Intravenous Versus Oral Antibiotic Prophylaxis Efficacy for Elective Laparoscopic Cholecystectomies: a Prospective Randomized Controlled Trial

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Abstract The aim of the present prospective randomized controlled trial is to compare the effectiveness of intravenous and oral antibiotic prophylaxis for cost and surgical site infection in elective laparoscopic cholecystectomy. Three hundred twenty patients were split into two groups as to include 160 patients in each, and they were evaluated in a prospective and randomized fashion. While one group was subjected to 1 g cefazolin via intravenous route during anesthesia induction, other group received 1 g cephalexin monohydrate via oral route 1 h prior to the operation. Demographic findings and operation results of the patients were compared by analyses. Our 320 patients (278 females and 42 males) received elective cholecystectomy and were followed up for a period of 6–26 months. Each group had 160 patients. Both groups were similar with regard to demographic characteristics and inclusion criteria. Among all, only five (1.5 %) cases demonstrated postoperative surgical site infection. Surgical site infection at postoperative period was determined in three (1.8 %) cases of intravenous prophylaxis group and two (1.2 %) cases of oral prophylaxis group. There was no statistically significant difference between the groups in terms of surgical site infection. Oral antibiotic prophylaxis can be used in elective laparoscopic cholecystectomy prophylaxis due to its cost-effective, reliable nature, and low surgical site infection rate.

Keywords Laparoscopic cholecystectomy · Antibiotic prophylaxis · Surgical site infection

Introduction

Currently, laparoscopic cholecystectomy is recognized as the gold standard in treatment of symptomatic gallstones by general surgery centers worldwide. Despite considerable low incidence (0.4–1.1 %) of surgical site infections in laparoscopic approach, prophylactic antibiotic therapy is still employed routinely in many clinics [1, 2]. In clean and clean-contaminated procedures, prophylactic administration of single-dose cephalosporin via intravenous (IV) route during single-dose anesthesia induction and just before the incision is recommended [3, 4]. There is not much clinical trial on this subject in the literature, and the existing ones aim to determine if preoperative antibiotic prophylaxis is needed in this surgery or not. There is only one study in the literature which investigates oral and IV prophylaxis. In the present study, we aim to determine whether oral or IV delivery of first-generation cephalosporin antibiotics would make a difference with regard to surgical site infections and costs among patients who received elective laparoscopic cholecystectomy due to symptomatic cholelithiasis [4].

Patients and Methods

Three hundred twenty patients who presented with cholecystitis to the Ankara Atatürk Teaching and Research Hospital between June 2007 and December 2008 and who received elective laparoscopic cholecystectomy were split into two groups (group A, 160 patients; group B, 160 patients) and included in our prospective and randomized study.

The following data on each patient were recorded: age, gender, BMI, gallbladder disease, blood biochemistry, presence of a biliary colic episode within 1 month before the surgery, American Society of Anesthesiologists (ASA) score, coexisting diseases, diabetes mellitus, length of postoperative

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hospital stay, gallbladder rupture, spillage of stones, histological findings of the gallbladder, drainage usage, gallbladder culture results, number and types of infections in cases that exhibited infection, and the microorganisms showing growth in the infection sites.

Patients above 18 years of age and with symptomatic cholelithiasis were included in the study, whereas patients who had β -lactam or cephalosporin allergy or hypersensitivity, acute cholecystitis or a history of emergency procedures, jaundice (bilirubin of >3 mg/dl), choledocholithiasis, history of an upper abdominal surgery or ERCP, leukocytosis (WBC of $\geq 12,500$), and a history of bile duct surgery, pancreatitis, hepatic disease, or prosthetic valve and the patients that used antibiotics within 7 days prior to the beginning of the study were excluded.

Surgical Procedure and Prophylaxis

All the patients who received laparoscopic cholecystectomy were operated on by standard four-trocar technique after establishing the same aseptic conditions. First group (group A) received 1 g IV cefazolin Na, whereas the second group (group B) received 1 g cephalexin monohydrate via oral route 1 h prior to the surgical procedure. Each gallbladder was removed through the trocar placed inferior to the xiphoid process during which samples were collected for the gallbladder cultures under sterile conditions. Those collected samples were sent to the microbiology laboratory.

