 ± 2.2% of children, exceeding to 2.1-3.7 norms in 5.1 ± 2.5% of adults, exceeding to 1 , 6-1,7 norms in 10,3 ± 3,4% of adults and 13,8 ± 3,7% of children, exceeding to 1,1-1,5 norms in 9,2 ± 3,1% of children. In this case, a decrease to 0.1-0.2 norms in 5.1 ± 2.5% of adults and 4.6 ± 2.2% of children, a decrease to 0.3-0.4 in 14.1 ± 3 , 9% of adults and 14.9 ± 3.8% of children, a decrease to 0.5-0.7 rates in 19.2 ± 4.5% of adults and 18.4 ± 4.2% of children, a decrease to 0, 8-0.9 rates in 10.3 ± 3.45 adults and 16.1 ± 3.9% of children. Thus, up to 50% of adults and children had a decrease in the level of TNF, and up to 20% – an increase, which is interesting and perhaps suggests that in about 50% of cases there is a risk of inadequate stimulation of the SR-link.

The average level of *cortisol* (Fig. 1) was: 510 (260.5) Me = 541 (281-740) in adults and 505.99 (258) Me = 541 (281-740) in children. That did not significantly exceed the parameters of the control group. Within the limits of the norm, the level of cortisol was 79.5 ± 4.6% of adults and 90.8 ± 3.1% of children, an excess of up to 1.2-1.3 norms was found in 10.3 ± 3.4% of adults and 4 , 6 ± 2.2% of children, an excess of 1.4-1.6 norms was found in 10.3 ± 3.4% of adults and 4.6 ± 2.2% of children. Thus, for a normal stress reaction, the level of cortisol is within normal limits, with a moderate excess in 20% of adults and 10% of children.

The mean *CTRF* values (Fig. 1) were: 21.64 (11.01) Me = 18.35 (17-22) in adults and 21.37 (10.59) Me = 18.7 (16.0-22.0) in children. That did not differ significantly from the norm. Thus, within the age limit, the CTRF level was 98.9 ± 1.2% for both adults and children. Thus, a normal stress reaction is characterized by a normal KTPF level.

The average level of *histamine* (Fig. 1) was: 1157 (719) Me = 1154 (985-1280) in adults and 1175.3 (205.69) Me = 1170 (1085-1290), which significantly exceeded normal indices. At the same time, within the norm, the histamine index was in 25.6 ± 4.9% of adults and 23.0 ± 4.5% of children. Exceeding up to 1.2-1.4 norms in 56.4 ± 5.5% of adults and 56.3 ± 5.3% of children; The excess to 1.5-1.8 norms in 17.9 ± 4.3% of adults 20.7 ± 4.3% of children. Thus, a normal stress reaction is characterized by an increase in the level of histamine in 75% of both adults and children.

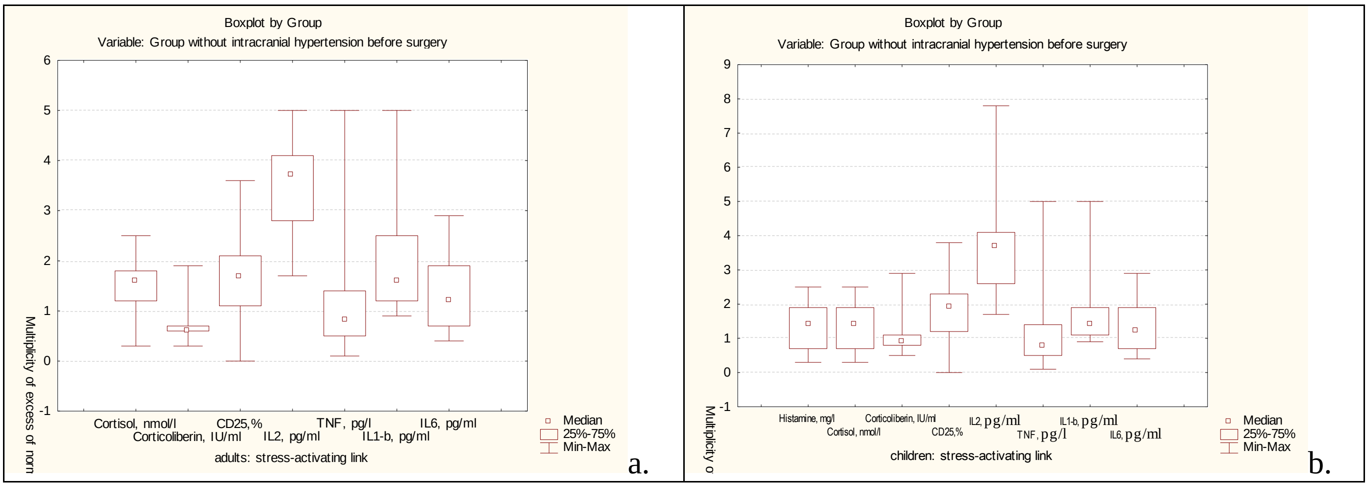

Fig. 1. The multiplicity of the excess of the stress-activating link of the stress system in adults and children (a – adults, b – children)

Thus, the first result of the study was the determination of the normal reaction of the SR-link of the stress system (Fig. 1a, b) (estimated normal stress response in adults and children), which was expressed in: normal level of cortisol (adrenal level), with an excess of 20 % Of adults and 10% of children; Normal level of CTRF (hypothalamic level); An increased level of histamine in 75% of both adults and children; The normal level of IL1 (with a possible increase to 4.0 in 25% of patients); The normal level of IL6 (with a possible increase to 3.0 in 20% of patients); Increased level of IL2 (typical reaction of the body to a stressful situation, requiring the activation of immune defense systems); Decrease in the level of TNF (in 50% of adults and children).

Comparative data of changes in mediators responsible for realizing the stress response (SR-link) after operation using total intravenous anesthesia (TIA) based on fentanyl and propofol (standard anesthesia group – SA).

Mean values *of IL1* (Fig. 2a, 3a) in the postoperative period tended to decrease from preoperative indicators and were within the normal range. The mean values were 2.7 (1.16) Me = 2.9 (2.1-3.3) in adults and 2.64 (1.15) Me = 2.8 (2.1-3.25) In children. Within the norm, the indicator was 97.0 ± 2.9% of adults (more than 20% before the operation) and 96.2 ± 3.7% of children (also 20% higher than before the operation). Thus, surgery / anesthesia led to the normalization of IL1 values in 95% of both adults and children, demonstrating a decrease in the index compared with preoperative data in 20% of patients.

