Antibiotic prophylaxis in elective laparoscopic cholecystectomy is useless
A prospective multicenter study

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Antibiotic prophylaxis in elective laparoscopic cholecystectomy is useless: a prospective multicenter study

AIM: *We performed a prospective study to evaluate the effect of antibiotic prophylaxis (AP) on the incidence of infection in elective laparoscopic cholecystectomy (LC).*
MATERIAL OF STUDY: *All patients were at low-medium anesthetic and infectious risk and underwent LC for benign disease. At induction of anesthesia 41 patients received ampicillin-sulbactam 3g, 40 patients received ciprofloxacin 400mg intravenously, and 53 patients received no AP.*
RESULTS: *Postoperative infection was observed in 11 patients (8.2%) in the entire study group. All observed infections were superficial surgical site infections (SSIs), always located at the umbilical incision. Infection occurred in 3 patients (7.3%) in ampicillin-sulbactam group, in 3 patients (7.5%) in ciprofloxacin group and in 5 patients (9.4%) in non-antibiotic group (p=0.916). Univariate analysis showed that duration of operation, placement of a drain and postoperative hospital stay were significantly associated with the development of SSIs. At multivariate analysis, only duration of operation was statistically significant in predicting SSIs.*
DISCUSSION: *The present study did not show any advantage in the use of AP, although in case of difficult surgery the risk of SSIs is increased, in particular in the umbilical incision. In all patients, the bile culture was sterile, then the infection of the umbilical site is not due to bacterial infection from the gallbladder.*
CONCLUSIONS: *AP in elective LC should not be routinely performed. A particular attention to the preoperative cleaning and topical antibiotic therapy of the umbilical area is advised.*

KEY WORDS: Antibiotic prophylaxis, Laparoscopic cholecystectomy, Surgical site infection (SSI).

Introduction

Laparoscopic cholecystectomy (LC) is the current preferred method of cholecystectomy.
LC has a low rate of postoperative surgical site infections (SSIs), probably owing to smaller wounds and minimal tissue damage, compared with the open procedure [1].
In the literature there is a growing consensus in avoiding the use of antibiotic prophylaxis (AP) in elective LC [2-6]. However, for some clinicians AP is still routinely used in elective LC in order to reduce the incidence of postoperative infections [7]. The evidence emerging from the literature is limited by the absence of well-designed randomized trials. In particular, inclusion of patients at high risk of acquiring infections from LC intervention is necessary for the generalizability of the results. However, due to the low risk of SSIs after elective LC a randomized trial is very difficult to perform, as it should recruit 3500-10.000 patients by intervention

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group to probe the equivalence between treatments [3,8].
White blood cell count (WBC) and absolute neutrophil count (ANC) are early-phase inflammatory indexes and are used for the early detection of postoperative infections following surgeries.
Cephalosporins are widely used as AP in LC. The organisms most commonly associated with infection after biliary tract procedures are Gram-negative *E. coli, Klebsiella* species, and enterococci. A considerable improvement of resistance of these bacteria to cephalosporins has been reported in recent years [9]. Ampicillin-sulbactam is effective against common gram-negative bacteria that colonize bile [10].
One study found that ampicillin-sulbactam was associated with significantly lower rates of infection compared with cefuroxime [11]. Ciprofloxacin showed similar results to cefuroxime in the setting of AP for open cholecystectomy [12].
We performed a prospective study comparing the use of ampicillin-sulbactam and ciprofloxacin as single-dose versus no antibiotic prophylaxis in elective LC.

Material and Method

The study conforms to the tenets of the Declaration of Helsinki.
From January 2012 to march 2014 all patients aged 18 years and older, submitted to elective LC at the three participating hospitals ("Sapienza"University of Rome, Polo Pontino, "A. Fiorini" Hospital Terracina, Italy; Hospital "P. Colombo," Velletri, Italy; "Nuova Itor" Clinic, Rome, Italy), were prospectively evaluated. Patients with acute cholecystitis, cholangitis, or pancreatitis were not included. If intraoperative common bile duct exploration or any other additional procedure were performed, patients also were excluded. The following clinical data were prospectively evaluated: age, sex, body mass index (BMI), indication for LC, comorbidities, American Association of Anesthesiologists (ASA) risk, and eventual administration and type of AP.

