Early versus delayed laparoscopic cholecystectomy for lithiasic acute cholecystitis during emergency admissions. Results of a monocentric experience and review of the literature.

Cholécystectomie laparoscopique précoce versus retardée pour cholécystite aiguë lithiasique pendant les admissions d'urgence. Résultats d'une expérience monocentrique et revue de la littérature.

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RÉSUMÉ

Introduction : Il est établi que le traitement standard pour cholécystite aiguë lithiasique est la cholécystectomie laparoscopie. Cependant, la question du délai de la cholécystectomie reste controversée.

But: Comparer les cholécystectomies précoces aux cholécystectomies retardées réalisées par voie laparoscopique, en matière de difficultés per-opératoires et de complications post-opératoires.

Méthodes : Entre le 1er Janvier 2007 et le 31 Décembre 2012, tous les patients opérées pour cholécystite aiguë au service de Chirurgie Générale et Digestive du CHU Farhat Hached et répondant à des critères d'inclusion et de non inclusion, ont été inclus dans une étude rétrospective. Ainsi, 184 patients ont été répartis en deux groupes selon que la chirurgie a eu lieu avant (groupe A) ou après (groupe B) les 72 heures qui ont suivi le début des symptômes. Nous avons procédé à la comparaison des deux groupes.

Résultats : Les deux groupes étaient comparables en termes de terrain, de présentation clinico-biologique, de grade de sévérité de la maladie et de constatations radiologiques. Le délai moyen de la chirurgie était de 111.6 heures après l'installation des symptômes. La durée opératoire était significativement plus allongée pour le groupe B (97 minutes versus 82.17 minutes ; p= 0.003). Il y avait plus de conversion pour le groupe B que pour le groupe A, sans que la différence ne soit significative (20 % versus 11.6 % ; p= 0.14). La mortalité dans notre série était nulle. Les complications post-opératoires spécifiques étaient comparables entre les deux groupes (infection de la paroi : 3 (B) versus 1 (A) ; fistule biliaire : 8 (B) versus 0 (A) ; p=NS). La durée du séjour hospitalier post-opératoire était significativement plus longue pour le groupe B (3.34 jours versus 1.84 ; p <10-3).

Conclusion : Le traitement laparoscopique précoce de la cholécystite aiguë lithiasique permet de réduire le coût de la prise en charge, la durée opératoire et le séjour hospitalier. Les taux de conversion et de morbidité post-opératoire sont comparables à ceux du traitement retardé.

Mots-clés : cholécystite aiguë lithiasique, cholécystectomie laparoscopique

SUMMARY

Background: It is established that the standard treatment for lithiasic acute cholecystitis is the laparoscopic cholecystectomie. However, the question of the timing of cholecystectomy remains controversial.

Aim: To compare early laparoscopic cholecystectomies (within 72 hours of symptom onset) and delayed laparoscopic cholecystectomies (beyond 72 hours) for lithiasic acute cholecystitis in terms of intra-operative difficulties and post-operative complications.

Methods: The patients operated on for acute cholecystitis, between January 2007 and December 2012, were included in a retrospective study. They were divided into two groups based on whether surgery was performed before (group A) or after (group B) 72 hours after the onset of symptoms. We conducted a comparison between the two groups.

Results: The two groups were comparable in terms of background, clinico-biological presentation, and radiological findings. The average time of surgery was 111.6 hours after symptom onset. Duration of surgery was significantly longer for group B (97 minutes versus 82.17 minutes, p = 0.003). There was more conversion in group B than in group A, without significant difference (20% versus 11.6%, p = 0.14). There were no deaths in our series. Specific post-operative complications were comparable between the two groups (wound infection: 3 (B) versus 1 (A), biliary fistula: 8 (B) versus 0 (A), p = Non significant). The post-operative hospital stay was significantly longer in group B (3.34 days versus 1.84, p <10-3).

Conclusion: In case of early laparoscopic cholecystectomy, the conversion rate and post-operative morbidity are comparable to the delayed treatment of acute cholecystitis. But the early surgery can reduce the cost of care, the duration of surgery and the hospital stay.

