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Adrenocorticotropic Hormone (ACTH) and Cortisol Monitoring as Stress Markers During Laparoscopic Cholecystectomy: Standard and Low Intraabdominal Pressure and Open Cholecystectomy

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ABSTRACT

Introduction: In this study we wanted to examine the hormonal responses due to stress exposure during laparoscopic cholecystectomy with standard (12-15 mm / Hg) (LCSP) and low (6-8 mm / Hg) (LCLP) intraabdominal pressure and open cholecystectomy (OC), with particular emphasis on stress hormone responses. **Aim:** Determination of adrenocorticotropic hormone (ACTH) and cortisol stress hormones before and after laparoscopic cholecystectomy with standard and low insufflation pressure, determination of ACTH and cortisol values before and after open cholecystectomy and comparison of ACTH and cortisol values between the patient sub-groups**. Methods:** In a prospective study conducted between July 2016 and February 2018, we involved 110 patients which were divided into two groups: 70 patients with laparoscopic cholecystectomy (LC) and 40 patients with open cholecystectomy (OC). The first group of patients was further divided into two subgroups of 35 patients, (subgroup LC with standard and subgroup LC with low intraabdominal pressure). All patients met the preset inclusion and exclusion criteria of the study. There were no statistically significant differences in the demographic characteristics of patients between the investigated groups. The stress hormones determined were adrenocorticotropic hormone (ACTH) and cortisol. **Results**: During the first, second and seventh day postoperative day (POD),ACTH values were significantly lower ($p < 0.0001$) in LCLP than in LCSP and OC groups. This was also the case for comparison in LCSP and OC groups. By comparing LC and OC groups during first, the second and seventh POD, there was a significant difference ($p < 0.0001$) in the ACTH levels. The concentration of this hormone was higher in the OC group in all three cases. The first, second and seventh POD were also statistically significant ($p < 0.0001$) in cortisol values and between LC and OC groups there was an increase in cortisol levels in patients operated by open method. There was also a significant difference ($p < 0.0001$) in cortisol values measured between LCLP and LCSP groups in the investigated days. Cortisol levels were higher in patients in the LCSP group. **Conclusion:** During open and laparoscopic cholecystectomy the response of the body to stress increased. The stress response of the organism during laparoscopic cholecystectomy was less than during open cholecystectomy. The stress response of the organism during laparoscopic cholecystectomy with low insufflation pressure (6-8mmHg) was less than during laparoscopic cholecystectomy with standard insufflation pressure (12-15mmHg).

Keywords: Cortisol, Cholecystectomy, pressure, abdomen.

1. INTRODUCTION

Laparoscopic cholecystectomy has shown numerous advantages over the open method: pain after surgery is significantly lower; the time of hospitalization is shorter and the patients return to work after laparoscopic surgery is faster; the quality of life of patients operated by the laparoscopic method is significantly better than the patients operated by the open method (1). However, the hormonal response of the organism of stress to laparoscopy has not been thoroughly investigated. Adrenocorticotropic hormone is a peptide hormone that is produced in the pituitary gland. It stimulates the formation and secretion of glucocorticoids (especially cortisol) from the adrenal cortex. The formation of glucocorticoids is regulated by various factors.

High blood glucocorticoid concentrations inhibit ACTH secretion by negative feedback mechanism (2). ACTH concentrations show daily differences, which are high in the morning and low in the evening. Cortisol represents 80% of all hydroxy-corticosteroids in the blood. Blood is bound to transcortin and albumin. Measurement of cortisol concentration is used to diagnose diseases and evaluate the function of adrenal gland, pituitary gland, and hypothalamus (3). Cortisol may be above the reference values in alcoholism, endogenous depression, anorexia, systemic illnesses, etc. Decreased cortisol values are found in the primary and secondary insufficiency of the adrenal gland.