The mean values of *IL6* (Fig. 2a, 3a) showed a decrease in the postoperative period, relative to preoperative data and relative to the norm. The mean IL6 was 3.9 (0.36) Me = 2.9 (2.1-4.4) in adults and 4.0 (0.4) Me = 2.8 (2.1-4.4) In children. The majority of patients were patients with a decrease to 0.1-0.2 norms – 51.6 ± 9.0% in adults and 58.3 ± 10.0% in children, a decrease to 0.2-0.4 norms Revealed in 45.2 ± 8.9% of adults and 35.7 ± 9.9% of children. Thus, surgery / anesthesia resulted in a marked decrease in IL6 in 95% of both adults and children, with a decline in the relative preoperative data in 90% of adults and 70% of children.

Changes *in IL2* (Fig. 2a, 3a) had a similar tendency to decrease with respect to preoperative data, but remained significantly higher than normal. The mean values were 0.28 (0.13) Me = 0.25 (0.19-0.35) in adults and 0.26 (0.14) Me = 0.24 (0.17-0.33) In children. Within the norm, the indicator was in 25.8 ± 7.9% of adults (more by 15% than before the operation) and 8.3 ± 5.6% of children (more by 5% than before the operation). The main group consisted of patients with an excess of 1.0-2.5 norms – 38.7 ± 8.7% of adults (more 5% than before the operation) and 62.5 ± 9.9% of children (20% more than Before the operation), exceeding to 2,6-4,0 norms in 9,7 ± 5,3% of adults and 25,0 ± 8,8% of children (less by 25% than before the operation), exceeding to 4,1- 6.5 norms in 25.8 ± 7.9% of adults (less by 20% than before the operation) and 4.2 ± 4.1% of children. Thus, in the postoperative period, the level of IL2 remained elevated, being within the normal range in 25% of adults (more by 15% than before the operation) and 8% of children (more by 8% than before the operation), on the whole, the indicator showed dynamics to decrease The degree of excess in comparison with preoperative data in 20% of adults and 25% of children.

Mean values of *TNFα* (Fig. 2a, 3a) were 8.18 (3.64) Me = 7.4 (5.4-10.10) in adults and 8.4 (3.93) Me = 7, 55 (5,4-10,25) in children. The majority of patients were patients with excess of normal indices up to 3.8-10 norms – 58.1 ± 8.9% of adults (more by 55% than before the operation) and 58.3 ± 10.1 children (55% more than Before the operation); With an excess of up to 2,1-3,7 norms – 38,7 ± 8,7% of adults (more by 30% than before the operation) and 33,3 ± 9,6% of children (more by 30% than before the operation). Thus, surgery / anesthesia in patients without ICH resulted in a significant increase in the level of TNFα in 95% of adults (more by 75% than before the operation) and 95% of children (more by 75% than before the operation), with the increase in the indicator relative to preoperative data In 50% of adults and children.

The level of *cortisol* (Fig. 2a, 3a), as a characteristic of the "adrenal level" of the stress response, in the postoperative period showed a significant increase in comparison with preoperative data and norm data. The mean values of cortisol (nmol / L) were 966 (160.94) Me = 962.0 (884, -1100.0) in adults and 988.63 (166.5) Me = 962.0 (884.0-1117 , 5) in children. Within the limits of the norm, the indicator was in 19,4 ± 7,1% of adults (less by 60% than before the operation) and 12,5 ± 6,8% of children (less by 75% than before the operation), exceeding to 1,2-1.3 norms were detected in 9.7 ± 5.3% of adults and 33.3 ± 9.6% of children (more by 30% than before the operation), exceeding to 1.4-1.6 norms in 58.1 ± 8.9% of adults (more by 45% than before the operation) and 33.3 ± 9.6% of children (more by 30% than before the operation), exceeding to 1.7-2.0 norms in 19.4 ± 7 , 1% of adults (15% more than before surgery) and 20.8 ± 8.3% of children (20% more than before surgery). Thus, surgery / anesthesia led to an increase in the level of cortisol in 80% of adults (more than 70% before the operation) and 85% of children (more by 80% than before the operation), with a corresponding increase in dynamics with respect to preoperative data.

The level of *CTRF* (Fig. 2a, 3a), characterizing the "hypothalamic level" of the stress response, significantly increased in the postoperative period both in relation to preoperative data and in relation to the norm. The mean values were 62.74 (17.84) Me = 68.0 (54.0-74.0) in adults and 62.88 (18.41) Me = 68.0 (48.0-74.0) In children. Within the norm, the indicator was 48.4 ± 9.0% of adults (less than 50% before the operation) and 45.8 ± 10.2% of children (less than 50% before the operation), exceeding the figure to 1, 2-1,5 norms were detected in 32,3 ± 8,4% of adults (more by 30% than before the operation) and 33,3 ± 9,6% of children (more by 30%), exceeding to 1,6-1 , 8 norms in 16.1 ± 6.6% of adults (more by 15% than before the operation) and 16.7 ± 7.6% of children (also more by 15%), exceeding to 1.9-2.5% In 3,2 ± 2,2% of adults and 4,2 ± 4,1% of children (an average of 5%). Thus, surgery / anesthesia resulted in a significant increase in the CTRF level in 50% of both adults and children, with the same increase in preoperative data.

The level of *histamine* (Fig. 2a, 3a), as a characteristic of the parasympathetic link (sympathetic-parasympathetic balance), of the stress-realizing part of the stress system, showed a tendency to decrease in the postoperative period in comparison with preoperative data, but exceeded the norm, demonstrating " Movement towards the limits of the norm. " The mean values were 693.32 (190.75) Me = 665.0 (478-870) in adults and 708.33 (190.4) Me = 704.50 (550.0-870.5) in children. Within the norm, the indicator was in 83.3 ± 6.6% of adults (more by 60% than before the operation) and 95.8 ± 4.1% of children (more by 70% than before the operation). Thus, surgery / anesthesia led to the normalization of the level of histamine in 80% of adults and 95% of children, with a positive trend of "striving for norm" and a decrease in the rate in 70% of adults and 75% of children.

