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INFLUENCE OF COMPONENTS OF ANESTHESIA ON DYNAMICS OF STRESS MARKERS IN GYNECOLOGICAL LAPAROSCOPIC SURGERY

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Abstract. Influence of components of anesthesia on dynamics of stress markers in gynecological laparoscopic surgery. Khalimonchyk V., Klygunenko O. *Surgical procedures are associated with a complexity of stress response characterized by neurohumoral, immulogic, and metabolic alterations. Objective: to evaluate the effect of combined intraoperative use of ketamine in low subnarcotic doses and dexketoprofen on intensity of the pain syndrome and dynamics of the stress response in gynecological laparoscopic surgery. A total of 45 patients scheduled for laparoscopic gynecological surgery under total intravenous anesthesia (TIA) were examined randomly and divided into 2 groups. Demographic characteristics, anthropometric data, functional status, duration of surgery and anesthesia were similar in all groups. Group 1 (n=25) patients received total intravenous anesthesia (TIVA) with propofol and fentanyl. Group 2 (n=20) patients received TIVA with additional administration of subanesthetic doses of ketamine and a single administration of 50 mg of dexketoprofen 30 minutes before the end of the surgery. Cortisol and blood glucose levels were evaluated before induction into anesthesia, after the main stage of operation, 2 and 24 hours after surgery. The intensity of postoperative pain was evaluated by VAS in 2 and 24 hours after surgery. The intensity of postoperative pain, concentration of serum cortisol 2 hours after surgery were significantly lower (p <0.05) in patients of group 2, compared to control (p<0,05). Differences of blood glucose levels between groups at the stages of the study were not identified. Combined intraoperative use of subanesthetic doses of ketamine and dexketoprofen at the end of the surgery provides a stress-protective effect. This is confirmed by the rapid normalization of serum cortisol levels and stable blood glucose levels after surgery and is manifested by a low level of postoperative pain syndrome.*

Реферат. Влияние компонентов анестезии на динамику маркеров стресса при лапароскопических операциях в гинекологии. Халимончик В.В., Клигуненко Е.Н. *Хирургическая травма вызывает стрессовую реакцию в организме и представляет собой сложный каскад нейроэндокринных, метаболических, коагуляционных, воспалительных и иммунных реакций. Цель исследования: оценить влияние комбинированного интраоперационного применения кетамина в субнаркотических дозах и декскетопрофена на интенсивность болевого синдрома и динамику стрессового ответа при проведении лапароскопических оперативных вмешательств в гинекологии. Обследовано 45 пациенток гинекологического профиля, которым проводились плановые лапароскопические оперативные вмешательства в условиях тотальной внутривенной анестезии (ТВА) с искусственной вентиляцией легких с использованием пропофола и фентанила. В зависимости от схемы интраоперационного обезболивания пациентки были разделены на две группы, сопоставимые по возрасту, антропометрическим данным, функциональному состоянию, продолжительности анестезии и оперативного вмешательства. Пациенткам I группы (n=25) проводилась стандартная ТВА; II группы (n=20) – ТВА с добавлением субнаркотических доз кетамина (до 0,5 мг/кг) и однократным введением декскетопрофена (50 мг) за 30 минут до окончания операции. Уровень кортизола и глюкозы крови определяли до индукции в анестезию, после окончания основного этапа операции, через 2 и 24 часа после операции. Интенсивность послеоперационного болевого синдрома оценивали по визуальной аналоговой шкале через 2 и 24 часа после операции. Интенсивность послеоперационной боли, концентрация кортизола в крови были ниже (p<0,05) через 2 часа*

после операции при комбинированном интраоперационном применении кетамина в субнаркотических дозах и декскетопрофена. Различий в уровне глюкозы между группами на этапах исследования не выявлено. Комбинированное интраоперационное применение субнаркотических доз кетамина и декскетопрофена в конце операции обеспечивает стресс-протективный эффект, что подтверждается быстрой нормализацией уровня кортизола в сыворотке крови, стабильным уровнем гликемии после операции и проявляется низким уровнем послеоперационного болевого синдрома.

Surgical trauma causes a stress response in the body and is a complex cascade of neuroendocrine, metabolic, coagulation, inflammatory and immune responses that increase the body's ability to recover. This stereotyped multilevel response to stress is modified by endogenous factors such as age, gender, previous health status, genome, and exogenous factors, including type, duration and invasiveness of surgery, anesthesia, infusion therapy, intensive care, etc. The interaction between endogenous and exogenous factors determines the variability of postoperative results and courses of recovery [12, 13].

