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Prospective Control Study of Clinical Effectiveness of Prophylactic Antibiotics in Laparoscopic Cholecystectomy on Infection Rate

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Purpose: This study evaluated the effectiveness of prophylactic antibiotics in elective laparoscopic cholecystectomy (LCC) for the reduction of postoperative infection rate.
Materials and Methods: Elective LCC was performed on 529 patients at Jeonbuk National University Hospital between April 2015 and August 2017. A total of 509 patients were enrolled based on the inclusion criteria. This prospective study compared the results for antibiotic group (AG) (n=249, cefotetan 1 g, 1 dose/prophylactic) and non-antibiotic group (NAG) (n=260).
Results: There were no significant differences in clinical characteristics between the two groups: AG and NAG (p=0.580, 0.782, and 0.325, respectively). Levels of C-reactive protein were higher in NAG compared to AG at postoperative day 2 (16.6±24.2 vs. 24.2±40.6; p=0.033). There were no significant differences in white blood cell counts and erythrocyte sedimentation rate. Fever ≥38°C on postoperative day 2 occurred in 3 (1.2%) and 9 (3%) patients in AG and NAG, respectively. One patient in each group had subhepatic fluid collection by abdominal computed tomography, but there was no evidence of infection. Two patients in NAG (3%) had serous wound drainage on postoperative day 14.
Conclusion: Our results showed no significant differences in patients receiving or not receiving prophylactic antibiotics during LCC. Therefore, it is not necessary to use prophylactic antibiotics during elective LCC in patients who meet the inclusion criteria.

Key Words: Laparoscopic cholecystectomy, prophylactic antibiotics, infection

INTRODUCTION

The Centers for Disease Control and Prevention recommend prophylactic antibiotics to reduce surgical site infections (SSIs) in surgery with a clean-contaminated wound, such as cholecystectomy.[1,2]

Several meta-analyses have evaluated randomized studies to elucidate the efficacy of prophylactic antibiotics in low-risk patients undergoing laparoscopic cholecystectomy (LCC). These studies have concluded that antibiotic prophylaxis is not warranted based on the lack of significant differences in the rate of postoperative infectious complications between patients with and without prophylactic antibiotic treatment.[3-11] However, most trials included in these meta-analyses had relatively small sample sizes and were statistically underpowered for the rare event of infections. Therefore, we conducted a prospective cohort study to assess the clinical efficacy of prophylactic antibiotics in preventing postoperative infectious complications in low-risk patients undergoing elective LCC.

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•The authors have no potential conflicts of interest to disclose.

MATERIALS AND METHODS

The study protocol was approved by the Institutional Review Board for Clinical Research of Jeonbuk National University Hospital (approval no. 2013-08-005-017).

Patient data

A total of 529 patients underwent elective LCC at the study center between April 2015 and August 2017. Inclusion criteria included diagnosed gallbladder stones and/or polyps at outpatient clinic. Exclusion criteria included history of jaundice; previous history suggestive of cholangitis including common bile duct stone and complicated cholecystitis; history of previous administration of antibiotics within 7 days such as antimicrobial resistance and history of being immunosuppressed; and suspicion of gallbladder malignancy.

Patients who received prophylactic antibiotics (antibiotic group, AG) were observed during early periods of the study (April 2015 to June 2016), and those not administered antibiotics (non-antibiotic group, NAG) were observed from July 2016 to August 2017. Patients in AG received 1 g of intravenous cefotetan immediately before skin incision, and those in NAG did not receive prophylactic antibiotic treatment.

Definition of infection

Postoperative course after admission was monitored, and patients were followed for 14 days after discharge. Body temperature was measured twice daily, excluding postoperative day 1. Infectious complications were defined as the presence of pyrexia with a body temperature of 38°C or leukocytosis (≥12000/mm^3), elevation of erythrocyte sedimentation rate (≥9 mm/h) and C-reactive protein (≥5 mg/L), and purulent drainage from the surgical site with or without positive cultures, as defined by the Centers for Disease Control and Prevention.[1,2]

Surgical procedures

Conventional LCC was performed on 54 patients. Standard skin preparation was achieved with 10% povidone-iodine solution. Periumbilical incision was used for conventional LCC, and transumbilical incision was used in cases with the single-incision method. Standard Calots' triangle dissections were made. The cystic duct and artery were doubly clipped proximally. After the cystic duct and artery were resected, bleeding control and saline irrigation were achieved. The gallbladder was extracted using an endoscopic retrieval bag through the umbilical trocar incision. The incision at the site of umbilicus was closed with 3–0 vicryl sutures, and other incisions were closed with a skin stapler or 2–0 nylon sutures. Drains were inserted in cases with gallbladder perforation and hemorrhage. All surgeries were performed by experienced surgeons.

Clinical data

Demographic data such as age, sex, and body mass index (BMI) were collected. Operative time, number of trocar insertions, as well as laboratory and radiologic findings were documented. Examinations for postoperative complications (including infection) were performed until hospital discharge. All patients were followed at the outpatient department for at least 14 days after surgery. In the present study, all adverse events were assessed according to the Clavien-Dindo classification of surgical complications. All adverse events are shown in Table 1.

