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ORIGINAL ARTICLE

Effect of antithrombotic therapy on postoperative outcome of 538 consecutive emergency laparoscopic cholecystectomies for acute cholecystitis: two Italian center's study

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Abstract
The risk of developing hemorrhagic complications during or after emergency cholecystectomy (EC) for acute cholecystitis (AC) in patients with antithrombotic therapy (ATT) remains uncertain. In this double-center study, we evaluated post-operative outcomes in patients with ATT undergoing EC. We retrospectively evaluated 538 patients who underwent laparoscopic EC for AC between May 2015 and December 2019 at two referral centers. 89 of them (17%) were on ATT. We defined postoperative complication rates, including bleeding, as our primary outcome. Mortality was higher in the ATT group. Morbidity was higher in the ATT group as well; however, the difference was not statistically significant. 12 patients (2%) experienced intraoperative blood loss over 500 ml and ten (2%) had postoperative bleeding complications. Two patients (< 1%) experienced both intraoperative and postoperative bleeding. On multivariate analysis, ATT was not significantly associated with worse postoperative outcomes. Antithrombotic therapy is not an independently associated factor of severe postoperative complications (including bleeding) or mortality. However, these patients still represent a challenging group and must be carefully managed to avoid postoperative bleeding complications.

Keywords Acute cholecystitis · Anticoagulation therapy · Antiplatelet therapy · Antithrombotic therapy · Bleeding complication · Emergency cholecystectomy · Laparoscopy

Introduction

The number of patients who required antithrombotic therapy (ATT), classified as antiplatelet therapy (APT) and anticoagulation therapy (ACT) for primary and secondary prevention of cardiovascular and/or cerebrovascular diseases, is increasing as the population ages.

Gallbladder disease is the most common indication for abdominal surgery in the elderly due to cholelithiasis prevalence increasing with age. Therefore, we can expect an increasing number of elderly patients needing emergency or elective surgical procedures for cholelithiasis [1, 2].

The risk of developing hemorrhagic complications during or after surgery in patients with ATT is still debated. While several studies have reported an increasing risk of perioperative bleeding with ATT [3–5], the safety and feasibility of surgery among patients with continuous aspirin therapy have also been reported recently in two randomized clinical trials regarding non-cardiac surgery [6, 7] and abdominal surgery [9, 10].

The guidelines of the American College of Chest Physicians recommend continuing aspirin in patients with moderate to high risk of cardiovascular events who undergo non-cardiac surgery [11].

This occurs in all patients undergoing emergency cholecystectomy (EC) when ongoing therapy cannot be stopped. Furthermore, the effect of APT or ACT on patients with systemic inflammation is unclear. Discordant results have been reported in the literature; Joseph et al. [12] found no significant difference regarding intraoperative bleeding,

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postoperative anemia, and blood transfusion among patients who underwent EC with or without ATT. Conversely, another report shows that the incidence of intraoperative blood transfusion was higher in the group continuing APT [13].

The aim of our paper is to deepen our understanding of this critical issue by evaluating outcomes in patients on prehospital ATT undergoing laparoscopic EC.

Methods

The study was designed as a case–control retrospective, observational study. Between May 2015 and December 2019, cholecystectomy was performed in 1622 patients at "St Orsola Hospital—Emergency Surgery Unit—University of Bologna" and "Umberto I" Hospital—Department of Surgical Sciences—La Sapienza University of Rome", sharing data in a common prospective database started in 2017. The study received approval from the hospital's institutional review board (156/2018/Oss/AOUBo, 18/04/18). Informed consent was obtained from every participant.

We selected 538 patients with acute cholecystitis (AC) out of those who underwent cholecystectomy at our institution; patients whose medical record was incomplete and those who did not have appropriate follow-up were excluded (Fig. 1). Diagnosis of AC was based on Tokyo Guidelines using clinical findings such as Murphy's sign, right upper quadrant mass, pain, tenderness, fever, elevated C-reactive protein, leukocytosis, and diagnostic imaging including ultrasonography, computed tomography (CT) with findings such as gallbladder enlargement, thickened gallbladder wall, or positive pericholecystic fluid [14–16].

