

The Concept of "Fast Track Surgery" as an Influencer on the Dynamics of Components of Stress-Realizing and Stress-Limiting Systems in the Perioperative Period

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Abstract: The concept of "Fast Track Surgery" has been of increasing interest, which implies accelerated recovery and a decrease in the frequency of postoperative complications, namely, a decrease in the body's stress response to surgery. The study aimed to assess the effect of Fast Track Surgery on the degree of surgical treatment trauma based on the dynamics of the functional integration of hormonal components of the stress-realizing / stress-limiting systems in the perioperative period. The study was conducted in 3 groups of patients. Groups of patients are comparable in age, sex, diagnosis of an underlying disease, degree of operative-anaesthetic risk ASA, intraoperative parameters, which allowed to carry out an analytical evaluation of the results of the study as objectively and reliably as possible. In the postoperative period, the maximum increase in stress-realizing system parameters in all groups was registered in patients after 1 day after surgery, less significant after LSSI-F: the concentration of daily excretion of dopamine exceeded the preoperative values by 1.2 times, epinephrine 2.0 times, norepinephrine in 1.3 times. Along with the activation of the stress-realizing system, a dynamic increase in the activity of the stress-limiting system was noted: after LSSI-F, the level of GABA increased by 1.3 times, after TSSI, the GABA secretion increased 1.2-fold. Laparoscopic SSI in combination with "Fast Track Surgery" contributed to a decrease in the intensity of the patient's stress response to the operating injury, which, in turn, significantly increased the effectiveness of simultaneous treatment and the quality of life of patients.

Keywords: Fast Track Surgery, simultaneous operations, combined pathology, stress-realizing and stress-limiting system.

INTRODUCTION

According to the literature data, in recent years there has been an increase in the number of patients who had combined surgical diseases [1]. The frequency of pathologies requiring simultaneous surgical correction is from 4.8 to 30%, which led to the growth of carried out in the performed simultaneous surgical interventions (SSI) by laparoscopic access [2, 3]. The main factor in the long recovery of the patient in the postoperative period is operational stress, and, as a consequence, a violation of the functions of organs and systems. In recent years, the concept of "Fast Track Surgery", implying an accelerated recovery and a

reduction in the frequency of postoperative complications through the use of special anesthesiological provision, non-narcotic anesthesia in the postoperative period, a reduction in infusion therapy, a minimally invasive surgical allowances, early oral nutrition, namely decreasing of stressful response of the body to surgical intervention, which, in turn, helps to reduce the duration of stay patient in hospital and rapid recovery of the quality of life [4-7].

In the process of adaptation to operational trauma, hormonal components of the stress-realizing and stress-limiting systems that unite the neuro-endocrine links play an important role, and therefore the evaluation of their functional integration in the SSI is an important marker for assessing the traumatic nature of the intervention. The stress-realizing system is a complex regulatory complex that helps to coordinate homeostasis under normal conditions and plays a key

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role in activating and coordinating all changes in the body that make up an adaptive response to stressors. According to modern data [8], this system consists of a central link (located in the brain) and two peripheral branches (hypothalamic-hypophyseal-adrenal system, the end product of which are glucocorticoids and the sympathetic department of the autonomic nervous system, the end product of this system are catecholamines - epinephrine and norepinephrine).

The activity and reactivity of this system are regulated by two main mechanisms: self-regulation (based on feedback) and external regulation (carried out by a stress-limiting system that can limit the activity of the stress-realizing system and excessive stress-realizing at the central and peripheral levels of regulation) [9]. The main central components of the stress-limiting system are, GABA-ergic system, opioidergic system, combining neurons in the hypothalamus and secretory cells in the pituitary gland, producing β -endorphin, substance-P [10]; serotonergic system - producing serotonin; epiphyseal hormone melatonin. Thus, resistance to stress damage is determined by the ratio of the activity of stress-realizing and stress-limiting systems, which is formed both based on the genetic characteristics of the organism and in the process of vital activity under the influence of various factors. In the available literature works, devoted to the study of the influence of "Fast Track Surgery" on the degree of traumatic surgical treatment on the basis of the dynamics of hormonal components of stress-realizing and stress-limiting systems in the perioperative period in patients with SSI us could not found , which conditioned the urgency of this study.