Samples for gallbladder culture were collected and sent to the microbiology laboratory under sterile conditions from gallbladders with infection, perforation, or spilled and scattered stones which were removed from the abdomen with the help of an endobag. In all these gallbladder operations, local peritoneal irrigation was performed with 0.9 % isotonic sodium. Hemovac drain was placed into the subhepatic region of each of those patients. All the incisions were closed with 2/0 nonabsorbable monofilament sutures.

The patients were scheduled for follow-up controls at 1, 2, 3, and 4 weeks after discharge and evaluated in terms of infection. Fever (fever of >38 °C twice a day at postoperative first day) and purulent discharge from the incision site were considered as complications of infection, whereas infections in the other systems and localizations such as the urinary system, respiratory system, and abdomen were evaluated, as well.

In our study, wound infections, deep and superficial surgical site infections, and abdominal cavity infections were regarded as organ or surface infections, as well. Cases that exhibited surgical site infection were treated with antibiotics.

Statistical Analysis

Each parameter was analyzed with SPSS 17.0 statistical program. All the categorical values were evaluated with Fisher's

exact test. Pearson chi-square test was applied where needed to. Two-tailed unpaired Student's *t* test was conducted for numerical values. $p < 0.005$ was recognized as statistically significant.

Results

Three hundred twenty (278 females and 42 males) patients who received elective laparoscopic cholecystectomy were followed up for 6 months.

Both groups were comprised of 160 patients, and they were similar to each other in terms of demographic characteristics and inclusion criteria. Postoperative surgical site infection was found in five (1.5 %) patients, while three (1.8 %) of those were in the intravenous prophylaxis group, and two (1.2 %) of those were in the oral prophylaxis group. No statistically significant difference was found between the groups relative to the surgical site infections.

While there were 142 females and 18 males in group A, there were 136 females and 24 males in group B. Mean age of the patients in groups A and B was 47.61 ± 13.68 (18–79) and 48.41 ± 12.98 (24–76), respectively. Mean BMI value was 28.40 ± 2.71 kg/m² (22–34) and 28.12 ± 3.26 kg/m² (21–34) in groups A and B, respectively. Operation length was 52 ± 8 min (40–75) and 49 ± 11 min (30–90) in groups A and B, respectively. Gallbladder perforation was observed in 12 and 25 cases in groups A and B, respectively. While seven cases in group A exhibited spillage of stones into the abdominal cavity, it was found in nine cases in the group B. Forty-three patients in group A and 28 patients in group B were found to have experienced a biliary colic episode within the preceding month. Hemovac drain was used in 31 patients of group A and 25 patients of group B. All of them were removed postoperatively at the first day. Surgical site infection was determined in three of group A patients and two of group B patients. Mean lengths of hospital stay for groups A and B were 1.32 ± 0.67 (1–7)°days and 1.23 ± 0.67 (1–8)°days, respectively. As coexisting disease was determined in 80 of patients in group A, group B had 54 such patients. There were 31, 119, and 3 of patients in group A were ASA 1, ASA 2, and ASA 3, respectively, while among group B, there were 64 ASA 1 patients, whereas 94 and 2 were ASA 2 and ASA 3, respectively (Table 1).

As growth was determined in 31 (19 %) of gallbladder cultures in group A, 24 (15 %) cultures showed growth in group B. The most frequently isolated bacteria were *Klebsiella oxytoca* (36 %) followed by *Escherichia coli* (20 %) (Table 2).

Patients who developed wound infection in group A were males at ages 27, 52, and 56; they had a BMI of 24, 31, and 27 kg/m², respectively, and an operation length of 50, 55, and 60 min, again respectively. All three cases presented to us at

Table 1 Characteristic of patients and surgical outcomes

	Group A (IV) Mean + SD	Group B (Oral) Mean + SD	<i>p</i> value	Signature (<i>p</i>)
Age, year	47.61±13.68	48.41±12.98	0.405	>0.005
BMI, kg/m ²	28.40±2.71	28.12±3.26	0.401	>0.005
DOS, min	52±8	49±11	0.405	>0.005
LOS, day	1.32±0.67	1.23±0.67	0.251	>0.005
Sex (M/F)	24/136	18/142	0.529	>0.005
Rupture of gallbladder	12/148	24/136	0.001	<0.005
Bile or gallstone spillage	7/153	9/151	0.004	>0.001
Infected bile	31/129	24/136	0.517	>0.005
Biliary colic	43/117	28/132	0.120	>0.005
Drain	31/129	25/135	0.560	>0.005
SSI	3/157	2/158	0.963	>0.005
ASA, score	64/94/2	31/119/10	0.003	<0.005
Concomitant diseases	80/80	59/101	0.950	>0.005
Diabetes mellitus	21/130	19/135	0.397	>0.005

