The Effect of Prophylactic Antibiotics on Post Laparoscopic Cholecystectomy Infectious Complications: A Double-Blinded Clinical Trial

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Type of article: Original

Abstract

Background: Laparoscopic cholecystectomy (LC) is one of the most common surgeries in laparoscopic surgery. Although, it is believed that LC has low-risk for post-operative infectious complications, the use of a prophylactic antibiotic is still controversial in elective LC.

Objective: To determine the impact of prophylactic antibiotics on postoperative infection complications in elective laparoscopic cholecystectomy.

Methods: In this double-blind, placebo-controlled, randomized, clinical trial, patients who were candidates for elective LC, from March 2012 to 2015, in four hospitals in Babol, Iran, were studied. Patients were allocated randomly to two groups, i.e., group C: Cefazolin (n = 182) and group P: placebo (n = 247). Group C received 1 g of Cefazolin 30 minutes before anesthesia and then, six and 12 hours after anesthesia. Group P patients received 10 ml of isotonic sodium chloride solution. Age, gender, type of gallbladder diseases (stone, polyp, or hydrops), the length of post-operative hospitalization, frequency of gallbladder rupture, the duration of surgery, and the kinds of complications associated with infections were collected for each patient in the two groups. The data were analyzed by IBM-SPSS version 20, using the t-test and the chi-squared test, and a p-value < 0.05 was considered as significant.

Results: There were no significant differences between the two groups in terms of gender (C versus P: 18 (9.9%) male versus 22 (9%); p = 0.74), age (C versus P: 43.75 ± 13.30 years versus 40.91 + 13.05; p = 0.20), and duration of surgery (C versus P: 34.97 ± 8.25 min versus 34.11 ± 8.39; p = 0.71). There were no significant differences between the two groups in the incidences of post-operative infection (C versus P: 3 (1.7%) versus 5 (2%); p = 0.99) and rupture of the gallbladder (C versus P: 14 (7.8%) versus 17 (6.8%); p = 0.85). No other post-operative systemic infectious complications (e.g., sepsis, pneumonia, or urinary tract infection) were found in either group.

Conclusion: For patients who underwent laparoscopic cholecystectomy (LC), prophylactic antibiotics had no important role in the prevention of infections; so these antibiotics apparently are not necessary in treatment, and they are not recommended for patients with laparoscopic cholecystectomy as low-risk selective antibiotics.

Trial registration: The trial was registered at the Iranian Clinical Trial Registry (http://www.irct.ir) with the IRCT identification number IRCT2013070413865N1.

Funding: This research was supported financially by the Research Council of Babol University of Medical Sciences.

Keywords: Antibiotic prophylaxis, Surgical wound infection, Laparoscopic cholecystectomy

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Received: December 03, 2015, Accepted: March 04, 2016, Published: May 2016
iThenticate screening: March 04, 2016, English editing: March 12, 2016, Quality control: May 02, 2016
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1. Introduction
In patients with symptomatic cholelithiasis during open cholecystectomy operations, the first choice for treatment should be laparoscopic cholecystectomy (1-2) because of the slight probability of post-operative infections due to the creation of tiny wounds as well as tissue damage, which is less common in LP than open surgery (1). Surgical site infections (SSIs) are infections that occur in the wound created by an invasive surgical procedure, and they are the common cause of healthcare-associated infections (1-4). Three meta-analyses based on the use of retrospective studies indicated that, after cholecystectomy, the mean ratio of infectivity by microorganisms in the wound sites was in the range of 0.4 - 1.1% (2-4). The use of prophylactic antibiotics in the study was shown to prevent surgical site infections (SSIs), thereby preventing the obvious infectious side effects in open cholecystectomy; of course, according to several surveys that have been conducted in various parts of the world, these antibiotics are neither appropriate nor necessary for this purpose (5-13). However, there is no consensus on these considerations, and many surgeons still use antibiotic prophylaxis in laparoscopic cholecystectomy and also recommend the administration of prophylactic antibiotics (13-18). However, these meta-analyses were conducted at a different time, and on studies with relatively small sample sizes. Cefazolin - a first-generation cephalosporin - has the favorable pharmacokinetic properties of sufficient distribution to the wall of the gallbladder and a high concentration in the bile (19, 20). Because of its low toxicity, broad-spectrum anti-microbial effect, and low cost, a single dose of the antibiotic cefazolin is effective in patients with open cholecystectomy and other biliary surgery (21, 22). Thus, it is the antibiotic that is recommended by the U.S. Center for Disease Control and Prevention as being suitable for preventing SSIs (23, 24). However, to date, the effectiveness of Cefazolin on post-LC infective complications remains unclear. The aim of this study was to determine the efficacy of prophylactic Cefazolin on the rate of post laparoscopic cholecystectomy infectious complications.

