

ORIGINAL PAPERS

Antibiotic prophylaxis in elective cholecystectomy: Protocol adequacy and related outcomes in a retrospective single-centre analysis

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ABSTRACT

Background: Antibiotic prophylaxis is an effective tool to reduce surgical infection rates. However, antibiotic prophylaxis in cholecystectomy is controversial when non-high risk patients are considered. This research aims to evaluate the adherence with antibiotic prophylaxis protocol in patients undergoing cholecystectomy, and its impact in the outcomes of surgical infection.

Methods: This single-center observational and retrospective study analyzed all elective cholecystectomy procedures carried out at the Fundación Alcorcón University Hospital in the period 2007-2014. Data were recovered from hospital records; rates of adherence to the available hospital protocols were evaluated for choice, initiation, duration, administration route and dosages of antibiotics, and the starting and duration of the prophylaxis.

Results: The overall adequacy rate to protocol was 72%. The adherence rates in both the administration route and dose were 100%. The most common violations of the protocol included the choice of antibiotic agent (19%), followed by the moment of initiating its administration (8.9%). The overall wound infection rate was lower in case of laparoscopy than in laparotomy cholecystectomy (1.4% vs. 4.3%, $p < 0.05$; odds ratio [OR] 0.29, 95% confidence interval [CI] 0.1-0.6). No relationship between adequacy of antibiotic prophylaxis and surgical infection rate was documented, neither considering overall gallbladder surgeries (crude OR 0.26, 95% CI 0.1-2.0), nor laparoscopy vs. open surgery (MH adjusted OR 0.24, 95% CI 0.2-2.1).

Conclusions: The overall adequacy rate to antibiotic prophylaxis protocol recommended for elective cholecystectomy in our hospital was high (72%). No significant association between the adequacy or antibiotic prophylaxis and surgical infection was found.

Key words: Cholecystectomy. Gallbladder surgery. Antibiotic prophylaxis. Surgical wound infection.

INTRODUCTION

Nosocomial infections, also called “health care-associated infections” or “HAIs” are major public health

concerns due to their associated morbidity, mortality and economic costs (1,2). Surgical site infections (SSIs) in our environment represent one of the most common HAIs together with respiratory and urinary tract infections (3). Both patients’ intrinsic and extrinsic factors relate with SSIs (4), for which incidences ranging from 1% in clean surgeries to 15% in dirty surgeries have been estimated (5,6). Incisional SSIs are classified according to their depth in affected tissues in superficial incisional, deep incisional, and organ/space (7).

Antibiotic prophylaxis is recognized as one of the most important preventive measures to reduce the incidence of SSI. It is indicated in clean-contaminated and contaminated surgeries and in some special cases of clean surgery (e.g. implants, immunosuppression and risky operative location such as neurosurgery and cardiac surgery) (8).

Antibiotic prophylaxis should ensure an adequate bactericidal antibiotic concentration in serum and in the surgical bed; therefore, doses of the drug should be repeated in case of prolonged surgery or hemodilution. However, the pre-operative dose is considered to be sufficient in most cases, but if a repeated antibiotic dose is needed, it should be administered before 24-48 hours from surgery. Antibiotic choice should be based on the spectrum of microorganisms most frequently involved in each surgical location, opting for the safer, cheaper and less likely to favor the emergence of drug-resistance bacteria. In order to ensure the effectiveness of antibiotic prophylaxis, its administration is usually protocolized, being not indicated in the case of a low risk gallbladder surgery (9). These interventions have an overall incidence of SSI of 1% to 3%, which range from 0.5% in laparoscopic to 6% in open surgery. A protocol for antibiotic prophylaxis is available in our hospital, according to which such prophylaxis is recommended only in case of gallbladder surgery in presence of associated risk factors, in agreement with most of the literature (10).

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The aim of this study was to evaluate the adherence of antibiotic prophylaxis in elective gallbladder surgery to our hospital's protocol, and to analyze the effect of the adequacy of prophylaxis schemes in clinical practice on the incidence of SSI.

PATIENTS AND METHODS

A retrospective observational study to assess the adherence to the institutional protocol of antibiotic prophylaxis in cholecystectomies performed at the Hospital Universitario Fundación Alcorcón was conducted. All consecutive patients undergoing scheduled cholecystectomy between January 1st, 2007 and December 31st, 2014 were considered.

Data collection was made from the patients' clinical records. Patients with suspected or confirmed infection at the time of the surgery (including acute cholecystitis or colangitis), those undergoing emergency cholecystectomy and patients who were receiving a non prophylactic antibiotic treatment were excluded.

An estimate of the sample size was made considering a confidence of 95%, an accuracy of 4%, an overall adherence to antibiotic prophylaxis protocol over 50% and a loss of 5% of patients' data. The number of patients considered to be analyzed was 631.