Surgical Management

Under general anesthesia, the abdomen was insufflated with CO_2 either with the use of the Veress needle or after the introduction of the first 10-mm trocar with the Hasson technique through an infraumbilical incision. The other 10-mm and two 5-mm trocars were inserted through appropriate subxiphoid, subcostal midclavicular, and subcostal anterior axillary incisions. The pneumoperitoneum pressure and CO_2 flow rate were set at 10 mmHg and 2 L/min, respectively. A standard retrograde cholecystectomy with previous isolation and section between 10-mm clips of cystic duct and artery was always performed. The gallbladder was always bagged and retrieved through the umbilical port. Placement of a drain in the subhepatic space was performed according to the preference of the operating surgeon. Five milliliters of bile was removed by suction with a sterile syringe from the gallbladder immediately after its surgical removal and sent to the microbiological laboratory. Bacteria were cultured and identified according to the standard protocol used in our clinical microbiology laboratories. The duration of the operation (from infraumbilical skin incision to pulling off the trocars), bile spillage, and additional complications also were recorded.

Postoperative Monitoring

White blood cell count (WBC) and absolute neutrophil count (ANC) and percentages were examined preoperatively and daily post-operatively until discharge, using an automated hematology analyzer (reference range 4-10,000 per microliter for WBC and 2,500-7,500 per microliter for ANC).
Postoperative problems and complications were recorded within 4 weeks after operation. Patients were reviewed at 1 week and 4 weeks postoperatively. In particular, superficial or deep incisional soft tissue SSI and intra-abdominal abscess (organ/space SSIs) were defined according to published criteria [13]. In case of SSI culture swabs were taken from the site involved. In the laboratory the swabs were processed as per the standard microbiological procedure and protocols.

Statistical Analysis

Statistical analysis was performed by using the χ^2 and Fisher exact test for categorical variables and the Kruskal-Wallis test for numerical variables. Spearman's rank correlation coefficient was applied to calculate correlation between duration of surgery and postoperative hospital stay. Statistical significance was set at the 0.05 level. Univariate analysis was performed for the identification of factors associated with SSIs. Factors considered significant in the univariate analysis were included in a multivariate analysis performed by using logistic regression for the identification of independent factors associated with SSIs.

Results

The characteristics of the study group are shown in Table I. Forty-one patients received ampicillin-sulbactam 3 g (group AS) and 40 patients received ciprofloxacin 400 mg (group C) intravenously at induction of anesthesia; 53 patients received no AP (group N). There was no statistically significant difference between the 3 groups

Table I - *Baseline demographic and clinical characteristics by treatment group.*

	Group AS (41 pts)	Group C (40 pts)	Group N (53 pts)	P†
Age, median (95% c.i.), years	48 (43.5 to 53.2)	51 (39.7 to 54.7)	46 (42.0 to 48.2)	0.626
Sex female, n. (%)	22 (53.7)	27 (67.5)	35 (66.3)	0.213
BMI, median (95% c.i.), kg/m2	27.2 (26.7 to 28.1)	27.6 (25.3 to 29.4)	26.2 (24.7 to 27.3)	0.467
Presence of co-morbidities, n. (%)	14 (34.1)	19 (47.5)	18 (34.00)	0.340
Gallbladder disease, n (%)				
Cholelithiasis	35 (85.4)	36 (90.0)	50 (94.3)	0.345
Gallbladder polyp	6 (14.6)	4 (10.0)	3 (3.7)	
ASA score, n (%)				
1	23 (56.1)	20 (50.0)	33 (62.3)	
2	16 (39.0)	15 (37.5)	17 (32.1)	0.571
3	2 (4.9)	5 (12.5)	3 (5.7)	
Duration of surgery, median (95% c.i.), min	115.0 (90.0 to 131.2)	90.0 (90.0 to 120.0)	90.0 (84.,5 to 105.5)	0.111
Intraoperative bile spillage, n (%)	6 (14.6)	3 (7.5)	2 (3.8)	0.161
Subhepatic drain, n (%)	16 (39.0)	11 (27.5)	12 (22.6)	0.215
Postoperative hospital stay, median (95% c.i.), days	3.0 (2.0 to 3.0)	3.0 (2.0 to 3.0)	2.0 (2.0 to 3.0)	0.261