Some studies have evaluated the influence of stress during laparoscopic and open cholecystectomy (4). The results vary depending on the study. Calvoet al (2012) compared the response of the organism to stress during laparoscopic cholecystectomy in patients who were under general anesthesia who were previously given spinal anesthesia and patients in the second group who were also under general anesthesia but previously given epidural anesthesia. Intraoperative values of cortisol, ACTH, adrenaline and catecholamine were significantly lower in the group that was cholecystectomized in combined general and spinal anesthesia (5). Preoperative oral nutrition decreases the body's response to stress after laparoscopic cholecystectomy. Patients who were fed the night before laparoscopic cholecystectomy had a significantly lower CRP increase and lower cortisol values within the first 48 hours after postoperative than those who were overnight fasted (6).

Therefore, we wanted to investigate the hormonal responses, the adrenocorticotropic hormone and cortisone secretion during laparoscopic cholecystectomy with standard (LCSP) and low intraabdominal pressure (LCLP) and open cholecystectomy (OC). Moreover, laparoscopic low-intra-abdominal pressure (LCLP) cholecystectomy has been shown to be more favorable in comparison to LCSP, especially in patients with high comorbidity (7).

2. AIM

This study had several aims; namely to:

a) Determine the markers of stress, adrenocorticotropic hormone (ACTH) and cortisol levels, before and after laparoscopic cholecystectomy with standard and low insufflation pressure.

b) Determine the value of adrenocorticotropic hormone and cortisol before and after open cholecystectomy.

c) Compare stress parameter values (ACTH and cortisol) after laparoscopic cholecystectomy with low insufflation pressure to the values of stress parameters after laparoscopic cholecystectomy with standard insufflation pressure and compare the obtained values with the values of stress parameters after open cholecystectomy.

3. METHODS

A prospective study was performed at the Surgery Clinic in Tuzla General Hospital during the period ranging from July 2016 to February 2018. Laparoscopic cholecystectomy surgeries were performed with three trocar; by the same surgical team, by standard (12-15 mm Hg) and low (6-8 mm Hg) insufflation pressure or by an open method in general endotracheal anesthesia. The study included 110 patients divided into three groups: 70 patients with laparoscopic method, 40 patients with open method (OH). The laparoscopic group of patients was further divided into two groups: 35 patients under standard intraabdominal pressure (LCSP) and 35 patients operated with laparoscopic low intraabdominal pressure (LCLP).

Fifty four (49%) were men, and fifty six were women (51%), The age of patients varied from 25 to 66 years with an average of 41±10.

Inclusion criteria for this study were: patients older than 18 years with clinical diagnosis of chronic cholecystolithiasis; all patients were selected by a consecutive method and were classified into groups I and II according to the ASA (Classification of the American Society of Anesthesiologists).

Excluding criteria for this study were: mental retardation of patients; patients under any type of pharmacotherapy; patients in whom the laparoscopic operation was converted into an open method; patients with calculus complications (acute inflammation, choledocholithiasis, billiary pancreatitis, secondary stenosis papillitis, and biliodigestive fistula). Patients with postoperative complications such as the biliary, vascular or intestinal injuries, jaundice, pancreatitis, residual stones and postcholecystectomy syndrome were excluded from the study.

Stress parameters, adrenocorticotropic hormone and cortisol were determined at the Department of Nuclear Medicine for preoperative, first, second and seventh postoperative day (POD). Data analyses were performed by standard descriptive and inferent statistics. Statistical hypotheses were tested with a significance level of $p < 0.05$. Three groups of data were analyzed and compared, and standard variance analysis (ANOVA) was used for their processing. When the ANOVA procedure revealed a statistically significant difference between the measured sizes, the Post Hoc test was applied. The Turkey test was used for multiple comparisons. Where appropriate, Student's 2-tailed T-test was used. Statistical data processing was done using Arcus Quick Stat Biomedical and Excel.

4. RESULTS

Analysis of ACTH values for the investigated groups is shown in Table 1.

Analysis of variance *(*ANOVA*)* shown that preoperatively ($P = 0.001$) and in all three PODs there was a statistically significant difference between the ACTH hormone concentration ($P < 0.0001$). During the first, second and seventh PODs, ACTH levels were significantly lower in the LCLP group than in LCSP and OC groups ($P < 0.0001$) (Table 2).