Following discharge, patients were followed up as far as 30 days. We reviewed their electronic medical records to monitor their progress and their attendance at hospital outpatient facilities, at emergency wards or at primary health care.

Study variables included age, sex, type of surgery (laparoscopic or open), duration of the intervention, different aspects of antibiotic prophylaxis (antibiotic administered, route, dose, start time of administration and duration of the prophylaxis), preoperative preparation-related aspects (preoperative antiseptic shower and mouthwash), patients' intrinsic risk factors (renal failure, diabetes mellitus, malignancy, chronic obstructive pulmonary disease, liver cirrhosis, obesity, and neutropenia), clinical complications, the presence or absence of infection according to the diagnostic criteria of the US Centers for Disease Control (CDC) (7) and the microorganisms involved.

A descriptive study of the sample was performed. Qualitative variables were described with frequency distribution (number and percentage) and compared using the Pearson's χ^2 -test or exact-Fisher's test when it did not meet application criteria. Quantitative variables were described as mean and standard deviation or median and interquartile range (IQR) when normality criteria were not met. Quantitative variables were compared using the Student's t-test or the Mann-Whitney U test in case of non-normality. Quantitative variables with more than two groups were compared with analysis of variance (ANOVA) or Kruskal-Wallis test if normality criteria were not met. The missing data are treated as missing values.

Adherence and adequacy of antibiotic prophylaxis to the protocol in force (Table I) were assessed, both overall and considering every component individually (including antibiotic administered, route of administration, dose, time of onset and duration of the prophylaxis). Overall prophylaxis was considered appropriate when all components were fulfilled according to the protocol. Patients were evaluated at discharge and the presence of SSI was also analyzed. The relationship between the adequacy or not of antibiotic prophylaxis

and the occurrence of SSI was assessed by crude odds ratio (OR) and adjusted Mantel-Haenszel OR (aOR). Data were collected on a specific data collection sheet created *ad hoc* and a relational and normalized Access® (Microsoft) recording database was designed. Data were analyzed using SPSS v19 (SPSS Inc., Chicago, IL, US) and a p value < 0.05 was considered as a significant difference.

This study based on review of medical records was developed according to the principles of the Declaration of Helsinki and was approved by the Hospital Ethics Committee for Clinical Research and the Research Committee.

RESULTS

We studied 1,532 patients undergoing surgical cholecystectomy between 2007 and 2014. Among the 1,532 patients, 766 (50%) fulfilled criteria for antibiotic prophylaxis and all of them (100%) received it. The demographic and clinical characteristics of all patients are shown in table II. Patients who received prophylaxis included 308 (40%) males and 458 (60%) females. The overall median age of these patients was 64 years (IQR = 46-74), being the median age for men 65 (IQR = 47-34) and for women 63 (IQR = 46-75) ($p < 0.05$).

Dealing with patients who received antibiotic prophylaxis, cholecystectomies were performed by laparoscopy in 590 (77%) patients and by laparotomy in 176 (23%). The incidence of conversion rate from laparoscopic to open surgery was 8% and was related to the difficult anatomical identification, thick gallbladder wall, elderly male, obesity and a history of previous abdominal surgery. Perforations of the gallbladder during cholecystectomy occurred in 18% of the patients.

Preoperative preparation was adequate according to the institutional protocol statements in 77% (95% CI: 75-79) of patients, with 90% adequacy of antiseptic shower and 40% of preoperative mouthwash.

Overall adequacy of antibiotic prophylaxis to the protocol was 72% (95% CI: 69-75). The main cause of non-adequacy to the protocol was an inadequate antibiotic choice (19%; 95% CI: 17-21), followed by time of onset (8%; 95% CI: 6-8) and duration (0.7%; 95% CI: 0.0-1.4). The rate of adequacy of prophylaxis antibiotic remained unchanged during the 7 year-study period.

Antibiotics given are depicted in figure 1. Amoxicillin-clavulanic was the antibiotic drug most commonly used (63%). Vancomycin was used in 5 patients who exhibited a previously known allergy to cephalosporins.

The overall incidence of surgical site infection was 1.96% (95% CI: 1.3-2.7) and there was no difference between SSI incidence in patients under antibiotic prophylaxis and patients not administering it. Patients who underwent laparoscopic surgery had an incidence of surgical site infection of 1.4% (95% CI: 0.6-2.3) whereas it was 4.3% (95% CI: 2.2-6.4) among those undergoing laparotomy. Laparoscopic surgery was therefore documented as a

Table I. Summary of antibiotic prophylaxis protocol for cholecystectomy

Guidelines ¹	Antibiotic	Dose	Route	Initiation
Standard	Amoxicillin-clavulanic	2 g	Iv ²	30-60 min prior to surgery
Allergic to beta-lactam antibiotics	Gentamicin	0.8 g	Iv	60-90 min prior to surgery

¹Indicated for patients considered at high risk (i.e. older than 70 years, choledocholithiasis and/or cholangitis, prior biliary instrumentation, diabetes mellitus, duration of intervention over 70 minutes and ASA > 2). ²Intravenous.

