

Infections after laparoscopic and open cholecystectomy: ceftriaxone versus placebo; a double blind randomized clinical trial

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ABSTRACT

Background: Gallstone disease is one of the most common gastrointestinal diseases requiring surgery with probable postoperative infection. The role of prophylactic antibiotics (AB) in prevention of infection is controversial. This study aimed to compare the manifestations, complications and outcomes of two groups of patients, those receiving prophylactic AB versus placebo, in order to determine whether antibiotic therapy is required.

Patients and methods: In this double blind randomized clinical trial, we studied 130 patients with symptomatic cholelithiasis or polyps of gallbladder admitted in Shohada-e-Tajrish Hospital, Tehran, Iran for cholecystectomy between 2006 and 2008. Patients were randomly assigned in two subgroups: the first group received 1gr ceftriaxone during induction of anesthesia and the second group received 10mL of isotonic sodium chlorides solution as placebo. All patients were followed for 4 weeks after surgery.

Results: The study population included 61 males and 69 females with the mean age of 49.3±9.6 and 51.8±9.9 years in treatment and placebo group, respectively. Of 130 bile culture results, 83 were negative. *Escherichia coli*, *Klebsiella* and *Staphylococcus aureus* were the most common cultured bacteria. There was no statistically significant difference in culture results between the patients received AB and placebo (*NS*). The surgical technique (open versus laparoscopic) did not influence the culture results.

Conclusion: It can be concluded that prophylactic antibiotics do not have any preventive effect on wound infection in a double blind setting. According to our findings, routine antibiotic prophylaxis as recommended for biliary surgery (open or laparoscopic cholecystectomy) is now questionable.

Keywords: Antibiotic, Cholecystectomy, Infection, Prophylaxis.
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INTRODUCTION

Gallstone disease is one of the most common gastrointestinal conditions requiring surgery. In the United States about 750,000 patients (10% of adult population) experience cholelithiasis and 500,000 cholecystectomies are performed annually. In Europe, 18.8% of women and 9.5% of men have

gallstones (1-5). Cholecystectomy is one of the most common treatments of gallbladder disease, which can be performed by either an open or laparoscopic approach. It is also one of the main causes of surgical site infection (SSI) (4-11).

Compared to open cholecystectomy (OC), laparoscopic cholecystectomy (LC) results in less pain, lower rates of nosocomial infection and SSI, shorter surgery time and hospital stay, reduced treatment costs, and a markedly lower death rate

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but higher rates of gallbladder and common bile duct injuries and 3-5% conversion rate to open surgery. It has also been suggested that longer time between diagnoses and treatment increases the risk of having complications (12-16).

Main complications of LC are major bleeding, wound infection, and biliary leakage or injury which is mostly seen in developing countries (11, 17-19). Surgeons' experience and patient selection are important determinants for complications (20).

Among surgical patients, SSIs account for 38% of nosocomial infections. It is estimated that SSIs develop in 2 to 5 percent of more than 30 million patients undergoing surgical procedures annually (2,11,17). Age, wound classes 3 and 4, ASA (American Society of Anesthesiology) score 3,4 and 5, surgery duration of >2 hours and complexity of surgery are main risk factors for SSI which can be reduced by minimally invasive procedures including LC (21,22). Although bile cultures are positive for bacteria in 50-75% of cases, bacterial proliferation may be a result of cholecystitis and not the precipitating factor but this matter is not clearly established (23).

This double blind randomized trial was conducted to compare the manifestations, complications and outcomes of cholecystectomy in two groups of patients, those who received AB and the other group that received placebo. Both groups were subdivided into two subgroups based on surgical technique (OC and LC). The ultimate goal of this study was to evaluate the role of bile infection in SSI and determine whether antibiotic therapy is needed in patients with gallstone.

PATIENTS and METHODS

In this randomized clinical trial, 196 patients with symptomatic cholelithiasis or polyps of gallbladder admitted in Shohada-e-Tajrish Hospital, Tehran, Iran for cholecystectomy between 2006 and 2008, were studied. Patients with acute cholecystitis based on three of the

following signs; abdominal pain in the upper right quadrant, Murphy's sign, leukocytosis >10000/mm³, and rectal temperature >38°C or <36.5°C as well as cholecystolithiasis (stones/sludge) or sonographic signs of cholecystitis (thickening and triple layer formation of the gall bladder wall) were included. Pregnant women, patients with jaundice at the time of diagnosis, coagulopathy, choledocholithiasis, portal hypertension, diabetes mellitus, immunosuppressive disorders, previous biliary surgery, biliary pancreatitis, history of antibiotic consumption within one week prior to surgery, allergic reaction/anaphylaxis to penicillin or cephalosporins, any acute emergency interventions, any contraindications for LC (previous history of abdominal surgery, choledocolithiasis), conversion from LC to OC and patients who did not agree with terms of study were excluded.

