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STRESS RESPONSE AND STATE OF COGNITIVE FUNCTIONS IN THE PERIOPERATIVE PERIOD IN ELDERLY PATIENTS DURING LAPAROSCOPIC CHOLECYSTECTOMY

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The aim. To investigate the dynamics of stress markers and the state of cognitive functions in the perioperative period during laparoscopic cholecystectomy in elderly patients.

Materials and methods. We examined 84 patients aged 68.1 ± 0.6 years, with diagnosed gallstone disease, acute cholecystitis, who underwent laparoscopic cholecystectomy. Patients were randomized into 2 groups: Group I – inhalation anesthesia based on sevoflurane with mechanical ventilation; Group II – TBA based on propofol with mechanical ventilation. Hemodynamic parameters, dynamics of stress markers (cortisol, insulin, glucose) and cognitive function were investigated.

Results. Glucose and insulin levels in both groups remained within normal limits at all stages of the study. The baseline cortisol level was higher than normal in both groups, but at 4, 5, 6 stages of the study decreased significantly compared with baseline values ($p < 0.001$).

In the study of cognitive functions by the Luria test and the MMSE scale, a significant decrease was found in both groups on the day after surgery.

According to the Luria test, the score in group I significantly decreased the day after surgery against the period before premedication by 8.7 % ($p < 0.001$), in group II – by 10.1 % ($p < 0.001$); according to the MMSE scale, the score in group I significantly decreased on the day after surgery against the period before premedication by 6.0 % ($p < 0.001$), in group II – by 6.3 % ($p < 0.001$).

On the fifth postoperative day, no significant differences in baseline values between the Luria test and the MMSE scale were detected.

Conclusions. The comparative analysis of the dynamics of stress marker levels in both groups revealed some advantages of general sevoflurane-based anesthesia in antistress protection of patients in the perioperative period during laparoscopic cholecystectomy compared with total intravenous anesthesia based on propofol. However, the effectiveness of anti-stress protection of both types of anesthesia was sufficient.

According to the correlation analysis, an inverse correlation was found between the state of cognitive functions in the postoperative period and the level of cortisol in the intraoperative period

Key words: inhalation anesthesia, total intravenous anesthesia, laparoscopic cholecystectomy, cortisol, insulin, glucose, cognitive dysfunction, elder patients

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1. Introduction

Modern requirements for anesthesia provide not only the possibility of perioperative analgesia, but also the prevention of possible complications and adverse effects associated with surgical stress [1]. Any surgery, from minimally invasive to major surgeries, is accompanied by tissue damage, blood loss, severe surgical stress response, and postoperative pain. The body's response to surgery is an increase in the content of stress hormones in the blood, such as cortisol, adrenaline, insulin, etc. [2].

Studies have found that the stress response is one of the key factors in the development of postoperative cognitive dysfunction [3, 4]. It is believed that an increase in markers of surgical stress response may indicate an increased risk of postoperative cognitive impairment – an adverse event caused by general anesthesia [5].

It should be noted that in the last decade there has been growing concern about the adverse effects of general anesthesia on the brains of elderly patients, as such

surgical patients often have postoperative cognitive impairment, which in turn can increase morbidity and mortality [6]. Postoperative cognitive impairment (PCI) is a disorder that develops in the early postoperative period, persists for days or weeks, rarely months, and is clinically manifested by memory impairment, difficulty concentrating and long-term attention, and impairment of such higher cortical functions. as thinking, speech, etc. The patient has problems with learning, decreased mental capacity, deteriorating mood, depression.

The medical and social significance of the study of stress response is also due to the fact that the pronounced stress response of the body to surgery increases the number of postoperative complications, prolongs hospital stays, increases the cost of treatment, impairs the quality of life of surgical patients, mostly elderly one [7].

The methods of general anesthesia, that are currently used, could be able to correct endocrine and metabolic disorders in the intraoperative period. At the same time, in recent years there has been a growing interest in

the impact of surgery and general anesthesia on the body of the elderly.

The system for assessing the severity of the stress response is a rather complex issue. Under general anesthesia, consciousness is switched off and there is no emotional coloration of pain. Under such conditions, monitoring the standard set of parameters (measurement of blood pressure, heart rate, determination of cardiac output, pulse oximetry, capnography) sometimes creates the illusion of good condition [8]. Determining the level of stress hormones is a recognized way to assess the state of the sympathoadrenal system of the body [9]. If non-invasive assessment of central hemodynamic parameters is available for most hospitals, laboratory assessment of the stress response, i.e. determination of stress hormone levels, is possible in a few hospitals. The issue of operational risk stratification remains relevant given that laboratory methods for many items are not always available.