Group AS, ampicillin/sulbactam; group C, ciprofloxacin; group N: no antibiotic prophylaxis; c.i., confidence interval; BMI, body mass index.
† Fisher's exact test and χ^2 for categorical data; Kruskall Wallis test for numerical variables.

in terms of sex, age, and body mass index, presence of co-morbidities, gallbladder disease, ASA score, and duration of surgery, intraoperative bile spillage, and use of subhepatic drain. Bile culture showed no bacterial growth in all cases.

Postoperative infection was observed in 11 patients (8.2%) in the entire study group. All observed infections were SSIs, always located at the level of the umbilical incision. Infection occurred in 3 patients (7.3%) in group AS, in 3 patients (7.5%) in group C and in 5 patients (9.4%) in group N (p=0.916).

The commonest organism responsible for SSIs was *Staphylococcus aureus* in 7 cases (63.6%) followed by *Enterococcus* in 3 patients (27.3%) and miscellaneous aerobic gram-positive bacteria in 1 subject (9.1%). Infection was treated in all patients by surgical debridement. No other postoperative systemic infectious complications (e.g., sepsis, pneumonia, or urinary tract infection) were found.

Fig. 1 and Fig. 2 demonstrated normal courses for postoperative changes regarding median WBC and ANC in the overall study group.

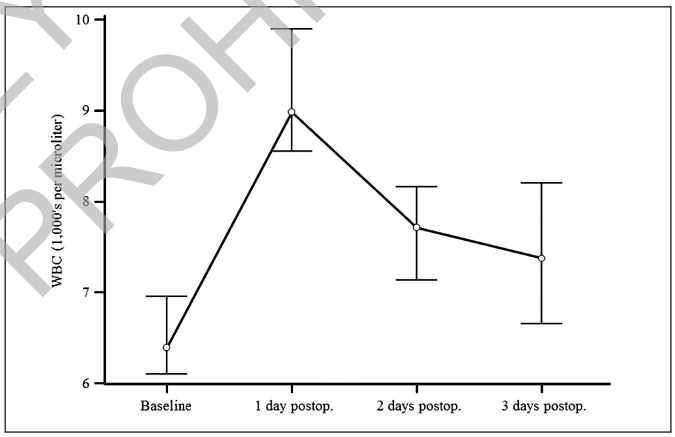

Fig. 1.: White blood cell count (WBC) at baseline and in the postoperative recovery in the overall study group.

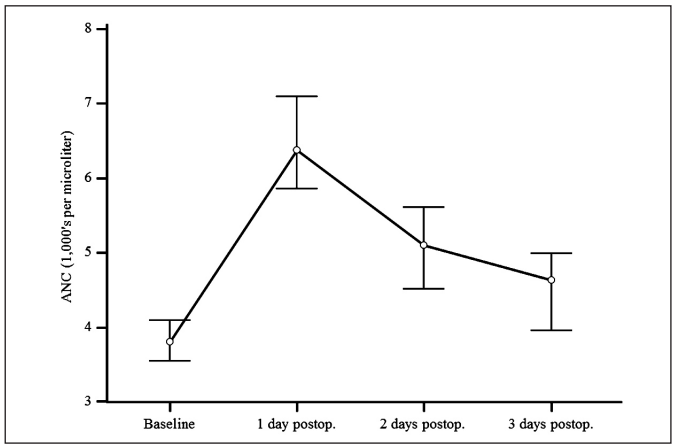

Fig. 2: Absolute neutrophil count (ANC) at baseline and in the postoperative recovery in the overall study group.

