

The role of histopathologic alterations of gallbladder wall in conversion cholecystectomy

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Abstract

Aim: We aimed to investigate the role of histopathologic alterations of gallbladder wall in conversion cholecystectomy.

Material and Methods: 3338 laparoscopic cholecystectomies and 121 conversion cholecystectomies that were performed between January 2008 and June 2017 in our hospital were evaluated. Patients were divided into 2 groups as laparoscopic and conversion cholecystectomy groups. Both groups were compared retrospectively by examining the histopathologic data of 140 patients were randomly analyzed.

Results: There was a statistically significant difference between the types of surgery according to necrosis, polymorfonuclear leucocytes, mononuclear cells, edema levels ($p < 0.01$). The incidence of polymorfonuclear leucocytes and mononuclear cells was at the marked and massive levels in cases with conversion cholecystectomy which were higher than in those with laparoscopic cholecystectomy. The rate of severe edema seen in conversion cholecystectomy was higher than in laparoscopic cholecystectomy ($p < 0.01$). There was a statistically significant difference between the types of surgery according to granulation tissue, neoangiogenesis and fibroblast levels ($p < 0.01$). There was a statistically significant difference between the necrosis-edema duple levels and Verhofstadt scores of the cases according to the operation type ($p < 0.01$).

Conclusion: Cholelithiasis histopathology that evaluates intra-mural factors has significant effects on conversion cholecystectomy with extra-mural factors. The increase in Verhofstadt score and Necrosis-Edema duple has been shown to increase the risk of conversion cholecystectomy surgery with great sensitivity. Preoperative superb microvascular imaging and contrast-enhanced ultrasound may helpful in detecting the necrosis and edema in the gallbladder wall which has also the potential to predict the risk of conversion cholecystectomy.

Keywords: Laparoscopic Cholecystectomy; Conversion Cholecystectomy; Histopathology.

INTRODUCTION

Laparoscopic cholecystectomy (LC) is gold standard operation for symptomatic cholelithiasis. Conversion cholecystectomy (CC), which is a transition from laparoscopy to open cholecystectomy, can not be avoided despite all preoperative investigations and precautions. The causes of LC to open surgery are still unclear (1). Conversion to OC is observed in 1-20% of patients (2-5). Currently, there are many studies investigating the causes of both preoperative, intraoperative and extra-mural causes of conversion (6-10,14-16).

In this study, we aimed to investigate the role of intra-mural histopathologic factors in CC.

MATERIAL and METHODS

Our study was started after acceptance of İstanbul Medeniyet University Göztepe Training and Research

Hospital ethics committee (2017 / 0327). One hundred forty patients ($n = 70$ women, $n = 70$ men) were randomly selected from 3459 patients who underwent LC and CC for symptomatic cholelithiasis between January 2008 and June 2017.

Patient selection was based on whether their last digit of hospital admission numbers were odd or even number by using of block randomization technique. Operation notes and histopathologic records of the patients were re-evaluated. Patients with symptomatic cholelithiasis with pathology results as acute and chronic cholecystitis were included in this study. Patients who were started as open cholecystectomy were excluded from the study.

Histopathological evaluation

Histopathological evaluation was performed by single pathologist who was blinded. Tissue samples from both groups which were obtained by 10% formalin fixation

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and paraffin embedded tissue blocks which was cut at a thickness of 4 mm and prepared for dyeing with hematoxylen-eosin (H & E) and Masson's trichrome re-evaluated. The modified Verhofstad scoring system was used for histopathological examination to determine the degree of inflammation in the gallbladder layers (11). Slides were examined for necrosis, edema, infiltration of polymorfonuclear leucocystes (PMNs), macrophages and mononuclear cells (MNLs), granulation tissue, neoangiogenesis, fibroblasts and collagen deposition. The Ehrlich and Hunt grading scale was used for fibroblastic

activity, neoangiogenesis and collagen deposits and was converted to the digital system of Philips et al. (12-13). Based on previous studies, the parameters are divided into four categories (0: normal / no, 1: mild, 2: moderate, 3: severe). In our study, necrosis, PMNs, MNLs, edema, mucosal epithelium, granulation tissue, neoangiogenesis, fibroblastic activity and collagen deposition were used as parameters. Because there are no muscularis mucosae and submucosa at the gallbladder, bridging between these layers was not evaluated during pathologic examination (14). (Table 1).