The aim of the research. To study the dynamics of levels of stress markers and the state of cognitive functions in the perioperative period during laparoscopic cholecystectomy in elderly patients.

2. Materials and methods

During 2019–2020, 84 patients diagnosed with gallstone disease (GD), acute cholecystitis, who underwent laparoscopic cholecystectomy, were examined at the CNE "City Clinical Hospital of Emergency Medical Care OI Meshchaninov" of Kharkiv City Council. (LC). The average age was 68.1 ± 0.6 years, the average duration of the operation was 61.1 ± 2.7 minutes.

Prior to the study, according to the Declaration of Helsinki, all patients were informed about the objectives and methods of the study. The study was approved by the Commission on Ethics and Bioethics within the Scientific and Methodological Council of the Kharkiv Medical Academy of Postgraduate Education (Minutes №3 of October 22, 2020).

Inclusion criteria: age of patients from 60 to 90 years, the presence of a confirmed diagnosis of GD, acute cholecystitis, physical status of the patient according to the classification of the American Society of Anesthesiologists (ASA) – I–III, coronary heart disease (CHD), atherosclerosis, hypertension I–II st., heart failure I–IIA st., I–II FC, absence of cardiovascular events in the anamnesis (myocardial infarction, acute cerebrovascular accident).

Exclusion criteria: patient age less than 60 or over 90, physical status of the patient according to the American Society of Anesthesiologists (ASA) - IV, diabetes mellitus, CNS disease, intracranial hypertension, mental illness, history of cardiovascular events (myocardial infarction, acute cerebrovascular accident), the patient's reluctance to participate in the study.

Depending on the type of anesthesia, patients were divided into 2 groups:

group I (n=42) – inhalation anesthesia based on sevoflurane (2–3 vol. %) with mechanical ventilation;

group II (n=42) – TBA based on propofol (2 mg / kg / h) with mechanical ventilation. In both groups, analgesia was performed with fentanyl (1 µg / kg / h), relaxation – atracurium (Table 1).

Table 1

Distribution of patients depending on the type of anesthesia

Group I (n=42)	Group II (n=42)
inhalation anesthesia based on sevoflurane (2–3 vol. %) with mechanical ventilation	TBA based on propofol (2 mg / kg / h) with mechanical ventilation
analgesia – fentanyl (1 µg / kg / h)	
relaxation – atracurium	

Monitoring of hemodynamic parameters consisted of determining heart rate (HR), systolic blood pressure (sBP), diastolic blood pressure (dBP), average blood pressure (ABP), cardiac output (SV). These measurements were performed using a monitor "Vismo PVM-2701" NIHON-KOHDEN (Japan).

These indicators were monitored continuously in real time throughout the anesthesia and surgery. However, for the analysis of the material the following stages were distinguished: stage 1 – before premedication; stage 2 – after premedication; stage 3 – intubation; stage 4 – the beginning of the operation; stage 5 – imposition of carboxyperitoneum (CP); stage 6 – the middle of the operation; stage 7 – extubation; stage 8 – 20 minutes after the operation.

Monitoring of stress response was performed by studying the level of stress markers (cortisol, insulin, glucose) at the following stages: stage 1 – before premedication, stage 2 – after premedication, stage 3 – intubation, stage 4 – start of surgery, stage 5 – imposition of carboxyperitoneum, stage 6 – the middle of the

operation, stage 7 – the end of the operation, stage 8 – 20 minutes after the operation, stage 9 – the day after the operation.

The level of cortisol in the serum was determined by enzyme-linked immunosorbent assay using test systems "Cortisol-ELISA-BEST (3964)" manufactured by LLC "Vector-Best-Ukraine"; insulin level – enzyme-linked immunosorbent assay using test systems "Insulin-ELISA-BEST (4002)" manufactured by "Vector-Best-Ukraine"; glucose level – glucose oxidase method using test systems "Glucose SPL 100" manufactured by LLC "SpineLab" (Ukraine). In the perioperative period, glucose infusion was not performed in patients.

Patients' cognitive function was assessed using neuropsychological scales: the 10-word memorization test by O. R. Luria and the Mini-Mental State Examination Scale (MMSE). The study of memory by the method of O. R. Luria uses a quantitative test of memorization of 10 words. The test is designed to diagnose auditory verbal memory.