ASA American Society of Anesthesiologists, DOS duration of surgery, LOS length of stay

4 days postoperative due to a discharge from the trocar site inferior to the xiphoid. Drainage and antibiotic treatment were applied to all of them. No microorganism growth was observed in their wound cultures.

Patients who developed wound infection in group B were females at ages 54 and 70; they had a BMI of 26 and 24 kg/m², respectively, and an operation length of 75 and 35 min, again respectively. The 54-year-old patient presented with a discharge from the umbilical trocar site at 3 days postoperative. Wound culture showed *Staphylococcus epidermidis* growth which was treated successfully with drainage and antibiotic treatment. The 70-year-old patient developed a lesion displaying discharge from the trocar site inferior to the xiphoid at 5 days postoperative which showed no growth in wound cultures and was successfully treated with drainage and

Table 2 Number (%) of organisms isolated

	Group A (n=160)	Group B (n=160)
No reproduction	129	136
<i>Klebsiella oxytoca</i>	12	8
<i>E. coli</i>	6	5
<i>Pseudomonas</i>	3	2
<i>Enterobacter</i>	3	3
<i>Enterococcus</i>	3	2
<i>Proteus</i>	2	2
<i>Staphylococcus aureus</i>	1	1
<i>Clostridium</i>	1	1

Table 3 Risk factors for infective complications

Risk factor	IV group, n=3	Oral group, n=2	<i>p</i>
Mean age	45±15.7	62±11.3	0.470
Sex M/F	3/0	0/2	0.000
BMI	27.3±3.5	25±1.4	0.500
DOS	55±5	55±28	0.930
Rupture of gallbladder	1/3	1/2	0.500
Bile or gallstone spillage	1/3	1/2	0.500
Drain	0	1	0.000
Diabetes mellitus	0	0	1.000
Biliary colic	0	1	0.000
Infected bile	1	0	0.000

DOS duration of surgery, BMI body mass index

antibiotic treatment. In these cases, second-generation cephalosporins administered orally, in accordance with the recommendations in the hospital infection control committee.

Cost Analysis

Prophylactic antibiotic cost in the oral group was 232.32 Turkish lire (TL) (106.5 euros) (0.65 euro for each patient), whereas it was 800 TL (366.9 euros) (2.29 euros for each patient) in the IV group. IV prophylaxis group was found to be 3.5-fold expensive than the oral group.

Discussion

While there are only a few studies which show that prophylactic antibiotic use reduces the postoperative complication rates in laparoscopic cholecystectomy [5, 6], there is no other randomized and controlled study that reveals a considerable effect of prophylactic antibiotic administration over postoperative infection complications in patients that received laparoscopic surgery [7–9].

Despite controversy surrounding the use of prophylactic antibiotics in laparoscopic cholecystectomy, 79 % of patients undergoing laparoscopic cholecystectomy have received prophylactic antibiotics preoperatively and 63 % received antibiotics postoperatively [10].

Many studies have evaluated this issue further with controversial results. Nine controlled studies on antibiotic prophylaxis with a total of 1,437 patients that also included laparoscopic cholecystectomy were evaluated in a meta-analysis from 2008 [11].

Catarci et al. summarized, in another review, that only a randomized multicenter trial could give an answer to whether an antibiotic prophylaxis can reduce the postoperative wound infection rate or not [12].

Except for one, all the prophylactic antibiotic studies on patients that received elective laparoscopic cholecystectomy are comparisons of IV antibiotic prophylaxis vs. placebo.

Zurbuchen et al. highlighted the oral prophylaxis concept among laparoscopic cholecystectomy patients for the first time and studied 151 patients in two groups by applying oral antibiotic prophylaxis to one group and IV antibiotic prophylaxis to the other group, and as a result of which, they found no significant difference between the groups with regard to post-operative infection complication rates [13].