Table 1. The modified histopathological assessment scale.

Score	Necrosis	PMN's	MNL's	Edema	Mucosal Epithelium	Granulation tissue	Neo-angiogenesis	Fibroblast	Collagen Deposition
0	None	Normal number	Normal number	None	Normal glandular	None	None	None	None
1	Small patches	Slight increase	Slight increase	Some	Normal cubic	Some	Partial	Partial	Partial
2	Some patches	Marked infiltration	Marked infiltration	Marked	Incomplete cubic	Marked	Moderate	Moderate	Moderate
3	Massive	Massive infiltration	Massive infiltration	Severe	Absent	Severe	Marked	Marked	Marked

PMN's: polymorfonuclear leucocystes. MNL's: mononuclear cells

Statistical analysis

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. Mann Whitney U test was used for two groups of descriptive statistical methods (Mean, Standard Deviation, Median, Frequency, Rate, Minimum, and Maximum) as well as quantitative data without normal distribution. Pearson Chi-square test and Fisher-Freeman-Halton test were used for comparison of qualitative data.

RESULTS

In our cholecystectomy serie, conversion rate was 3.4% (n = 121). Grade 3 - 6 adhesions were observed as the factors of causing CC in 71.9% (n:87) of these patients. Other causes of CC in patients were; scleroatrophic gallbladder 4.9% (n:6), 4.9% brids due to previous operations (n:6) , intraoperative bleeding 4.1% (n:5) , laparoscopic instrumentation problems 4.1% (n:5), porcelain gallbladder 1.6% (n:2) , iatrogenic bile duct injury 1.6% (n:2), additional lesions in the liver 1.6% (n:2), iatrogenic small bowel injury %1.6 (n:2), unsecured clipping due to wide cystic channel %1.6 (n:2), giant (over 20 cm long diameter) gallbladder, 0.8 % (n:1) general condition disorder due to bradycardia 0.8% (n:1), respectively.

According to pathology, 8.5% of patients (n:12) were reported as acute calculous cholecystitis. All patients with acute cholecystitis were in the CC group. Remaining patients (n:128) were reported as chronic calculous cholecystitis.

There was a statistically significant difference between the types of surgery according to necrosis, PMNs, MNLs,

edema levels (p <0.01). Necrosis was not observed at laparoscopic procedures. However, cases of CCs' were with 28.6% small, 24.3% some, and 7.1% were massive necrosis, respectively. The incidence of PMNs and MNLs were at the marked and massive levels in cases with CC which were higher than in those with LC (p <0.01). The rate of severe edema seen in CC was higher than in LC. A statistically significant difference was found between the types of mucosal epithelium (p <0.01).

The incidence of incomplete cubic and absent mucosal epithelium in cases with CC was higher than in LC. There was a statistically significant difference between the surgical types according to granulation tissue levels (p <0.01). The incidence of granulation tissue as marked and severe levels in cases with CC was higher than in cases with LC.

There was a statistically significant difference between the types of surgery according to neoangiogenesis and fibroblast levels (p <0.01). The rate of moderate and marked neoangiogenesis, collagen accumulation and fibroblast levels were observed in CC which were higher than in LC (Table 2).

There was a statistically significant difference between Verhofstadt scores (p<0.01). The Verhofstadt scores of CC group were higher than the group of LC.

There was a statistically significant difference between the necrosis-edema (NE) duple levels of the cases according to the operation type (p <0.01). The NE duple of CC group was higher than the group of LC (Table 3).

Table 2. Evaluation of descriptive characteristics according to the operation type