ACTH values preoperatively and postoperatively for LC and OC groups are shown in Table 3.

ACTH	Group	N	Xsr	SD	Min	Max
Preoperative	LCLP	35	16,76	6,28	10,00	32,10
	LCSP	35	16,15	5,07	10,00	32,20
	OC	40	21,75	8,08	11,50	44,00
First POD	LCLP	35	66,07	17,81	20,50	94,30
	LCSP	35	82,32	16,84	48,40	120,10
	OC	40	100,94	12,17	79,40	129,40
2nd POD	LCLP	35	63,58	17,90	16,40	100,10
	LCSP	35	80,01	16,72	40,00	100,40
	OC	40	100,42	13,06	76,80	140,70
7th POD	LCLP	35	37,25	14,83	8,80	66,60
	LCSP	35	60,59	18,91	22,20	84,20
	OH	40	81,10	12,34	55,50	100,40

Table 1. ACTH hormone values before and after surgery

ACTH			P
Preoperative	LCLP	LCSP	0,922
		OC	0,005*
	LCSP	OC	0,001*
First POD	LCLP	LCSP	<0,0001*
		OC	<0,0001*
	LCSP	OC	<0,0001*
2nd POD	LCLP	LCSP	<0,0001*
		OC	<0,0001*
	LCSP	OC	<0,0001*
7th POD	LCLP	LCSP	<0,0001*
		OC	<0,0001*
	LCSP	OC	<0,0001*

Table 2. Results of multiple testing of statistical significances between themean values of ACTH hormone concentration in different patient subgroups (Table 2). * Statistically significant

		ACTH				
		N	Min	Max	Xsr	S D
Preopera-tively	LC	70	10,00	32,20	16,46	5,67
	OC	40	11,50	44,00	21,75	8,08
First POD	LC	70	20,50	120,10	74,19	19,05
	OC	40	79,40	129,40	100,94	12,17
2nd POD	LC	70	16,40	100,40	71,79	19,08
	OC	40	76,80	140,70	100,42	13,06
7th POD	LC	70	8,80	84,20	48,92	20,56
	OC	40	55,50	100,40	81,10	12,34

Table 3. ACTH values preoperatively and postoperatively for LC and OC groups

The statistically significant difference in ACTH in LC group was observed preoperatively and the first POD (t = 24.3, df = 138, P <0.0001). The preoperative values of ACTH in the OC group were statistically significantly different compared to the first POD (t = 34.29, df = 78, P <0.0001). The Student's t-test revealed statistically significant difference in ACTH levels in the LC group preoperatively and the second POD (t = 23.26, df = 138, P <0.0001).

Cortisol	Group	N	Xsr	SD	Min	Max
Preopera-tive	LCLP	35	412,91	132,30	220,00	690,00
	LCSP	35	438,11	146,34	137,00	700,00
	OC	40	515,08	98,41	310,00	710,00
First POD	LCLP	35	994,66	164,07	500,00	1300,00
	LCSP	35	1059,97	245,26	167,00	1410,00
	OC	40	1246,03	159,90	996,00	1527,00
2nd POD	LCLP	35	938,29	176,53	440,00	1250,00
	LCSP	35	1049,63	240,27	194,00	1400,00
	OC	40	1198,95	156,22	876,00	1550,00
7th POD	LCLP	35	663,14	134,79	350,00	880,00
	LCSP	35	778,94	191,90	160,00	1000,00
	OC	40	914,58	129,73	590,00	1110,00

Table 4. Cortisol values before and after surgery for the investigated groups

Cortisol			Statistics	P
Preoperatively	LCLP	LCSP	<0	0,681
		OC	<0	0,002*
	LCSP	OC	<0	0,026*
1th POD	LCLP	LCSP	<0	0,334
		OC	<0	<0,0001*
	LCSP	OC	<0	<0,0001*
2nd POD	LCLP	LCSP	<0	0,045*
		OC	<0	<0,0001*
	LCSP	OC	<0	0,003*
7th POD	LCLP	LCSP	<0	0,006*
		OC	<0	<0,0001*
	LCSP	OC	<0	0,001*

