Biohumoral and endocrine parameters in assessment of surgical trauma in open and laparoscopic cholecystectomy

Metabolički i endokrini parametri u proceni hirurške traume kod otvorene i laparoskinske holecistektomije

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Abstract

Background/Aim. Every surgical procedure causes metabolic, endocrine, and hemodynamic stress in the organism. The aim of this work was to assess the extent of trauma following each of the two types of cholecystectomy (traditional/open and laparoscopic) by measuring palette of biochemical parameters. Methods. This prospective, single-center study included 120 patients subjected to elective cholecystectomy during the period of one year. Sixty patients were treated laparoscopically and 60 traditionally. Biohumoral and endocrine parameters were determined from 24-hour urine and blood. We measured adrenaline, noradrenaline, metabolites of corticosteroid hormones (17-hydroxyl and 17-keto steroids), C-reactive protein (CRP), albumin, glycemia, creatine-phosphokinase (CPK), lactate-dehydrogenase (LDH), red blood cells sedimentation and serum concentration of potassium. Results. We observed significantly lower levels of adrenaline (p < 0.01), noradrenaline (p < 0.05), dopamine (p < 0.01), 17-hydroxyl (p < 0.01) and 17-keto steroids (p < 0.01), glycemia (p < 0.01), CPK (p < 0.01), LDH (p < 0.01) and red blood cells sedimentation (p < 0.01) following laparoscopic cholecystectomy compared to traditional one. Significant increase in CRP levels was recorded postoperatively in both groups (p < 0.05), as well as significant decrease in serum albumin values (p < 0.05). Duration of the hospitalization following laparoscopic cholecystectomy was significantly shorter (p < 0.01). Conclusion. The intensity of organism response is proportional to the intensity of surgical trauma. Metabolic, tissue and neuroendocrine response of organism to trauma has lower intensity after laparoscopic cholecystectomy.

Key words: cholecystectomy; cholecystectomy, laparoscopic; intraoperative period; biological markers; blood chemical analysis.

Zaključak. Intenzitet odgovora organizma je proporcionalan intenzitetu hirurške traume. Metabolički, biohumoralni i endokrini odgovor organizma značajno je nižeg nivoa nakon laparoskopske intervencije.

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Introduction

Every surgical intervention represents a stress and causes a severe metabolic, endocrine and hemodynamic reaction of organism. The intensity of operative trauma can be tracked by monitoring, identification and quantification of various metabolites. Surgical intervention as a stress model causes dynamic exposure to neuroendocrine metabolic and biohumoral substances which are in correlation with duration and intensity of trauma. Negative balance of nitrogen with a consequential catabolism of proteins, glyconeogenesis, reduced utilization of glucose, retention of water and salt and lipolysis are the parameters that determine the organism reaction to trauma.

Neuroendocrine response to trauma is realized in three pathways: via the sympathetic nervous system, that influences energy mobilization by stimulating the secretion of adrenalin, noradrenalin, glucagon and inhibiting secretion of insulin using renin-angiotensin system 1–3; by balancing hormones which are secreted over the hypothalamus, stimulating secretion of ACTH and growth hormone 1 and by stimulating magnocelular nucleus of hypothalamus and releasing vasopressin from the hypophysis. With the increase of endorphine, causing endanalgesia, these reactions confirm the organism adaptation to the stress provoked by surgical intervention 4–6.

Cholelithiasis is the most common disease of hepatobiliary system. According to Schirmer et al. 7, 20 million people in the USA have gallbladder disease and 500,000 cholecystectomies are done per year with the mortality of 3% due to manifested complications. Since the first traditional cholecistectomy, surgeons have tried to use a minimally invasive approach to decrease the intensity of surgical trauma. Since 1985 laparoscopic cholecystectomy has been accepted as the gold standard in the therapy of calculous cholecystitis 5, 6, 8–10. Laparoscopic cholecistectomy is used instead of traditional one and mini-laparotomic cholecystectomy because better effects, minimal operative traumatism, shorter postoperative recovery and a significant esthetical effect 4, 6, 10–12. Operative mortality in developed countries is not expected to be higher than 0.2–0.5%.

The reduction of risk connected with the laparoscopic approach can be achieved with the recognition of anatomic variation of hepatobiliary system, intraoperative visualization, an experienced surgical team and a suitable choice of operative approaches. Operative incision being smaller in patients treated laparoscopically contributes to the lower level of surgical trauma. Pneumoperitoneum can be an additional factor of traumatism. Carbon dioxide has a small irritating effect on peritoneum but also causes distension of parietal peritoneum, elevation of diaphragm, reduction of alveolo-capillary membrane and hypoventilation with consequently respiration acidosis as a result 13.