2. Material and methods
2.1. Study design
This was a double-blinded, randomized, clinical trial conducted on patients who were candidates for elective LC due to symptomatic gallbladder stones or polyps and who were referred to four major hospitals in Babol, Iran, from March 2012 to March 2015.

2.2. Study population
The inclusion criteria were ages more than 18 years old and a first-time abdominal surgery. The exclusion criteria were patients who were younger than 18 and older than 75, antibiotic consumption in seven days before the LC, immune compromised patients, history of acute cholecystitis in the six months prior to admission, concomitant cholelithiasis, intrahepatic duct stones, evidence of cholangitis and/or obstructive jaundice and gallstone pancreatitis, previous biliary tract surgery or previous endoscopic retrograde colangiopancreato- garphy within a week before the surgery, diabetes mellitus, massive bleeding during surgery, converting laparoscopy to laparotomy, cephalosporin or beta-lactam allergy, sensitivity, or anaphylaxis, major thalassemia, and empyema.

2.3. Sample size determination
According to previous studies that showed an overall rate of infection of 1.1% (4), we estimated a sample size of 167 in each group using a value of 0.05 with a power of 80% and a precision of 1%.

2.4. Blinding and allocation
Patients were allocated randomly using closed envelopes that contained one of the intervention protocols. They were allocated to two groups, i.e., group C: Cefazolin group (n = 182) and group P: Placebo group (n = 247) (Figure 1). The intervention plan of each group was prepared by a nurse who was not a member of our research team, and the plan was delivered to the anesthesiologist. The patients were not aware of the type of solution that was used. The medical staff and the patient were unaware of the content of the solution.

2.5. Interventions
Group C patients received 1 gr of Cefazolin 30 minutes before anesthesia and and then, six and 12 hours after anesthesia. Group P patients received 10 ml of isotonic sodium chloride solution with the same prescribing method of Cefazolin. Operations were conducted on all of the patients using reusable laparoscopic instruments that were sterilized with ethylene oxide. The skin was prepared with a 10% povidone-iodine solution. LC was done with a 4-trocar standard technique; a 10-mm trocar was placed with the open technique through an infra-umbilical incision (Hasson). A 2-0 non-absorbable, monofilament suture was used to close the incision, but the other ones were applied under direct vision as follows: 5-mm trocar on the midclavicular line, 10-mm trocar in the epigastrium, and 5-mm
trocar in the right flank in line with the gallbladder fundus; the extraction hole created by the trocar in the epigastric region was opened to remove the ruptured gallbladders that had severe inflammation and friability using a plastic bag and positional peritoneal irrigation without any drain, and 3-0, non-absorbable, monofilament sutures were used in the other incisions.

Figure 1. CONSORT diagram showing how the patients undergoing laparoscopic cholecystectomy were recruited and handled during the course of the study

2.6. Outcomes
Before the interventions, the subjects’ genders and ages were documented. During the operation, surgery time and evidence of ruptured gallbladder also were recorded. The post-operative course was monitored, and the duration of hospital stay and any evidence of superficial SSI or any incidents, such as fever (> 38 °C, temperature taken twice a day, excluding the first postoperative day), infection of the trocar site (purulent drainage from the surgical sites), and intra-abdominal collection of pus were recorded in checklists. After being discharged from the hospital, the patients underwent weekly, clinical, post-operative monitoring for SSI for a one-month period.

2.7. Ethics
This study was approved by the Ethics Committee of Babol University of Medical Sciences, and all of the subjects’ parents were informed regarding the details of the study, and they signed a consent form. This study was registered in the Iranian Registry of Clinical Trials with the registration number of IRCT 20130704138651.

2.8. Statistical analysis
All of the variables had a normal distribution. Statical analysis, such as the t-test, chi-squared test, and ‘Fisher exact test,’ as appropriate, were done using IBM-SPSS version 20 considering a p-value < 0.05 as significant.

3. Results
3.1. Baseline characteristics
Four hundred and twenty-nine patients, including 40 males and 389 females with a mean age of 42.08 ± 13.1 years, were enrolled in two groups, i.e., Group C (n = 182) and Group P (n = 247). There was no statistically significant difference between the two groups in term of gender (p = 0.74), age (p = 0.2), or the duration of surgery (p = 0.17) (Table 1).
physician

The risk of infectious complications increased in patients who had ruptured gallbladders (p = 0.001) and in male patients (p = 0.03) (Table 2).