In the present study, we aimed to reveal the reliable and cost-effective nature of oral prophylactic antibiotics. Thus, we designed a prospective and randomized study that would enable us to evaluate 320 patients scheduled for elective laparoscopic cholecystectomy in two groups. No complication or intolerance associated with the drug was observed among our patients. Cephalexin monohydrate is generally well tolerated. Nausea and vomiting was not observed in patients with preoperative period. We were so sure that the oral prophylaxis of patients in the group.

Surgical site infection was found in three (1.8 %) patients of prophylactic IV antibiotic group and two (1.2 %) patients of the oral antibiotic group. Our results were consistent with the postoperative surgical site infection rates reported for laparoscopic cholecystectomy in the literature [14, 15].

Moreover, we determined oral prophylaxis group as 3.5 times cost-effective than IV prophylaxis group. Zurbuchen et al. reported 20-fold cost-effective oral prophylaxis compared with the IV prophylaxis [13]. We believe that this difference between our studies was due to the differences between countries.

Positive culture rate in patients with gallstone is 10–20 % [16]. Thirty-one (19 %) patients in group A and 24 (15 %) patients in group B demonstrated growth in their gallbladder cultures. The most frequently isolated microorganism was *K. oxytoca* (36 %) followed by *E. coli* (20 %) (Table 2).

No correlation was found between postoperative infection complications and microbiology. As five patients in the study group exhibited surgical site infection, only one of them showed growth in gallbladder culture.

In terms of patients that developed infection complications, mean age was 62 ± 11.3 in the oral group and 45 ± 15.7 in the IV group. Two patients with surgical site infection in the oral prophylaxis group were female, whereas three patients with surgical site infection in the IV prophylaxis group were all male. There was no significant difference between those groups in terms of BMI, operation length, and complications such as gallbladder rupture and spillage of stones into the abdomen. While there was one patient subjected to drain usage and developed surgical site infection in the oral prophylaxis group, another patient who suffered biliary colic and demonstrated surgical site infection was also in the oral prophylaxis group; moreover, one patient who exhibited growth

in the gallbladder culture alongside surgical site infection was in the IV prophylaxis group. Some authors mention the following as risk factors for infection complications: >60 years of age, DM, and history of a biliary colic in the preceding month [9, 17]. In the current study, only one patient above 60 years of age in the oral prophylaxis group demonstrated surgical site infection. Moreover, another patient in the oral prophylaxis group who suffered biliary colic episode within the preceding month showed surgical site infection. There was no significant difference between the groups (Table 3).

Many studies in the literature found no correlation between wound infection and bile culture, spillage of stones into the abdominal cavity, and gallbladder perforation. Koc et al. noted stone spillage rate as 19.5 %; however, they found no correlation with the surgical site infection [9]. In the current study, we determined similar results. Fourteen of 16 patients with spillage of stones into the abdomen demonstrated no complication, while the remaining two showed surgical site infection. One of those two patients was in the IV prophylaxis group, while the other was in the oral prophylaxis group; there was no statistically significant difference. Two of the 36 patients with gallbladder perforation exhibited surgical site infection. Moreover, one of those two patients was in the IV prophylaxis, and the other, in the oral prophylaxis group; there was no statistically significant difference (Table 3).

Gold-Deutch et al. found only umbilical port infection in 2 of 247 patients in their study and observed no growth in their bile cultures [18]. In the present study, cultures of 55 patients showed growth, and only one of the patients with a surgical site infection demonstrated growth in the bile culture (IV prophylaxis group).

Mechanical tissue trauma and contamination of skin flora have been shown to be other important factors for surgical site infection [9, 18–21]. In our study of patients, we had no mechanical skin trauma and skin flora contamination.

Conclusion

Oral antibiotic prophylaxis can be used in elective laparoscopic cholecystectomy prophylaxis due to its cost-effective, reliable nature, and low surgical site infection rate.