The aim of this study was to assess impact of each of the two types of cholecystectomy (open or laparoscopic) to the extent of operative stress and trauma in the patients being electively operated on due to their chronic calculous cholecystitis, by performing comparative analyze of the pallet of neuroendocrine, metabolic and tissue indicators.

Methods

This prospective, single-center, randomized study included 120 patients with the indication of chronic calculous cholecystitis who were electively operated on during the one year period in the Surgery Department, General Hospital in Berane, Republic of Montenegro, after approval by the local Ethics Committee.

The patients were divided into two groups: the experimental group including the patients treated with laparoscopic and the control group including those treated with open cholecystectomy. The groups were standardized by the number of patients and clinical parameters. The written informed consent was obtained from all the patients included in the study. If patients wanted to reconsider their participation in the trial, they were excluded on the day of admission.

Inclusion criteria implied symptomatic cholecystolithiasis (confirmed by ultrasonography), age of 18 or older at recruitment, ASA (American Society of Anesthesiologists) score of 1 or 2, no known relevant allergies, and signed informed consent letter. Exclusion criteria were less than 18 years, choledocholithiasis (presented with icterus, alcoholic feces, and/or bilirubin level of twice the upper limit of normal), cholangitis, known pregnancy, moderate to severe systemic disease (ASA score of 3 or higher), known cirrhosis of the liver, history of abdominal malignant neoplasm, previous upper abdominal surgery (precluding laparoscopic approach) and psychiatric disease that might make follow-up or completion of questionnaires unreliable.

Assuming no differences in primary outcome measures, sample size calculation was based on differences of costs 6, 14, 15. For this purpose, the direct costs of the first 30 patients in the trial were calculated to estimate a likely range of differences in costs and their standard deviations. On this basis, we estimated that 120 patients divided in 2 groups would be enough to detect a difference of 10% in direct costs using an α of 0.05 and a β of 0.9.

All the patients were operated under general anesthesia and passed the standard preoperative preparation. In the patients operated on traditionally the length of skin incision was 13 cm, approaching through the right upper quadrant with the standard operative technique.

Biohumoral parameters as a measuring response to trauma were determined from urine and blood samples in a biochemical laboratory in Berane. The levels of adrenaline, noradrenaline, dopamine, metabolites of corticosteroid hormones (17-hydroxy and 17-keto steroids) were determined on the postoperative day 1 in the 24-hour urine by HPLC method. In the postoperative morning 1 and 2, blood samples were taken from every patient to determine C-reactive protein (CRP) and albumin. C-reactive protein was defined by enzyme immunoassay technique. Albumins were determined according to the electrophoresis method on paper. Metabolic and tissue parameters of response to trauma, such as: glycemia, creatine phosphokinase (CPK), lactate dehydrogenase (LDH), red blood cells (RBC) sedimentation and serum concentration of potassium, were determined from the same blood samples.

The obtained values were statistically evaluated using descriptive and analytical statistics (program SPSS version 10 for Windows).

Student’s t-test, linear correlation, analysis of variance (ANOVA), Mann-Whitney test, U-test and logistic regression were used.

Results

In both groups 2/3 of all the patients were females with no statistically significant difference in gender structures among the groups. The average age of the patients in the experimental group was 56 (SD = 9.95) years and in the control group 61 (SD = 8.65) years. The patients in the control group were statistically significantly older than those in experimental one (p < 0.05). The average body weight of patients who were traditionally operated on was 73 (SD = 7.91) kg, and of those in the experimental group 69 (SD = 8.06) kg, showing no statistical difference between the groups (p > 0.05). There was no significant difference in the operative procedure duration (p = 0.074), being 60.7 (SD = 8.25) minutes and 61.68 (SD = 7.31) minutes in the experimental and the control group, respectively. The duration of hospital treatment of patients who were laparoscopically operated was significantly shorter (p < 0.01), being 3.1 ± 0.9 days comparing with 5.4 ± 1.2 days in the control group.