MMSE is widely used in most modern epidemiological and clinical studies for screening and evaluation of cognitive impairment, which confirms its validity and suitability. The MMSE scale consists of a number of subtests that make it possible to quickly and effectively assess the orientation in time, place, as well as the state of short-term, long-term memory, language function, gnosis, praxis. The total score is calculated by summing the scores for individual subtests.

Studies of cognitive function were performed three times: stage 1 – before surgery, stage 2 – the day after surgery, stage 3 – on the fifth day after surgery.

The obtained data were analyzed using statistical processing using the computer program SPSS19 for Windows and methods of descriptive statistics. The Shapiro-Wilk test was used to determine the nature of the distribution of the obtained data. Data are presented in the form of $M \pm m$ (average value \pm average error of the average value). In the process of studying the dynamics of indicators relative to baseline levels, Student's t-test was used for dependent samples, and in intergroup comparisons, Student's t-test was used for independent samples. Pearson's correlation coefficient was determined to study the correlation. Differences were considered statistically significant at $p < 0.05$.

3. Research results

In terms of hemodynamics, patients did not differ significantly between groups at the stages of the study.

However, at the end of the operation, the average blood pressure (ABP) in group II was significantly higher than in group I ($p < 0.05$) and amounted to 99.3 ± 1.6 mm Hg. In contrast, ABP in group I was 95.3 ± 1.4 mm Hg. This may be due to the fact that the average wake-up time in group II was shorter – 10.7 ± 1.6 vs 6.6 ± 1.2 min ($p = 0.044$).

The results of the study indicate that the initial values of glucose levels in both groups were within normal limits. The level of glucose at the beginning of the operation and the imposition of CP, in the middle of the operation and at the end of the operation significantly decreased compared to baseline values in both groups ($p < 0.001$). But the values of glucose levels in patients of group I were significantly lower than in patients of group II after premedication ($p = 0.037$), at the time of intubation ($p = 0.033$), in the middle of the operation ($p = 0.046$) and 20 min after surgery ($p < 0.001$).

Cortisol levels at baseline were higher than normal in both groups. But the indicators of cortisol levels at the beginning of the operation and the imposition of CP, in the middle of the operation and at the end of the operation significantly decreased compared to baseline values in both groups ($p < 0.001$). Cortisol levels in patients of group I were significantly lower than in patients of group II at the time of intubation ($p = 0.045$), in the middle of the operation ($p = 0.042$), at the end of the operation ($p < 0.001$) and 20 min after surgery ($p < 0.001$) (Table. 2).

Table 2

Dynamics of levels of stress markers at the stages of the study

Stages of the research	Group	Indicators of stress response				
		Glucose, mmol/l	Cortisol, mmol/l	Insulin, μ od/ml	C/I	HOMA
Before premedication	I	5.4 ± 0.1	685.2 ± 12.5	7.4 ± 0.1	92.9 ± 1.7	1.7 ± 0.1
	II	5.5 ± 0.1	702.2 ± 11.4	7.4 ± 0.1	94.3 ± 1.7	1.8 ± 0.1
After premedication	I	$4.9 \pm 0.1^*$	594.4 ± 10.1	7.1 ± 0.1	83.7 ± 1.6	1.6 ± 0.1
	II	5.2 ± 0.1	608.8 ± 16.6	7.0 ± 0.1	87.9 ± 2.7	1.6 ± 0.1
Intubation	I	$5.4 \pm 0.1^*$	$618.9 \pm 21.9^*$	7.3 ± 0.1	85.7 ± 3.2	1.7 ± 0.1
	II	5.6 ± 0.1	668.5 ± 10.4	7.3 ± 0.1	92.6 ± 2.4	1.8 ± 0.1
The beginning of the operation	I	4.7 ± 0.1	503.8 ± 9.3	7.2 ± 0.1	70.7 ± 1.7	1.5 ± 0.1
	II	4.8 ± 0.1	521.1 ± 11.1	7.1 ± 0.1	74.2 ± 1.8	1.5 ± 0.1
Imposition of CP	I	4.7 ± 0.1	504.0 ± 9.3	7.1 ± 0.1	70.9 ± 1.7	1.5 ± 0.1
	II	4.8 ± 0.1	518.1 ± 12.1	7.1 ± 0.1	72.9 ± 1.8	1.5 ± 0.1
The middle of the operation	I	$4.4 \pm 0.1^*$	$361.3 \pm 5.9^*$	$8.5 \pm 0.1^*$	$42.9 \pm 0.8^*$	1.6 ± 0.1
	II	4.6 ± 0.1	395.7 ± 15.4	8.1 ± 0.1	49.4 ± 2.0	1.6 ± 0.1
The end of the operation	I	4.9 ± 0.1	$445.7 \pm 7.4^{**}$	$8.2 \pm 0.1^*$	$55.0 \pm 1.2^{**}$	1.8 ± 0.1
	II	5.1 ± 0.1	499.5 ± 7.5	7.8 ± 0.1	65.5 ± 1.5	1.8 ± 0.1
In 20 minutes after surgery	I	$5.1 \pm 0.1^{**}$	$550.1 \pm 9.5^{**}$	7.4 ± 0.1	$74.8 \pm 1.7^{**}$	1.7 ± 0.1
	II	5.4 ± 0.1	616.8 ± 9.2	7.3 ± 0.1	84.5 ± 1.4	1.7 ± 0.1
The next day after surgery	I	4.7 ± 0.1	486.4 ± 14.4	7.1 ± 0.1	67.2 ± 2.2	1.5 ± 0.1
	II	$4.5 \pm 0.1^*$	514.6 ± 21.9	7.2 ± 0.1	73.0 ± 3.5	1.4 ± 0.1