Key-words
Lithiasic acute cholecystitis ; Laparoscopic cholecystectomy

It is now established that the standard treatment for lithiasic acute cholecystitis is surgery [1]. However, the question of the timing of cholecystectomy remains controversial. Currently, there are three attitudes towards this disease. The first, which is the oldest, is an elective surgery after an initial medical treatment allowing the retrocession of the inflammatory phenomena, during a second hospitalization. The second is a delayed cholecystectomy, scheduled during the same hospitalization. The third is an early cholecystectomy, as soon as possible after admission. In our current practice, we operate acute cholecystitis during the index hospitalization. It is exceptional that we defer intervention to a second hospitalization. More and more studies focus on the timing of cholecystectomy during the same hospitalization: should it be performed in acute phase or scheduled after a few days of medical treatment?

The purpose of this study was to compare early laparoscopic cholecystectomies (within 72 hours of symptom onset) and delayed laparoscopic cholecystectomies (beyond 72 hours) for lithiasic acute cholecystitis, in terms of intra-operative difficulties and post-operative course.

METHODS

This is a retrospective study, which involved patients operated on in the Department of General and Digestive Surgery of *Farhat Hached* University Hospital of *Sousse* (Tunisia) for lithiasic acute cholecystitis. We looked at files of all patients operated on between January 1st, 2007 and December 31st, 2012. We identified 2027 patients operated on for biliary lithiasis including 346 acute cholecystitis (17%). Out of these 346 cases, 184 patients had the inclusion criteria.

We included all patients with clinical, biological and radiological criteria of lithiasic acute cholecystitis: pain with or without right upper quadrant guarding, a Murphy's sign, a temperature > 37.5°C, leukocytosis ≥ 10 000 elements/mm^3 and / or increased CRP, ultrasound findings (gallstones, gallbladder wall thickening, gallbladder distension, peri-vesicular effusion, non dilated biliary tract, sonographic Murphy's sign), and the pathological examination of operative specimens.

Have not been included in this study patients with Mirizzi syndrome, with a history of abdominal surgery, with common bile duct stones (with or without acute cholangitis), having (or having had) acute pancreatitis, with generalized peritonitis and with unexploitable files.

The endpoints were intra-operative difficulties (localized peritonitis, duration of surgery, difficulties in Calot's triangle dissection, intra-operative bleeding, adhesions, pediculitis and conversion to open cholecystectomy) and postoperative course (wound infection, biliary fistula, medical complications, overall hospital stay, post-operative hospital stay and incisional hernia).

Two groups were defined: group A gathering patients operated on within 72 hours of symptom onset (n = 69); group B with patients operated on beyond 72 hours (n = 115).

We conducted a comparison between the two groups.

All patients underwent laparoscopic cholecystectomy using the same procedure: supine position, legs spread apart, the operator between the legs and the assistant in the left side of the patient. Four trocars are used: epigastric and right hypochondrium (5 mm), umbilicus and left hypochondrium (10 mm). The pneumoperitoneum's pressure was maintained at 12 mmHg. In case of conversion to open cholecystectomy, the incision was a right subcostal one. The duration of surgery was measured in minutes from the insufflation to the exsufflation of carbon dioxide or to the wound closure in case of conversion to open cholecystectomy.

We entered the data on the software package *Epi Info* (version 8). Comparing the quantitative variables was made by the Student's t-test; the comparison of qualitative variables was performed using the Chi-squared test, Yates' chi-squared test and F-test. The threshold for statistical significance was set at 5% and the difference was considered as significant as of $p < 0.05$. The timing of cholecystectomy was measured from symptom onset.

RESULTS

Both groups A and B were comparable concerning demographic, clinical and para-clinical (biological and radiological) data. They only differed by the timing of cholecystectomy (Table 1). The average time between symptom onset and surgery was 111.6 hours. For group A, the average was 53.2 hours. Group B had an average of 146.7 hours.

