ORIGINAL ARTICLE

Serum cholecystokinin levels can be a predictive factor for difficult cholecystectomy: Decreased cholecystokinin receptor levels

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ABSTRACT

BACKGROUND: Laparoscopic cholecystectomy (LC) is being performed frequently in general surgery practice. Estimation of difficult cholecystectomy is very important to take precautions against complications. Cholecystokinin (CCK) is an important enzyme for gallbladder motility. CCK receptor is the target for CCK. Fibrosis and emptying problems of gallbladder are related with difficult cholecystectomies. We aimed to evaluate the association between plasma CCK and difficult cholecystectomy and try to explain the mechanism.

METHODS: Prospective cross-sectional study was conducted on a group of patients with cholelithiasis Patients who underwent elective cholecystectomy were classified into easy, difficult and very difficult preoperatively using LC difficulty scores. Pre-operative gallbladder empting ratios were measured by ultrasonography. Serum C-reactive protein, and postprandial serum CCK and pancreas polypeptide levels were measured before the operation. Operation data including operation times, adhesion scores, and complications were collected. Tissue CCK receptor levels and tissue fibrosis scores were obtained.

RESULTS: Easy, difficult, and very difficult LC (DLC) groups were consisted of 34, 28, and 8 patients, respectively. Gallbladder emptying was 60% in easy LC group, but 15% in very DLC group. Plasma CCK levels in easy group (37.4 pg/ml) were significantly lower than plasma CCK levels of difficult (58.6 pg/ml), and very difficult groups (66.23 pg/ml). Tissue CCK receptor levels of easy, difficult, and very difficult were 372.4, 178.3, and 144.1 ng/100 mg, respectively. Adhesion scores and fibrosis scores of very difficult group were significantly higher than other groups. Operation times were significantly longer in very difficult group. There were two conversions to open in very DLC group (25%).

CONCLUSION: CCK is a reliable parameter for determining the difficulty of LC. Decreased CCK receptor levels with fibrosis of gallbladder are the probably responsible mechanism.

Keywords: Cholecystokinin; cholecystokinin receptor; difficult cholecystectomy; gallbladder motility; laparoscopic cholecystectomy.

INTRODUCTION

Laparoscopic cholecystectomy (LC) can decrease postoperative pain, shorten the postoperative ileus period, and lead to earlier oral intake and earlier return to normal activities with better cosmesis. LC is the most common procedure for gallstone diseases.[1] Nevertheless, LC can result in conversion to open cholecystectomy. In difficult cases serious complica-

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tions can be seen when dense adhesions appear at the cystic pedicle; Fibrotic and contracted gallbladder; Or inflamed gall bladder.[2] For this reason, difficult procedures are defined depending on conversion rates, iatrogenic injuries, bile spillages, and operation times.[3] Defining difficult LC (DLC) preoperatively can help surgeons to prepare for intraoperative challenges, optimize surgical plan, improve patient counseling, increase operation room efficiency, schedule for long hospital stay, plan operation techniques, and identify patients eligible for resident training.[2–4]

The previous studies have identified several predictors for DLC including conversion rates, operation times, subjective difficulties, and risk-assessment models.[4,5] Most of the risk-assessment models includes parameters such as C-reactive protein (CRP), white blood cell count (WBC) or symptoms and findings of cholecystitis, pancreatitis, and cholangitis with inflammation and fibrosis around the cystic pedicle.[5,6] Among all this risk models, the difficulty depends on fibrosis.

Plasma cholecystokinin (CCK) is the main factor for post-prandial gall bladder emptying. CCK interacts with the CCK receptor-A (CCK-A) in the gall bladder leading to contraction of the gall bladder.[7] Reduced expression of CCK-A can cause impaired contractility in patients with gallstones.[8] A negative linear correlation between postprandial plasma CCK and CCK-A has been shown in patients with cholesterol stone in gall bladder.[9] The aim of this study is to evaluate whether the plasma CCK level can be a predictor factor for DLC and to investigate the relationship between fibrosis of gall bladder and plasma CCK level, tissue CCK-A levels, and DLC.