The pathogenic nature of the surgical stress response has been proven, which significantly impairs the postoperative period and prolongs the rehabilitation time of patients. Surgical stress response is the main cause of postoperative dysfunction of various organs and systems which dictates the need to find approaches to its correction [2]. In this regard, limiting the severity of the surgical stress response becomes one of the leading tasks of anesthesia and postoperative intensive care [6].

The reaction to "stress" begins with the activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system through afferent nerves from the site of tissue damage [14]. This leads to increased secretion of adrenocorticotropic hormone, cortisol, catecholamines and inflammatory mediators.

The role of cortisol in stressful situations is to temporarily increase energy production by limiting processes that are not required for immediate survival [8]. Cortisol increases glucose levels due to gluconeogenesis, suppresses the immune system, increases the metabolism of fats, proteins and carbohydrates [5].

Conventional mechanisms that support glucose homeostasis become ineffective in the postoperative period. Increased levels of cortisol lead to the development of insulin resistance and hyperglycemia, which have a significant impact on wound healing processes and to increased morbidity and mortality after surgery [4].

Cortisol is one of the most commonly used markers of the level of adaptive response (stress). Plasma cortisol concentrations may increase 2-10 times after induction of anesthesia, during surgery and postoperatively and returns to normal within 24 hours after surgery; however, depending on the severity of the surgical trauma, it may remain elevated for 72 hours [1]. The degree of cortisol increase in blood was found to be generally proportional to the severity of the injury. There is a clear correlation between surgical stress and cortisol levels in patients undergoing surgery [8].

Pain as one of the consequences of acute trauma can be involved in the realizatrion and maintenance of stress responses to surgical trauma. Adequate pain control cannot be achieved without normalizing hormonal homeostasis. Cortisol secretion during a non-pain-related stress reaction can avert attention from a concurrent pain stimulus, thus suppressing pain, whereas cortisol secretion in response to pain (i.e. when pain is a stressor) can enhance pain and cause fear-based fear formation [3]. In addition, pain-induced reflex responses can lead to impaired pulmonary, immunological, and metabolic functions. Thus, the relief of acute pain may also reduce the response to operative stress and improve treatment outcomes.

The aim of the study is to evaluate the effect of combined intraoperative use of ketamine in subnarcotic doses and dexketoprofen at the end of surgery on the intensity of pain syndrome and the dynamics of stress response during laparoscopic surgery in gynecology.

MATERIALS AND METHODS OF RESEARCH

On the basis of Endotechnomed LLC Medical Center "Clinic Garvis" (Chief - Doctor of Medical Sciences, Professor Bereznytsky YaS), 45 patients aged 21 to 60 years were examined in the period from 2015 to 2017 (mean age 41.1±2.1 years). Criteria for inclusion in the study: age from 20 to 60 years, planned surgical gynecologic intervention by laparoscopic method in the conditions of total intravenous anesthesia (TIVA) with artificial lung ventilation (IVL). Exclusion criteria: decompensated extragenital pathology, oncologic pathology, diabetes mellitus, hyperthyroidism, mental illness (schizophrenia, acute psychosis), hypersensitivity to drugs used during anesthesiology, surgical conversion, refusal to participed.

By age, anthropometric data, functional status, duration of anesthesia and surgery groups did not differe (Table 1).

Table 1

General characteristics of patients by groups (M±m)

Finding	Group I (n=25)	Group II (n=20)
Age (years)	40,9±3,53	41,0±3,58
Weight (kg)	68,31±4,87	67,0±6,04
Height (cm)	163,34±2,26	163,81±2,57
IMT	25,67±1,91	24,9±1,99
ASA I / II	3 / 22	1 / 19
Duration of surgery, min.	118,75±11,81	119,05±16,56
Duration of general anesthesia, min.	134,44±12,86	131,90±16,71

All patients underwent surgery under TIVA with IVF with propofol and fentanyl. Anesthesia induction, muscle relaxation, tracheal intubation, and mechanical ventilation were performed according to conventional methods. Depending on the scheme of intraoperative analgesia, women were randomly divided into two groups. Group I patients (n=25) were given standard TIVA; Group II (n=20) – TIVA with addition of ketamine (0.3-0.5 mg/kg) onto the skin incision and repeated bolus administration (0.2-0.3 mg/kg) 30-40 minutes after and single administration of dexketoprofen (50 mg) 30 minutes before surgery. The rate of infusion of propofol was adjusted to maintain the target bispectral index (BIS) in the range of 40-55. Propofol infusion was stopped at the end of surgery before the last sutures were applied to the skin. The neuromuscular block was supported by the administration of non-depolarizing muscle relaxants in the recommended doses.