Thus, the following result of the study was the evaluation of the reaction of the SR-link of the stress system (Fig. 2a, 3a) to the surgical intervention (surgical stress) using standard TIA variants (group SA). It was revealed: an increase in the level of cortisol in 80% of adults (more by 70% than before the operation) and 85% of children (more by 80% than before the operation), with a corresponding increase in dynamics with respect to preoperative data; An increase in the CTRF level in 50% of both adults and children, with an increase in relative preoperative data; Normalization of histamine levels in 80% of adults and 95% of children, with a decrease in 70% of adults and 75% of children; Normalization of IL1 indices in 95% of both adults and children; A decrease in the IL6 level in 95% of both adults and children, with a decrease in the relative preoperative data in 90% of adults and 70% of children; Increased level of IL2, with dynamics to decrease in comparison with preoperative data in 20% of adults and 25% of children; An increase in TNFα in 95% of adults (75% more than before surgery) and 95% of children (75% more than before surgery), with an increase in the rate of preoperative data in 50% of adults and children.

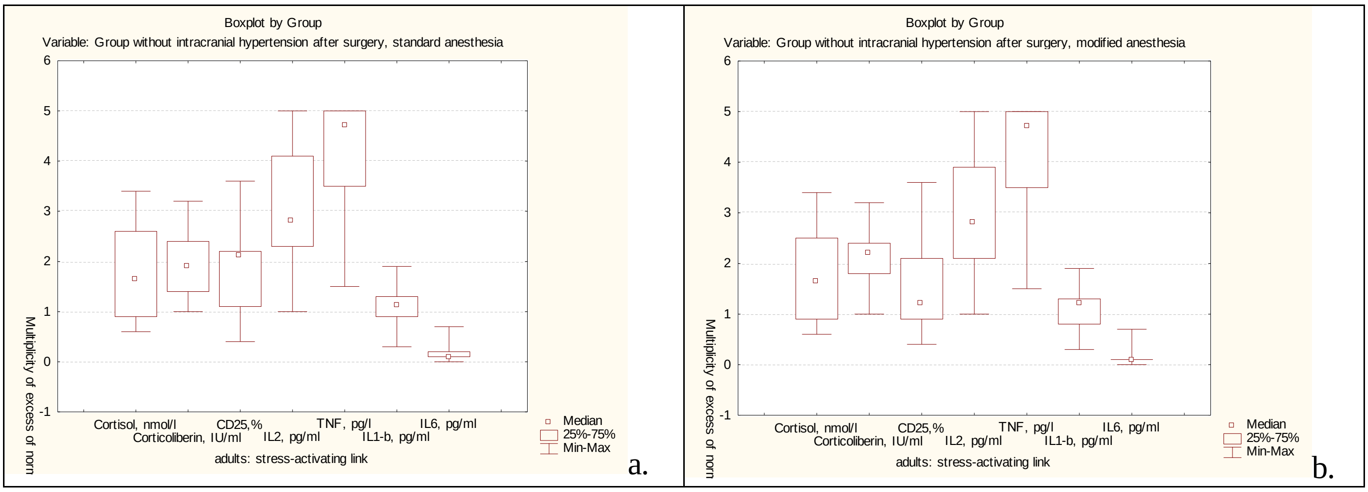

Fig. 2. Changes in the stress-activating link in adult patients of the general surgical profile (a – after surgery, standard anesthesia, b – after surgery, modified anesthesia, where 1 – average values of normal indicators)

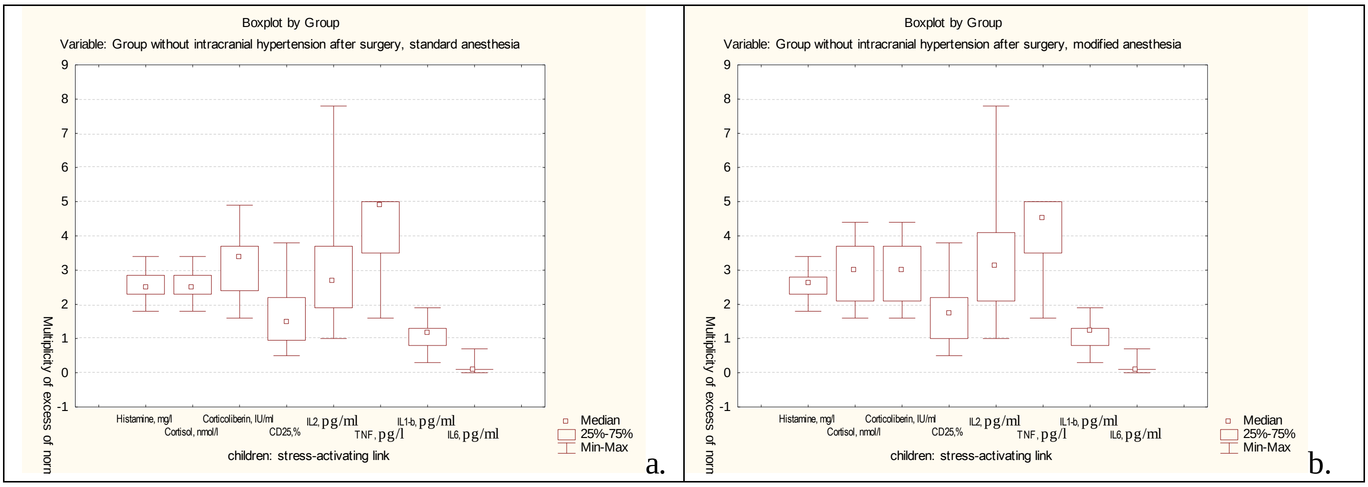

Fig. 3. Change in the indicators of stress-activating link in children of general surgical profile (a – after surgery, standard anesthesia, b – after surgery, modified anesthesia, where 1 – average values of normal indices)

Comparative data of changes in mediators responsible for realizing the stress response (SR-link) after surgery using modified anesthesia (TIA) based on fentanyl, ketamine, sodium oxybate and propofol (MA group).