MATERIALS AND METHODS

This prospective descriptive clinical cohort study was approved by local Ethical Committee (KOU KAEK 2015/72) and performed in Kocaeli University School of Medicine Department of General Surgery. The committee waived the need for individual consent because of prospective nature of the study. Patients who underwent elective LC for gallbladder stones were included in the study. We collected the patients during 6 months period. During this 6 month period, we excluded patients who underwent gastric and duodenum operations; Patients with inflammatory bowel diseases, diabetes mellitus, autoimmune diseases, cirrhosis, cancer; Patients using ursodeoxycholic acid and history of somatostatin; And also the patients with history of endoscopic retrograde cholangiopancreatography and vagotomy from the study. Ultrasonography was performed on the patients included in the study while they were fasting and full, 1 week before their planned surgery. Fasting and post-prandial blood biochemistry analyzes were performed.

To predict the difficulty of LC, the scoring system which was developed by Randhawa and Pujahari[4] and validated by Gupta et al.[5] was used (Table 1).[10,11] Age, sex, history of acute cholecystitis, body mass index (BMI), existence of abdominal scars, palpable gallbladder, wall thickness, the volume of gallbladder, and identifying pericholecystic fluid or stones during fasting were studied in this scoring system. Ultrasonography evaluation was performed by same expert radiologist (SÇ). One day before the operation day, in the morning, following at least 12 h fasting, the patients were evaluated for gallbladder volume. Thirty minutes after eating 100 gr Ensure plus chocolate shake (Abbot Lab, Chicago, USA), the gallbladder volume was remeasured to find the emptying ratio.[11] Pre-operative blood samples were taken for measurement of liver function tests, CRP levels, and pancreas polypeptide (PP) levels in fasting state. Post-prandial (30 min after eating breakfast containing one egg, toast, and orange juice in the morning) blood samples were taken to measure postprandial CCK levels. These evaluations were done during preparation of the patients in last week of the operation. Serum CCK and PPs levels were measured with a CCK immunoassay kit (Phoenix Pharmaceuticals, California, USA). All patients were treated by same surgeons (TUY, SÇ), together. One (TUY) is experienced in hepatopancre-

Table 1. Factors used for grading difficulty score in laparoscopic cholecystectomy

		Score
History		
Age	≤50 years	0
	>50 years	1
Sex	Male	1
	Female	0
History of hospitalization	Yes	4
for acute cholecystitis	No	0
Clinical parameters		
BMI	<25	0
	25–27.5	1
	>27.5	2
Abdominal scar	No	0
	Infraumblical	1
	Supraumblical	2
Palpable gallbladder	Yes	1
	No	0
Sonography		
Wall thickness	Thin <4 mm	0
	Thick ≥4 mm	2
Pericholecystitic collection	No	0
	Yes	1
Impacted stone	No	0
	Yes	1

Score 0–5 easy, 6–10 difficult, 11–15 very difficult. Table is taken from Gupta N et al.[5]

aticobiliary (HPB) surgery for 14 years and European HPB board certificated and other (SÇ) is last year resident. The operation times were divided into three periods: Time from trocar placement to dissection of Calot triangle (trocar to dissection), time from dissection of Calot triangle to placement of last clip to cystic duct (Calot dissection), and time from last clip to removal of gallbladder from abdomen (gallbladder bed dissection).

Subjective intra-operative adhesion scores were determined according to subjective clinical findings:

- Grade 0: Complete absence of adhesions
- Grade 1: Localized filmy easily separable adhesions
- Grade 2: Localized filmy separable adhesions with moderate traction
- Grade 3: Dense, extensive adhesions
- Grade 4: Adhesions of the visceral organs to the abdominal wall.