Gallbladder distension was found intra-operatively in 153 patients (83.2%) of whom 59 (38.5%) in group A and 84 (61.4%) in group B. There was no significant statistical difference between the two groups (p = 0.85). A hepatic pediculitis was mentioned in operative reports of 23 patients in group A (33.3%) and 51 patients in group B (44.3%). It was more frequent during the first 24 hours (66.7% of patients operated on during the first 24 hours). There was no significant difference between the two groups (p = 0.14). Gallbladder adhesions (with the greater omentum, duodenum, right colic flexure, etc.) were observed in 19 patients in group A (27.5%) and 51 patients in group B (44.3%). The difference was statistically significant (p = 0.025). Localized peritonitis was found among 4 patients in group A (5.8%) and 12 patients in group B (10.4%), with no significant statistical difference (p = 0.28). In our study, we counted 108 (58.7%) inflammatory gallbladders (congestive wall and clear content), 36 (19.6%) suppurative cholecystitis (phlegmonous wall and / or purulent content) and 40 (21.7%) gangrenous cholecystitis.

Table 1: Summary of the characteristics of the two groups.

Characteristics	Group A (n=69)	Group B (n=115)	p
Timing of cholecystectomy* (hours)	53.2	146.7	
Age (extremes)	50.2 years	56.8 years	0.412
Sex ratio (M/F)	(18/51) 0.35	(34/81) 0.42	0.612
Antecedents			
Hypertension	18 (26.1%)	34 (29.6%)	0.612
Diabetes	10 (14.5%)	21 (18.3%)	0.509
ASA			
ASA I	34 (49.3%)	47 (40.9%)	0.371
ASA II	31 (44.9%)	55 (47.8%)	0.401
ASA III	4 (5.8%)	13 (11.3%)	0.156
Cause (s) of the delay (Group B):			
Delay of admission		20 (17.4%)	
Delay of diagnosis		69 (60%)	
Patient refusal		5 (4.3%)	
Anaesthetic problem		13 (11.3%)	
others		17 (14.7%)	
Clinical symptoms			
Fever	40 (58%)	76 (66.1%)	0.27
RUQ tenderness/guarding	69 (100%)	113 (98.3%)	0.31
Murphy's sign	24 (34.8%)	39 (33.9%)	0.9
Jaundice	1 (1.4%)	6 (5.2%)	0.26
Laboratory findings			
High WBC count	52 (75.4%)	86 (74%)	0.93
High CRP	34 (49.3%)	79 (69.3%)	0.07
Cytolysis	17 (27.8%)	32 (32.3%)	0.553
Cholestasis	6 (11.1%)	11 (12.35%)	0.823
US signs			
Gallstones	68 (98.6%)	111 (96.5%)	0.652
GB distension	51 (73.9%)	89 (77.4%)	0.592
GB wall thickening	56 (81%)	97 (84.3%)	0.63
Double-layered GB wall	18 (26%)	25 (21.7%)	0.5
Peri-vesicular effusion	3 (4.3%)	9 (7.8%)	0.537
Sonographic Murphy's sign	21 (30.4%)	23 (20%)	0.108
Diameter of the CBD (mm)	5.88	5.69	0.61

*Measured from symptom onset
RUQ: Right upper quadrant; WBC: White blood cell; CRP: C-reactive protein; US: Ultrasonographic; GB: gallbladder; CBD: Common bile duct

According to operative reports, cholecystectomy was considered as difficult in 27 patients (14.7%). Difficulties in the dissection of Calot's triangle were encountered in 5 patients in group A (7.2%) and 22 patients in group B (19.1%). The statistical difference between the 2 groups was significant (p = 0.027). A problem of intra-operative bleeding was reported in 2 patients in group A (2.9%) and 10 patients in group B (8.9%). The difference was not significant between the two groups (p = 0.22). The bleeding had not been quantified, and no blood transfusion was required. A conversion to open cholecystectomy was required in 31 patients (16.8%): 8 patients in group A (11.6%) and 23 patients in group B (20%). There was no significant difference between the 2 groups (p = 0.14). The causes of conversion were an intra-operative bleeding (group A: 2 versus group B 10), difficulties in Calot's triangle dissection (group A: 5 versus group B: 12), a refractory hypercapnia (group A: 1) and a doubt about a biliary injury (group B: 1).