The average postoperative value of adrenaline in the experimental group was 45.5 nmoL/24h urine, with minimal value of 16.0 and maximum of 66.0 nmol/24h urine. The controls had the average value of adrenaline 167.0 nmol/24h urine, showing statistically highly significant difference (p < 0.01). The values of noradrenaline in the experimental group were balancing from minimal value of 150.0 to a maximal one of 640.0 nmol/24h urine, while the values of noradrenal in the control group were significantly higher (438.9; SD = 146.48 nmol/24h urine; p < 0.05) (Figure 1). In the experimental group average value of dopamine was 1,519.4 nmol/24h urine, while the average value in the controls was 2,286.7 nmol/24h urine being statistically significantly higher (p < 0.01). The patients from the experimental group have had average value of 17-OH steroids of 83.9 (SD = 20.25) nmol/24h urine, while the average value in the controls was 117.3 (SD = 15.36) nmol/24h urine also showing significant statistical difference (p < 0.01) (Figure 1). The average values for 17-keto steroids in the experimental group (169; SD = 45.61 nmol/24h urine) and the controls (284; SD = 42.14 nmol/24h urine) were also statistically highly different (p < 0.01) (Figure 1).

The average serum glucose value was also significantly different (p < 0.01) being 4.4 (SD = 0.77) mmol/L in the experimental group vs 6.6 (SD = 0.73) mmol/L in the control group. Difference between average value of serum CPK in experimental group and controls was highly statistically significant (p < 0.01), like the difference between average values of LDH (p < 0.01) (Figure 2). The average value of serum potassium in the experimental group was 4.27 (SD = 0.64) mmol/L. The average value of potassium in the control group was 4.45 (SD = 0.41) mmol/L and there was no statistically significant difference (p > 0.05) between groups. The average value of red blood cells sedimentation in the experimental group was 16.57 (SD = 3.98), while in the control group was 18.97 (SD = 3.24). Comparing the values between the groups a highly statistically significant difference (p < 0.01) was proven. There was no significant difference in preoperative CRP (p > 0.05) levels. Nevertheless, in both groups significant CRP increase was postoperatively recorded (p < 0.05). Preoperative albumin levels showed no significant difference between the groups (p > 0.05). Postoperative values in both groups were significantly lower (p < 0.05).

Discussion

Surgical trauma entails a complex answer by the organism including releasing of metabolic, tissue, endocrine, and immunologic substances. Tracking these processes we can track the organism answer to trauma as well. The intensity of organism reaction to surgical trauma is proportional to
the trauma intensity. Quantification of some of endocrine, immunologic, tissue, and metabolic parameters was found to correlate with the intensity of surgical trauma itself.²⁶–²⁹

More specific factors are tissue and immunological factors, which are produced in the initial phase of organism reaction to trauma. The liver synthesizes proteins in increased concentration, ie reactants. The reactant group consists among others of haptoglobin and fibrinogen as normal constituents of plasma. The values of albumin, C-reactive protein, α2 acid glycoprotein, transferrin and macroglobulin are changing. Tissue mediators (cytokines) including interleukins (IL) IL-1, IL-2, IL-6, IL-8, IL-10, and tumor necrosis factor (TNF) are created by phagocytes and histiocytes.²⁰,²¹ These mediators increase the production of reactant group proteins but also of prostaglandins, which belong to the group of humoral messengers, participating in catabolic processes in the organism. Recently, focus is on the thial cells (oxygen radicals, NO) but also on cellular and humoral answer to trauma, including values of immunoglobulins and T lymphocytes. Analyses show different dynamics of their plasma concentrations after the operation. Tracking these changes can show us how organism reacts to surgical trauma.

Gender structure of the studied patients was expected, considering the prevalence of gall-bladder diseases, recognized to be more frequent in female population. The patients had average weight value above that of general population, being important factor in the etiology of calculous gall-bladder.²²,²³

Laparoscopic surgery demands more time, usually leading to longer procedure duration, but after procedure hospitalization is shorter²⁴–²⁶, as proved in this study as well.

Surgical intervention induces endocrine response of the organism via sympathetic nervous system promoting the secretion of adrenal in and noradrenaline. It also stimulates excretion of ACTH and growth hormone via hypothalamus.²⁷ Increase of catecholamine levels in postoperative period verified in this study is expected as previously proven in other studies. It is also interesting that adrenaline values in laparoscopic cholecystectomy are significantly higher in patients who are operated by mini-laparotomy cholecystectomy.²⁸ This difference is explained by the effects of pneumoperitoneum, gastric distension and parietal peritoneum dilatation which lead to stimulating of stress reaction in organism. The phenomenon of stomach gas pillar in abdomen causes compression of portal system and the system of the lower hollow vein leading to lung hyperperfusion, and a disorder of ventilation/perfusion ratio in alveoli by diaphragm uplifting. Absorbed CO₂ also has system effects on the center for respiration and induces respiratory acidosis causing high production of catecholamine as the answer to trauma.²⁹ It is known that noradrenaline metabolism is different than adrenaline metabolism. Noradrenaline values grow very slowly, but they stay on higher levels for a long period of time.¹–³,²⁷,²⁸ A wide range of adrenaline and noradrenaline values detected in both the examined group and the controls can be explained by individual differences in stress reaction. From the other hand, the average noradrenaline level being higher in the controls tells us that stress provoked by procedure is much higher when it is done by traditional way.