Conversion to open cholecystectomy, bile leakage, and choledochal injury were noted. Two longitudinal strips (3×15 mm) parallel to the longitudinal axis were obtained from the middle of gallbladder body. Histological evaluation was performed for histological fibrosis score by using the method defined by Barcia et al.[12] The reviewing pathologist was blinded to the study. Other tissue samples were used to measure the amount CCK-A receptor by solid phase ELISA (Santa Cruz Biotechnology, Texas, USA).

The patients were grouped into three according to difficulty scores: Easy, difficult, and very difficult. The parametric results were given as mean±SEM. The plasma CCK and PP levels were given as pg/ml. Tissue CCK-A levels were given as ng/100 mg. The parametric values of groups were compared with ANOVA, and post hoc Tukey. Nonparametric values of groups compared with Kruskal-Wallis test. The ROC curve was plotted according to the CCK plasma levels of the enrolled patients. According to the area under ROC curve and the 95% confidence interval of the area, the accuracy of the tests was evaluate based on statistical tests. Optimal cutoff point was calculated according to better positive predictive value. Data were analyzed by SPSS 20.0 (Chicago, IL, USA). P<0.05 was considered statistically significant.

RESULTS

We included 70 patients. The mean age was 50.8±13.6 years. The mean BMI was 26.7±6.3 kg/m^2. Patients were grouped according to pre-operative difficulty scores. The easy group, difficult group, and very difficult group had 34, 28, and 8 patients, respectively. The mean age, sex distribution, and mean BMI values are given in Table 2. Pre-operative PP levels among easy, difficult, and very difficult groups were 0.22, 0.21, and 0.19 pg/mL, respectively. There is no significant difference between PP levels of groups (p=0.9).

Pre-operative CRP levels among groups are shown in Figure 1. The mean CRP levels of the very DLC group were higher than the other groups, but the difference is not significant (p=0.06). The mean plasma CCK levels of easy LC, DLC, and very DLC were 37.4, 58.6, and 66. 23 pg/ml, respectively. The mean plasma CCK levels of the very DLC group were significantly higher than the easy LC group (p=0.012) (Fig. 2). However, there is no significant difference between very difficult and difficult groups (p=0.3). Optimal cutoff point was determined as 48.6 pg/ml according to positive predictive value 91.6%. This value can be cutoff limit for difficult cholecystectomy. Pre-operative gallbladder emptying showed that gallbladders in the easy LC group empty better than DLC and very DLC groups after meal (p=0.002 and p=0.001 respectively, Fig. 3). Nearly 60% of gallbladders empty in the easy LC group; This ratio decreases up to 15% in the very DLC group.

The mean tissue CCK-A levels of easy LC, DLC, and very DLC were 372.4, 178.3, and 144.1 ng/100 mg, respectively. The mean tissue CCK-A amount in the easy LC group is significantly higher than the difficult and very DLC groups (p=0.001 and p=0.0001, respectively, Fig. 4). However, there is no significant difference in the mean CCK-A values between difficult versus very DLC groups (p=0.8). Histological fibrosis scores of easy LC, DLC, and very DLC were 1.7, 2.4, and 3.5, respectively. The histologic mean fibrosis score is significantly higher in the very DLC group than difficult and easy LC groups (p=0.03 and p=0.01, respectively, Fig. 5). The mean intraoperative subjective adhesion scores of easy LC, DLC, and very DLC were 1.3, 2, and 4, respectively. The mean intraoperative subjective adhesion mean score is signif-

Table 2. Mean age, mean BMI, and sex distribution of groups

	Easy group (n=34)	Difficult group (n=28)	Very difficult group (n=8)	Total (n=70)
Mean age (years)	47.9±12.8*	51.21±11.6	61.6±18.8	50.83±13.6
BMI (kg/m^2)	25.4±6.8	28.1±4.1	25.2±8.2	26.7±6.3
Sex distribution (male/female)	7/27	17/11	5/3	29/41
Conversion to open cholecystectomy (n=3)	1		2	3

BMI: Body mass index.

icantly higher in the very DLC group than difficult and easy LC groups (p=0.03 and p=0.01, respectively, Fig. 6). Time periods for stages of operations among groups are compared in (Fig. 7). There is no significant difference between groups in trocar to dissection and gallbladder bed dissections (p=0.8, ANOVA). However, the time period in Calot dissection is significantly longer in very DLC groups versus DLC and easy LC groups [p=0.003 and p=0.001, respectively, Fig. 7).