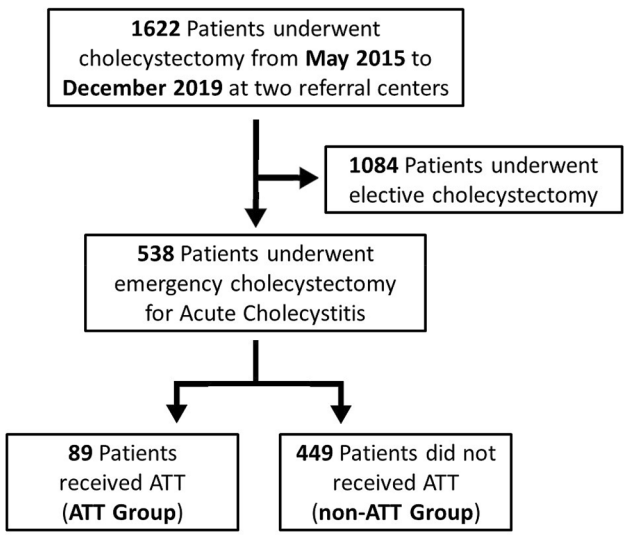

Fig. 1 Diagram of the current study

Surgeries were performed by 7 experienced surgeons and by 23 different surgical residents under supervision.

Patients with APT generally underwent surgery without reversal of the effect of antiplatelets. In contrast, patients with ACT and increased INR usually received preoperatively vitamin K (INR > 1.5) or fresh frozen plasma (INR > 3) without waiting for the INR normalization before surgery.

Collected data included age and gender, comorbidities, vital signs and laboratory parameters on admission, physical examination findings, results of preoperative imaging, surgical treatments, and postoperative outcomes.

The patients' general well-being was assessed based on American Society of Anesthesiologists (ASA) score [17].

Postoperative complications were categorized and assessed using Clavien–Dindo classification [18]. Postoperative bleeding complications included gastrointestinal (GI) bleeding, abdominal bleeding, and abdominal wall hematoma. Gastrointestinal bleeding was defined as symptomatic bleeding from the digestive tract such as hematemesis or melena accompanied by a significant drop in hemoglobin level and requiring red blood cell transfusion and/or therapeutic intervention.

Abdominal bleeding was diagnosed due to a bloody abdominal drain or abdominal distention with radiologic findings associated with a significant drop in hemoglobin level.

We defined postoperative complication rates, including bleeding, as our primary outcome. Background, peri-operative conditions and post-operative outcomes were collected and compared between patients with ATT (ATT group) and those without ATT (Non-ATT group) to identify differences between the two groups.

Statistical analysis

Data were reported as median (range) for continuous variables and proportions for categorical variables. Comparisons of the continuous variables between the two groups were conducted using Mann–Whitney *U* test. Chi-squared test or Fisher's exact probability test were used for comparison of categorical variables. Univariable and multivariable logistic regression analyses were used to assess risk factors affecting the primary outcome. The level of statistical significance was set at 0.05. All statistical analyses were performed using SPSS package software (SPSS version 11, Chicago, IL, USA).

Results

Preoperative characteristics, surgical procedures and postoperative outcomes of the 538 patients included in the study are listed in Tables 1, 2 and 3.