References

1. Shea JA, Berlin JA, Bachwich DR, Starosick RN, Malet PF, McGuckin M, Schwartz JS, Escarce JJ (1998) Indications for and outcomes of cholecystectomy: a comparison of the pre and postlaparoscopic eras. *Ann Surg* 227:343–350
2. No Author (1991) A prospective analysis of 1518 laparoscopic cholecystectomies. The Southern Surgeons Club. *N Engl J Med* 324 (16):1073–1078

3. Nichols RL (2001) Preventing surgical site infections: a surgeon's perspective. *Emerg Infect Dis* 7:220–224
4. Mangram AJ, Horan TC, Pearson ML et al (1999) Guideline for prevention of surgical site infection, 1999. Hospital Infection Control Practices Advisory Committee. *Infect Control Hosp Epidemiol* 20:250–280
5. Shindholimath VV, Seenu V, Parshad R, Chaudhry R, Kumar A (2003) Factors influencing wound infection following laparoscopic cholecystectomy. *Trop Gastroenterol* 24:90–92
6. Al-Abassi AA, Farghaly MM, Ahmed HL, Mobasher LL, Al-Manee MS (2001) Infection after laparoscopic cholecystectomy: effect of infected bile and infected gallbladder wall. *Eur J Surg* 167:268–273
7. Harling R, Moorjani N, Perry C, MacGowan AP, Thompson MH (2000) A prospective, randomized trial of prophylactic antibiotics versus bag extraction in the prophylaxis of wound infection in laparoscopic cholecystectomy. *Ann R Coll Surg Engl* 82:408–410
8. Kuthe SA, Kaman L, Verma GR, Singh R (2006) Evaluation of the role of prophylactic antibiotics in elective laparoscopic cholecystectomy: a prospective randomized trial. *Trop Gastroenterol* 27:54–57
9. Koc M, Zulfikaroglu B, Kece C, Ozalp N (2003) A prospective randomized study of prophylactic antibiotics in elective laparoscopic cholecystectomy. *Surg Endosc* 17:1716–1718
10. McGuckin M, Shea JA, Schwartz JS (1999) Infection and antimicrobial use in laparoscopic cholecystectomy. *Infect Control Hosp Epidemiol* 20:624–626
11. Choudhary A, Bechtold ML, Puli SR, Othman MO, Roy PK (2008) Role of prophylactic antibiotics in laparoscopic cholecystectomy: a meta-analysis. *J Gastrointest Surg* 12:1847–1853
12. Catarci M, Mancini S, Gentileschi P, Camplone C, Sileri P, Grassi GB (2004) Antibiotic prophylaxis in elective laparoscopic cholecystectomy. Lack of need or lack of evidence? *Surg Endosc* 18(4):638–641
13. Zurbuchen U, Ritz J-P, Lehmann KS, Groene J, Heidari M, Buhr HJ, Germer C-T (2008) Oral vs intravenous antibiotic prophylaxis in elective laparoscopic cholecystectomy—an exploratory trial. *Langenbecks Arch Surg* 393:479–485
14. Chuang SC, Lee KT, Chang WT, Wang SN, Kuo KK, Chen JS, Sheen PC (2004) Risk factors for wound infection after cholecystectomy. *J Formos Med Assoc* 103(8):607–612
15. Rotermann M (2004) Infection after cholecystectomy, hysterectomy or appendectomy. *Health Rep* 15(4):11–23
16. Chang WT, Lee KT, Wang SR et al (2002) Bacteriology and antimicrobial susceptibility in biliary tract disease: an audit of 10-year's experience. *Kaohsiung J Med Sci* 18(5):221–228
17. Higgins A, London J, Charland S et al (1999) Prophylactic antibiotics for elective laparoscopic cholecystectomy: are they necessary? *Arch Surg* 134:611–613
18. Gold-Deutch R, Mashiach R, Boldur I et al (1996) How does infected bile affect the postoperative course of patients undergoing laparoscopic cholecystectomy? *Am J Surg* 172:272–274
19. den Hoed PT, Boelhouwer RU, Veen HF et al (1998) Infections and bacteriological data after laparoscopic and open gallbladder surgery. *J Hosp Infect* 39:27–37
20. Illig KA, Schmidt E, Cavanaugh J et al (1997) Are prophylactic antibiotics required for elective laparoscopic cholecystectomy? *J Am Coll Surg* 184:353–356
21. Colizza S, Rossi S, Picardi B et al (2004) Surgical infections after laparoscopic cholecystectomy: ceftriaxone vs ceftazidime antibiotic prophylaxis. A prospective study. *Chir Ital* 56:397–402