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


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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.
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. Ceftriaxone is 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 ceftriaxone 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 CO2 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 CO2 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 $\chi^2$ 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 1. 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
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 \textit{Staphylococcus aureus} in 7 cases (63.6%) followed by \textit{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.

**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)
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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

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>SSI (11 pts.)</th>
<th>No SSI (123 pts.)</th>
<th>P†</th>
<th>Odds ratios (95% c.i.) multivariate analysis</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (95% c.i.), years</td>
<td>50 (36.0 to 62.4)</td>
<td>47 (44.0 to 50.0)</td>
<td>0.458</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex female, n. (%)</td>
<td>6 (54.5)</td>
<td>78 (63.4)</td>
<td>0.797</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, median (95% c.i.), kg/m2</td>
<td>26.5 (23.9 to 34.6)</td>
<td>27.2 (26.2 to 27.7)</td>
<td>0.961</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of co-morbidities, n. (%)</td>
<td>4 (36.4)</td>
<td>47 (38.2)</td>
<td>0.839</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA score, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5 (45.5)</td>
<td>71 (57.8)</td>
<td>0.733</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>5 (45.5)</td>
<td>43 (34.9)</td>
<td>0.733</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1 (9.0)</td>
<td>9 (7.3)</td>
<td>0.733</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of surgery, median (95% c.i.), min</td>
<td>150 (129.6 to 171.8)</td>
<td>90 (90.0 to 105.0)</td>
<td>0.001</td>
<td>1.031</td>
<td>0.000</td>
</tr>
<tr>
<td>Intraoperative bile spillage, n (%)</td>
<td>1 (9.0)</td>
<td>10 (8.1)</td>
<td>0.644</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subhepatic drain, n (%)</td>
<td>7 (63.6)</td>
<td>4 (3.3)</td>
<td>0.022</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative hospital stay, median (95% c.i.), days</td>
<td>3.0 (3.0 to 3.0)</td>
<td>2.0 (2.0 to 3.0)</td>
<td>0.009</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SSI, surgical site infection.
† Fisher’s exact test and χ² for categorical data; Kruskall Wallis test for numerical variables.
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.

References

12. Agrawal CS, Sehgal R, Singh RK, Gupta AK: Antibiotic pro-
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