Conversion to open cholecystectomy occurred in three cases. The inability to expose the anatomy due to bleeding was seen in one case in the easy LC group during Calot dis-

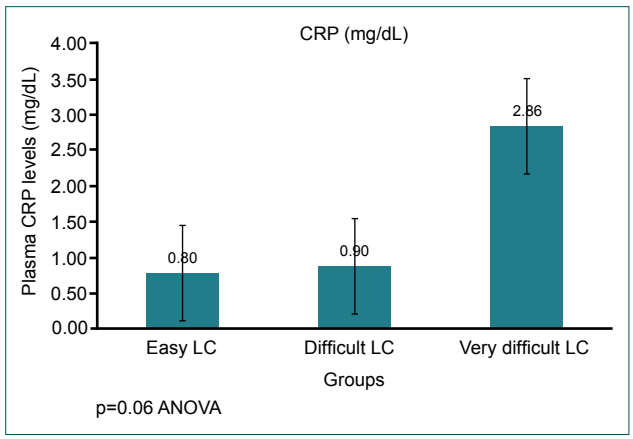

Figure 1. Mean plasma CRP levels of groups. P=0.06 ANOVA.

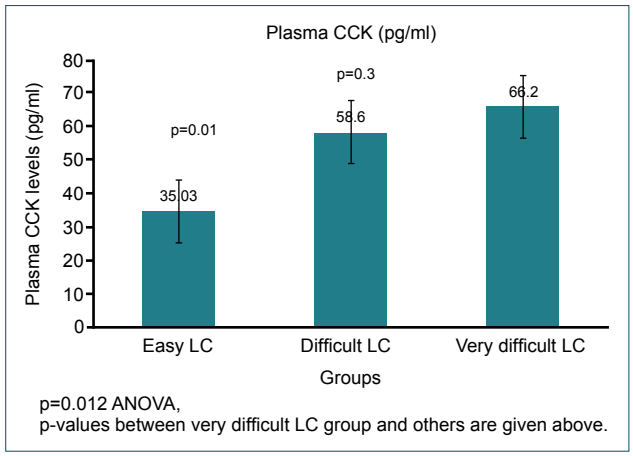

Figure 2. Mean plasma CCK levels of groups. P-values between difficult LC group and others are given above.

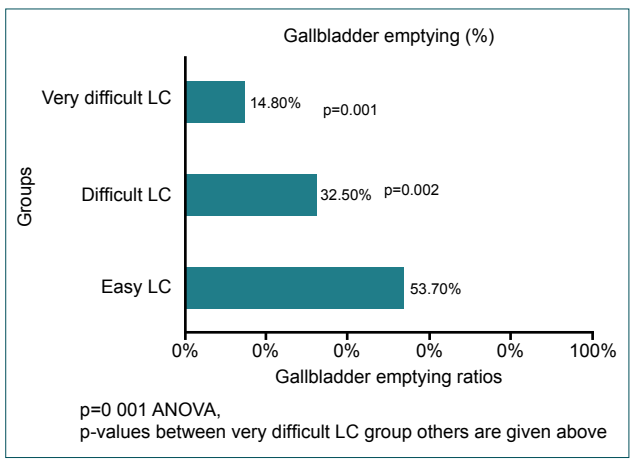

Figure 3. Preoperative gallbladder emptying ratio of groups in ultrasonography evaluation.