The study aimed to evaluate the effect of "Fast Track Surgery" on the degree of traumatic of surgical treatment based on the dynamics of functional integration of hormonal components of stress-realizing / stress-limiting systems in the perioperative period after performed simultaneous surgical interventions at combined abdominal and anterior abdominal wall diseases.

MATERIALS AND METHODS

Based on informed consent, following the standards of the Ethics Committee of the Russian Federation, a prospective, randomized controlled trial of 586 patients aged 18 to 72 years old who underwent planned SSI with combined diseases of the abdominal cavity, pelvis and the anterior abdominal wall. The criteria for inclusion in the study were: 1) age over 18; 2) the

planned nature of the intervention; 3) physical status by ASA; 4) the transferred isolated, simultaneous laparoscopic and traditional (open) surgical interventions for the combined pathology of the abdominal cavity organs and the anterior abdominal wall; 5) absence of acute inflammatory diseases, 6) absence of psychic, psycho-organic and exogenous diseases of the brain; 7) signed informed consent to participate in the study. The average age of patients was 49.2 ± 6.9 years. Among them 420 (71.7%) were women and 166 (28.3%) were men. The first group consisted of 196 patients who underwent laparoscopic SSI using the "Fast Track Surgery" program. The second group consisted of 195 patients who underwent laparoscopic cops with traditional management in the perioperative period. The third group consisted of 195 patients who underwent traditional SSI with traditional maintaining during the perioperative period. In terms of the severity of surgical pathology and comorbid somatic diseases, 29 (4.9%) patients were classified as I, 241 (41.2%) as II, 224 (38.2%) as III and 92 (15.7%) of the patient - to the 4th degree of operational and anesthetic risk according to ASA. The demographic profile of patients is presented in Table 1.

Table 1: The Demographic Profile of Patients

Index	Group 1	Group 2	Group 3
Age	48.2 \pm 6.9	49.3 \pm 6.6	50.0 \pm 6.9
Gender (F:M)	139:57	141:54	140:55
Total	196	195	195

Groups of patients were comparable in age ($p = 0.807$, two-sided t-criterion of Student), sex ($p = 0,94$, χ^2), diagnosis of underlying disease ($p = 0,895$, χ^2), degree of operative-anesthetic risk ASA ($p = 0,737$, χ^2), intraoperative parameters ($p = 0,806$, χ^2), which allowed to carry out an analytical evaluation of the results of the study as objectively and reliably as possible.

In all patients, the basic surgical disease was chronic calculous cholecystitis (CCC). The structure of the concomitant surgical pathology is presented in Table 2.

In 249 (63.6%), a comorbid somatic pathology was established, in the structure of which was dominated by hypertension, diabetes, obesity, hypothyroidism, chronic stomach diseases, chronic pyelonephritis, varicose veins of the lower extremities. The index of comorbidity Charlson averaged 5.6 ± 0.84 .

Table 2: Structure of Concomitant Surgical Pathology of Abdominal Organs

concomitant surgical pathology	LSSI-F	LSSI	TSSI
CCC + adhesive disease	47 (24.0%)	48 (24.6%)	54 (27.7%)
CCC+ postoperative herniation of the anterior of the abdominal wall	44 (22.4%)	45(23.1%)	40 (20.5%)
CCC+ umbilical hernia + adhesive disease	31(15.8%)	26 (13.3%)	23 (11.8%)
CCC+ nonparasitic liver cyst	12 (6.1%)	13 (6.7%)	15 (7.7%)
CCC+ cyst of the upper pole of the kidney	14 (7.1%)	11 (5.6%)	13 (6.7%)
CCC+ inguinal hernia + adhesive disease	13 (6.6%)	12 (6.2%)	9 (4.6%)
CCC+ sliding hernia of the esophageal aperture opening	12 (6.1%)	11(5.6%)	9 (4.6%)
CCC+ abdominal hernia	9 (4.6%)	10 (5.1%)	13 (6.7%)
CCC+ echinococcosis of the liver	8 (4.1%)	11 (5.6%)	9 (4.6%)
CCC+ postoperative ventral hernia + adhesive disease	4 (2.0%)	6 (3.1%)	6 (3.1%)
CCC+ nonspecific ulcerative colitis	2 (1.0%)	2 (1.0%)	4 (2.1%)
Total	196	195	195