Having explained surgical methods and study protocol, patients were assigned in two groups by a table of random numbers among the patients' name list. First group received 1gr ceftriaxone during induction of anesthesia and the second group received 10ml of isotonic sodium chlorides solution as placebo. Laboratory tests (complete blood count/diff, aspartate and alanine aminotranferase, serum billirubin, and alkaline phosphatase) were checked before surgery. All surgeries were performed with the same surgical team who were expert in both approaches. In each group patients were randomly divided into two subgroups: Group A underwent OC and group B had LC. None of the patients received extra dosage of antibiotics (AB) during or after surgery. Both patients and questioners were blind to surgical approach and administered drugs.

In OC, we removed the gall bladder after right subcostal incision. In patients with previous history of icter, liver function tests elevation and serum amylase or common bile duct diameter >10mm, common bile duct exploration and T-tube drainage was achieved. LC was performed by Angelo-

American method with reusable tools. Gall bladder was dissected with electro cauterization. No routine intraoperative cholangiography was performed during laparoscopy. Bile secretion was cultured in all patients.

We followed all patients for four weeks after surgery. The bile culture results were compared between groups. In cases with wound infection we compared the site of surgery and infection, class of infection and treatment. Data were analyzed using SPSS (version 16.0, Chicago, Illinois, USA). T-test, chi square, and Fisher's exact test were used, when appropriate. P values less than 0.05 were considered significant.

RESULTS

Totally, 196 patients enrolled of whom 66 were excluded. Of 130 studied patients, 66 received prophylactic antibiotic and 64 received placebo. Meanwhile, 32 patients of treatment group and 31 of placebo group underwent OC.

The study population included 61 males and 69 females with the mean age of 49.3 ± 9.6 and 51.8 ± 9.9 years in treatment and placebo group, respectively. Female to male ratio in the treatment and placebo group was 35/31 and 34/30, respectively. Table 1 represents the demographic features of patients of both groups. As shown, ASA score, body weight, duration of surgery, surgical complications (rupture of bladder, bile or stone spillage, wound infection, biloma, intra abdominal abscess, portal herniation and post operative icter), hospital stay, frequency of subhepatic drains, and histopathological characteristics were not significantly differed between groups (table 1).

Bile infection, rupture of gallbladder, spillage of gallstone or bile, the need for sub hepatic drainage and surgical site infection were the most frequent complications (table 2). Mean surgical time and hospital stay were longer in OC group, however the difference did not reach a statistically significant level.

Table 1. Demographic and disease characteristics of patients undergoing open/laparoscopic cholecystectomy with/without prophylactic antibiotic

Characteristics*	OC(n=63)		LC(n=67)	
	AB (n=32)	Placebo (n=31)	AB (n=34)	Placebo (n=33)
Age (yr)	49.2	51.9	49.3	51.6
Sex				
Female	17(27)	17(27)	18(26.9)	17(25.3)
Male	15(23.8)	14 (22.2)	16 (23.9)	16 (23.9)
Body weight (kg)	62.3	62.1	62.6	62.2
Gallstone	24	20	23	21
Gallbladder polyp	8	11	11	12
ASA score				
1	16	14	17	15
2	12	12	13	13
3	4	5	5	5
Cholecystitis				
Acute	8	7	9	8
Chronic	17	14	19	16
Empyema	5	6	4	6
Hydropse	2	4	2	3

OC: open cholecystectomy; LC: laparoscopic cholecystectomy;

AB: antibiotic; ASA: American Society of Anesthesiology

* No statistically significant difference was noted between groups.

Table 2. Complications and outcome of surgery in patients undergoing open/laparoscopic cholecystectomy with/without prophylactic antibiotic

Complications*	OC(n=63)		LC(n=67)	
	AB (n=32)	Placebo (n=31)	AB (n=34)	Placebo (n=33)
Infected bile	11	12	12	13
Intraoperative rupture of gallbladder	8	6	9	7
Spillage of bile/ gallstone	7	6	8	6
Subhepatic drain	5	4	6	5
Surgical site infection				
Subhepatic fluid	1	0	1	0
Infection of incision	0	1	1	1
Operation time (min)	71.4	72.7	69.3	68.4
Hospital stay (day)	3.46	3.53	4.54	3.57

* No statistically significant difference was noted between groups.

OC: open cholecystectomy; LC: laparoscopic cholecystectomy;

AB: antibiotic.

Of 130 bile culture results, 83 were negative (table 3). *E coli*, *Klebsiella* and *Staphylococcus aureus* were the most common cultured bacteria. Nevertheless, differences in culture results were not statistically significant between patients receiving AB and the placebo group, regardless of the surgical approach.

Totally, 3 patients in the treatment and two in placebo group developed surgical site infection,

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however only one had positive culture result (table 4). The incidence of SSI were not statistically significant between the two groups ($p>0.05$), thus, prophylactic antibiotics had no protective effect against bile infection or complications of surgery. This was also true in all four subgroups suggesting that this conclusion is valid regardless of the surgical approach.