In the adult group, the response of the SR-link of the stress-system unit was expressed in: the level of *cortisol* (Fig. 2b) was 1022.3 ± 171.1; Me = 998.0 (685.0 – 1325.0) nmol / L, with a significant increase in the content from preoperative data (χ2 = 80.4, df = 4, p <0.001), without significant difference with the comparison group (SA) . The level of *histamine* (Fig. 2b) was 690.1 ± 196.4; Me = 665.0 (412.0 – 1085.0) mg / l, with a significant decrease to normal (χ2 = 57.7, df = 3, p <0.001), without significant difference with the comparison group (SA). The *CTRF* level (Fig. 2b) was 62.15 ± 19.83; Me = 59.0 (32.0 – 98.0) IU / ml, with a significant increase in the content from preoperative data (χ2 = 44.3, df = 3, p <0.001), without significant difference with the comparison group (SA). The level of *IL2* (Fig. 2b) was 0.30 ± 0.14; Me = 0.25 (0.09-0.70) pg / ml, with a significant increase from the norm (p <0.001), without significant difference with preoperative data and the comparison group (SA). The level of *TNF* (Fig. 2b) was 8.13 ± 3.95; Me = 7.40 (2.40 – 17.70) pg / l, with a significant increase in the content from preoperative data (χ2 = 99.8, df = 8, p <0.001), without significant difference with the comparison group (SA). The level of *IL1-b* (Fig. 2b) was 2.70 ± 1.01; Me = 2.70 (0.70-4.70) pg / ml with a significant decrease to normal (χ2 = 57.7, df = 3, p <0.001), without significant difference with the comparison group (SA). The level of *IL6* (Fig. 2b) was 0.47 ± 0.47; Me = 0.33 (0.1-2.1) pg / ml with a significant decrease below the norm (χ2 = 112.8, df = 4, p <0.001), without significant difference with the comparison group (SA).

In the group of children, the reaction of the SR-link of the stress-system unit was expressed in: the level of cortisol (Fig. 3b) was 988.6 ± 166.5; Me = 962.0 (685.0 – 1325.0) nmol / L, with a significant increase in the content from preoperative data (χ2 = 89.3, df = 3, p <0.001), without significant difference with the comparison group (SA) . The level of histamine (Fig. 3b) was 708.3 ± 190.4; Me = 704.5 (412.0 – 1085.0) mg / l, with a significant reduction to normal (χ2 = 76.8, df = 3, p <0.001), without significant difference with the comparison group (SA). The level of KTPF (Fig. 3b) was 62.88 ± 18.41; Me = 68.0 (32.0 – 98.0) IU / ml, with a significant increase in the content of preoperative data (χ2 = 51.7, df = 2, p <0.001), without significant difference with the comparison group (SA). The level of IL2 (Fig. 3b) was 0.26 ± 0.14; Me = 0,24 (0,09 – 0,70) pg / ml, with a significant increase from the norm and from preoperative data (χ2 = 7.99, df = 3, p = 0.046), without significant difference with the comparison group SA). The level of TNF (Fig. 3b) was 8.40 ± 3.93; Me = 7.55 (2.40 – 17.70) pg / l, with a significant increase in the content from preoperative data (χ2 = 134.0, df = 9, p <0.001), without significant difference with the comparison group (SA). The level of IL1-b (Fig. 3b) was 2.64 ± 1.15; Me = 2.80 (0.70-4.70) pg / ml with a significant decrease to normal (χ2 = 17.7, df = 2, p <0.001), without significant difference with the comparison group (SA). The level of IL6 (Fig. 3b) was 0.40 ± 0.40; Me = 0.28 (0.1-2.1) pg / ml with a significant decrease below the norm (χ2 = 138.4, df = 5, p <0.001), without significant difference with the comparison group (SA).

Thus, in spite of different numerical data, the reaction of the stress-realizing link of the stress system under the influence of a modified version of anesthesia (another combination of drugs for general anesthesia) under the conditions of identical surgical stress can be estimated as "typical", without significant differences in the response by age And the direction of changes in the average data, between the applied types of anesthesia (Fig. 4). This characterizes the reaction as a stress-realizing (hyper-stress) – protective, which made it possible to determine the "norm of pathology" for the reaction of the SR-link of the stress system, starting from which it became possible to evaluate the reaction of the stress system in other pathologies and species (combinations) Anesthesia. It was proved that combinations of drugs for general anesthesia (in manufacturer's recommended dosages) could not influence the activity of the SR-link of the stress system in patients of the general surgical group.

For visual presentation of the changes, the coefficients of exceeding the stress-system indicators were summarized, calculating the difference in the changes from preoperative data (Δ before-SA and Δ before-MA) (Fig. 4).

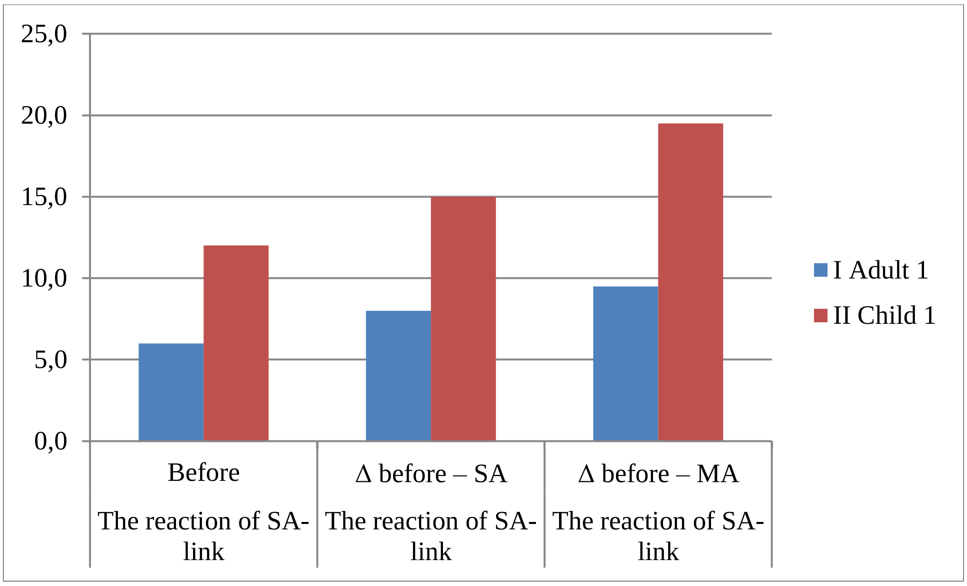

Fig. 4. The total typical evaluation of the reaction of the stress-activating -link of stress system («pathology norm») in adults and children in the preoperative period and after standard and modified anesthesia, where the indicators within the limits of the norm are taken as 1, the excess of the indicator (times deviations from the norm) – «+2, +4, etc.», decrease in the indicator (times by deviations from the norm) – «-2, -4, etc.», the value of the indicator, which has up to 50% of the results within the norm, And the remaining increase is «+0,5», the value of the indicator, which has up to 50% of the results of the decrease from the norm – «-0,5»

Comparative data of the initial change of mediators responsible for the limitation of stress response (SL-link).