In the process of work, general-clinical, clinical-laboratory and statistical methods were used. The level of the stress-realizing system state indicators was studied by daily excretion of catecholamines with urine by the method of high-performance reversed-phase liquid chromatography on liquid chromatograph Waters 590 (NGO "Chemavtomatika"). The collection of urine was carried out for 24 hours in a container with the addition of a preservative (10 ml sulfuric acids). The content of the main central indicators of the state of the stress-limiting system was determined in the blood serum, the samples of which were stored in a frozen state at -200C. The level of the neurotransmitter system of gamma-aminobutyric acid (GABA) was studied by a competitive three-phase enzyme immunoassay using the original idio-type-anti-idiotypic ELI-N-test test system (Russia). The concentration of β -endorphin in the blood serum was determined in the morning on an empty stomach. An enzyme immunoassay (Bachem-BCM Diagnostics test system, manufactured by Peninsula Laboratories, LLC, USA) was used. The control points of the study were: immediately before the operation; 1st, 2nd and 5th postoperative day.

Statistical processing of the data obtained during the research was carried out using the statistical package SPSS 19.0. As descriptive statistics for quantitative data, the arithmetic mean(M) was used as a measure of the central tendency, the standard deviation and the standard error as measures of variability (m (\pm)). To determine the statistical

significance of differences in mean values of the criterion, the Student's test was used (for unrelated or linked samples, depending on the task). The calculations were carried out in the Medstat licensed software, with a preliminary check of the distribution of the series of data on the normality of the distribution with the criterion W by Shapiro-Wilk's. In this statistical package, Student's criterion provides for corrections for a possible dispersion inequality with an insignificant difference in distribution from the normal one.

RESULTS AND DISCUSSION

In the course of studying the dynamics of the components of the stress-realizing and stress-limiting systems, the following peculiarities were established (Table 3): in the preoperative period, dopamine, epinephrine and norepinephrine values significantly exceeded the values in CG and made up in LSSI-F $200.3 \pm 11.6 \mu\text{g} / \text{day}$ ($p = 0.010$), $16.4 \pm 2.0 \text{mcg} / \text{day}$ ($p = 0.049$), $51.1 \pm 5.0 \text{mcg} / \text{day}$ ($p = 0.043$), respectively; with LSSI, the level of dopamine was $205.7 \pm 11.9 \text{mcg} / \text{day}$ ($p = 0.004$), adrenaline was $17.8 \pm 2.4 \text{mcg} / \text{day}$ ($p = 0.026$), norepinephrine - $51.5 \pm 5.1 \mu\text{g} / \text{day}$ ($p = 0.040$) and at TSSI - $202.4 \pm 11.4 \mu\text{g} / \text{day}$ ($p = 0.006$), $16.9 \pm 2.2 \mu\text{g} / \text{day}$ ($p = 0.041$), $51.8 \pm 5.2 \text{mkg} / \text{day}$ ($p = 0.038$), respectively, while the level of excretion of catecholamines in the study groups was almost the same ($p > 0.05$).