Statistical analysis

All statistical analyses were performed using SPSS ver. 21 (IBM Corp., Armonk, NY, USA). Chi-squared test was used to analyze categorized variables, and Fisher's exact test was used when the expected frequency was less than five in a cell. Two-tailed unpaired Student's t test was used to analyze continuous variables. Significance was defined as a p value<0.05.

RESULTS

The study included 526 consecutive patients who underwent LCC at our institution. After the exclusion of 17 patients who did not meet the inclusion criteria, the remaining 509 patients either received (AG; n=249) or did not receive (NAG; n=260) preoperative prophylactic antibiotics. There were no significant differences in clinical characteristics between the two groups: AG (male/female ratio, 103/146; mean age, 51.0±13.6 years; mean BMI, 25.1±3.9 kg/m^2) and NAG (male/female ratio, 109/151; mean age, 51.3±14.0 years; mean BMI, 25.0±3.6 kg/m^2) (p=0.580, 0.782, and 0.325, respectively).

There were no significant intergroup differences in the parameters of operation such as operative times, number of incisions, trocar insertion, and number of drains (p=0.081, 0.072, 0.427, and 0.124, respectively).

Gallbladder stones and polyps were diagnosed in 130 (52%) and 91 (36%); and 153 (58%) and 88 (34%) in the AG and NAG, respectively. Mixed types were diagnosed in 28 (12%) and 19 (8%) in the AG and NAG, respectively (Table 2).

White blood cell counts and erythrocyte sedimentation rates

Table 1. Data Collection Protocol During Follow-Up Period

	Pre-op	Op day	POD1	POD2	POD14
Enrollment					
Permission	O				
Exclusion					
Criteria	O				
Laboratory data					
WBC counts	O		O	O	O
ESR, CRP	O		O	O	O
Symptom					
Fever	O	O	O	O	O
Dyspnea	O	O	O	O	O
Wound	O	O	O	O	O
Radiologic data					
Chest X ray	O		Suggestive of infection sign		
Abdominal CT					

WBC, white blood cell; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; CT, computed tomography; POD, postoperative day.

showed no significant differences between the two groups until postoperative day 14. The levels of C-reactive protein were higher in NAG than in AG at postoperative day 2 (16.6±24.2 vs. 24.2±40.6; p=0.033), with no significant differences on other postoperative days (Table 3).

Fever ≥38°C on postoperative day 2 occurred in 3 (1.2%) and 9 (3%) patients in AG and NAG, respectively. Two patients in NAG (3%) had serous wound discharge on postoperative day 14, but bacteria were not identified. One patient (0.4% vs. 0.3%; AG vs. NAG) in each group had subhepatic fluid collection by abdominal computed tomography, but there was no evidence of infection. SSIs did not occur in either group. The total complication rates were 1.6% (AG) and 4.6% (NAG), respectively (p=0.058). No other major complications, such as postoperative bleeding and bile leakage, were observed in either group during hospital stay (Table 4).

DISCUSSION

In the present study, the rate of total postoperative complications was 1.6% (AG) and 4.6% (NAG), respectively; which was comparable with the complication rate including SSIs of 1.4% to 7.9% reported in previous studies.[1,3,4] Postoperative infections, including SSIs, did not occur in either group in the present study. Our findings agree with past other studies which showed that patients undergoing LCC may not require antibiotic prophylaxis due to the low postoperative infection rate.[12,13]

Administration of single-dose intravenous cephalosporin during anesthesia induction or immediately before incision in the operating room is recommended for patients undergoing clean or clean-contaminated procedures.[14,15] Third-generation cephalosporins have several advantages compared to cefotetan, such as better concentration in bile and increased sensitivity to gram-negative bacteria.[16,17] However, cefotetan can provide enough effect for the prevention of postoperative infectious complications in patients undergoing elective cholecystectomy.[18]

The use of drains and incision methods (such as transumbilical incision) are important factors related to infection. Although drain insertion is useful in managing bile leakage of gallbladder

Table 2. Clinical Characteristics of AG and NAG

Characteristic	AG (n=249)	NAG (n=260)	p value
Age (yr)	51.0±13.6	51.3±14.0	0.782
Sex (M:F)	103:146	109:151	0.580
BMI (kg/m^2)	25.1±3.9	25.0±3.6	0.325
Operative time (min)	34.5±11.0	35.7±15.2	0.081
Single incision (%)	25 (10)	29 (11)	0.072
Trocar insertion (n)	2.2±0.80	2.2±0.82	0.427
Drain insertion (%)	14 (6)	21 (8)	0.124
GB stone (%)	130 (52)	153 (58)	0.211
GB polyp (%)	91 (36)	88 (34)	0.458
GB stone+polyp (%)	28 (12)	19 (8)	0.054

AG, antibiotics group; NAG, non-antibiotics group; BMI, body mass index; GB, gallbladder.