Risk Factors for Surgical Site infection

Univariate analysis showed that duration of operation, placement of a drain and postoperative hospital stay were significantly associated with the development of SSIs. At multivariate analysis, only duration Duration of surgery and postoperative hospital stay are significantly related of operation was statistically significant in predicting SSIs (Table II). (rho= 0.570, 95% c.i. 0.444 to 0.675; P=0.000)

Table II - *Risk factors for surgical site infection.*

Risk factor	SSI (11 pts.)	No SSI (123 pts.)	P†	Odds ratios (95%c.i.) multivariate analysis	P
Age, median (95% c.i.), years	50 (36.0 to 62.4)	47 (44.0 to 50.0)	0.458		
Sex female, n. (%)	6 (54.5)	78 (63.4)	0.797		
BMI, median (95% c.i.), kg/m2	26.5 (23.9 to 34.6)	27.2 (26.2 to 27,7)	0.961		
Presence of co-morbidities, n. (%)	4 (36.4)	47 (38.2)	0.839		
ASA score, n (%)					
1	5 (45.5)	71 (57.8)			
2	5 (45.5)	43 (34.9)	0.733		
3	1 (9.0)	9 (7.3)			
Duration of surgery, median (95% c.i.), min	150 (129.6 to 171.8)	90 (90.0 to 105.0)	0.001	1.031 (1.013 to 1.051)	0.000
Intraoperative bile spillage, n (%)	1 (9.0)	10 (8.1)	0.644		
Subhepatic drain, n (%)	7 (63.6)	4 (3.3)	0.022		
Postoperative hospital stay, median (95% c.i.), days	3.0 (3.0 to 3.0)	2.0 (2.0 to 3.0)	0.005		

SSI, surgical site infection.
† Fisher's exact test and χ^2 for categorical data; Kruskall Wallis test for numerical variables.

Discussion and Comments

The present study did not show any advantage in administering AP in elective laparoscopic surgery in order to reduce postoperative infections. Infection rates after LC range from 0% to approximately 7% [14]. In elective LC global infection rates are 4.7% and SSIs occurred in 2.9% of cases [3]. The most part of infections are of minor clinical importance, such as subcutaneous abscess or urinary tract infections. In the present series we observed only superficial infections of the umbilical wound, successfully treated with surgical revision. The potential benefit of AP in this setting has a limited clinical importance and is largely counterbalanced by the adverse effects, in particular the risk for further stimulating the development of resistant bacteria.

Several risk factors, associated with postoperative SSIs, are reported in the literature and include performance of emergency procedures, longer procedure duration, intraoperative gallbladder rupture, age >70 years, obesity, conversion of laparoscopic to open cholecystectomy, higher ASA classification (≥3), bacteria in the bile, episode of biliary colic within 30 days before the procedure, reintervention in less than a month for noninfectious complications [14]. The exclusion of emergent cases and the absence of conversion to laparotomy and noninfectious complications requiring surgery may explain the lack of serious SSIs in our series.

The biliary tract is usually sterile. Patients with bacteria in the bile at the time of surgery may be at higher risk of postoperative infection. However, no relation between the infection of the bile and postoperative infective complications was reported [15,16]. The absence of bile infection in our study group may have contributed to reduce the severity of postoperative SSIs.

WBC and ANC are widely used as an index of infection [17]. In our series both WBC and ANC were within the range of normal values during the early recovery. The absence of significant postoperative infections in our study group may support the use of these simple parameters to improve the early diagnosis of postoperative infections. If WBC and ANC are above the normal range, further diagnostic tools such as blood culture should be recommended in order to confirm the suspicion of infection and start appropriate antibiotic therapy.