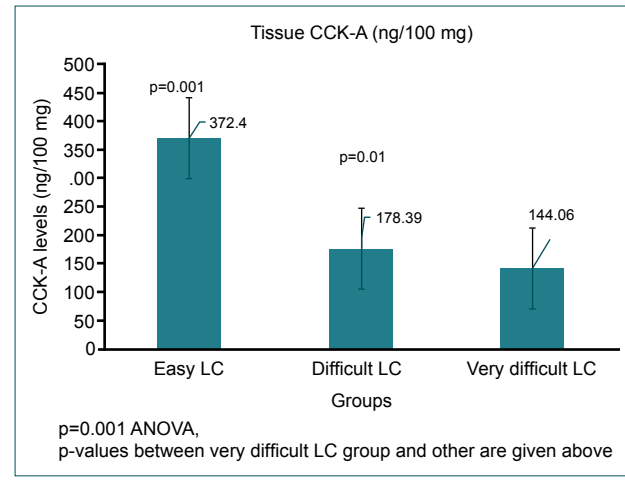

Figure 4. Mean tissue CCK A levels among groups.

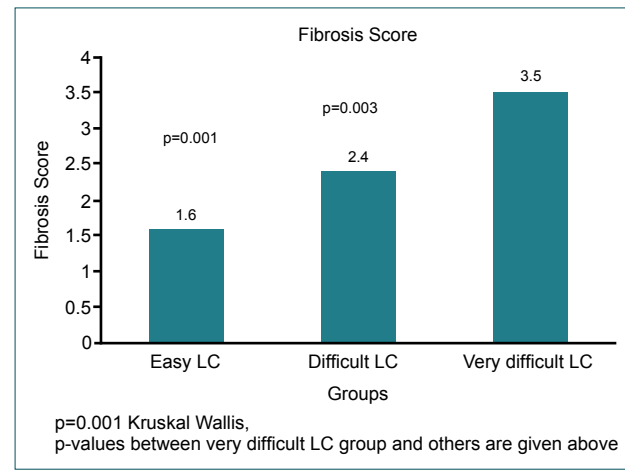

Figure 5. Mean histological fibrosis scores of groups among groups.

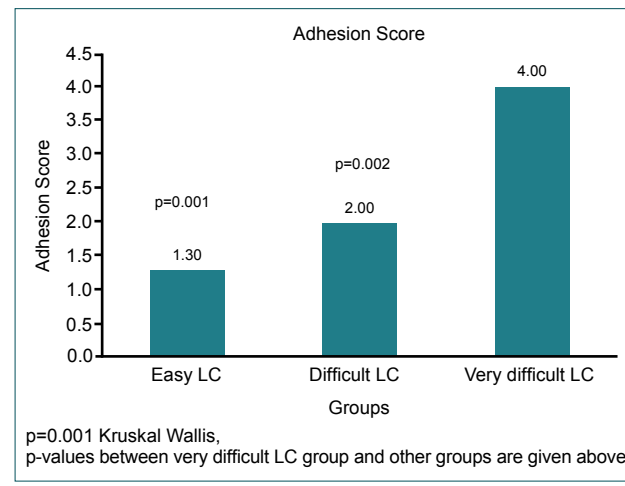

Figure 6. Mean intraoperative adhesion scores of groups.