Note: * – significant differences between groups I and II, $p < 0.05$; ** – significant differences between groups I and II, $p < 0.001$.

Insulin levels in both groups remained within the reference values at all stages of the study, but their values in group I patients were significantly higher than in group II patients in the middle ($p = 0.004$) and at the end of surgery ($p = 0.012$).

The HOMA index in both groups remained within normal limits at all stages of the study.

Cortisol-insulin index (C/I) in both groups significantly decreased at the beginning of the operation and the imposition of CP, in the middle of the operation, at the end of the operation and 20 min after the operation compared to baseline ($p < 0.001$), which also indicates adequate anti-stress protection during anesthesia in both groups. However, C/I values in group I patients were

significantly lower than in group II patients in the middle of the operation ($p=0.004$), at the end of the operation ($p<0.001$) and 20 min after the operation ($p<0.001$).

The dynamics of changes in cognitive functions was also studied.

According to the Luria test, patients of group I at the stage before premedication memorized 7.5 ± 0.1 words, the next day after surgery – 6.8 ± 0.1 words ($p<0.001$), on the fifth day after surgery – 7.3 ± 0.1 words ($p>0.05$). In group II at the stage before premedication patients memorized 7.6 ± 0.1 words, the day after surgery – 6.9 ± 0.1 words ($p<0.001$), on the fifth day after surgery – 7.5 ± 0.1 words ($p>0.05$).

According to the MMSE scale in group I, the score at the stage before premedication was 28.2 ± 0.2 points, the day after surgery – 26.6 ± 0.2 points ($p<0.001$), on the fifth day after surgery – 28.1 ± 0.2 points ($p>0.05$). In group II, the result was at the stage before premedication 28.8 ± 0.2 points, the next day after surgery – 27.1 ± 0.2 points ($p<0.001$), on the fifth day after surgery – 28.7 ± 0.2 points ($p>0.05$).

4. Discussion of research results

One of the main issues that remains in the focus of anesthesiologists is the problem of protecting patients from surgical trauma and the adequacy of general anesthesia. In elderly patients, homeostatic balance is easier to change under the influence of exogenous stimuli, such as surgical stress. The presence of comorbidity, the accession of the syndrome of senile asthenia, which is accompanied by severe depression of life, age-related changes in the neurohumoral system increase the frequency of complications in the development of surgical stress. Excessive and prolonged surgical stress can significantly worsen the physical and mental condition of elderly patients. This is why their functional recovery after surgery may be more difficult against young patients. Therefore, it is extremely important to minimize this impact by reducing the duration of hospitalization.

Surgery significantly stimulates endogenous cortisol secretion [10]. The constant increase in glucocorticoid levels affects cognitive functions [11], therefore, prolonged and severe stress response in elderly patients may play an important role in the development of PCI.

Cortisol is widely used as a marker of surgical stress, because its secretion is proportional and positively correlates with the amount of painful stimulation [12]. In the process of physiological aging, the number of glucocorticosteroid receptors in the hypothalamus gradually decreases. This weakens this negative feedback mechanism, which inhibits further secretion of corticosteroids [13]. Loss of glucocorticoid receptors and weakening of the feedback mechanism make the elderly more prone to chronic hypersecretion of corticosteroids and cognitive impairment after surgery. In patients who have undergone non-cardiac surgery, elevated cortisol levels are associated with cognitive dysfunction in the early postoperative period [14]. This is confirmed by a negative correlation between plasma cortisol levels and MMSE assessment in elderly patients 7 days after surgery due to hip fracture under spinal anesthesia [15].