Activation of the stress-realizing system is explained by the presence of psychoemotional (neurogenic)

Table 3: Dynamics of Hormonal Components of Stress-Realizing and Stress-Limiting Systems, Depending on the Method of Surgical Intervention and Features of the Perioperative Period

Index	Group LSSI-F					Group LSSI					Group TSSI					
	II	1 day	2 day	5 day	ИП	1 day	2 day	5 day	II	1 day	2 day	5 day	11	12	13	
Dopamine, mcg / day	200.3±11.6 P ₂₁ =0.010	244.3±10.2 P ₃₂ =0.005	219.9±10.0	188.3±9.6 P ₅₃ <0.001 P ₅₄ =0.024	205.7±11.9 P ₆₁ =0.004	272.8±10.1 P ₇₃ =0.048 P ₇₆ <0.001	249.2±10.5 P ₈₄ =0.045 P ₈₆ =0.007	205.7±9.9 P ₉₇ <0.001 P ₉₈ =0.003	202.4±11.4 P _{10,1} =0.006	359.4±11.4 P _{11,3} <0.001 P _{11,7} <0.001 P _{11,10} <0.001	342.5±11.6 P _{12,4} <0.001 P _{12,8} <0.001 P _{12,10} <0.001	257.0±10.4 P _{13,5} <0.001 P _{13,9} <0.001 P _{13,10} <0.001 P _{13,11} <0.001 P _{13,12} <0.001				
Adrenaline, mcg / day	16.4±2.0 P ₂₁ =0.049	32.9±2.1 P ₃₂ <0.001 P ₃₃ =0.004	24.2±2.1 P ₄₂ =0.008 P ₄₃ =0.004	16.4±2.2 P ₅₃ <0.001 P ₅₄ =0.011	17.8±2.4 P ₆₁ =0.026	42.8±2.4 P ₇₃ =0.002 P ₇₆ <0.001	34.4±2.3 P ₈₄ =0.001 P ₈₆ <0.001 P ₈₇ =0.012	25.1±2.4 P ₉₅ =0.008 P ₉₆ =0.033 P ₉₇ <0.001 P ₉₈ =0.006	16.9±2.2 P _{10,1} =0.041	51.3±2.6 P _{11,3} <0.001 P _{11,7} =0.012 P _{11,10} <0.001	44.5±3.0 P _{12,4} <0.001 P _{12,8} =0.008 P _{12,10} <0.001	35.8±2.8 P _{13,5} <0.001 P _{13,9} =0.004 P _{13,10} <0.001 P _{13,11} <0.001 P _{13,12} <0.035				
Norepinephrine, Mgg / day	51.1±5.0 P ₂₁ =0.043	61.3±3.9 P ₃₂ =0.047	51.9±5.1	42.1±3.9 P ₅₃ =0.003	51.5±5.1 P ₆₁ =0.040	71.5±5.4 P ₇₆ =0.008 P ₇₃ =0.048	62.5±5.2 P ₈₄ =0.005	53.5±4.1 P ₉₅ =0.045 P ₉₇ =0.009	51.8±5.2 P _{10,1} =0.038	89.4±5.5 P _{11,3} <0.001 P _{11,7} =0.017 P _{11,10} <0.001	73.2±5.2 P _{12,4} =0.004 P _{12,10} <0.001 P _{12,11} =0.034	59.7±5.4 P _{13,5} =0.018 P _{13,11} <0.001				
GABA, pmol / ml	689.3±22.5 P ₂₁ <0.001	898.9±22.6 P ₃₂ <0.001	871.2±22.9 P ₄₂ <0.001	849.3±22.7 P ₅₂ <0.001	688.9±22.6 P ₆₁ <0.001	876.9±22.6 P ₇₆ <0.001	864.7±22.8 P ₈₆ <0.001	851.1±22.6 P ₉₆ <0.001	689.7±22.8 P _{10,1} <0.001	799.7±22.7 P _{11,3} =0.002 P _{11,7} =0.017 P _{11,10} <0.001	789.7±22.8 P _{12,4} =0.013 P _{12,8} =0.021 P _{12,10} =0.002	791.8±18.2 P _{13,5} =0.049 P _{13,10} <0.001				
Endorphin, nmol / ml	28.9±3.9	53.9±4.0 P ₃₂ <0.001	44.7±3.8 P ₄₂ =0.004	37.2±4.0 P ₅₃ =0.004	28.6±3.7	51.6±3.7 P ₇₆ <0.001	33.0±3.6 P ₈₄ =0.027 P ₈₇ <0.001	47.2±3.7 P ₉₅ =0.045 P ₉₆ <0.001 P ₉₈ =0.007	28.7±3.9	41.7±3.9 P _{11,3} =0.030 P _{11,10} =0.019	32.8±3.6 P _{12,4} =0.024	29.1±4.0 P _{13,11} =0.033				