Port-site infection is a minor complication that affects 1.1-7.9% of patients after LC [18,19]. The commonest organisms responsible for port-site infection in our study was *Staphylococcus aureus* and *Enterococcus,* suggesting intrinsic source from skin. This datum underscores the importance of skin preparation to surgery with a particular attention to the cleaning of the umbilical area. Topical antibiotics may be effective in this setting [20].

There is conflicting evidence in the literature about the improved risk of port-site infection, if drains are placed [21,22]. In the present study drains were placed, if surgery was difficult and/or intraoperative bile spillage occurred. Obviously, difficult surgery improves the surgical time. This may explain the fact that drain placement was not recognized as an independent risk factor for SSIs at multivariate analysis. We found that the only independent factor was duration of surgery. Operative time longer

than the 75th percentile of other operations of the same type is a recognized risk factor for SSIs [23]. AP does not reduce the rate of umbilical wound infection with respect to bag extraction of the gallbladder [19]. The routine use of bag extraction of the gallbladder in our case series may have contributed to the evidence of no effect of AP in this setting.
Postoperative hospital stay was showed to affect SSIs at univariate analysis in our case series. However, it was strictly related to operative time, as reported in the literature [24].
The main limitation of the present study is the absence of randomization and the limited number of patients observed with a consequent low number of SSIs. However, the prospective design and the absence of lost-to-follow-up patients are a significant strength.

Conclusions

The present study supports the evidence against AP in elective laparoscopic surgery. In case of difficult surgery the risk of SSIs is increased, in particular in the umbilical incision. A particular attention to the preoperative cleaning and topical antibiotic therapy of the umbilical area is advised.

Riassunto

In letteratura c'è un crescente consenso nell'evitare l'utilizzo della profilassi antibiotica (PA) nella colecistectomia per via laparoscopica elettiva (CLE). Tuttavia, la PA è ancora ampiamente utilizzata allo scopo di ridurre l'incidenza di infezioni postoperatorie. Abbiamo eseguito uno studio prospettico di comparazione tra utilizzo di ampicilina-sulbactam, ciprofloxacina e assenza di PA nei pazienti a basso-medio rischio anestesiologico (ASA I-III) e infettivo (patologie croniche in buon compenso) sottoposti a CLE per patologia benigna (litiasi e polipi).
A 41 pazienti sono stati somministrati 3g di ampicillina-sulbactam e.v., 40 pazienti hanno assunto 400mg di ciprofloxacina e.v. e 53 pazienti non hanno effettuato nessuna PA.
Nell'intero gruppo di studio si sono registrati 11 casi (8,2%) di infezione postoperatoria. Tutte le infezioni hanno coinvolto unicamente il sito chirurgico e, in particolare, l'incisione ombelicale. L'infezione si è verificata in 3 pazienti (7,3%) nel gruppo ampicilina-sulbactam, in 3 pazienti (7,5%) nel gruppo ciprofloxacina e in 5 pazienti (9,4%) nel gruppo non sottoposto a PA (p=0.916). All'analisi statistica univariata la durata dell'intervento chirurgico, il posizionamento di un drenaggio e la degenza ospedaliera, si sono dimostrati significativamente associati all'insorgenza di infezioni postoperatorie. All'analisi statistica multivariata unicamente la durata dell'intervento chirurgico è risultato significativamente associato all'insorgenza di infezioni del sito chirurgico.
La PA nella CLE non è consigliabile. In caso di difficoltà durante l'intervento chirurgico, il rischio di infezione del sito chirurgico è aumentato, in particolare nella sede dell'incisione ombelicale. Si raccomanda una particolare attenzione alla disinfezione preoperatoria dell'area ombelicale anche con l'utilizzo di antibiotici per via topica.

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