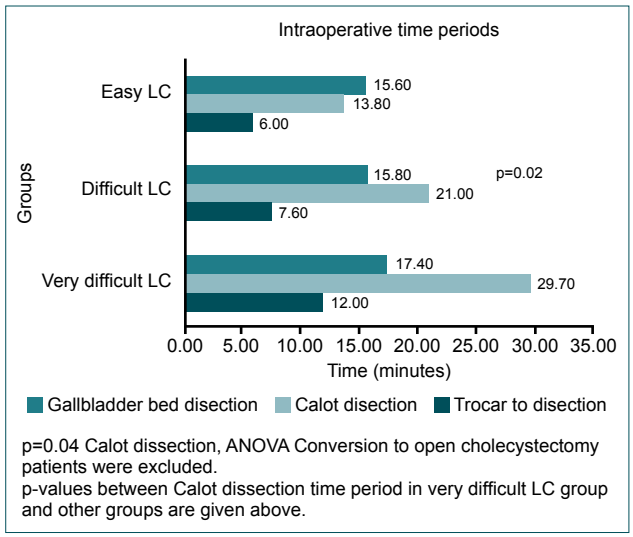

Figure 7. Intraoperative time periods of stages of operation among groups (minutes).

section (2% conversion rate). Two cases in the very DLC group were converted to open cholecystectomy because of an inability to dissect the dense adhesions (25% conversion rate). Delineation of Calot triangle was not achieved. Cystic artery, choledoch, and cystic duct were not seen. The time period measurement was not done in patients with conversion to open cholecystectomy. Although these cases were elective LC cases, three cases had increased gallbladder wall thickness and increased WBC. However, none of the cases fulfilled the acute cholecystitis criteria.[13]

DISCUSSION

Since the first LC from Philip Mouret in 1987, the complication rate and conversion rate in LC are now remarkably low at 2–6%.[14] Although the complication rate decreases with experience, there is still an important amount of complications related to LC. DLC are the main reasons for complications, conversions, blood loss, long operative time, and long hospital stays. There have been a number of scoring or prediction systems proposed to predict the probability of conversion.[15] Male gender, abdominal tenderness, previous abdominal operation, age over 60 years, acute cholecystitis, and obesity are risk factors for conversion.[15] Patients with none of these predictors have a 1.5% conversion probability, but this rose to 9.3% in the presence of acute cholecystitis and elevated alkaline phosphatase (ALP). It rose to 27.5% if acute cholecystitis was accompanied by elevated WBC counts and ALP.[16] For these reasons, during the preoperative evaluation-especially for emergency cases - surgeons search the patients for possible acute cholecystitis. Acute cholecystitis requires special treatment, and thus most surgeons take precautions against possible complications. However, in elective cases, patients may not show acute cholecystitis criteria.[13] Here, fibrosis is the main factor for DLC. Thus, we chose the scoring system from Randhawa and and Pujahari[4] Several other scoring systems have criteria including acute cholecystitis.[16] In our study, DLC groups have an increased operative time especially in Calot dissection, which is related to dense adhesion. Our study showed that increased intraoperative adhesions and increased Calot dissection time are seen in DLC. Difficulty is a subjective finding, but here in this study, the operations are performed by the same team and major difficulty outcomes such as operation time and conversion to open can be regarded as difficulty parameters. We noted that increased adhesion score, fibrosis, and conversion to open cholecystectomy much more seen in difficult cases. This scoring system is beneficial in estimating the difficulty. The difficulty depends on the fibrosis and adhesions around the Calot area. The difficult LCs mostly related with injury and conversion to open. The rate of injury and conversion could be up to 1% and 30% respectively in the literature.[3] Our conversion to open rate is 25%.

Gallbladder emptying is a parameter that defines the contraction capacity of gallbladder. Contraction capacity can be measured with in vitro techniques or through radiologic volumetric changes of gallbladder after meal.[9] To measure the volume of GB, ultrasonography and cholescintigraphy are the mostly preferred methods.[17] There have been several studies that measure the volume of GB in the literature by ultrasonography.[18,19] The contraction capacity of gallbladder decreases during inflammation and fibrosis in smooth muscles of the gallbladder.[20] Thus, it is a parameter for evaluation of cholecystitis. In our study, the emptying capacity of DLC group was significantly lower than the other groups. The previous studies showed that the emptying ratios of the non-contraction groups were <40%.[9] In our study, all of the patients in DLC were <30% emptying ratios. The serum CRP levels did not showed any significant difference among groups, but the DLC group had higher CRP levels than the others. Although none of the patients had symptoms of acute cholecystitis, there is continued inflammation in gallbladders in difficult cases.