Table 1 Pre-operative characteristics of patients

	Overall ($n=538$)	ATT group ($n=89$)	Non-ATT group ($n=449$)	p value
Age (years)[a]	60.8 ± 17.2	76.1 ± 9.3	57.8 ± 16.8	**< 0.01**
Age > 65 years	237 (44%)	77 (86%)	160 (35%)	**< 0.01**
Male sex	264 (49%)	54 (60%)	210 (47%)	**0.02**
BMI (kg/m^2) [a]	26.0 ± 4.1	25.9 ± 3.8	26.0 ± 4.2	*0.83*
ASA class [18]				
I–II	*320 (59%)*	*18 (20%)*	*300 (66%)*	**< 0.01**
III–IV	*218 (41%)*	*71 (80%)*	*149 (34%)*	
Comorbidity	331 (62%)	81 (91%)	254 (56%)	**< 0.01**
Cardio-vascular	*247 (46%)*	*81 (91%)*	*166 (37%)*	**< 0.01**
Diabetes	*64 (12%)*	*21 (24%)*	*43 (10%)*	**< 0.01**
COPD	*44 (8%)*	*17 (19%)*	*27 (6%)*	**< 0.01**
CRF	*22 (4%)*	*8 (9%)*	*14 (3%)*	**0.02**
Obesity	*62 (12%)*	*8 (9%)*	*54 (12%)*	*0.47*
Previous abdominal surgery	61 (11%)	13 (15%)	48 (11%)	*0.28*
Previous upper abdominal surgery	27 (5%)	5 (6%)	22 (5%)	*0.79*
Previous AC	238 (44%)	36 (40%)	202 (45%)	*0.48*
Previous pancreatitis	89 (17%)	7 (8%)	82 (18%)	**0.02**
Previous ERCP	161 (30%)	34 (38%)	127 (28%)	*0.08*
Murphy's sign	362 (67%)	68 (76%)	294 (%)	*0.27*
Fever (> 38.0°)	255 (47%)	46 (%)	209 (%)	*0.42*
Laboratory tests				
WBC ($\times 10^9$/L)[a]	*11.08 ± 5.45*	*12.42 ± 6.56*	*10.95 ± 5.18*	**0.02**
Platelets ($\times 10^9$/L)[a]	*248.03 ± 90.84*	*234.84 ± 92.09*	*260.17 ± 93.78*	**0.02**
INR[a]	*1.53 ± 6.94*	*1.77 ± 1.16*	*1.11 ± 0.29*	**< 0.01**
Amylase (U/L)[a]	*127.06 ± 320.32*	*142.30 ± 304.54*	*163.10 ± 503.34*	*0.71*
Lipase (U/L)[a]	*151.76 ± 841.84*	*225.34 ± 648.72*	*387.98 ± 1689.54*	*0.37*
Bilirubine (mg/dL)[a]	*1.16 ± 1.17*	*1.94 ± 2.28*	*1.41 ± 1.91*	**0.02**
CRP (mg/dL)[a]	*6.01 ± 9.26*	*11.99 ± 11.89*	*8.73 ± 12.35*	**0.02**
CRP > 0.5 (mg/dL)	326 (61%)	31 (34%)	201 (45%)	*0.10*
WBC > 10 ($\times 10^9$/L)	232 (43%)	56 (63%)	270 (60%)	*0.64*

Values in parentheses are percentages unless indicated otherwise

Values given in italics are not statistically significant

[a]Values are mean ± SD

The cohort of patients had a mean age at surgery of 60.8 ± 17.2 years, 49% were male. A total of 89 patients (16.5%) continued ATT until surgery. Table 4 shows the indications for the administration of antithrombic agents. In particular, myocardial infarction and atrial fibrillation were the most common indications of APT or ACT (40.4%). Percutaneous coronary intervention (PCI) was the second leading cause with 7.8%. Cerebral infarction, pulmonary embolism, coronary artery bypass grafting and deep venous thrombosis were less frequent.

Table 1 shows the perioperative characteristics of patients. The average age of patients in the two groups ranged from 76.1 years in the ATT group to 57.8 years in the Non-ATT group. The gender distribution was significantly different ($p < 0.01$) between the two groups: male patients were more frequent in the ATT group (86%).

The overall comorbidity rate differed significantly between the two groups ($p < 0.01$): in the ATT group, 91% of patients had a cardiovascular risk factor compared to 56% of patients in the other group ($p < 0.01$). Obesity was the only comorbidity that did not differ significantly between the two groups. Not surprisingly, also ASA classification differed significantly ($p < 0.01$) between the groups.