Table 5. Results of multiple testing of statistical significance between the mean values of cortisol hormone concentration. * Statistically significant

Cortisol						
Group		N	Min	Max	Xsr	S D
Preopera-tively	LC	70	137,00	700,00	425,51	139,07
	OC	40	310,00	710,00	515,08	98,412
1th POD	LC	70	167,00	1410,00	1027,31	209,73
	OC	40	996,00	1527,00	1246,03	159,9
2nd POD	LC	70	194,00	1400,00	993,96	216,67
	OC	40	876,00	1550,00	1198,95	156,22
7th POD	LC	70	160,00	1000,00	721,04	174,64
	OC	40	590,00	1110,00	914,58	129,73

Table 6. Cortisol values preoperatively and postoperatively for LC and OC groups

The preoperative ACTH values in the OC group were statistically significantly different compared to the other postoperative day (t = 32.39, df = 78, P <0.0001).

Student's t-test analysis further revealed a significant difference in ACTH levels in the LC group preoperatively and seventh POD (t = 12.73, df = 138, P <0.0001). The preoperative ACTH values in the OC group were significantly different compared to the seventh postoperative day (t = 24.45, df = 78, P <0.0001).

Comparison of the ACTH values of LC and OC groups in the first, second and seventh PODs revealed a significant difference in ACTH levels by comparing the LC and

OC group of patients with the first postoperative day (t = 7.99, df = 108, P <0.0001), the second POD = 8.42, df = 108, P <0.0001) and seventh POD (t = 14.27, df = 108, P <0.0001).

Analysis of cortisone hormone values by study groups

Cortisol values before and after surgery for the investigated groups are shown in Table 4.

Preoperatively (P = 0.002) and in all three POD days there was a statistically significant increase in the cortisol levels (P <0.0001*).* Analysis of variance *(*ANOVA*)* shown that during the first POD, cortisol was not significantly different between LCLP and LCSP groups (P = 0.334). Cortisol levels were however significantly lower in the LCLP group than in the OC group (P <0.0001). Statistically, LCSP group had significantly lower cortisol levels than the OC group (P <0.0001).

During the second POD, the cortisol levels were significantly lower in the LCLP group than in the LCSP group (P = 0.045) (Table 5) . Cortisol in the LCSP group was significantly lower than in the OC group. Seven POD the cortisol in the LCLP group was statistically lower than in the LCSP (P = 0.006) group and in the OC group (P <0.0001). Cortisol in the LCSP group was statistically significantly lower than in the OC group (P = 0.001).

After the first POD, a statistically significant difference in cortisol levels was established in the LC group preoperatively and the first POD (t = 20.01, df = 138, P <0.0001). Preoperative cortisol values in the OC group were significantly different compared to the first postoperative day (t = 24.62, df = 78, P <0.0001). After the second POD, a significant difference in cortisol levels was determined in the LC group preoperatively and in the second POD (t = 18.47, df = 138, P <0.0001). Preoperative values of cortisol in OC group were significantly different compared to other PODs (t = 23.43, df = 78, P <0.0001).

After the seventh POD, the Student's t-test analysis revealed a significant difference in LC preoperative and seventh POD (t = 11.08 df = 138, P <0.0001). The preoperative values of cortisol in the OC group were statistically significantly different on the seventh POD (t = 15.52, df = 78, P <0.0001). Comparison of the cortisol values in the LC and OC groups in the first, second and seventh PODs revealed a significant difference between LC and OC group cortisol during the first POD (t = 5.71, df = 108, P <0.0001), the second POD (t = 5.25, df = 108, P <0.0001) and the seventh POD (t = 6.11, df = 108, P <0.0001) (Table 6).