CCK constitutes the major hormonal stimulus for postprandial gallbladder emptying mainly through CCK receptors in a dose-dependent manner. CCK receptor A is the main receptor found in smooth muscles of gallbladder. Although it can be stimulated by cholinergic system and gastrin hormone, the potency of CCK is 1000–fold higher.[21] Decreased CCK receptors are related with decreased contraction of gallbladder.[8,9,22] In these studies, patients with gallbladder emptying <50% have decreased CCK receptors. Patients in the DLC group have emptying ratios <50%. The natural question that arises is whether inflammation destroys the CCK receptors or whether decreased receptors and the consequent decreased motility predisposes the gallbladder to stone formation and inflammation. Some authors state that a decreased CCK receptor is the primary mechanism of hypomotility and stone formation.[8,22] Upp et al.[22] investigated the lymphocyte infiltration for inflammation score, and Ding et al.[8] evaluated the inflammation and thought that the decreased levels of CCK receptor were due to diabetes mellitus. While Upp

et al.[22] support the main route of stone formation through decreased CCK receptors, all noncontractors have inflammation, but only 15% of contractors have moderate or severe inflammation. Faridi et al.[23] showed that patients with gallstones but without inflammation have higher CCK receptors levels than the normal gallbladders that are extracted from donor hepatectomy. However, if the inflammation occurs, then the CCK receptor levels decrease significantly.[24] The inflammation in gallbladder lead to increased lipid peroxidase, prostaglandin E2, and superoxide dismutase that damage constituents of the plasma membrane of muscle cells and CCK receptors as well.[24] Of course, altered CCK receptor functions can also be seen in diabetes, obesity, celiac, total parenteral nutrition, pregnancy, and result with hypomotility of gallbladder. We thought that CCK levels are decreasing in the presence of inflammation. In our study, inflammation and fibrosis have shown a decreased amount of CCK receptors. Patients with decreased CCK receptor have significantly reduced gallbladder emptying.

Plasma CCK is responsible for gallbladder emptying. Plasma CCK levels mostly increase after protein and fat uptake and gallbladder construction can only start with plasma levels of 2 pg/ml.[21] Plasma CCK levels have been shown to be increased in non-contractor gallbladders.[9,25] Here, we similarly found that plasma CCK levels were increasing in the non-contracting group significantly higher than the contracting group. Plasma CCK concentration may reach the peak at a specific postprandial time and remain constant for a period of time. This is important for gallbladder emptying. Decreased CCK-A in gallbladder might be responsible for decreased combination of CCK and abnormally increased plasma CCK. This mechanism is also shown in patients with increased CCK levels in patients with cholecystectomy.[26] We showed that plasma CCK levels are increasing because of decreased CCK-A. Thus, plasma CCK levels might be helpful to evaluate gallbladder function and related fibrosis in gallbladder.

PPs are secreted from pancreas and mainly offer self-regulatory functions in the pancreas. PPs are increased by exercise, fasting, protein meal, and hormone-active pancreas tumors.[27] PP also acts as a CCK antagonist and also influences the postprandial gallbladder motor function. Any factor that can alter PP can influence plasma CCK levels and gallbladder function. However, there is no significant difference between the PP of groups.

Our study confirmed that difficult cholecystectomy is related with increased fibrosis and adhesions and results in an increased operation time and conversion rate. Plasma CCK levels can be a parameter to estimate the difficulty of LC through the mechanism of CCK receptor A decreases during gallbladder inflammation. Limitations of our study are lack of evaluation of serum CCK changes before and after meal. According to our results, future studies about effects oral CCK agonists to gallbladder motility can be arranged.

Conclusion

Our findings demonstrated that fibrosis in gallbladder is related with difficult cholecystectomy. Tissue CCK receptor levels are decreasing with increasing fibrosis. Serum CCK levels are shown to be higher in DLC cases. Serum CCK might be a tool for estimation of DLC.