Table 2 summarizes the intraoperative characteristics of the study cohorts. The overall median operative time was 93.1 ± 38.6 [30–303] min. There was a trend toward longer duration of surgeries in the ATT group; in particular, median operative time was 108.9 ± 42.4 min in the ATT

Table 2 Surgical and pathological characteristics of population

	Overall ($n=538$)	ATT group ($n=89$)	Non-ATT group ($n=449$)	p value
AC (TG2018)				
Grade I	*254 (47%)*	*42 (47%)*	*212 (47%)*	*1.00*
Grade II	*269 (50%)*	*44 (50%)*	*225 (50%)*	*0.91*
Grade III	*15 (3%)*	*3 (3%)*	*12 (3%)*	*0.72*
Cholecystectomy				
Open	107 (20%)	26 (29%)	81 (18%)	**0.02**
Laparoscopic	431 (80%)	63 (71%)	368 (82%)	
Conversion to open	*80 (18%)*	*20 (32%)*	*60 (16%)*	**< 0.01**
Intra-operative blood loss > 500 ml	12 (2%)	4 (4%)	8 (2%)	*0.12*
Duration of procedure (min)[a]	93.1 ± 38.6	108.9 ± 42.4	90.1 ± 37.1	**< 0.01**
Duration of procedure > 90 min	263 (49%)	58 (65%)	205 (46%)	**< 0.01**

Values in parentheses are percentages unless indicated otherwise

Values given in italics are not statistically significant

[a]Values are mean ± SD

Table 3 Postoperative characteristics of population

	Overall ($n=538$)	ATT group ($n=89$)	Non-ATT group ($n=449$)	p value
Death in hospital	12 (2%)	6 (7%)	6 (1%)	**< 0.01**
Complication (Clavien–Dindo)	97 (18%)	21 (23%)	76 (17%)	*0.09*
Grades I–II	75 (14%)	16 (17%)	59 (13%)	*1.00*
Grades III–IV	22 (4%)	5 (6%)	17 (4%)	
Post-operative bleeding	10 (2%)	2 (2%)	8 (2%)	*0.68*
Hospital stay (days)[a]	7.2 ± 9.3	3.0 ± 3.6	5.3 ± 6.6	**< 0.01**
Discharge at home	454 (84%)	67 (75%)	387 (86%)	**< 0.01**

Values in parentheses are percentages unless indicated otherwise

Values given in italics are not statistically significant

[a]Values are mean ± SD

Table 4 Indications for the administration of antithrombic agents

	No. of patients	%
Myocardial infarction	36	40.4
Atrial fibrillation	36	40.4
Percutaneous coronary intervention	7	7.8
Cerebral infarction	3	3.3
Pulmonary embolism	3	3.3
Coronary artery bypass grafting	2	2.2
Deep venous thrombosis	2	2.2
Total	89	100.0

group and 90.1 ± 37.1 min in the Non-ATT group, with significant differences between the two groups ($p < 0.01$). Four hundred and thirty-one patients (80%) were treated laparoscopically and 107 patients (20%) using an open approach. More patients were selected for open cholecystectomy in the ATT group ($p = 0.02$). In the ATT group 20 patients (32%) were converted from laparoscopic to open surgery. Open conversion rate was significantly higher in the ATT group ($p < 0.01$).

Post-operative outcomes are shown in Table 3. Twelve patients died in hospital after surgery: six in each group ($p < 0.01$). All patients died due to multi-organ failure, both in the ATT group and in the Non-ATT group. In particular, all patients had very poor general conditions at the time of surgery; ten patients had ASA score III and two ASA score IV. All patients of the ATT-group had cardiovascular disease, two also had COPD and a third patient had CRF in addition to BPC and cardio-vascular disease. We found gangrenous cholecystitis in eight patients and their death occurred due to septic shock; four of them died after a re-intervention.

Post-operative complications occurred in 97 patients (8.9%) of our overall study cohort. Seven patients had a

reintervention. In five patients the reoperation was due to haemoperitoneum, while in two cases an exploratory laparoscopy was performed: one for a sub-glissonian hematoma in the absence of a clear source of bleeding and one for an abdominal collection.