In this study, glucose and insulin levels in patients in both groups at the study stages were within the refer-

ence range. However, the level of cortisol at the initial stage of the study was higher than normal in both groups, due to the presence of preoperative stress, fear and unpleasant emotions. However, cortisol levels at the beginning of surgery and CP, in the middle of surgery and at the end of surgery were significantly reduced compared to baseline in both groups ($p<0.001$), which may indicate sufficient anti-stress protection of both types of anesthesia. However, cortisol levels in patients of group I were significantly lower than in patients of group II at the time of intubation ($p=0.045$), in the middle of the operation ($p=0.042$), at the end of the operation ($p<0.001$) and 20 min after surgery ($p<0.001$). Thus, a comparative analysis of the dynamics of stress marker levels in both groups revealed some advantages of general sevoflurane-based anesthesia in antistress protection of patients in the perioperative period during laparoscopic cholecystectomy compared with total intravenous anesthesia based on propofol with mechanical ventilation.

In the process of studying cognitive functions according to the Luria test and the MMSE scale, a significant decrease was found in both groups on the day after surgery. According to the Luria test, the score in group I significantly decreased on the day after surgery against the period before premedication by 8.7 % ($p<0.001$), in group II – by 10.1 % ($p<0.001$); according to the MMSE scale, the assessment in group I significantly decreased on the next day after surgery against the period before premedication by 6.0 % ($p<0.001$), in group II – by 6.3 % ($p<0.001$).

On the fifth day after surgery, no significant differences from baseline in the Luria test and the MMSE scale were found.

As a result of the correlation analysis, patients of group I showed a moderate inverse correlation between the result of the Luria test in stage 3 of the study (fifth postoperative day) and cortisol levels in stage 3 of the study, at the time of tracheal intubation -0.392 ; $p=0.010$). In group II patients, a moderate inverse correlation was found between the MMSE test result in stage 3 of the study (fifth postoperative day) and cortisol levels in stage 8 of the study, which coincides with the time of tracheal extubation ($r=-0.365$; $p=0.017$).

M. L. Piekarska et al. [16] found a direct relationship with an increased risk of postoperative complications from the level of cortisol secretion. However, no correlation was found between the decrease in cortisol levels and the age of the patients.

D. L. Mu et al. [17] showed an association between high plasma cortisol levels on the first day after coronary artery bypass graft surgery and an increased risk of cognitive impairment in the early postoperative period. Patients with a cortisol concentration of 690 nmol/l had a higher risk of PCI ($p<0.001$).

The opposite results reached S. Glumac et al. [18] in a prospective cohort study of patients who underwent planned heart surgery. Cortisol levels were determined the day before surgery, 1 day after surgery (08-00, 16-00 and 24-00), for 3 and 5 days. The study did not find a significant correlation between the duration and severity of the cortisol response to surgery and the occurrence of early PCI. This study had several possible limitations because it investigated the association of cortisol levels

with the appearance of only early PCI, while the cause of later cognitive impairment may include not only the effects of surgery but also the effects of physiological aging, progression of cardiovascular or cerebrovascular disease.

According to N. K. Hashmi and M. V. Podgoreanu [19], surgical stress affects the body of elderly patients, increasing the risk of postoperative complications. This is directly related to the processes of wound healing and recovery of the patient in general [20]. Anesthesia and postoperative analgesia only partially relieve the stress response after surgery, which negatively affects the quality of life of patients [21]. However, laparoscopic surgery causes a less stable acute phase and an immune response against open procedures, as well as a reduction in postoperative pain and the length of hospital stay [22, 23].

Study limitations. The small number of examined patients does not allow to disseminate the obtained data to the entire patient population, which requires further research.

Prospects for further research. Further study of the effect of hormonal markers of stress in the perioperative period on the state of cognitive functions in elderly patients is needed.

5. Conclusions

A comparative analysis of the dynamics of stress marker levels in both groups revealed some advantages of general sevoflurane-based anesthesia in antistress protection of patients in the perioperative period during laparoscopic cholecystectomy compared with total intravenous anesthesia based on propofol with mechanical ventilation. However, the effectiveness of anti-stress protection of both types of anesthesia was sufficient.

According to the correlation analysis, an inverse correlation was found between the state of cognitive functions in the postoperative period and the level of cortisol in the intraoperative period.

Conflict of interests

The author declares no conflict of interests.

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