Table 3. Laboratory Findings between AG and NAG

	AG (n=249)	NAG (n=260)	p value
WBC (mm^3)			
Preoperative	8645.3±2973.1	8936.1±3399.4	0.391
POD1	8887.9±3061.9	9008.3±3074.1	0.715
POD2	8645.3±2582.6	7557.1±2645.4	0.377
POD14	8645.3±1431.7	6855.2±1778.4	0.481
ESR (mm/h)			
Preoperative	14.8±15.6	16.4±15.5	0.305
POD1	16.1±12.3	14.8±11.3	0.305
POD2	16.8±11.4	17.6±12.3	0.507
POD14	16.4±15.2	14.9±13.8	0.311
CRP (mg/L)			
Preoperative	12.6±25.0	12.3±28.8	0.893
POD1	16.9±20.2	16.8±21.0	0.385
POD2	16.6±24.2	24.2±40.6	0.033
POD14	3.6±7.9	4.3±12.9	0.500

AG, antibiotics group; NAG, non-antibiotics group; POD, postoperative day; WBC, white blood cell; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

Table 4. Occurrence of Postoperative Outcomes according to Clavien-Dindo Classification between AG and NAG

	Postoperative fever*		Wound discharge†		Abdominal fluid collection‡		Surgical site infection		Total§	
	AG	NAG	AG	NAG	AG	NAG	AG	NAG	AG	NAG
Grade I	2	8	0	2	0	0	0	0	2	10
Grade II	1	1	0	0	0	0	0	0	1	1
Grade IIIa	0	0	0	0	1	1	0	0	1	1
Grade IIIb	0	0	0	0	0	0	0	0	0	0
Grade IVa	0	0	0	0	0	0	0	0	0	0
Grade IVb	0	0	0	0	0	0	0	0	0	0
Grade V	0	0	0	0	0	0	0	0	0	0
Total (%)	3 (1.2)	9 (3)	0 (0)	2 (3)	1 (0.4)	1 (0.3)	0 (0)	0 (0)	4 (1.6)	12 (4.6)

AG, antibiotics group; NAG, non-antibiotics group.
*AG vs. NAG; p=0.164, †AG vs. NAG; p=0.116, ‡AG vs. NAG; p=0.415, §AG vs. NAG; p=0.058.

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perforation and hemorrhage, it may cause infection. In our study, the drain insertion rate in NAG was higher than that in AG, but there is no significant difference (6% vs. 8%; p=0.124). This may have resulted from the short duration (mostly 2 days) of drain insertion.

In terms of incision method, transumbilical incision may have a higher incidence rate of wound infection compared to periumbilical incision.

We have tried a transumbilical approach in single-incision procedures for patients with no previous history of abdominal surgery. Our resulted showed no significant difference between AG and NAG with the use of a single incision. Serous wound discharge of a single-incision site occurred in only one patient in NAG. Many complications may occur after discharge, as most patients are discharged within a few of days after surgery. Therefore, complications related to infections may be missed if patients are not carefully followed. To prevent overlooking these complications, strict follow-up protocols should be established. In the present study, all of the enrolled patients were followed, which allowed the detection of all complications. Follow-up rates should be an important consideration in trials. Importantly, no patient was lost to follow-up in the present study.

The study had several limitations. Patients were not included in the study if they showed a high leukocyte count, fever on admission, previous history of endoscopic retrograde cholangiopancreatography, and findings of empyema or gangrenous gallbladder during surgery. Therefore, the study findings cannot be applied to patients undergoing surgery for complicated cholecystitis who initiate antibiotic treatment during admission to the emergency department. Future studies with a different design are warranted to investigate this patient population. Second, this was a single-center study, and selection bias cannot be avoided.

The rate of postoperative complications, including SSIs, is rare and does not appear to be reduced further by the routine use of antibiotics in the present study of patients undergoing LCC. Based on the findings of recent studies as well as the current study, we have adopted the protocol of not administering prophylactic antibiotics in patients undergoing elective LCC at our institution.

In the present study of 509 low-risk patients undergoing elective LCC, prophylactic antibiotics did not significantly reduce the postoperative infection rate. This should be confirmed in future multicenter trials.

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AUTHOR CONTRIBUTIONS

Conceptualization: Jae Do Yang and Hee Chul Yu. Data curation: Jae Do Yang and Hee Chul Yu. Formal analysis: Jae Do Yang and Hee Chul Yu. Funding acquisition: Jae Do Yang and Hee Chul Yu. Investigation: Jae Do Yang and Hee Chul Yu. Methodology: Jae Do Yang and Hee Chul Yu. Project administration: Jae Do Yang and Hee Chul Yu. Resources: Jae Do Yang and Hee Chul Yu. Software: Jae Do Yang and Hee Chul Yu. Supervision: Jae Do Yang and Hee Chul Yu. Validation: Jae Do Yang and Hee Chul Yu. Visualization: Jae Do Yang and Hee Chul Yu. Writing—original draft: Jae Do Yang. Writing—review & editing: Jae Do Yang and Hee Chul Yu. Approval of final manuscript: all authors.

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