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Elective Laparoscopic Cholecystectomy Nearly Abolishes the Postoperative Hepatic Catabolic Stress Response

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Objective

Surgery results in a catabolic state of postoperative stress, where the efficiency of the liver to convert amino acids to urea is increased. This study measured the metabolic consequences of the less traumatic laparoscopic surgery in elective cholecystectomy compared with traditional open surgery technique.

Summary Background Data

The authors previously have shown that open cholecystectomy doubles the urea synthesis measured by the means of the functional hepatic nitrogen clearance. Glucagon and cortisol increased by 50% ($p < 0.05$) and 75% ($p < 0.05$), respectively, after open cholecystectomy.

Methods

Patients undergoing uncomplicated elective laparoscopic cholecystectomies were included. Preoperatively and on the first postoperative day, blood and urine samples were drawn every hour under basal conditions and during amino acid infusion. The urea synthesis rate was calculated from the urea excreted in urine and accumulated in total body water. Functional hepatic nitrogen clearance was quantified as the slope of the linear relation between blood amino-N concentration and the urea synthesis rate. The results were compared with an historic matched group of patients who underwent open cholecystectomies and were studied by the same protocol.

Results

The laparoscopic cholecystectomy increased the functional hepatic nitrogen clearance by only 25%, (from 8.7 ± 0.9 to 11.1 ± 1.5 mL/sec [mean ± SEM; $p < 0.05$]), compared with a doubling after open cholecystectomy (from 9.4 ± 0.9 to 17.6 ± 3.3 mL/sec [$p < 0.05$]). The difference between the groups was significant ($p < 0.05$). Neither glucagon nor cortisol increased significantly after laparoscopic cholecystectomy.

Conclusions

The laparoscopic technique results in a much smaller postoperative hepatic catabolic stress response and probably reduced tissue loss of amino-N. This may be important for the more rapid convalescence and reduced postoperative fatigue.

Laparoscopic cholecystectomy has become the preferred method to remove the gallbladder. Its advantages include less patient discomfort, shorter hospital stay, and shorter interval to return to work.[1-3] Furthermore, the procedure results in a shorter period of postoperative ileus[4] and less impaired pulmonary function.[5]

Little is known as to why these clinical benefits may emerge, and the metabolic consequences of the laparoscopic surgery are largely unknown.

We have previously studied the hepatic catabolic stress response after open cholecystectomy.[6-8] Urea synthesis increases, despite a fall in blood amino-N concentration, indicating a hepatic condition with increased efficiency of amino-N removal. This can by quantified by means of the slope of the linear relation between blood amino-N concentration and urea synthesis rate—i.e, functional hepatic nitrogen clearance (FHNC),[9] that doubles after open cholecystectomy.[6-8]

This change in liver function plays a primary role for postoperative catabolism. The phenomenon is assumed to be a result of the surgical stress and to some extent, mediated via the hormonal responses to surgery.[10]

The purpose of this study was to measure FHNC and circulating hormones before and after laparoscopic cholecystectomy and to compare the results with those from patients undergoing open cholecystectomies.

MATERIALS AND METHODS

Patients

Eight patients took part in the study (four men and four women); uncomplicated gallbladder stones were verified by ultrasonography. The patients had no other known diseases. They underwent elective laparoscopic cholecystectomies because of abdominal discomfort. The study group was matched by age and body weight, with the control group consisting of patients (n = 16) included in an earlier study.[8] The average age in the study group was 45 years (range 31–63 years) and the average body weight was 73 kg (range 45–97 kg), compared with 42 years (range 34–59 years) and 77 kg (range 55–92 kg) in the control group. The patients in the control group underwent elective open cholecystectomies under the same indications and were investigated according to exactly the same protocol.

Protocol

Subjects acted as their own control. They were investigated preoperatively and on the first postoperative day, after an 8-hour fast with free access to tap water. Each investigation lasted for 5 hours and consisted of 1 hour with observation under basal conditions (no amino acid infusion), 1 hour with infusion of an amino acid mixture (Primmer + Co, Erlangen, Germany) at 41.2 μmol-N/(min × kg body weight), and 3 hours at a rate of 22.3 μmol-N/(min × kg).