The average level of *serotonin* (Fig. 5a, b), as a powerful endogenous antistress and neuroprotective factor (blockade of the glutamate cascade, due to interaction with NMDA receptors) was 1096.62 (30.9-14) Me = 999.0 (945 -1187.0) in adults and 1095.82 (302.6) Me = 999.0 (965-1200.0), which, although it tended to exceed, but within the norm was 70.5 ± 5.2 % Of adults and 99.4 ± 0.6% of children. It is characteristic that 30% of adults noted an excess of this indicator (a feature associated with age, the course of a typical pathophysiological reaction). Thus, up to 1.4-1.8 serotonin levels were elevated in 14.1 ± 3.8% of adults; Up to 1,1-1,3 norms in 15,4 ± 4,1% of adults.

β-endorphin (Fig. 5a, b), the mean β-endorphin values (pmol / L) were: 2.98 (0.97) Me = 3.0 (2.3-3.3) in adults and 2 , 94 (0.94) Me = 2.9 (2.2-3.2), which, on the whole, tended to decrease relative to the norm group. The level of β-endorphin was within the normal range in 65.4 ± 5.4% of adults and 64.4 ± 5.1% of children. Nevertheless, a decrease to 0.5-0.6 norms revealed 10.3 ± 3.4% of adults; A moderate decrease to 0.7-0.8 norms in 24.4 ± 4.9% of adults and 25.3 ± 4.7% of children. Thus, a moderate decrease in the level of β-endorphin detected in patients with a moderate "inhibition" of the central SL response may be a variant of the normal course of the stress response when stimulation of the stress-realizing link of the stress system is necessary for an adequate physiological response.

The mean values *of IL4* (Fig. 5a, b) were: 5.23 (4.64), Me = 4.15 (1.99-6.60) in adults and 5.17 (4.41) Me = 4 , 2 (2,2-5,2) and significantly exceeded the age norm, which can be considered a variant of a normal stress response, when along with stress-realizing mechanisms, stress-limiting, equalizing and regulating responses are triggered in strength. In 25.6 ± 4.9% of adults and 31.0 ± 5.0% of children, the indicator was normal. Thus, over 10 norms were diagnosed in 5.1 ± 2.5% of adults and 4.6 ± 2.2% of children; The excess to 6.0-10.0 norms in 10.3 ± 3.4% of adults and 4.6 ± 2.2% of children; Excess to 3.1-5.0 norms in 24.4 ± 4.9% of adults and 14.9 ± 3.8% of children; Excess to 1.5-3.0 norms in 34.6 ± 5.4% of adults and 42.5 ± 5.3% of children; The excess to 1.3-1.4 norms in 5.7 ± 2.5% of children. Thus, the excess of the IL4 index (in 70% of patients) can be considered as a prognostically favorable direction of the stress-limiting reaction of the stress system aimed at the regulation of the T and B immunity systems, monocyte-macrophage system (MMS). The level of increase, possibly, depends on the strength of aggressive influence, the question of the duration of the favorable influence of the revealed changes remains open.

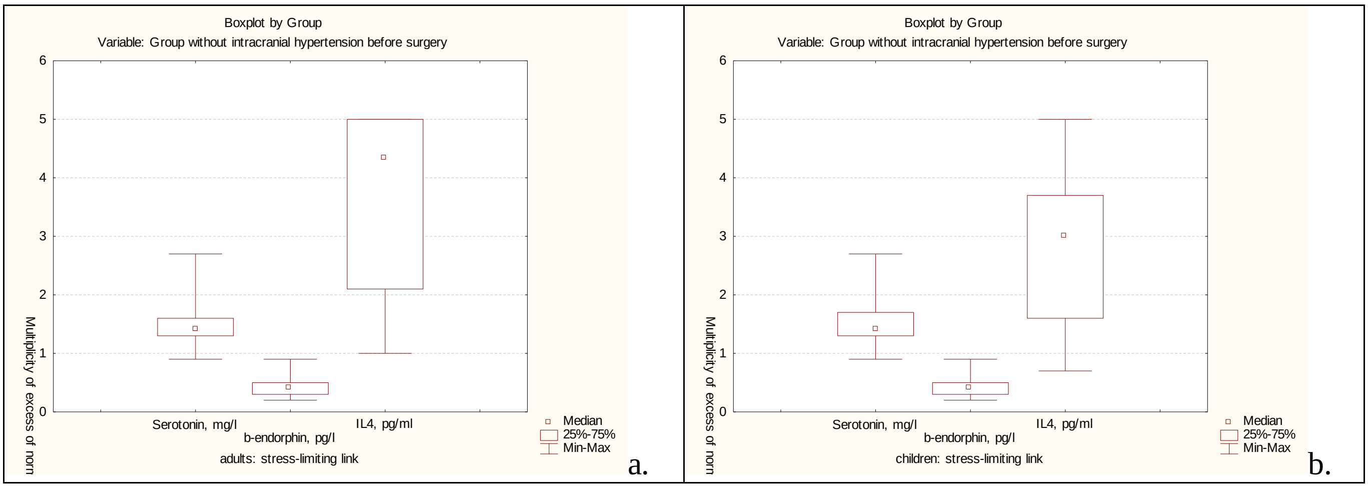

Fig. 5. Multiplicity of excessing indicators of the stress-limiting link of the stress system in adults and children (a – adults, b – children)

Thus, the following result of the study was the determination of the normal response of the SL-link in the stress system (Fig. 5a, b) (estimated normal stress response in adults and children), which was expressed in: normal serotonin levels in children and an increase in 30% of adults A characteristic of a typical pathophysiological reaction associated with age, which demonstrates the "vulnerability" of the SL link in adults); Reduction of β-endorphin level (a discussion on the need to enhance opioid exposure in order to prevent inadequate anesthesia); An increase in IL4 mean values.

Comparative data of changes in mediators responsible for the limitation of the stress response (SL-link) after operation using total intravenous anesthesia (TIA) based on fentanyl and propofol (standard anesthesia group – SA).

Mean values of *IL4* (Fig. 6a, 7a) were significantly elevated in the postoperative period both in relation to preoperative data and in relation to the norm, "balancing" the multidirectional changes in the system of stress-realizing / pro-inflammatory cytokines (see Fig. 2, 3). The mean IL4 was 4.62 (2.37) Me = 5.2 (2.2-5.89) in adults and 4.88 (2.17) Me = 5.2 (4.16-5.96) In children. Within the norm, the indicator was in 22.6 ± 7.5% of adults and 20.8 ± 8.3% of children (less by 10% than before the operation); The main group consisted of patients with excess to 3.1-5.0 norms – 58.1 ± 8.9% of adults (more by 30% than before the operation) and 16.7 ± 7.6% of children (without dynamics); And with an excess of 1.5-3.0 norms (more in children) – 9.7 ± 5.3% of adults (less than 25% before the operation) and 62.5 ± 9.9% of children (more by 20 % Than before the operation); The excess to 6.0-10.0 norms – in 9.7 ± 5.3% of adults. Thus, despite the increased average rates, in the postoperative period in patients of the SA group, the level of IL4 had a dynamics to decrease. Operation / anesthesia resulted in a significant increase in IL4 in 75% of adults and 80% in children (more than 10% before surgery) – a normal "protective" response of the SL link, with a decrease in the rate of preoperative data in 5% of adults and 10% Children – the prevalence of the destructive effect of SA activation on the SL reaction.