During the operation, ECG monitoring, heart rate (HR), non-invasive blood pressure (BP), pulse oximetry (SpO2), capnography (EtCO2) were performed. Depth of anesthesia was monitored using a BIS-index (BISX Module monitor, BIS ™ Covidient, USA), and depth of neuro-muscle block - TOF monitoring (TOF-Watch®SX, Organon, Ireland).

Post-operative analgesia in all groups was performed with the introduction of dexketoprofen. A modified visual analog scale (VAS) was used to assess pain. The basic goal was to maintain a PPS less than 3 points. Serum cortisol concentration was determined by enzyme-linked immunoassay using standard kits (Cortisol ELISA, DRG, Germany) according to the manufacturer's instructions. Glucose content was determined by the enzymatic method.

Control points: stage 1 – before induction of anesthesia, stage 2 – after the main stage of surgery, stage 3 – 2 hours after surgery, stage 4 – 24 hours after surgery.

To determine the regional standard, 20 women aged 39.8±3.5 years without serious chronic diseases were examined.

Ethical aspects of the work were approved at the meeting of the Committee on Biomedical Ethics of the SE "Dnepropetrovsk Medical Academy of the Ministry of Health of Ukraine" (protocol No. 2 of February 12, 2015).

Statistical analysis of the primary database was performed using parametric and non-parametric statistics. The normality of the distribution of quantitative indicators was checked using the Kolmogorov-Smirnov criterion. Quantitative data with normal distribution are presented as arithmetic mean and standard deviation (M±Sd). Non-normal distributions were described using median (Me) and interquartile range (25%; 75%). For statistical analysis, the Kruskal-Wallis method, the Mann-Whitney U-test, Wilcoxon test were used. Value $p<0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

The indicators obtained during the study were compared with those of healthy volunteers (reference values), which were taken as normal. We also conducted an intergroup comparison of the results obtained (Table 2).

Baseline serum cortisol levels were 150.0 (124.6; 162.0) ng/ml in patients of group I and 184.6 (105.8; 352.1) in group II, which was lower than the reference values. No significant differences in cortisol concentrations were found in the intergroup comparison.

After completion of the main stage of surgery, there was a significant increase in the content of cortisol in patients in both groups. Thus, when using standard TIVA, the hormone level exceeded baseline and norm by 114.9% and 64.4% respectively, and with intraoperative administration of ketamine as an adjuvant – by 114.1% and 101.5%. There were no significant differences between the groups.

Table 2

Dynamics of stress markers at stages of investigation

Stage	Group I (n=25)	Group II (n=20)	Reference values
	Cortisol ng/ml		
1	150,0 (124,6; 162,0)	184,6 (105,8; 352,0)	196,15 (141,67; 306,43)
2	322,4 (211,9; 360,3)#	395,3 (187,1; 482,9)#	
3	398,7 (345,7; 495,5)#	292,5 (194,3; 417,9)*	
4	262,3 (143,6; 317,9)#	185,7 (170,4; 303,3)	
	Glucose, mmol/l		
1	3,8 (3,7; 4,5)	4,30 (4,2; 4,8)	4,82 (3,78; 5,10)
2	4,9 (4,6; 5,7)#	5,62 (5,3; 6,5)#	
3	5,6 (5,1; 6,3)#	5,2 (4,6; 5,9)	
4	5,0 (4,3; 6,4)#	4,3 (3,5; 5,4)	

Note: * p<0,05 – compared between grpups; # p<0,05 – compared with 1 stage.

Two hours after surgery a tendency for a further increase in serum cortisol concentration, was maintained in control patients. Cortisol content increased by 23.7% compared to the previous stage and probably exceeded the initial values by 165.8%, the norm – by 103.3%. At the same time, against combined intraoperative use of ketamine in subnarcotic doses and dexketoprofen at the end of surgery, cortisol levels were reduced by 26.0% from the previous stage, and unreliably exceeded baseline and reference values by 58.5% and 49.1%, respectively,. However, cortisol content in patients in group II was significantly lower by 26.6% compared with the control group.

On day 1 after surgery in the first group of patients, the concentration of cortisol decreased significantly by 34.2% compared to the previous stage, but exceeded ($p<0.05$) preoperative and reference rates (by 74.8% and 33.7%, respectively). In group II patients, cortisol content decreased by 36.5% ($p> 0.05$) compared to the previous stage and returned to baseline values.

The level of glycemia in patients of I and II groups before surgery was not significantly different and was 3.8 (3.7; 4.5) and 4.3 (4.2; 4.8) mmol/l, respectively. This was below the reference value by 22.0% and 10.8%, respectively ($p> 0.05$). We did not find any significant differences between the glucose levels at the study stages.