Severe complications (Clavien grades III–IV) and mild complications (Clavien grades I–II) were prevalent in the ATT group. However, no significant differences were recorded between the two groups. The overall median hospital stay was 7.2 ± 9.3 (range 1–59) days.

Looking at the results of Table 3, the number of deaths and average hospital stay were higher in the ATT group than in the other group; on the contrary, surgical complications and post-operative bleeding were not affected by ATT.

Therefore, we performed a logistic regression to understand if ATT was a significant predictor of mortality, morbidity and discharge at home. The results are shown in Table 5.

Age > 80 years (OR 1.905; $p = 0.036$), WBC > 10 × 10^9/L (OR 1.629; $p = 0.033$), ASA scores III–IV (OR 1.841; $p = 0.043$) and severe cholecystitis (OR 2.024; $p = 0.017$) were independently associated with an increased risk of post-operative morbidity.

The presence of comorbidities (OR 4.500; $p = 0.062$) was the only factor independently associated with mortality. In our series, patients with overall comorbidities had a risk of death 4.5 times higher than patients without comorbidities. The presence of ATT is not a significant factor on its own, as it is associated with the comorbidity that it is meant to treat.

Finally, the presence of comorbidities (OR 0.529; $p = 0.051$) and ASA scores III–IV (OR 0.478; $p = 0.006$) were factors independently associated with discharge at home (protective factors).

On multivariate analysis, our results demonstrated that ATT was not a factor independently associated with mortality, morbidity and discharge at home.

Discussion

The optimal management of surgical patients on ATT remains undefined. Surgical treatment represents a "surgical dilemma", especially in the emergency setting, because all anticoagulants can cause bleeding [19].

Performing an emergent operation on patients with ATT is known to be associated with the development of hemorrhagic complications and higher rate of conversion from laparoscopic to open surgery [3, 8, 20]. On the other hand, discontinuing ATT increases the risks of postoperative thrombotic events and also a delay in surgery is associated with higher postoperative morbidity [21, 22].

When considering EC for AC in patients under ATT, it is important to consider not only the effect of ATT but also the inflammatory status (i.e., the duration of abdominal pain or grade of AC). Patients with AC have inflamed tissues with a high tendency to bleed and a modified anatomy that leads to higher morbidities and mortality, as reported in many papers [23, 24].

Table 5 Factors significantly influencing morbidity, mortality and discharge (logistic regression model)

Parameter	Mortality		Morbidity		Discharge at home	
	p value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)
Age > 80 years	NS	–	0.036	1.905 (1.043–3.482(	NS	–
Male sex	NS	–	NS	–	NS	–
ATT	NS	–	NS	–	NS	–
Comorbidity	0.062	4.500 (0.925–21.903)	NS	–	0.051	0.529 (0.279–1.022)
Cardio-vascular	NS	–	NS	–	NS	–
Diabetes	NS	–	NS	–	NS	–
COPD	NS	–	NS	–	NS	–
CRF	NS	–	NS	–	NS	–
WBC > 10 (× 10^9/L)	NS	–	0.033	1.629 (1.0.9–2.554)	NS	–
PCR > 0.5 (mg/dL)	NS	–	NS	–	NS	–
ASA 3–4	NS	–	0.043	1.841 (1.018–3.327)	0.006	0.478 (0.282–0.810)
Timing (within 3 days)	NS	–	NS	–	NS	–
Mild cholecystitis	NS	–	NS	–	NS	–
Moderate cholecystitis	NS	–	NS	–	NS	–
Severe cholecystitis	NS	–	0.017	2.024 (1.135–3.612)	NS	–
Open procedure	NS	–	NS	–	NS	–
Laparoscopic procedure	NS	–	NS	–	NS	–
Conversion to open	NS	–	NS	–	NS	–

Many surgeons recommend that surgery for AC should be performed within the first 96 h, when the "edematous phase" predominates [25, 26]. The Tokyo Guidelines 2018 [14, 27, 28] recommended early laparoscopic cholecystectomy within 72 h from onset of symptoms, to decrease conversion rates and postoperative complications. As we showed in a previous paper, we can have similar post-operative outcomes if procedures are performed earlier than or nearly after 72 h from the onset of symptoms [29]. In this study, we only enrolled patients undergoing emergency procedures, but our results showed no statistical differences in intraoperative blood loss or postoperative complications in either the univariate analysis or the multivariate analysis.