The *serotonin* level (Fig. 6a, 7a) was 670.94 (322.56) Me = 741.0 (254-947) in adults and 673.13 (311.24) Me = 471.0 (537.5- 947.0) in children. Within the norm, the indicator was in 74.2 ± 7.9% of adults and 79.2 ± 8.3% of children (less by 20% than before the operation); A decrease to 0.6-0.8 norms was found in 12.9 ± 6.0% of adults (more by 10% than before the operation) and 4.2 ± 4.1% of children; A decrease to 0.3-0.5 rates in 12.9 ± 6.0% of adults (20% more than before surgery) and 16.7 ± 7.6% of children (more by 15% than before surgery). Thus, surgery / anesthesia led to a decrease in serotonin levels in 25% of adults and 20% of children, demonstrating a decline in the relative preoperative data in 55% of adults and 20% of children, which characterizes the decrease in the SL potential.

The level of *β-endorphin* (Fig. 6a, 7a) in the postoperative period was significantly increased in comparison with preoperative data and tended to exceed the norm values. The mean values were 12.52 (3.92) Me = 13.2 (9.2-16.2) in adults and 12.38 (4.04) Me = 13.65 (9.0-16.05) In children. Within the limits of the norm, the indicator was in 41.9 ± 8.9% of adults (less by 25% than before the operation) and 37.5 ± 9.9% of children (less by 25% than before the operation), exceeding to 1,2-1.5 norms were found in 45.2 ± 8.9% of adults (more by 45% than before the operation) and 50.0 ± 10.2% of children (more by 50% than before the operation), excess to 1.6- 2,0 norms in 12,9 ± 6,0% of adults (more by 10% than before the operation) and in 12,5 ± 6,5% of children (more by 10% than before the operation). Thus, the operation / anesthesia led to a significant increase in the level of β-endorphin in 55% of adults and 60% of children, which demonstrates the adequacy of the opioid effect on the receptors of the SL-link in the stress system.

Thus, the following result of the study was an evaluation of the response of the SL-link of the stress system (Fig. 6a, 7a) to the surgical intervention (surgical stress) using standard TIA variants (group SA). A decrease in serotonin levels in 25% of adults and 20% of children (decrease in the SL potential and the need for additional activation via NMDA receptors), an increase in β-endorphin in 55% of adults and 60% of children (adequacy of opioid stimulation of the SL link), An increase in IL4 in 75% of adults and 80% of children (with a decrease in 5% in adults and 10% in children, the need for additional stimulation via GABA receptors).

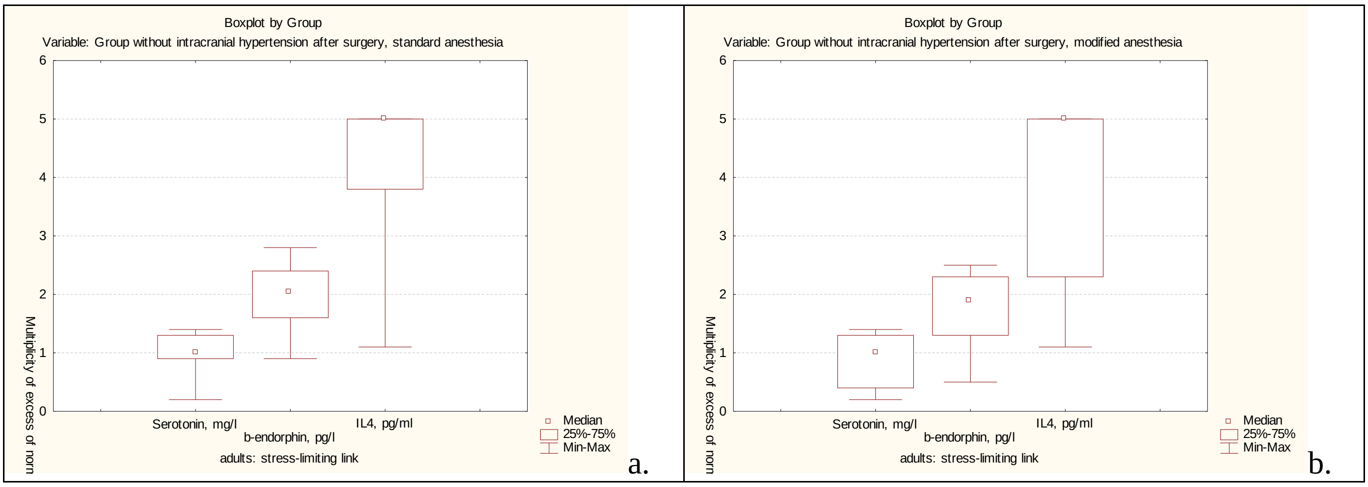

Fig. 6. Changes in the indicators of stress-limiting link in adult patients of general surgical profile (a – after surgery, standard anesthesia, b – after surgery, modified anesthesia, where 1 – average values of normal indices)