Table 2. Comparison of the two groups of patients with and without infectious complications during one-month follow-up after laparoscopic cholecystectomy

| Characteristics       | Infectious complications (n=8) | No complications (n=421) | p-value |
|-----------------------|-------------------------------|--------------------------|---------|
| Gender, male/female   | 3 (37.5%) / 5 (62.5%)         | 37 (8.8%) / 384 (91.2%)  | 0.03    |
| Age, year (mean ± SD) | 45.88 ± 15.88                 | 42.05 ± 13.17            | 0.41    |
| Rupture of Gallbladder| 3 (37.5%)                     | 28 (6.7%)                | 0.01    |
| Duration of Operation | 37.5 ± 11.33                  | 34.42 ± 8.22             | 0.30    |
| Length of Stay, day   | 1.00 ± 0.0001                 | 1.02 ± 0.14              | 0.74    |

4. Discussion

Our data showed that the overall rate of SSIs after LC was just 1.9%, and it was not related to the use of a Cefazolin (1 g), which was lower than the rate of post-LC SSIs that has been reported in the literature, i.e., about 0.4% and 6.3% (4, 6, 8, 13, 15, 24). The patients treated with or without prophylactic antibiotics showed different rates of SSIs, i.e., about 1.7% and 2.1%, respectively, but the difference was not statistically significant. Actually, these differences were lower than the rates reported in other studies on open cholecystectomy (4, 25). In open cholecystectomy and other biliary surgery, Cefazolin is an effective antibiotic (18, 19). Also, studies have shown that, for induction of anesthesia or immediately before cutting in clean or clean-contaminated procedures, cephalosporin should be administered intravenously as a single dose (22). However, the aim of antimicrobial prophylaxis is to reduce the number of microorganisms to such an extent that the defense mechanism of the host can effectively prevent infection by the contaminating microorganisms; it is not to completely eradicate microorganisms from the tissue (26). Whether antibiotic prophylaxis has any effect on the occurrence of postoperative infections in LC remains controversial (2, 4, 5, 7, 14, 15, 27-30). Infectious side effects in laparoscopic cholecystectomy can be prevented mainly by administering prophylactic antibiotics (14-16), and these results were contrary to other findings obtained from several prospective surveys, so that the use of these antibiotics is unnecessary due to the low rates of infection during LC (4, 5, 7, 34). The various benefits of laparoscopy categorized as an elective method include less postoperative pain, shorter hospital stay, faster resumption of food intake and work, and a significant reduction in perioperative infectious complications (1, 31-33). Similar to previous studies, our results showed that there were no significant differences in the infection rate between the two groups of users of prophylactic antibiotic. Many reports also have indicated that wound infections are not related to rupture of gallbladders (5, 35). However, like other studies, our study also demonstrated that ruptures of the gallbladder contributed to the increased rates of postoperative infections (38, 39). Perforation during gallbladder surgery is attributed to traction, grasping, dissection, and removal of the gallbladder, which is likely to occur in 11 to 35% of LC cases (4, 7, 14, 34). In this study, rupture of the gallbladder occurred in 7.7 and 6.9% of patients in groups C and P, respectively. There was a significant
association between intraoperative gallbladder rupture and SSI \((p = 0.001)\), whereas many reports have indicated that wound infections were not related to rupture of the gallbladder \((5, 35)\). Patients with laparoscopic interventions treated by antibiotic prophylaxis were examined by Goldfan and Birkenmeier in 1990 within 98 randomized works, and they concluded that these antibiotics are not necessary in low-risk patients \((37)\). According to the results of this and other studies, it should be noted that the causes of the low incidence of infections after laparoscopy can be attributed to minor surgical trauma, patient mobilization, faster resumption of permitted nutrition, and avoiding the administration of prophylactic antibiotics \((7, 9)\). Other researchers have shown that major infectious complications, such as bile leak, intra-abdominal abscesses, and acute pancreatitis, usually are caused by technical problems instead of prophylactic antibiotics, so various parameters, including the delicacy of surgical techniques and other non-antibiotic-based physical and prophylactic methods, are considered more significant in the prevention process \((7, 8, 36)\). Other substantial factors of SSIs are associated with mechanical damage to tissues and contamination with the microflora from the skin \((5, 10, 25, 35, 36)\).

5. Conclusions
Considering the low rate of observed post-LC operation SSI in this study and the fact that there was no significant different between the two groups of patients who used prophylactic antibiotics and those who did not, it seems that the use of Cefazolin does not lower the rate of SSIs. Therefore, the use of prophylactic antibiotics is not recommended for patients undergoing LC.

Acknowledgments:
We thank Mrs. Sakineh Kamali Ahangar, who is on the staff of the Clinical Research and Development Group at Shahid Beheshti Hospital in Babol, Iran, for her scientific support during this trial.

Funding:
This research was supported financially by the Research Council at Babol University of Medical Sciences. The authors received no financial assistance for the authorship and publication of this article.

Trial registration:
The trial was registered at the Iranian Clinical Trial Registry (http://www.irct.ir) with the IRCT identification number IRCT2013070413865N1.

Conflict of Interest:
There is no conflict of interest to be declared.

Authors’ contributions:
All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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