An intra-operative cholangiography was performed on one patient in group A (doubt about common bile duct stones) and 5 patients in group B (doubt about common bile duct stones in 4 patients; about a biliary injury in one patient). The difference was not significant between the two groups (p = 0.52). It was normal in 2 patients and non contributory in 4 patients. The establishment of a cystic duct drain was performed for 2 patients in group A (2.9%) and 15 patients in group B (13%). The difference was significant (p = 0.02). The cystic duct drain was kept every time cholangiography was not contributory (4 patients) or not done because not available (13 patients).

A sub-hepatic drainage was considered necessary for 12 patients in group A (17.4%) versus 33 patients in group B (28.7%), with no significant statistical difference (p = 0.08).

For group A, the mean duration of surgery was 82.17 minutes with extremes of 35 and 155 minutes. For Group B, the mean duration was 97 minutes (40 to 220 minutes). The difference between the two groups was statistically significant (p = 0.03).

The mean overall hospital stay in group A was 3.44 days (2 to 6 days). For Group B, it was 5.91 days (2 to 30 days). The difference was statistically significant with $p < 10^{-3}$. The mean post-operative hospital stay in group A was 1.84 days (1 to 5 days). In Group B, it was 3.34 days (1 to 29 days). The difference was also statistically significant between the 2 groups ($p < 10^{-3}$).

The median follow up was 14 months (6 to 42 months). We counted 8 cases of early post-operative complications (4.3%), one in group A (1.4%) and 7 in group B (6%). No surgical, endoscopic or radiological reintervention was recorded. No deaths have been noted. For group A, we observed one case of wound infection (1.4%). In Group B, we counted three infections of the subcostal incision (2.6%), 8 external biliary fistula (7%) dried up spontaneously after 4 days on average (3 to 7 days) and two cardiac decompensation (1.7%). Later, we found 2 incisional hernias on the right subcostal scar, one case for each group. No cases of residual lithiasis were observed. There was no significant statistical difference between the 2 groups in our series in terms of early and late post-operative complications.

Pathological examination showed 82 simple cholecystitis, 52 phlegmonous cholecystitis and 50 gangrenous cholecystitis.

Table 2 summarizes the results of our series comparing the two groups.

Table 2 : Results of the surgery in the two groups.

Results	Group A (n=69)	Group B (n=115)	p
Duration of surgery (minutes)	82.17 (35 to 155)	97 (40 to 220)	0.003
Surgical findings			
Gallbladder appearance			
Inflammatory	49 (71.0%)	59 (51.3%)	0.012
Suppurative	6 (8.7%)	30 (26.1%)	0.004
Gangrenous	14 (20.3%)	26 (22.6%)	0.615
Difficulties in Calot's triangle dissection	5 (7.2%)	22 (19.1%)	0.027
Intra-operative bleeding	2 (2.9%)	10 (8.7%)	0.217
Adhesions	19 (27.5%)	51 (44.3%)	0.025
Localized peritonitis	4 (5.8%)	12 (10.4%)	0.280
Pediculitis	23 (33.3%)	51 (44.3%)	0.140
Conversion to open cholecystectomy	8 (11.6%)	23 (20%)	0.140
Intra-operative cholangiography	1 (1.4%)	5 (4.3%)	0.520
Biliary drainage	2 (2.9%)	15 (13%)	0.021
Sub-hepatic drainage	12 (17.4%)	33 (28.7%)	0.084
Post-operative course		3 (2.6%)	
Wound infection	1 (1.4%)	8 (7%)	0.518
Biliary fistula	0		0.065
Medical complications	0	2 (1.74%)	0.118
Incisional hernia	1 (1.4%)	1 (0.87%)	0.691
Overall hospital stay (days)	3.44 (2 to 6)	5.91 (2 to 30)	<10-3
Post-operative hospital stay (days)	1.84 (1 to 5)	3.34 (1 to 29)	<10-3
Pathological examination			
Simple	40 (58.0%)	42 (36.5%)	0.005
Phlegmonous	14 (20.3%)	38 (32.2%)	0.081
Gangrenous	15 (21.7%)	35 (30.4%)	0.199