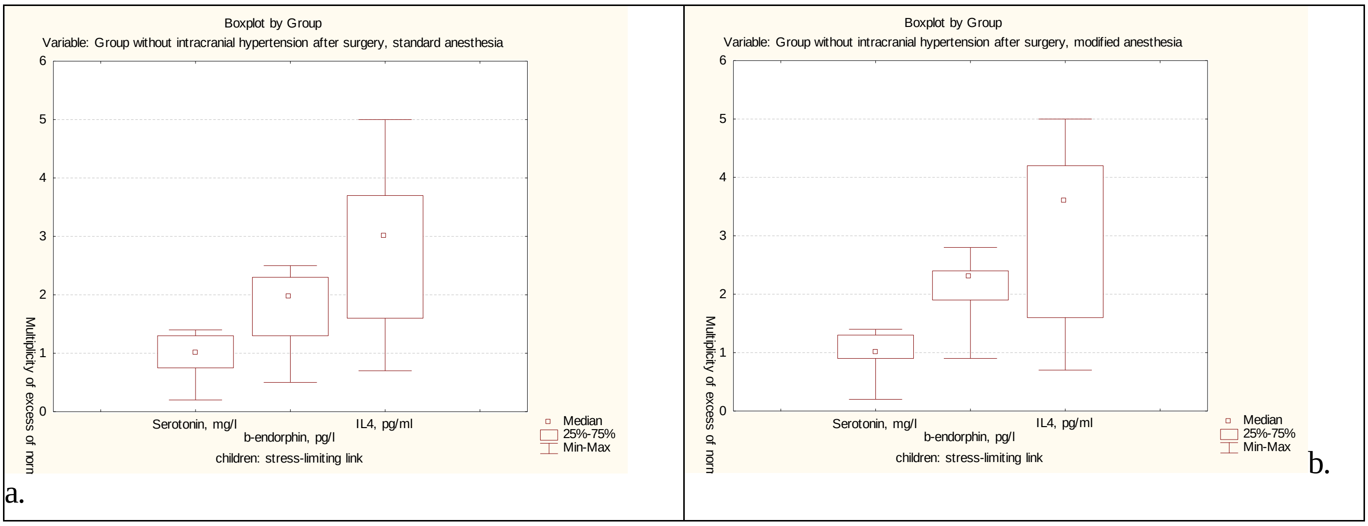

Fig. 7. Changes in the stress-limiting link in children of the general surgical profile (a – after surgery, standard anesthesia, b – after surgery, modified anesthesia, where 1 – mean values of normal indicators)

Comparative data of changes in mediators responsible for the limitation of the stress response (SL-link) after surgery using modified anesthesia (TIA) based on fentanyl, ketamine, sodium oxybate and propofol (MA group).

In the group of adult patients in the postoperative period (MA group), the reaction of the SL-link of the stress system was expressed in: a significant decrease to the norm of *serotonin* level (Fig. 6b) (mean values 709.8 ± 290.7, Me = 747.0 (112 , 0 – 999.0)), compared with preoperative data ($\chi2$ = 27.7, df = 4, p <0.001), without significant difference with the comparison group (SA), with a tendency to decrease the degree of decline in 10% in Group MA (p = 0.064).

The level of *β-endorphin* (Fig. 6b) was 14.39 ± 3.90; Me = 14.90 (6.50 – 19.80) pmol / L, with a significant excess of preoperative data ($\chi2$ = 83.6, df = 4, p <0.001), without significant difference with the comparison group (SA).

The level of *IL4* (Fig. 6b) was 4.96 ± 2.48; Me = 5.20 (1.04 – 9.80) pg / ml with a significant excess of preoperative data ($\chi2$ = 18.4, df = 4, p = 0.001), without significant difference with the comparison group (SA).

In the group of children in the postoperative period (MA group), the response of the SL-link of the stress system was expressed in: a significant decrease in the level of *serotonin* (Fig. 7b) (mean values 673.1 ± 311.2, Me = 741.0 (112.0 – 999.0)), compared with preoperative data (χ2 = 23.0, df = 2, p <0.001), without significant difference with the comparison group (SA).

The level of *β-endorphin* (Fig. 7b) was 12.38 ± 4.04; Me = 13.65 (3.80 – 17.80) pmol / l, with a significant excess of preoperative data (χ2 = 115.1, df = 4, p <0.001), without significant difference with the comparison group (SA), with The tendency to increase the degree of excess in 20% (p = 0.052) in the MA group.

The level *of IL4* (Fig. 7b) was 4.88 ± 2.17; Me = 5.20 (1.04 – 9.80) pg / ml with a significant excess of preoperative data (χ2 = 11.4, df = 5, p = 0.044), without significant difference with the comparison group (SA).

Thus, as in the case of the SA-link reaction described above, the reaction of the stress-limiting (SL) – link of the stress system under the influence of a modified variant of anesthesia (another combination of drugs for general anesthesia) under identical surgical stress can be estimated as " ", Without significant differences in the response by age and direction of changes in mean data, between the types of anesthesia used (Fig. 8). The reaction can be evaluated as stimulation of the SL-link, identical stimulation of the SR-link, for leveling the destabilizing effect of SR-stimulation. Unlike the SR-link, the tendency of combinations of drugs for general anesthesia to affect the activity of the SL-link receptors has been revealed, that is, the application point for drugs has been shown, with the prospect of developing techniques (new combinations) that can affect serotonin metabolism.

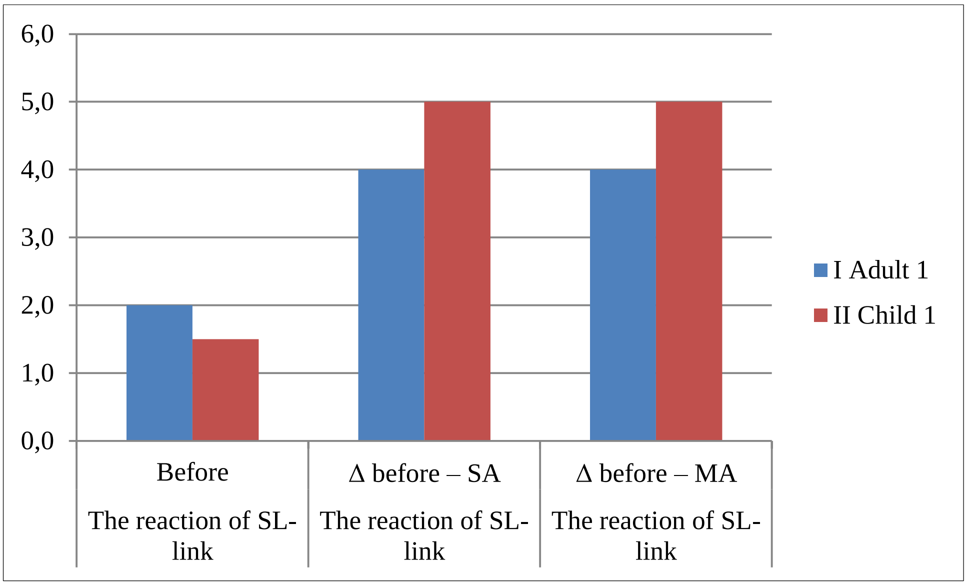

Fig. 8. The total typical evaluation of the response of the SL-link of the stress system (the «pathology norm») in adults and children in the preoperative period and after standard and modified anesthesia, where the parameters within the limits of the norm were taken as 1, the excess of the indicator (times deviations from the norm) – «+2, +4, etc.», decrease in the indicator (times by deviations from the norm) – «-2, -4, etc.», the value of the indicator, which has up to 50% of the results within the norm, And the remaining increase is «+0,5», the value of the indicator, which has up to 50% of the results of the decrease from the norm – «-0,5»

The main result of the study is that the data for the first time have been obtained that allow us to evaluate the normal reaction of the stress system links and the stress system as a whole ("stress rate" or "rate of pathology") for surgery (surgical stress) and combinations of drugs for general Anesthesia (Fig. 9).