Venous blood samples were drawn from the arm not used for infusion, at the start of the investigation and every half hour thereafter.

After initial emptying of the bladder, urine was collected quantitatively every hour. During the fasting period the night after the operation, the patients were given 1000 mL of isotonic NaCl intravenously.

Clinical Procedures

The patients were sedated with benzodiazepines and anesthetized with fentanyl-thiopental and dinitro-oxide or halothane. In the laparoscopic cholecystectomy group, muscle relaxation was performed with either suxamethonium or atracurium. The average anesthesia time was 102 ± 14 minutes (mean ± SEM) in the laparoscopic cholecystectomy group and 76 ± 14 minutes in the open cholecystectomy group.

Cholecystectomies were performed according to standard procedures and were uncomplicated in all included cases. There was no blood loss requiring transfusion. The systolic blood pressure did in no case fall below 100 mm Hg. No patient had a postoperative temperature above 38 C. No patient had pains requiring use of opioids.

Analyses

Total amino-nitrogen concentration in blood was determined by the dinitrofluorobenzene method (coefficient of variation of analyses 1.25%)[11] and urea by the urease-berthelot method (coefficient of variation 1%).[12]

Serum cortisol was determined by radioimmunoassay (Orion Diagnostica, Finland). Serum insulin and plasma glucagon were measured by radioimmunoassay, with the modification that polyethylene glycol used for separation.[13] Intra- and interassay coefficients of variance were less than 5% and 10%, respectively.

Calculations

For each urine collection period, the urea nitrogen synthesis rate was calculated as urinary excretion rate of urea (E) corrected for accumulation of urea in total body water (A) and fractional hydrolysis of urea in the gut (L)[9]:

$$UNSR = (E + A)/(1 - L)$$

Total body water was estimated from body weight,

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Table 1. PLASMA CONCENTRATION OF TOTAL α-AMINO NITROGEN (AAN), UREA-NITROGEN SYNTHESIS RATE (UNSR) AND N-EXCHANGE PREOPERATIVELY AND ON THE FIRST POSTOPERATIVE DAY IN PATIENTS AFTER LAPAROSCOPIC AND OPEN CHOLECYSTECTOMY

		Laparoscopic Cholecystectomy (n = 8)		Open Cholecystectomy (n = 16)	
		Preoperative	Postoperative	Preoperative	Postoperative
P-AAN (mmol/L)	Fasting	3.1 ± 0.1	2.9 ± 0.1†	2.9 ± 0.1*	2.5 ± 0.1†
	AA-load	4.9 ± 0.1*	4.4 ± 0.2†	5.3 ± 0.1*	4.3 ± 0.1†
UNSR (μmol/s)	Fasting	10.0 ± 3.3‡	10.1 ± 1.3	6.9 ± 1.0‡	11.5 ± 2.2
	AA-load	27.1 ± 2.3‡	28.4 ± 2.9	27.0 ± 1.4‡	35.2 ± 0.9
N-exchange		92 ± 5	96 ± 6	84 ± 3*	115 ± 5

* Preoperative value *vs.* postoperative value $p < 0.05$;
† Change in value preoperatively to postoperatively open cholecystectomy *vs.* laparoscopic cholecystectomy $p < 0.05$;
‡ Change in value preoperatively to postoperatively open cholecystectomy *vs.* laparoscopic cholecystectomy $p < 0.05$.
Values are mean ± SEM.

body height, and age.[14] Fractional hydrolysis of urea in the gut (L) was taken to be 17%.[15]

Hepatic amino-nitrogen conversion was assessed by the FHNC.[16] This was calculated for each investigation as the slope of the relation between urea-nitrogen synthesis rates and the corresponding average total blood α-amino-nitrogen concentrations during the same time periods within which urea synthesis was determined. Calculations of FHNC were based on at least four sets of data, each based on a time period of about 1 hour.

The metabolic N-exchange was calculated during the last 3 hours of infusion as the percentage of infused amino-N, appearing as urea-N.

Statistical Analyses

Difference between groups were evaluated by two-tailed t test of means or paired test as appropriate. P values less than 0.05 were considered statistically significant. Values are given as mean ± SEM.