DISCUSSION

Our study has certain shortcomings. The first one is a methodological limit, since it is a retrospective observational descriptive study, on the low-scale level evidence. It may contain a few measurement bias related to the validity and reliability of the measuring instrument. The second limit is the small size of our population. However, it allowed the identification of the specific subject of our article by the comparison of the two groups. The feasibility of early cholecystectomy for acute cholecystitis has already been proven. We have shown that the rate of conversion to laparotomy and that of post-operative morbidity are not higher than in case of a delayed surgery. The overall hospital stay and the duration of surgery are significantly shorter.

Nowadays, and with a high level of recommendation (grade A), the superiority of early laparoscopic treatment of acute cholecystitis is established. This concerns essentially the duration of surgery, the intra-operative difficulties, the overall cost and post-operative complications [1].

A review of the literature, regarding duration of surgery, finds results in favor of early cholecystectomy. The study of Zhu [2] found significant shorter duration for the group of early cholecystectomy (44.1 minutes versus 66 minutes). Similar results were published by Koo [3] and Serralta [4]. However, Gelbard [5] concluded that there was no significant difference in terms of duration of surgery between the two groups (84.1 minutes for early vs 84.3 minutes for the delay, p = 0.129). The results of our study demonstrate significant superiority of early cholecystectomy versus delayed one in terms of operative duration with an average of 82.17 minutes for early treatment versus 97 minutes for the belated treatment (p = 0.03). This could be explained by the difficulties encountered during surgery. Indeed, gallbladder adhesions were observed in 27.5% of patients in group A and 44.3% of patients in group B, with a significant statistical difference (p = 0.025). Table 3 summarizes the data of the literature comparing the duration of surgery.

Intra-operative bleeding may occur during the dissection of Calot's triangle or be related to a wound of the liver. This risk is even more important if there are adhesions and severe locoregional inflammation [6]. The rate of

incident is variable in the literature; it is 1.5% according Arvieux [7] and 3.8% for Pessaux [8]. In our series, intra-operative bleeding was reported in 6.4% of cases. However, few studies have focused on the comparison of intra-operative bleeding between early and delayed laparoscopic cholecystectomy for acute cholecystitis. According to Chandler [9], delayed cholecystectomy is more often complicated of intra-operative bleeding (299 ml vs 81 ml, p <0.05).

Table 3 : Comparison of operative duration between early and delayed laparoscopic cholecystectomy for acute cholecystitis in the literature.

Series	Duration (minutes)		P
	EC	DC	
Zhu [2]	44.1	66.4	<0.01
Serralta [4]	74.7	93.4	0.008
Gelbard [5]	84.1	84.3	NS
Our series	82.17	97	0.03

EC: Early cholecystectomy; DC: Delayed cholecystectomy; NS: No significant

The rate of conversion to laparotomy during laparoscopic cholecystectomy for acute cholecystitis varies between 5 and 20% in the literature [10]. In our series, the conversion was necessary in 31 patients (16.8%), this accords with the literature data. Most randomized studies of the literature concluded to the superiority of early cholecystectomy in terms of conversion to laparotomy. We quote the randomized trial published in 2003 by Serralta [4], including 169 patients, and having found a higher conversion rate in case of delayed surgery cholecystectomy (p = 0.001). It is the same for Eldar [11], who showed that the conversion rate was 23% for early surgery and 47% for delayed surgery with a significant difference (p = 0.022). Similar results were found by Koo [3] (12% versus 30%, p = S) and Willsher [12] (3.47% versus 27.02%, $p < 10^{-3}$). However, for Cheema [13], the conversion rates were close between the two groups (29% versus 23%) with no significant difference (p = 0.919).