Moreover, patients with ATT are frequently elderly patients with decreased functional reserve due to comorbidities. Complication rates have been reported in the literature to be between 18 and 35% and mortality up to 13% [30–32]. In this study, the average age of the patients with ATT was higher than that of the Non-ATT group. Moreover, in the multivariate analysis, age > 80 was a statistically significant factor for post-operative complications. We believe that this discrepancy is due to the greater fragility of elderly patients often leading to poor post-operative outcomes. This in turn might be secondary to the higher numbers of serious coexisting medical conditions and consequent higher ASA classification, as well as the frequently higher ATT at the time of surgery [33–35].

Several large randomized controlled trials reported that 0.6–3.8% of patients treated with aspirin alone experienced major GI bleeding, whereas the same is true for 0.6–4.8% of patients treated with ACT [36]. The rate of postoperative bleeding in our cohort (2%) is on the higher end of the range of reported incidences, mainly because the patient population in the current study was in the emergency setting with severe gallbladder inflammation.

Recently, surgical techniques have improved and new surgical devices for hemostasis have been developed. These devices were developed to be used in liver resections, but they are effective in stopping bleeding from the gallbladder bed during EC [13].

Our results indicate that intraoperative bleeding related to ATT therapy can be controlled during surgery thanks to these new devices and meticulous hemostasis.

Indeed, in our study, there were no significant differences in intraoperative bleeding; however, the average operative time was longer for the ATT group. This shows how performing an accurate hemostasis, while lengthening surgeries, influenced short-term results. The control of intraoperative bleeding is essential to achieve a safe postoperative clinical course in every patient, but particularly in patients receiving ATT.

There were no differences in the number of minor or major complications. The incidence of intraoperative bleeding is higher in cases with severe AC; however, the relationship was not found to be statistically significant. AC can lead to serious local complications such as gangrenous cholecystitis, liver abscess, biliary peritonitis or emphysematous cholecystitis (grade II) and/or organ dysfunction such as circulatory failure, consciousness disorders, respiratory failure, renal failure, liver failure or blood clotting disorder due to cholecystitis (grade III) [14, 15].

This reflects that bleeding caused by severe local inflammation can be difficult to control [13].

In our study, no significant differences were collected between the two groups due to the grade of AC.

There are many limitations to our study. First of all, it is a retrospective study. In addition, despite being conducted at two institutions, the sample size is small. Finally, we did not include patients who were selected for conservative management in the emergency setting. Further studies are needed to better evaluate the safety and feasibility of EC in patients with ATT and which therapeutic option is most appropriate for patients with high risk of perioperative bleeding.

Conclusion

The optimal management of patients on ATT with AC still remains indefinite. Our results have shown that fears of bleeding complications are unwarranted. Laparoscopic EC may be the treatment of choice for patients who are on ATT as well as for those who are not. We conclude that EC is an effective surgical option in patients with ATT, but controlling intraoperative bleeding is essential for a safe postoperative outcome.

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Author contributions SV, AL, MC, GP, RC, VDA, and VT conceptualized and designed the study, acquired, and analyzed data, interpreted the study results, drafted the manuscript, and critically revised the manuscript for important intellectual content. EG, APP, RB, DDN, and AU acquired and analyzed data, and interpreted the study results.

Compliance with ethical standards

Conflict of interest All authors declared that they have no potential conflict of interest.

Financial support and sponsorship All authors declared that they no receive financial support and sponsorship.

Ethical approval All procedures performed in the participants of our study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study received approval from the hospital's institutional review board (156/2018/Oss/AOUBo, 18/04/18).

Informed consent Our study received approval from the hospital's institutional review board (156/2018/Oss/AOUBo, 18/04/18). Informed consent was obtained from every patient included in this cohort of study.

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