RESULTS

Fasting and amino acid infusion-stimulated blood amino-nitrogen concentration did not change between the pre- and first postoperative day in the patients undergoing laparoscopic cholecystectomies, whereas they decreased by 16% and 19%, respectively ($p < 0.05$) after open cholecystectomy (Table 1).

Fasting urea-N synthesis rate did not change after laparoscopic cholecystectomy, but increased by 66% after open cholecystectomy ($p < 0.01$). The amino acid stimulated urea-N synthesis rate increased by a factor of approximately 3 in all cases, but the resulting level was 25% higher after open cholecystectomy ($p < 0.05$; Table 1).

Laparoscopic cholecystectomy increased FHNC by approximately one fourth ($p < 0.05$), whereas open cholecystectomy nearly doubled it ($p < 0.02$; Fig. 1).

The N-exchange was below 100% and did not change after laparoscopic cholecystectomy; however, open cholecystectomy increased it to above 100% (Table 1).

Fasting blood glucose concentration decreased by 25% after laparoscopic cholecystectomy and increased by 25% after open cholecystectomy ($p < 0.05$; Table 2).

Fasting glucagon was lower in the laparoscopic chole-

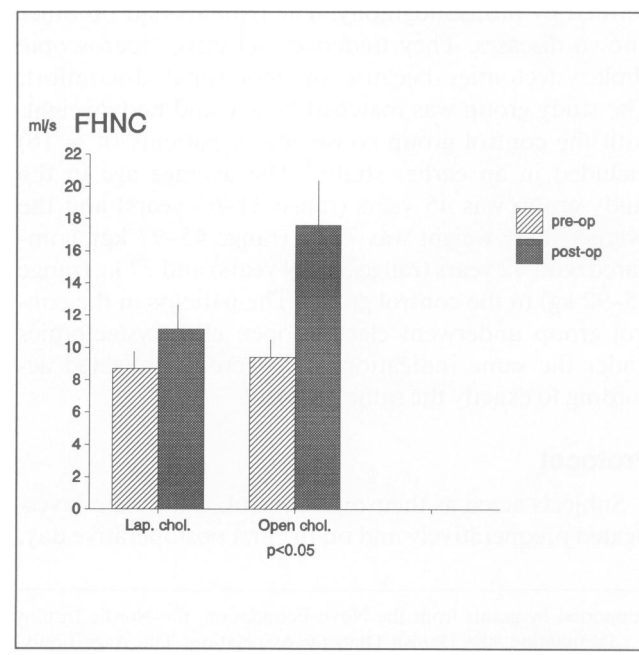

Figure 1. Functional hepatic nitrogen clearance preoperatively and on the first postoperative day after laparoscopic (n = 8) and conventional open cholecystectomy (n = 16) (mean ± SEM).