Table II. Demographic and clinical characteristics of the patients receiving antibiotic prophylaxis (n = 766)

Characteristic	Value
Age: Median; IQR ¹	64; 46-74
Age > 70 (%)	56
Genre (%): male; female	40; 60
Diabetes (%)	14.8
Renal failure (%)	2.2
Malignancy (%)	7.5
COPD ² (%)	3.5
Obesity (%)	13.8
Liver cirrhosis (%)	0.1
Neutropenia (%)	0.1
Laparoscopy (%)	77
Laparotomy (%)	23
Conversion rate (%)	8
Perforations (%)	18
ASA > II ³ (%)	19
Mean stay (days)	5.4

¹Interquartile range. ²Chronic obstructive pulmonary disease. ³American Society of Anesthesiologists Index.

protective factor for SSI when compared with open surgery (OR = 0.29; 95% CI: 0.1-0.6). According to the location of incisional primary SSI, 7 cases were superficial SSI, 4 deep incisional SSI, and 4 additional cases organ-space incisional SSI. There were no readmissions due to SSI, so infections diagnosed after discharge were superficial and did not require it.

Microorganisms involved in the incisional primary SSI are shown in table III. An overall of 23 microbiological isolates were performed in 13 infected patients, and 6 of them had polymicrobial infections. *Escherichia coli* constituted the bacteria most commonly isolated, followed by *Klebsiella pneumoniae* and *Enterococcus faecium*. Two additional patients exhibited a clinical diagnosis of infection, characterized by an open and oozing surgical wound, but with no positive microbiological culture.

No statistically significant relationship between the adequacy of antibiotic prophylaxis and the incidence of surgical site infection was found (OR = 0.26; 95% CI: 0.1-2.0). Stratifying by type of intervention did not change this result (aOR 0.24; 95% CI: 0.2-2.1).

Identified intrinsic risk factor of the patients for SSI included renal failure (2.2%), diabetes mellitus (14.8%), malignancy (7.5%), chronic obstructive pulmonary disease (3.5%), liver cirrhosis (0.1%), obesity (13.8%) and neutropenia (0.1%). Patients with concomitant neoplasia had a significant increased risk of SSI (OR = 9.05; 95% CI: 4.2-19.3).

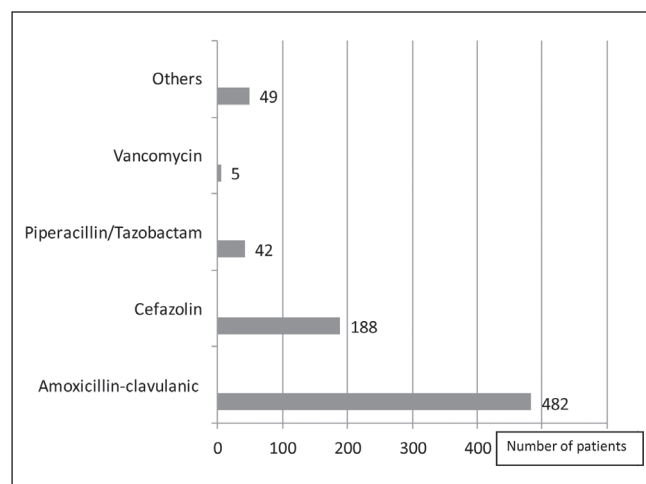


Fig. 1. Drugs administered as antibiotic prophylaxis. Endoscopic submucosal tunnel dissection).

Table III. Etiology of surgical site infections (n = 23)

Microorganism	Cases (n)	%
<i>Escherichia coli</i>	11	47.8
<i>Klebsiella pneumoniae</i>	3	13.1
<i>Enterococcus faecium</i>	3	13.1
<i>Staphylococcus aureus</i>	2	8.8
<i>Morganella morganii</i>	1	4.3
<i>Proteus mirabilis</i>	1	4.3
Methicillin-resistant <i>Staphylococcus aureus</i>	1	4.3
<i>Enterobacter cloacae</i>	1	4.3
Total	23	100

DISCUSSION

Antibiotic prophylaxis is one of the major measures to reduce the rates of surgical site infection although its impact in gallbladder surgery remains under discussion, as shown in clinical trials, systematic reviews and meta-analysis (10-12). In general terms, antibiotic prophylaxis is restricted to patients undergoing cholecystectomy with associated risk factors. These include coexistence of choledocolithiasis and/or cholangitis, age over 70 years, duration of intervention over 70 minutes, prior biliary instrumentation, American Society of Anesthetics index (ASA) > 2 and diabetes mellitus (13-16).