		Operation Type		p
		LC(n=70) n (%)	CC(n=70) n (%)	
Gender	Female	35 (50.0)	35 (50.0)	^a 1.000
	Male	35 (50.0)	35 (50.0)	
Necrosis	None	70 (100)	28 (40.0)	^b 0.001**
	Small	0 (0)	20 (28.6)	
	Some	0 (0)	17 (24.3)	
	Massive	0 (0)	5 (7.1)	
PMN	Normal	60 (85.7)	3 (4.3)	^a 0.001**
	Slight	10 (14.3)	20 (28.6)	
	Marked	0 (0)	20 (28.6)	
	Massive	0 (0)	27 (38.6)	
MNL	Normal	1 (1.4)	0 (0)	^b 0.001**
	Slight	46 (65.7)	2 (2.9)	
	Marked	22 (31.4)	52 (74.3)	
	Massive	1 (1.4)	16 (22.9)	
Edema	None	3 (4.3)	0 (0)	^b 0.001**
	Some	28 (40)	1 (1.4)	
	Marked	34 (48.6)	17 (24.3)	
	Severe	5 (7.1)	52 (74.3)	
Mucosal epithelium	Normal glandular	24 (34.3)	4 (5.7)	^a 0.001**
	Normal cubic	22 (31.4)	13 (18.6)	
	Incomplete cubic	15 (21.4)	35 (50)	
	Absent	9 (12.9)	18 (25.7)	
Granulation tissue	None	66 (94.3)	31 (44.3)	^b 0.001**
	Some	3 (4.3)	15 (21.4)	
	Marked	1 (1.4)	18 (25.7)	
	Severe	0 (0)	6 (8.6)	
Neoangiogenesis	None	40 (57.1)	4 (5.7)	^a 0.001**
	Partial	24 (34.3)	21 (30.0)	
	Moderate	5 (7.1)	32 (45.7)	
	Marked	1 (1.4)	13 (18.6)	
Fibroblast	None	29 (41.4)	0 (0)	^a 0.001**
	Partial	31 (44.3)	16 (22.9)	
	Moderate	10 (14.3)	26 (37.1)	
	Marked	0 (0)	28 (40.0)	
Collagen deposi-tion	None	55 (78.6)	20 (28.6)	^a 0.001**
	Partial	11 (15.7)	19 (27.1)	
	Moderate	3 (4.3)	16 (22.9)	
	Marked	1 (1.4)	15 (21.4)	

LC: Laparoscopic Cholecystectomy. CC: Conversion Cholecystectomy. ^a Pearson Chi-square test. ^bFisher-Freeman-Halton Test. **p<0.01

Table 3. Evaluation of Verhofstadt Score and Necrosis-Edema Duple levels according to operation type

		Operation Type		p
		LC (n=70)	CC (n=70)	
Verhofstadt Score	Min-Max	1-18	6-26	0.001**
	Mean±SD	5.80±3.40	16.19±5.42	
Necrosis-Edema	Min-Max	0-3	1-6	0.001**
	Mean±SD	1.58±0.69	3.71±1.30	

LC: Laparoscopic Cholecystectomy. CC: Conversion Cholecystectomy. Mann Whitney U Test. **p<0.01

From this point of view, it was considered to calculate the cut-off point for Verhofstadt score and the NE duple. According to the surgical procedure, the cut-off point for the Verhofstadt score was 7 and above. If 7 point was selected for cut-off value of Verhofstadt score; sensitivity 98.57%; specificity 67.14%; positive predictive value 75.00; the negative predictive value was 97.92 and the accuracy

was 82.86 (Table 4). According to the operation, the cut-off point 2 and above was determined for NE duple. If 2 point was selected for cut off value of NE level; sensitivity 98.57%; specificity 44.29%; the positive predictive value was 63.89 and the negative predictive value was 96.88 and the accuracy was 71.43.

Table 4. Diagnostic screening tests for Verhofstadt Score and Necrosis-Edema and ROC curve results

Diagnostic Scan								
	Cut off	Sensitivity	Specificity	PPV	NPV	Area	95% CI	P
VS	≥ 7	98.57	67.14	75.00	97.92	0.949	0.917-0.982	0.001**
NE	≥ 2	98.57	44.29	63.89	96.88	0.911	0.865-0.957	0.001**

VS: Verhofstadt Score. NE: Necrosis-Edema. Pearson Chi-square test. PPV: Positive Predictive Value. NPV: Negative Predictive Value. CI: Confidence Interval

DISCUSSION

The reasons for CC are not fully understood (1). Transition rates up to 20% have been reported (2-5). It was reported CC increases in the cases where the Calot triangle can not be adequately revealed due to inflammation, fibrosis and adhesions (6,7). Factors such as previous upper abdominal surgery, pericholecystic fluid, bile duct dilatation, cholestasis, hepatomegaly, acute cholecystitis and emergent cholecystectomy must alert surgeon about complicated surgery (15,16) On the other hand, Chang's recent study was not justified the inflammation grading system for CC decision (17). This has led us to investigate role of the histopathology of gallbladder wall in the decision of conversion. Although CC is a decision during surgery, it is understood that this condition may not always due to extrinsic factors. Inflammation related factors, such as stage 3 - 6 adhesions, sclero-atrophic and porcelain gallbladder are the well known causes of conversion. Surgeon's decision to open procedure roots from surgeon's experience and clinical sense during laparoscopies, too. However some of extra-mural factors are generally due to intra-mural inflammatory processes. Verhofstadt scale which has wide spectrum of tissue inflammatory parameters was preferred for histopathologic examination in the current study.