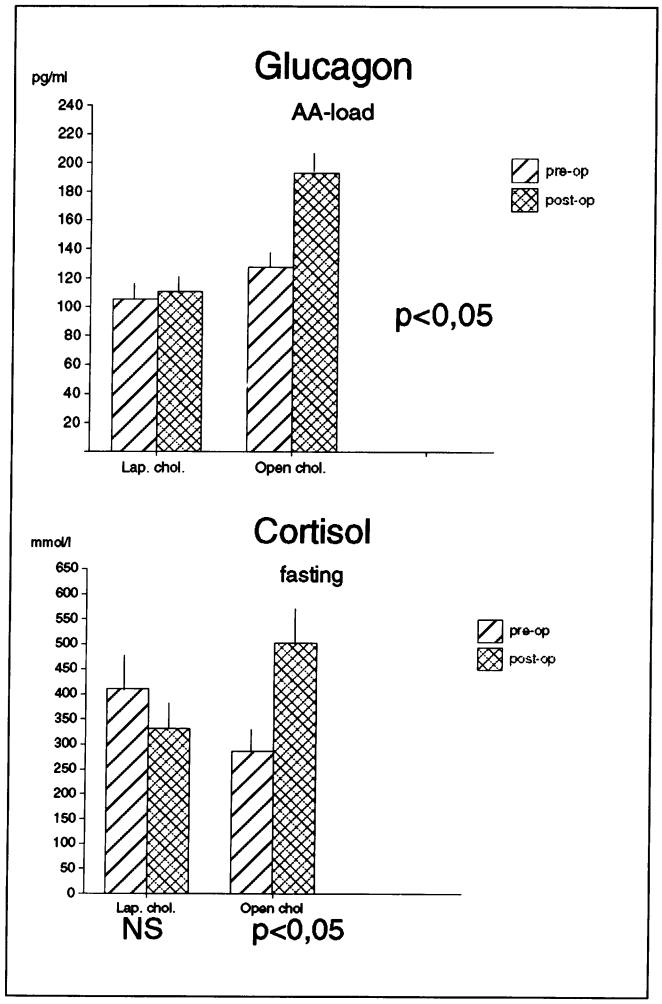

Figure 2. Glucagon and cortisol preoperatively and on the first postoperative day after laparoscopic and conventional open cholecystectomy.

cystectomy group than in the open cholecystectomy group, both before and after surgery. Amino acid-stimulated glucagon was the same before and after laparoscopic cholecystectomy, whereas the postoperative value was 50% higher after open cholecystectomy ($p < 0.05$; Table 2).

Neither fasting nor amino acid-stimulated cortisol concentration increased after laparoscopic cholecystectomy, whereas the fasting value increased by 75% ($p < 0.05$) after open cholecystectomy (Table 2; Fig. 2).

Fasting insulin was lower in the laparoscopic cholecystectomy group (Table 2). Amino acid infusion increased insulin to the same value before and after laparoscopic cholecystectomy, but to a value two times higher after open cholecystectomy ($p < 0.05$).

DISCUSSION

The laparoscopic cholecystectomy increased the hepatic nitrogen conversion only slightly, as opposed to the doubling after open cholecystectomy. The widespread acceptance of the laparoscopic techniques mostly is the result of the early discharge of the patients, which, despite being a political decision, often is taken to reflect less postoperative stress. This study documents that the patients operated via the laparoscope are subject to less metabolic stress.

Hepatic nitrogen conversion was quantified by means of the FHNC. Functional hepatic nitrogen clearance expresses the efficiency of the liver in converting α-amino-N into urea. By urea synthesis, nitrogen is irreversibly made unavailable for protein synthesis. In catabolic states such as postoperative stress, active inflammatory bowel disease, and insulin-dependent diabetes mellitus, FHNC is increased markedly.[6,7,17] This contributes toward negative nitrogen balance with loss of body proteins. Correspondingly, the N-exchange, which is an expression of how much of the infused amino-N is lost as urea, indicated a net loss of body nitrogen after open cholecystectomy. This did not occur in the laparoscopic cholecystectomy group.

The mediation of the increase in FHNC in catabolic situations involves the classical "catabolic hormones" (glucagon, cortisol, catecholamines), prostaglandins, cytokines, and afferent neural reflexes.[10] The postoperative increase in FHNC after open cholecystectomy can be abolished completely through a combined neurohormonal blockade.[8]

This study shows that the laparoscopic technique resulted in a much smaller postoperative amino-N loss. The most likely explanation is that the laparoscopic technique resulted in smaller increases of catabolic hormones. This suggestion is supported by the results of an investigation made on a patient, who was excluded from the laparoscopic cholecystectomy group because of a complicated course, (temperature 38.5 C and a small preoperative intraperitoneal bleeding). In this patient, the catabolic hormones rose as after open cholecystectomy (data not shown), and the postoperative FHNC doubled.

Glucagon stimulates urea synthesis[18-19] and is elevated after surgery.[10] The reduced postoperative level of glucagon during amino acid stimulation probably is important for the reduced hepatic stress response after laparoscopic cholecystectomy.

Cortisol increases urea synthesis, mobilizes amino acids from skeletal muscle proteins,[20-23] and potentiates the stimulating effect of glucagon on urea synthesis. Fasting cortisol was not changed by laparoscopic cholecystectomy, whereas it increased after open cholecystectomy. This probably also is important for the reduced hepatic stress response.