5. DISCUSSION

Laparoscopic cholecystectomy is a method of choice in the treatment of chronic cholecystitis. However, the hormonal responses and the secretion of adrenocorticotropic hormone and cortisol during laparoscopic surgery has not been fully elucidated. The stress hormone markers that were evaluated in this study were ACTH and cortisol hormones.

In this study, from the aspect of ACTH hormones and cortisol as stress markers, we could conclude that the response of the organism to stress during laparoscopic cholecystectomy was lower than during open cholecystectomy and that the response to the stress during laparoscopic cholecystectomy with low insufflation pressure (6-8mmHg) was lower than during laparoscopic cholecystectomy with standard insufflation pressure (12-15mmHg).

In a prospective study of 50 patients, conducted by Sessa and associates in 2019, perioperative analgesia, which implies use of remifentanil, reduces the neuroendocrine stress response of the organism during laparoscopic cholecystectomy. Contrary to our study, ACTH, cortisol and other hormones, such as prolactin and growth hormone were monitored. The blood in which the stress parameters were analyzed was drawn three times immediately before the patients were taken into the operating room, then during the operative procedure and at the moment of trocar placement in the abdomen and 1-hour post surgical procedure. In our study, ACTH and cortisol levels were lower than during the standard procedure and at the time of placing the trocar; however one hour after the end of the surgery, there was an increase in ACTH and cortisol values in the examined patients (8).

Luo and associates (2002) measured the concentration of cortisol, insulin, CRP in 26 patients with chronic cholecystitis. The patients were divided into two groups. In the first LC group there were 14 patients and in the other OC group, 12 patients. In the first postoperative day, cortisol levels were significantly higher in the OC group compared to the LC group. In addition, postoperatively during the second, third and fourth postoperative days, there were significantly higher CRP, cortisol and insulin levels in the OC group than the LC group (p <0.05) (9). Laparoscopic surgeries therefore appear to result in a smaller stress and metabolic response of the organism, which is advantageous in terms of the role of stress hormone, body balance in the organism and energy response of the organism.

Hormones cortisol and ACTH were significantly increased in the first postoperative hours after open and laparoscopic cholecystectomy. In the prospective study conducted in 2005, patients were divided into two groups, laparoscopic, which counted 17 patients and open with 14 patients (4). Two hours postoperative cortisol concentrations were statistically higher in the group of patients who were laparoscopically operated in comparison to the open group (p <0.05). This result could not be compared with the results in our study because we did not measure the levels during such a nearly postoperative period. However, in the postoperative period of 24 and 48 hours, when concentrations of these hormones were measured in both groups, we could conclude that the concentration of ACTH and cortisol were both statistically significantly higher in the group that was operated by the open approach in comparison to the laparoscopic group. These results also confirm the conclusion of this study that the hormonal response to stress (ACTH and cortisol) in the postoperative period, the first and second postoperative days was significantly higher in patients who were treated using the open

method of surgery. Thus, our study and the above-mentioned study give preference to the laparoscopic method from the standpoint of the hormonal responses of the organism to stress. Ordinance of epidural anesthesia can postoperatively significantly reduce the pain intensity to the patient. In addition, the reduced response of the organism to stress in terms of lower cortisol concentrations, lower paresthesia, and faster re-establishment of the bowel movements after surgery were observed after injection of 125% levobupivacaine epidural in patients with intestinal resection (10). This study can not be compared with ours except in the cortisol comparison, but it can be fueled by some future research that will eventually lead to the use of possibly epidural anesthesia during cholecystectomy.

6. CONCLUSION

From our data, we can draw conclusions that during open and laparoscopic cholecystectomy, the body's response to stress is increased. The stress response of the body to the laparoscopic cholecystectomy is however lower than during open-cholecystectomy. The stress response to laparoscopic cholecystectomy with low insufflation pressure (6-8mmHg) is also lower than during laparoscopic cholecystectomy with standard insufflation pressure (12-15mmHg) suggesting that these may hold promise for faster surgical recovery.

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