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Ethics Committee Approval: This study was approved by the Kocaeli University Faculty of Medicine Clinical Research Ethics Committee (Date: 10.03.2015, Decision No: 2015/72).

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Authorship Contributions: Concept: T.U.Y., F.C.E.; Design: T.U.Y., F.C.E., Ç.V.; Supervision: T.U.Y., N.Z.U.; Resource: T.U.Y., N.Z.U.; Materials: .U.Y., F.C.E., S.Ç., E.A., S.Ça.; Data: Ç.V., S.Ç., E.A., S.Ça., BYB; Analysis: E.A., S.Ç., BYB, S.Ça.; Literature search: S.Ç., Ç.V., S.Ça.; Writing: T.U.Y., F.C.E., S.Ç.; Critical revision: N.Z.U.

Conflict of Interest: None declared.

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ORİJİNAL ÇALIŞMA - *ÖZ*

Serum kolesistokinin düzeyi, zor kolesistektomi için belirleyici faktör olabilir: Azalmış kolesistokinin reseptör düzeyleri

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AMAÇ: Laparoskopik kolesistektomi (LK), genel cerrahinin sık yapılan ameliyatlarındandır. Olası komplikasyonlara karşı önlem almak için, zor kolesistektomiler belirlenmelidir. Kolesistokinin (CCK), safra kesesi boşalmasında rol oynayan önemli bir hormondur. Safra kesesinde bulunan kolesistokinin reseptörleri, CCK için temel hedeftir. Safra kesesinde fibrozis zor kolesistektomilerdeki en önemli sorundur. Bu çalışmanın amacı, zor kolesistektomi ile plazma kolesistokinin düzeyi arasındaki ilişkiyi incelemek ve olası mekanizmayı açıklamaya çalışmaktır.
GEREÇ VE YÖNTEM: Elektif laparoskopik kolesistektomi ameliyatına alınacak hastalar daha önceden belirlenen skorlama sistemine göre kolay, zor ve çok zor laparoskopik kolesistektomi olarak gruplandırıldı. Ameliyat öncesi safra kesesi boşalması ultrasonografi ile değerlendirildi. Serum CRP, tokluk serum CCK ve pankreas polipeptid düzeyleri operasyon öncesi ölçüldü. Operasyon süreleri, yapışıklık skorları ve ameliyattaki komplikasyonlar incelendi. Doku CCK reseptör düzeyleri ve safra kesesi dokularında fibrozis düzeyleri belirlendi.
BULGULAR: Kolay, zor ve çok zor LK grupları sırasıyla 34, 28 ve 8 hastadan oluşuyordu. Safra kesesi boşalması kolay LK grubunda %60 iken çok zor LK grubundan %15 olarak belirlendi. Kolay LK grubunda (37.4 pg/ml) ortalama plazma CCK düzeyleri, zor LK grubu (58.6 pg/ml) ve çok zor LK grubuna (66.23 pg/ml) göre belirgin daha düşüktü. Doku CCK reseptör düzeyleri kolay, zor ve çok zor LK gruplarında sırasıyla 372.4, 178.3, and 144.1 ng/100 mg ölçüldü. Doku yapışıklık skoru ve operasyon süreleri çok zor LK grubunda belirgin daha fazla ölçüldü. Çok zor LK grubunda iki hastada (%25) açığa geçiş görüldü.
TARTIŞMA: Serum CCK düzeyi, LK zorluğu belirlemek için bir parameter olarak kullanılabilir. Zor LK'da artmış fibrozis ile birlikte azalmış CCK reseptör düzeyleri bu mekanima için muhtemel sebep olabilir.
Anahtar sözcükler: Kolesistokinin; kolesistokinin reseptörü; laparoskopik kolesistektomi; safra kesesi boşalması; zor kolesistektomi.

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