In the series of Koo [3], it was shown that early cholecystectomy significantly reduces the overall hospital stay, and specifically the post-operative stay of patients. Similarly, the study of Willsher [12] concluded that early cholecystectomy in the first 48 hours has a lower hospital stay (3.7 days versus 5.6 days, p = 0.003). However, other studies have shown that delaying cholecystectomy beyond 72 hours of symptom onset does not significantly lengthen the hospital stay compared to the early treatment [2, 5, 11]. A single recent study, made by Serralta [4] contradicted previous results. It showed a longer post-operative hospital stay in patients treated early (<72 hours): 5.3 days versus 3.6 days (p = 0.045). This could be explained by the non-randomized nature of the study which includes a selection bias concerning different experience in laparoscopic surgery of surgeons who operated on the two groups. In case of diabetes, the hospital stay was significantly more elongated in delayed cholecystectomy compared to early cholecystectomy (p <0.001) [5].

According to the meta-analysis of Wu, early laparoscopic cholecystectomy appears as safe and effective as delayed cholecystectomy. However early cholecystectomy might be associated with lower hospital stay, fewer work days lost, and greater patient satisfaction [14].

A comparison of the overall hospital stay between early and delayed laparoscopic cholecystectomy is made in table 4.

Table 4 : Comparison of the overall hospital stay between early and delayed laparoscopic cholecystectomy for acute cholecystitis in the literature.

Study	Overall hospital stay (days)		P
	EC	DC	
Zhu [2]	7.5	12.1	NS
Serralta [4]	5.3	3.6	0.045
Gelbard [5]	1.9	3.9	0.078
Eldar [11]	6.5	6.67	0.596
Willsher [12]	3.7	5.6	0.003
Our series	3.44	5.91	<0.001

EC: Early cholecystectomy; DC: Delayed cholecystectomy; NS: No significant

Concerning morbidity, the post-operative course of laparoscopic cholecystectomy for acute cholecystitis is usually uneventful. Indeed, the rate of post-operative mortality ranges from 0 to 0.28% and the overall rate of post-operative morbidity reported in the literature varies between 12% and 14.7% [15, 16].

Biliary injuries are the most dreadful complication during laparoscopic cholecystectomy. These are serious injuries, of which the evolution is uncertain. Biliary fistula may be related to an injury of the common bile duct, to a dislocation of clips of the cystic duct stump, or to a bile canaliculus in the gallbladder bed (duct of Luschka) [17]. The series found in the literature, as represented in table 5, did not show any difference in the rate of this complication between the two groups [5, 18-22].

Table 5 : Comparison of biliary fistula between early and delayed laparoscopic cholecystectomy for acute cholecystitis in the literature.

Series	Biliary fistula		P
	EC	DC	
Gurusamy [18]	0.5 %	1.4 %	0.54
Lai [19]	0	0	NS
Lo [20]	0	2 %	NS
Kolla [21]	5 %	0	NS
Johansson [22]	0	1.4 %	NS
Our series	0	3.4 %	0.065

EC: Early cholecystectomy; DC: Delayed cholecystectomy; NS: No significant

The incidence of wound infection varies from 2% to 7% [16]. The main results of the literature showed no significant difference between early and delayed treatment in terms of occurrence of wound infection. Indeed, Zhu [2] found 2.94% wound infection in the early group against 2.02% in the delayed group (p = 0.755). Eldar [11] and Willsher [12] found similar results. However, in diabetics, Gelbard [5] showed a significant increase in the rate of surgical site infection in case of delayed cholecystectomy (4.93% versus 2.77%, p=0.034).

The study of Haltmeier showed that early laparoscopic cholecystectomy in patients older than 65 years with significant comorbidities is associated with shorter postoperative stay and no increase in postoperative complications [23].

The main studies, comparing the rate of post-operative peritonitis and intra-peritoneal collections between early and delayed cholecystectomy affirm no significant statistical difference [3, 11, 12, 18].

CONCLUSION

The early laparoscopic management of acute cholecystitis has now demonstrated its superiority over delayed treatment. The feasibility is well established, the rate of conversion to open cholecystectomy and post-operative morbidity are not higher than in delayed surgery. The duration of surgery and the hospital stay are however significantly shorter and the cost of treatment is therefore lower. This early surgery reduces the rate of medical treatment failure of and of biliary peritonitis. It must therefore be regarded as the gold standard in the surgical management of acute cholecystitis.

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