Edema and necrosis, duple of parameters in the Verhofstadt scale, can give an idea about the status of the gallbladder in the preoperative period. This duple was evaluated separately in the current study. Edema and necrosis of gallbladder can be evaluated with careful ultrasonography before operation (18,19). The presence of this duple in the preoperative period may be effective in preventing the surgeon's insistence about laparoscopy during the operation.

Grade 3 - 6 adhesions, scleroatrophic gallbladder, porcelain gallbladder and giant gallbladder were the main conversion reasons in our study. Moreover, these kind of situations are the exploratory findings that enforce surgeon to convert open surgery. All of these situations

occur after acute and chronic inflammatory processes. It is obvious that increase in PMNs, MNLs, collagen deposition, fibrosis, edema with or without necrosis in the gallbladder walls are essential components of acute and chronic cholecystitis. There are three clinical subtypes of cholecystitis which are acute, subacute and chronic cholecystitis. Surgeon's diagnosis is clinical and radiologic at the preoperative period. However, precise diagnosis is at postoperative period after histopathologic evaluation. Histopathology of acute cholecystitis is with PMNs infiltration, marked epithelial changes, edema with or without necrosis. Histopathology of chronic cholecystitis is with MNLs, chronic fibrosis and Rokitansky- Aschoff sinuses (20-23). As we see, there are some changes from acute cholecystitis to chronic cholecystitis.

Surgeons are generally abstaining from subacute period cholecystectomies because of perioperative complications. There is no histopathologic prediction system for CC. It is not feasible to predict conversion even during laparoscopic exploration until Calot angle is fully dissected. This situation sometimes causes time and money loss with catastrophic complications. It is clear that we need more precise prediction system in the preoperative period. However, it is quite difficult to determine some of Verhofstadt scoring system's components in the preoperative period for today. Determining PMNs, MNLs and fibroblasts in this period is nearly impossible. But it is well known from inflammation canon that PMNs are more intense in the acute phase, whereas MNLs and chronic fibrosis with fibroblasts are more common in the subacute and chronic phases of cholecystitis (20-23). For this reason it is not important to demonstrate these cellular parameters and can be conceded as positivity during preoperative period according to patients' clinical and radiologic findings. Today tissular collagen density can be demonstrated with more careful radiologic evaluations such as collagen-binding molecular magnetic resonance imaging (24). In this point of view nearly all Verhofstadt's scale components can be disclosed properly at the preoperative period.

In the present study, histopathologic evaluation of the gallbladder wall revealed significantly lower necrosis, PMNs, MNLs and edema levels in the LC than in CC group. On the other hand, incomplete cubic and absence of mucosal epithelium, tissue granulation, neo-angiogenesis, fibroblast accumulation and collagen deposition were significantly higher in CC group. All these findings suggest that intra-mural factors are the primary cause of augmentation in gallbladder wall inflammation and provide a positive contribution to CC. According to our study it is obvious that increase in Verhofstadt score and NE duple has been shown to increase the risk of CC surgery with great sensitivity. This study has importance to point out the relevance between intra-mural histopathologic factors and some extra-mural factors in CC for the first time in literature.

In the present study, the small size sample and its retrospective nature has presented some limitations. On the other hand, non-operational factors associated with histopathology of diseased gallbladder effect on the risk of CC assessment were analyzed in detail.

CONCLUSION

In conclusion, it can be said that intra-mural factors such as histopathology of diseased gallbladder has a significant and primary role on the risk of CC with other extra-mural factors. Preoperative superb microvascular imaging and contrast-enhanced ultrasound may be helpful in detecting the necrosis and edema in the gallbladder wall which has also the potential to predict the risk of CC.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: Our study was started after acceptance of İstanbul Medeniyet University Göztepe Training and Research Hospital ethics committee (2017 / 0327).

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