Note. 1. II is the initial indicator in the preoperative period; 2. Blank - comparison of II with control group, blue - intergroup comparison of dynamics at one research stage; red - the dynamics in the group, depending on the research stage.

tension in patients before the operation, the main result of which is the release of catecholamines - the basic stress hormones that help mobilize the functions of organs and tissues responsible for adaptation-compensatory reactions and ensure their energy supply, i.e. functioning under new conditions. The values of GABA and β -endorphin were slightly lower in comparison with CG and amounted to LSSI-F – 689.3 ± 22.5 pmol/ml, 28.9 ± 3.9 pmol/ml, respectively, for LSSI – 688.9 ± 22.6 pmol/ml and 28.6 ± 3.7 pmol/ml, respectively, at TSSI – 689.7 ± 22.8 pmol/ml and 28.7 ± 3.9 pmol/ml, respectively, but these changes were not carried out ($p > 0.05$), which indicated the presence of distress and insufficient reserves of a modulating endogenous link, which limiting stressor manifestations in conditions of chronic somatic disease.

In the postoperative period, the maximum increase in stress-realizing system parameters in all groups was registered in patients after 1 day after surgery, less significant after LSSI-F: the concentration of daily excretion of dopamine exceeded the preoperative values by 1.2 times (after LSSI 1.4 times, $p = 0.048$, TSSI 1.8 times, $p < 0.001$), epinephrine 2.0 times (2.4, $p = 0.002$ and 3.0 times, $p < 0.001$, respectively), norepinephrine in 1.3 times (after LSSI 1.4 times, $p = 0.002$, TSSI - 1.7 times $p < 0.001$). Along with the activation of the stress-realizing system, a dynamic increase in the activity of the stress-limiting system was noted: after LSSI-F, the level of GABA increased by 1.3 times (β -endorphin 1.9 times, after LSSI the same picture was observed (in 1.3 and 1.8 times, respectively), after TSSI, the GABA secretion increased 1.2-fold and was significantly lower in comparison with LSSI-F ($p = 0.002$) and LBR ($p = 0.017$), β -endorphin 1.5-fold and was statistically significantly different from the values of LSSI-F ($p = 0.03$).

Despite the statistically significant growth of the studied hormones, both after traditional and laparoscopic SSI, LSSI-F performed in a greater degree to normalize the functional-adaptive (compensatory) capabilities of the organism: already on the 2nd day after the operative intervention, the values of dopamine decreased in 1.1 times, norepinephrine by 1.0 times, did not have significant differences from preoperative indices ($p > 0.05$) and exceeded the results after LSSI ($p = 0.045$, $p = 0.005$, respectively), which were obtained only after 5 days and TSSI ($p < 0.001$, $p = 0.004$, respectively). Positive dynamics of the daily excretion of adrenaline was also observed in all

groups, but the index after the performed TSSI was significantly higher in comparison with LSSI-F ($p < 0.001$) and LSSI with the traditional perioperative period ($p = 0.008$). After the LSSI-F, the level of GABA increased by 1.3 times and was significantly higher in comparison with TSSI ($p = 0.013$), β -endorphin - 1.6 times concerning preoperative values and statistically significantly exceeded the LSSI values ($p = 0.027$) and TSSI ($p = 0.024$).