Insulin seems not to be a direct regulator of urea synthesis.[24-26] The slight hyperinsulinemia after open cholecystectomy probably is secondary to the slight hypergly-

Table 2. PLASMA GLUCAGON, INSULIN, CORTISOL, B-GLUCOSE PREOPERATIVELY AND ON THE FIRST POSTOPERATIVE DAY AFTER LAPAROSCOPIC AND OPEN CHOLECYSTECTOMY

		Laparoscopic Cholecystectomy (n = 8)		Open Cholecystectomy (n = 16)	
		Preoperative	Postoperative	Preoperative	Postoperative
Glucose (mmol/L)	Fasting	4.9 ± 0.7	3.6 ± 0.6	4.5 ± 0.1*	5.7 ± 0.3
	AA-load	4.4 ± 0.4	4.1 ± 0.4	4.8 ± 0.1	5.7 ± 0.2
Glucagon (ng/mL)	Fasting	34 ± 4†	38 ± 5†	92 ± 6†	97 ± 9†
	AA-load	105 ± 11	111 ± 14	128 ± 10*	193 ± 15
Cortisol (nmol/L)	Fasting	410 ± 57‡	332 ± 34	287 ± 34	503 ± 56†
	AA-load	376 ± 44	374 ± 73	216 ± 22	399 ± 57
Insulin (mU/L)	Fasting	8 ± 2	7 ± 1†	15 ± 2*	20 ± 2†
	AA-load	14 ± 3*	19 ± 7	15 ± 2*	39 ± 6

* Fasting or AA-load values before operation *vs.* after operation $p < 0.05$;
† Fasting *vs.* AA-load values $p < 0.05$;
‡ Preoperative *vs.* postoperative NS.
Values are mean ± SEM.

cemia, resulting from the increased hepatic amino acid conversion as also reflected in the higher urea synthesis. The simultaneous hyperinsulinemia and hyperglycemia after open cholecystectomy also may be aggravated by postoperative insulin resistance.[27] Insulin sensitivity is reported to decrease by only 20% after laparoscopic cholecystectomy, compared with 50% after open cholecystectomy ($p < 0.01$).[28]

Catecholamines were not measured in this study, but infusion of catecholamines to a level two times as high as those usually seen after surgery does not change the dynamics of urea synthesis in rats.[29] Neither cytokines were measured. The effect of interleukin-1 on urea synthesis evidently depends on cortisol,[10] which only increased after open cholecystectomy. The individual effects of the other cytokines on urea synthesis are not clear. Prostaglandins might play a regulating role, because they accelerate the effects of glucagon and cortisol on urea synthesis.[30] Whether the laparoscopic technique influence these factors differently from open cholecystectomy is not known.

Our study uses an historic but well-matched control group (open cholecystectomy group). It would have been desirable with a true control group, but this will not be possible to obtain after the advent of the laparoscopic cholecystectomy. Eighty-five percent of cholecystectomies and probably nearly all elective cases are performed laparoscopically.[2]

The difference in fasting glucagon and insulin between the study group and the control group probably is not caused only by interassay variations between the two analysis series because the amino acid stimulated values were comparable. Patient adherence to fasting regimen may have been less strict in the open cholecystectomy group. Because the preoperative FHNC does not differ between the groups, however, the difference in fasting hormones is not important for the validity of the results.

The anesthesia technique was the same in both groups, but the anesthesia time in the laparoscopic group was 50% longer than in the open cholecystectomy group. This shows either that anesthesia is not in itself a heavy stress factor or that the small increase in FHNC in the laparoscopic group might have been smaller, or even absent, had the anesthesia time been the same.

The laparoscopic operation technique for cholecystectomy, compared with open surgery, almost abolishes the postoperative hepatic catabolic stress response. This may, to some extent, result from the changes in glucagon and cortisol responses. The smaller increase in hepatic urea synthesis probably results in a reduction of postoperative amino-N loss, as indicated by the normalization of the N-exchange. This may be important for uncomplicated convalescence and amelioration of postoperative fatigue. It still is unknown whether these observations can be paralleled to other laparoscopic operations, particularly to those performed in patients with pre-existing metabolic stress, such as infection, or patients undergoing reoperation.

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