Steroid response to trauma can also be objectified by average values of 17-keto steroids and 17-OH steroids in 24-hour urine. Steroid answer of high intensity is a reflection of total stimulus and it represents more reliable and objective parameter than it is the case with catecholamine. The results obtained in this study showing a significant difference between the steroid response to trauma in open and laparoscopic cholecystectomy are going in favor of laparoscopic surgery as a less stress-inducing method.

Although parameters of metabolic and tissue answer do not have high significance as factors of endocrine answer, their tracking in this study gave us a number of statistical importance which is fully in line with the results from previous researches. Hyperglycemia is a phenomenon of surgical trauma. In 1877, Claude Bernard described hyperglycemic reaction in patient who experienced hemorrhagic crisis. It has been proven that every trauma, high infection and sepsis is followed by a hyperglycemic reaction, and that the degree of hyperglycemia is proportional to the intensity of trauma.³,²⁹ Just after trauma, the organism wants to secure energy resource and that is the main reason for hyperglycemic reaction happen. At early stages of postoperative procedure, there is a changed metabolism of carbohydrates. There is also an increased splanchnic output (emptying of the deposit in circulation) and decreased utilization of glucose at periphery. During trauma, hyperglycemic reaction is initiated by a catecholamines, cortisol, glucagon, vasopressin, growth hormone and somatostatin as well as insulin.¹–³,²⁹ Cortisol and catecholamine increase resistance of periphery tissues on effects of insulin (whose secretion is decreased) and therefore decrease acceptance of glucose at periphery. A high level of glycemia detected in both groups of patients is explained by these processes and higher glycemia values in the patients who were traditionally operated on come as a consequence of more extended trauma during the procedure.

When during surgical trauma comes to an increased destruction of muscle cells, there is a higher level of CPK. Muscle cells contain LDH and aminotransferases as well as CPK. When other muscle diseases are absent, ie myocardial infarction or liver disease, then the increase of CPK level shows the degree of muscle damage depending on surgical procedure.³⁰,³¹ Higher CPK in traditionally operated on patients comes from longer incision causing bigger destruction of muscle tissue. Lactate dehydrogenase is an intracellular enzyme which catalyzes processes of carbohydrate metabolism. After surgical trauma, there is a high LDH level. Increase of LDH level is explained by a release of the enzyme from the tissues which were destroyed during the operation, or local trauma which was done on the liver parenchyma (if operations are done on that anatomic area). Higher LDH measured in the controls group is in favor of less extended tissue destruction in laparoscopic approach being one advantage more.

The increase of serum potassium of operated patients were statistically significantly lower in laparoscopic than in

open operation trauma, but we also have to be aware that other metabolic factors can increase the levels of potassium.

Red blood cells sedimentation as an unspecific parameter of the organism answer to trauma is considered important for tracking patients after operation. Minimal traumatizing effect of laparoscopic operative procedure gives statistically significant lower RBC sedimentation values.

Also, there are changes in metabolism and biosynthesis of liver proteins after trauma. C-reactive protein is the main reactant of acute phase answer, and due to its sensitivity and prompt jump of CRP after trauma, it enables us to track intensity of trauma. C-reactive protein have shown increase in both groups but contrary to RBC sedimentation there were no significant differences in its levels between the groups. As expected in postoperative period average albumin level is proportional to the intensity of trauma. 1–3.

Cholecystectomy, as one of the most common abdominal operations, has a small morbidity and mortality. Regardless of well defined technique and standardized procedures precaution is necessary. According to previous studies, during elective operations, percentage of complications is 6–12% and, generally speaking, percentage of complications in this research is in line with the indications and age of patients. Highest number of complications is connected to laparotomic incision. They belong to the group of unspecific complications in which dominate: hematoma, fistulas and granuloma around stitched material, infection and difficulties with wound healing and pain 4–6, 11, 32, 33. In our patients regardless operative procedure used no postoperative complications were observed.

Conclusion

The intensity of the organism response is proportional to the intensity of surgical trauma. Metabolic, tissue and neuroendocrine response of the organism to trauma has much lower intensity after laparoscopic cholecystectomy. Although the advantages of laparoscopic surgery are well-known these results are speaking in favor of minimal invasive surgery in so far most complete way.

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Declaration of interest

Authors have no conflict of interest to declare.

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