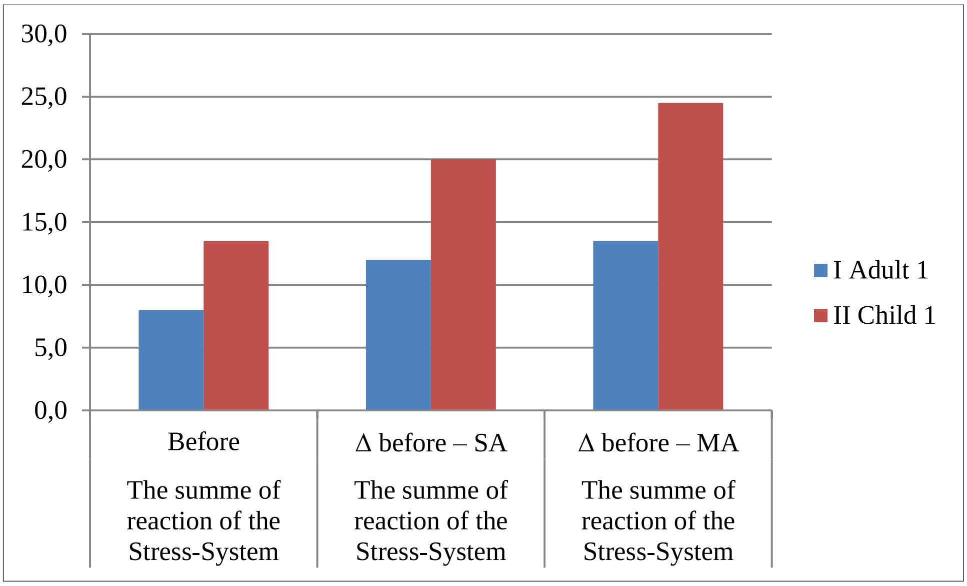

Fig. 9. The total typical evaluation of the reaction of the stress system in adults and children (the «pathology norm» or «stress norm») in the pre- and postoperative periods (SA and MA), where the indices within the norm are taken as 1, – deviation from the norm) – «+2, +4, etc.», decrease in the indicator (times by deviations from the norm) – «-2, -4, etc.», the value of the indicator, which has up to 50% Results within the limits of the norm, and the remaining increase is «+0,5», the value of the indicator, which has up to 50% of the results of the decrease from the norm – «-0,5»

According to the data obtained (see Fig. 9), the normal reaction of the stress system is characterized by synchronous activation of the SR and SL links, that is, the concept of "vegetative balance" is defined. Based on these data, it becomes possible to evaluate the reaction of the stress system in various clinical situations. It has been revealed that the point of application of preparations for general anesthesia is the SL-link of the stress system, which allows using the new term "stress-limiting" anesthesia, which differs from the term "general anesthesia" in assessing the adequacy of anesthesia, and not just "depth of anesthesia." The data obtained can be a platform for assessing the adequacy of new combinations of drugs for general anesthesia in various clinical situations associated with the initial disruption of the activity of the stress-system links.

Conclusions

1. The normal initial reaction of the SR-link of the stress system was determined (the normal stress-typical stress response in adults and children) on preoperative (psycho-emotional) and pain (traumatic) stress, which is expressed in: normal level of cortisol (adrenal level); Normal level of CTRF (hypothalamic level); Increased level of histamine; The normal level of IL1; The normal level of IL6; Increased IL2; A decrease in the level of TNFα.

2. The normal initial reaction of the SL-link of the stress system was determined which was expressed in: normal serotonin level in children and increase in 30% of adults (a typical pathophysiological reaction associated with age, which demonstrates the "vulnerability" of the SL-link in adults); Reduction of β-endorphin level (a discussion on the need to enhance opioid exposure in order to prevent inadequate anesthesia); An increase in IL4 mean values.

3. A typical reaction of the SR-link of the stress system to the surgical intervention (surgical stress) was carried out using standard variants of TIA (SA group) and modified variants (MA group). It was revealed: increased cortisol level, increased CTRF level, normalization of histamine level, normalization of IL1 indices, lowering of IL6 level, increased level of IL2, increase of TNFα level.

4. A typical reaction of the SL-link of the stress system to the surgical intervention (surgical stress) was carried out using standard TIA variants (group SA) and modified variants (MA group). A decrease in the level of serotonin (decrease in the SL potential and the need for additional activation via NMDA receptors), an increase in β-endorphin level (adequacy of opioid stimulation of the SL-link), an increase in IL4 in 75% of adults and 80% of children

(the need for additional stimulation through GABA receptors).

5. The "norm of pathology" (or "stress-norm") of the reaction of the SR-link was first defined-stress-realizing (hyper-stress) - protective, starting from which it became possible to evaluate the reaction of the stress system in another pathology and species (combinations) Anesthesia. It was proved that combinations of drugs for general anesthesia (in manufacturer's recommended dosages) could not influence the activity of the SR-link of the stress system in patients of the general surgical group.

6. For the first time, the "pathology norm" (or "stress rate") of the SL-link reaction (stress-restriction activation) was determined, which can be evaluated as normal when it is identical to the SR-stimulation, to level out the destabilizing effect of SR-stimulation, That is, autonomic stabilization is achieved. Unlike the SR-link, the tendency of the combination of drugs for general anesthesia to affect the activity of the SL-link receptors has been revealed, the "point of application" for drugs has been shown, with the prospect of developing techniques (new combinations) capable of affecting serotonin metabolism in the brain.

7. It is possible to introduce a new concept – stress-limiting anesthesia, which is necessary, due to the received data that "depth of anesthesia" and "adequacy of anesthesia" – these are not identical concepts. Preparations for general anesthesia affect, first of all, the activity of the SL-link of the stress system and it is due to their combinations based on the initial activity of the stress system that it is possible to achieve adequate stress-limiting anesthesia.

Conflicts of interest

The authors have no conflict of interest to declare.

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