In this study we have evaluated the adequacy of antibiotic prophylaxis to the institutional protocol in patients undergoing cholecystectomy. This is an important measure to assess the quality of standards of care in clinical practice. In fact, in some countries, such as France, the evaluation of the adequacy of antibiotic prophylaxis according to the predefined protocol of each center is mandatory (17). Our results indicate that the overall compliance with the antibiotic prophylaxis protocol in our hospital was 72.2%. The adequacy of administering the antibiotic of choice was 80.9%, the doses and route of administration adequacy rates were 100%, with a time of initiation and duration of the prophylaxis rates of 91.9% and 99.3%, respectively. These data are similar to those from other studies conducted in our country (18) and slightly better than those obtained by Diaz-Agero et al. in a multicenter study conducted in hospitals in the region of Madrid and sponsored by the Madrid Society of Preventive Medicine and Public Health (19). In this last study an overall adequacy rate of 71% was observed and no antibiotic prophylaxis was administered at 1.5% of patients to whom it should be given, compared to 0% in our study. Anesthesiologists are in charge of the administration of antibiotic prophylaxis at our hospital, and they were not aware of the fact that this study was carried out, so we could control the Hawthorne effect.

We obtained a SSI overall rate of 1.96%, which was significantly lower than the figures provided nationwide according to data from INCLIMECC (Indicadores Clínicos de Mejora Continua de Calidad), a multicenter prospective observational study on the incidence of nosocomial infection program that provided a 3.63% SSI rate in gallbladder surgery (20).

Data from the National Surgical Quality Improving Program of the American College of Surgeons (ACS NSQIP) has been communicated by Ingraham et al. (21): A 2.0% SSI rate was reported among the 65,511 patients who underwent cholecystectomy between 2005 and 2008, feature slightly superior to that provided in our research. When patients operated by laparoscopy or laparotomy were separately evaluated, Ingraham et al. also found lower infection rates in patients operated with laparoscopy compared to laparotomy (1.3% vs. 8.4%, respective-

ly). Our infection rates for laparotomy were significantly lower (4.3%). In contrast, the National Healthcare Safety Network/American CDC, reported a SSI rate lower to ours, with a 0.56% overall surgical site infection in patients undergoing cholecystectomy between 2006 and 2008 (22). Other studies have reported higher results than ours (23). The relatively high rate of open cholecystectomy in our patients (23%) may be due to the fact that we have treated elderly patients with comorbidity and previous abdominal surgery. Younger patients without comorbidity or previous laparotomy in waiting list are offered being referred for surgery to other concerted hospitals.

We found no significant differences in SSI rate according to the adequacy of antibiotic prophylaxis. Our data agree with studies that raise doubts regarding the effectiveness of antibiotic prophylaxis in this kind of surgical intervention (10-12). In addition, the most common reason of inadequacy was the election of the antibiotic of choice, so the possibility of the selected drug having enough efficacy against the microorganisms causing infection in our centre should be considered. Regarding the preoperative preparation, an antiseptic shower was applied in a high percentage of patients, and a greater inadequacy occurred with antiseptic mouthwash. This particular measure mainly prevents from postoperative pneumonia, so it does not influence the prevention of incisional SSI. Finally, as in parallel to other series reviewed (9,11,13), the microorganisms isolated in our study were the most often identified in such kind of surgical procedures, including *Escherichia coli* (47.8%), *Klebsiella pneumoniae* (13.1%) and *Enterococcus faecium* (13.1%).

Our study has the limitation that a prospective follow-up of patients after discharge was not made. Our evaluation of the incidence of SSI rates was done at the time of hospital discharge, so the estimation of the incidence of infection may have been underestimated because we could not rule out an infection occurring within the after surgery 30 days period usually considered for wound infection in interventions without implants. However, the primary goal of our research was to assess the adherence and adequacy rates to the antibiotic prophylaxis protocol in our hospital; since it does not depend on the temporal tracking, we consider our results to be accurate and unbiased.

As a result of this study a series of measures have been launched and they are currently under a follow-up period. The feedback of our results was made to the Surgery Department involved in this research and the protocol for antibiotic prophylaxis and preoperative preparation are being reviewed. The effects of these interventions will be reported in due course.

We conclude that the adequacy of antibiotic prophylaxis in our hospital was high but it can be improved. Its continuous assessment, as well as incidence of SSI, allows for the revision and improving of institutional protocols, in order to continuously improve the quality and safety of patients' care.

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