Table 3. Results of bile culture in patients undergoing open/laparoscopic cholecystectomy with/without prophylactic antibiotic

Culture result *	OC(n=63)		LC(n=67)	
	AB (n=32)	Placebo (n=31)	AB (n=34)	Placebo (n=33)
No growth	20	20	22	20
<i>E coli</i>	4	3	4	3
<i>Klebsiella pneumoniae</i>	3	2	3	2
<i>Pseudomonas aeruginosa</i>	1	0	1	1
<i>Enterobacter</i>	0	1	0	1
<i>Proteus mirabilis</i>	0	1	0	1
<i>Staphylococcus aureus</i>	2	2	2	2
<i>Streptococcus</i>	0	1	1	1
<i>Enterococcus</i>	1	0	1	1
<i>Clostridium</i>	0	1	0	1

* No statistically significant difference was noted between groups.

OC: open cholecystectomy; LC: laparoscopic cholecystectomy; AB: antibiotic.

Table 4. Demographic and disease characteristics of patients with SSI in open/laparoscopic cholecystectomy group with/without prophylactic antibiotic

No Bile culture results	SSI class	Clinical manifestation	Age (yr)	Sex	Surgical technique	Spillage of bile/gallstone
1 Neg.	II	AC	38	F	LC(- AB)	Neg.
2 Pos.	III	empyema	50	F	LC(+AB)	Neg.
3 Neg.	II	AC	41	M	LC(+AB)	Neg.
4 Neg.	II	AC	52	M	OC(+AB)	Neg.
5 Neg.	III	AC	50	F	OC(-AB)	Neg.

OC: open cholecystectomy; LC: laparoscopic cholecystectomy; Neg.: negative; Pos.: positive; (-AB): without antibiotic (placebo group); (+AB): with antibiotic; SSI: surgical site infection; AC: acute cholecystitis; F: female; M: male.

DISCUSSION

Cholelithiasis is a common gastrointestinal disease worldwide. The prevalence and incidence increases with age and 20% of adults over 40 years old suffer from biliary calculi. The age-adjusted female-to-male ratio for gallstone disease is 2.9 between the ages of 30 and 39 years, but it decreases to 1.2 between the ages of 50 and 59

years (4). In this study 130 patients were randomly assigned in two groups, received antibiotic prophylaxis or placebo, and underwent either OC or LC. Patients were alike for background variables.

In our study, the result of bile culture was positive in 36.2% of patients, while the main cultured bacteria were: *E. coli*, *Klebsiella* and *Staphylococcus aureus*. These results were in agreement with other studies. In a study in Honolulu, among 501 cases of cholecystectomy, 46.7% of patients had positive bile culture with dominance of *E. coli*, *Klebsiella*, *Enterobacter*, *Enterococcus*, *Clostridium perfringens* and staphylococci. Wound infection was mostly seen in men and 65% of cases had the same organism in both bile and infected wound (24). In Ahmadian et al study, 57.5% of cultures were positive for pathogenic bacteria, and in 14% more than one bacterium was isolated. *E. coli* and staphylococci were the most common aerobic bacteria and *Clostridium* species and streptococci were the most common anaerobic isolated bacteria (25).

In another study Sattar et al evaluated the frequency of infection in cholelithiasis. Thirty six percent (36%) of patients had positive bile culture. *E. coli* (17 patients) followed by *Klebsiella* (9), *Pseudomonas* (6), *Staphylococcus aureus* (2), *Salmonella* (1), and *Bacteroids fragalis* (1) were the most frequent isolated bacteria. Most of the organisms were highly sensitive to the second generation cephalosporins and quinolones. They concluded that both endogenous and exogenous contamination were the causes of wound sepsis. Nevertheless, the infection of bile did not increase the risk of postoperative wound infection when prophylactic perioperative antibiotics were used (26). In our study, 5 patients had infection of surgical incision site with primary manifestation of acute cholecystitis (n=4) and empyema (n=1), however only one had positive bile results and there was no correlation between bacteribilia and SSIs, a finding that was described in other studies

as well (27,28). In our setting, spillage of bile or gall bladder stones occurred in 21.2% and 20.3% of patients in the treatment and placebo group, respectively, however spillage did not contribute to a higher SSI rate. All five patients with SSIs did not have rupture of gallbladder, so infectious complications were not predictable. Many reports have also indicated that wound infections are not related to bile culture, rupture of gallbladder, or spillage of gallbladder stones or bile (27,28). Therefore, the cause of SSIs in these five patients could be in part explained by inadequate skin preparation, aseptic manipulation, and incomplete homeostasis.

The role of prophylactic AB in prevention of infection is controversial. Although many studies show that prophylactic AB is not necessary in elective, non complicated LC, others believe that it can be useful in reduction of SSI after cholecystectomy in high risk populations (29). Our data also showed that it is not necessary to prescribe antibiotics before wound closure in order to decrease the incidence of SSIs in elective cholecystectomy. In elective cases, additional doses are generally recommended only when surgery lasts longer than 2 to 3 hours (30). On the other hand, prolonged use of prophylactic antibiotics may induce bacterial resistance, change normal bile flora, cost more, and increase further opportunistic nosocomial infections and SSIs (27).

In conclusion, prophylactic AB did not have any preventive effect on wound infection. This fact was demonstrated regardless of surgical approach. Therefore, routine antibiotic prophylaxis as recommended for biliary surgery (open or laparoscopic cholecystectomy) in general is now questionable.

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