Against the background of standard TIVA, glucose concentrations increased during the 2nd and 3rd stages. Thus, at the end of the traumatic stage, the level of glycemia was higher by 30.1% against baseline and by 1.45% against normal values.

2 hours after surgery, the glucose content increased by 13.9% compared to the previous stage and probably exceeded the baseline values and norm by 48.1% and 15.6%, respectively. On day 1 after surgery, glucose content decreased by 9.7% from the previous stage, but exceeded preoperative by 33.8% and by 4.36% norm ($p>0.05$).

In combined intraoperative use of sub-narcotic doses of ketamine and dexketoprofen after the traumatic stage of surgery, glucose content increased significantly by 30.7%, which exceeded the reference values by 16.6%. In subsequent stages, there was a gradual decrease in glycemia to baseline values. Thus, 2 hours after surgery, the blood glucose concentration decreased by 7.7% from the previous stage, but exceeded the preoperative level and norm by 20.7% and 7.68%, respectively. 24 hours after surgery, glucose content decreased significantly (by 17.5%) from previous values to baseline level, exceeding the norm by 11.2% ($p>0.05$).

Before surgery in patients of both groups, the pain was absent. 2 hours after surgery, patients in the control group experienced mild pain at rest and moderate when moving (2.8 (1.6; 3.5) points and 3.3 (2.5; 4.3) points, respectively). In patients of group II on the background of combined intraoperative use of ketamine in sub-narcotic doses and dexketoprofen, the pain level was 1.0 (0; 1.5) points at rest and 2.0 (1.0; 2.1) points when moving, which indicated about the absence of pain at rest and a slight pain when moving. Overall, the intensity of PPS by VAS in group II was probably lower (64.3% at rest and 39.4% when moving) compared to group I. The level of pain at rest and when moving 24 hours after surgery between the groups was not significantly different and made up 1.4 (1.0; 2.0) and 2.0 (1.5; 2.6), respectively, in patients of group I and 1.0 (1.0; 1.8) and 1.5 (1.0; 2.2) – group II. The time to first administration of analgesic in patients in group I was 26.9±1.8 minutes, in group II analgesic was administered after 234.3±29.2 minutes ($p<0.05$).

General anesthesia does not completely eliminate the stress response due to surgical trauma, since the hypothalamus and pituitary gland respond to harmful stimuli, even with deep anesthesia, but may limit it [9].

The increase in serum cortisol concentration during surgery occurred regardless of the anesthetic regimen. The most probable reason for this is the inability to provide absolute neurovegetical blockade with the anesthetics used, and in patients of group II - possibly also due to the sympathomimetic effect of ketamine.

The maximal increase in baseline cortisol and glucose levels in patients when using standard TIVA 2 hours after surgery is associated with the renewal of pain impulsation and activation of the sympathetic component of the autonomic nervous system due to the short duration of the analgesic effect of fentanyl [7]. This was confirmed by the development of moderate and severe postoperative pain and the need for "rescue" anesthesia in the first hours after surgery. Thus, when performing standard TIVA using propofol and opioids, there is a lack of post-anesthetic analgesia. The decrease in the concentration of stress markers occurred on day 1 after surgery and was accompanied by a decrease in the intensity of pain by VAS, which indicated a sufficient level of analgesia.

Against the background of combined intraoperative use of sub-narcotic doses of ketamine and dexketoprofen at the end of surgery, a decrease in cortisol and glucose was observed within 2 hours after surgery, and 24 hours after, their concentration reached baseline. This was accompanied by the absence of pain at the stages of the study, testified to adequate postoperative analgesia and proved the effectiveness of the scheme of anesthesia used.

An analysis of the dynamics of PPS revealed that the combined intraoperative use of sub-narcotic doses of ketamine and dexketoprofen at the end of surgery significantly prolonged the duration of the pain-free period compared with the control group. The analgesic properties of sub-narcotic doses of ketamine have been confirmed in many clinical trials [10] and are due to a decrease in central sensitization caused by tissue damage and a decrease in the development of opioid tolerance. Nonsteroidal anti-inflammatory drugs do not have a direct effect on the classical stress response, but they affect the synthesis of arachidonic acid metabolites involved in various stages of the stress response [11].

CONCLUSIONS

1. The combined intraoperative use of sub-narcotic doses of ketamine and dexketoprofen at the end of surgery provides a stress-protective effect, as evidenced by the rapid normalization of serum cortisol and steady-state glycemia after surgery.
2. The use of ketamine in sub-narcotic doses and dexketoprofen at the end of surgery in intraoperative analgesic regimens ensures low levels of pain in the early term after laparoscopic gynecologic surgery.

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