The less pronounced intensity of the endocrine and metabolic response to operational trauma and the synergism of changes in the stress-realizing / stress-limiting systems in the LSSI-F group allowed earlier to limit the pathological manifestations of operational stress at the central and peripheral levels of regulation and after 5 days after surgery provided a complete restoration of the content of hormonal components. At the same time, the indicators not only did not have statistically significant differences from the preoperative values but also reached the CG parameters ($p > 0.05$). After LSSI, there was also a positive trend, however, changes in adrenaline, noradrenaline and β -endorphin were less pronounced in comparison with LSSI-F ($p = 0.008$, $p = 0.045$, $p = 0.045$, respectively). The dynamics of GABA indices were characterized by the inertness of the changes, while the neurotransmitter values did not have statistically significant differences from preoperative ($p > 0.05$).

After TSSI, the trend towards normalization of the parameters studied was recorded, namely, the concentration of dopamine decreased by 1.4 times, adrenaline by 1.4 times, noradrenaline by 1.5 times, less pronounced in comparison with LSSI-F ($p < 0.001$, $p < 0.001$, $p = 0.018$) and LBR ($p < 0.001$, $p = 0.004$, $p > 0.05$). At the same time, the values of dopamine and adrenaline significantly exceeded preoperative indices ($p < 0.001$). Changes in the stress-limiting system indicators were characterized by increased activation of the GABA-ergic structure and inhibition of the synthesis of β -endorphin to preoperative values. The heterogeneity (antagonism) of the changes in the stress-limiting system indicators indicated a lack of activity in the neurotransmitter-endorphins opioid links of the endogenous system and pronounced desynchronization, which indicated a stress reaction and a "depletion" of the ability of β -endorphin to limit the activity of the stress system. This fact, in our opinion, is due to immobilization stress, physical discomfort and affective tension, which patients experience after the TSSI.

Thus, in the course of the comparative analysis, a general trend was established: the transferred simultaneous surgical interventions caused intensification of the stress-realizing and stress-limiting systems on the 2nd day with the subsequent inclination to normalization by 5 days. In this case, laparoscopic SSI in combination with "Fast Track Surgery" contributed to a decrease in the intensity of the patient's stress response to the operating injury, which, in turn, significantly increased the effectiveness of simultaneous treatment and the quality of life of patients. The fact that when comparing the features of the functional integration of the hormonal components of the stress-realizing and stress-limiting systems after traditional and laparoscopic PSB did not reveal the significant advantages of the latter, it indicates that a more significant role in improving the results of surgical treatment is played by a block of perioperative management of patients, aimed at early mobilization and recovery of the patient, rather than the method of operational access.

This article has provided an overview of the current evidence for "Fast Track Surgery" (FTS) methodology in a range of surgical procedures. The concept of FTS rehabilitation is now established as safe and effective. Patients treated according to FTS principles can expect a faster recovery without increased adverse events. Other benefits of the FTS approach include a reduction in complications, fatigue, pain, and hospital expenses. However, despite clear benefits of FTS care, implementation in daily practise has been slow. Several cross-sectional surveys have documented that perioperative care is still traditional in many institutions [11-19]. Thus, the authors suppose that our study provides better evidence. Our meta-analysis shows some favourable results and conclusions regarding the effects of FTS after laparoscopic surgery.

CONCLUSIONS

The comparative analysis of the dynamics of hormonal components of stress-realizing and stress-limiting systems after laparoscopic and traditional simultaneous surgical interventions made it possible to establish differences that are more dependent on the features of perioperative period management than on the mode of operation. The combined use of laparoscopic simultaneous interventions and the multimodal concept of "Fast Track Surgery" is the least traumatic, contributing to a decrease in the intensity of the endocrine metabolic response to surgical trauma, which, in turn, significantly improves the effectiveness

of simultaneous treatment and the quality of life of patients. Synergism of changes in stress-realizing / stress-limiting systems in the postoperative period allows in earlier terms limit pathological manifestations of operational stress at the central and peripheral levels.

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Received on 09-07-2019

Accepted on 19-09-2019

Published on 18-11-2019

DOI: <https://doi.org/10.6000/2292-2598.2019.07.04.3>

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