Prophylactic Antibiotics for Elective Laparoscopic Cholecystectomy

Are They Necessary?

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Hypothesis: Prophylactic antibiotic treatment in elective laparoscopic cholecystectomy does not lower the already low infection rate associated with this procedure.

Design and Setting: Prospective double-blind randomized trial at a community-based training hospital.

Patients: Four hundred fifty patients undergoing elective laparoscopic cholecystectomy were randomized into 1 of 3 treatment arms: (1) preoperative cefotetan disodium, 1 g intravenously; (2) preoperative cefazolin, 1 g intravenously; and (3) intravenous placebo. There were no demographic differences between groups in age, smoking history, American Society of Anesthesiologists score, infection risk class, time of antibiotic administration prior to surgery, and type of skin preparation.

Interventions: Laparoscopic cholecystectomy was attempted in all cases; however, 10 patients required conversion to an open cholecystectomy and they were included in the statistical analysis. Preoperatively, all patients were randomized in a blinded manner and received cefotetan, cefazolin, or placebo intravenously.

Results: There were 10 postoperative infections. In the cefotetan group, there were 3 cases of superficial surgical site infections. In the cefazolin group, there were 2 superficial surgical site infections—1 pneumonia and 1 rhinosinusitis. In the placebo group, there were 2 superficial surgical site infections and 1 urinary tract infection. The overall infection rate in this series was 2.4%. Follow-up was performed at routine postoperative visits and by telephone contact. Data were evaluated using the χ² test and analysis of variance with Duncan post hoc test (P<.05).

Conclusion: Based on our data, use of prophylactic antibiotics does not decrease the rate of wound infections in elective laparoscopic cholecystectomy.

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The use of prophylactic antibiotics reduces wound infections in elective open cholecystectomies. Taragarona et al found no difference in the rate of infections with the prophylactic use of broad-spectrum penicillins vs cephalosporins. They reported a wound infection rate of 6.5% in low-risk patients undergoing open cholecystectomy without prophylactic antibiotics.

Elective laparoscopic cholecystectomy has a low risk for infection, but many surgeons still use prophylactic antibiotics. We postulated that use of prophylactic antibiotics in elective laparoscopic cholecystectomy would not lower its already low infection rate. This study was designed to determine the infection rate in patients undergoing elective laparoscopic cholecystectomy. This controlled study was conducted comparing cefotetan or cefazolin with placebo.

RESULTS

In the 25-month study period, 450 patients were selected for the study protocol. Four hundred twelve patients were evaluable after randomization into 1 of 3 arms. A total of 137 patients received cefotetan; 140 received cefazolin; and 135 received placebo. The 3 groups were well matched for the demographics listed in the "Patients and Methods" section (Table 1). Thirty-eight patients were excluded from the statistical analysis for protocol violations. The cefotetan group excluded 13 patients, the cefazolin group excluded 11, and the placebo group excluded 14 (Table 2). Seventy-eight percent of study patients received their study medication within 60 minutes of surgery.

There was no statistical difference between the 3 groups for superficial, deep, or distant infections (P>.05). The cefotetan group (137 patients) had 3 superficial surgical site infections for a 2.2%
PATIENTS AND METHODS

PATIENTS

Following institutional review board approval of the protocol, all patients undergoing elective laparoscopic cholecystectomy at Exempla Saint Joseph Hospital, Denver, Colo., from January 1, 1995, to February 2, 1997, were evaluated for the protocol. Four hundred fifty patients having elective laparoscopic cholecystectomy were selected for a double-blind randomized prospective study. Group 1 received cefotetan disodium, 1 g intravenously; group 2 received cefazolin, 1 g intravenously; and group 3 received 50 mL of isotonic sodium chloride solution.

When the patient was confirmed for the study, the Saint Joseph Pharmacy randomly selected a sealed envelope and delivered the appropriate solution to the preoperative holding area. The medical staff and the patient were unaware of the identity of the solution. Patients were given the study medication by the anesthesiologist or operating room nurse prior to surgery.

Laparoscopic cholecystectomy was planned for all patients. The only allowed variables were number and location of port sites, disposable or nondisposable trocars, intraoperative cholangiograms, port site used for gallbladder removal, and method of skin preparation and closure.

The following data were collected on each patient: age, sex, skin preparation technique, times of antibiotic administration, time of skin incision, number and location of ports, disposable or nondisposable trocars, type of skin closure, duration of operation, American Society of Anesthesiologists classification, wound infection risk classification, intraoperative cholangiograms, bile spillage, gallbladder histological findings, conversion to open cholecystectomy, length of hospital stay, body mass index, and evidence of infection.

All patients were examined by an attending surgeon 7 to 10 days after surgery and were followed up for 30 days after the procedure. Infections were classified as superficial surgical site, deep surgical site, and distant. A superficial surgical site infection is defined as erythema and/or purulent drainage at the surgical site above the fascia. A deep surgical site infection is defined as purulent material deep to the fascia or near the gallbladder fossa. A distant infection is defined as any infection remote to the surgical site. The attending surgeon obtained cultures at his or her discretion.

Inclusion criteria in the protocol were all patients scheduled for elective laparoscopic cholecystectomy aged between 18 and 80 years, without biliary colic and meeting no exclusion criteria.

Exclusion criteria were patients younger than 18 years and older than 80 years; pregnant or lactating women; β-lactam or cephalosporin allergy, sensitivity, or anaphylaxis; antibiotic therapy within 48 hours prior to surgery; evidence of acute cholecystitis, cholangitis, or obstructive jaundice; previous biliary tract surgery; evidence of choledocholithiasis; history of prosthetic valves or joints; contraindication to laparoscopic cholecystectomy as determined by the attending surgeon; and patients determined to be at increased risk of infection secondary to their medical condition.

DATA ANALYSIS

A sample size of 450 patients (150 patients per treatment arm) was predicted to detect a significant difference in the wound infection rate between the 3 arms. The sample size was based on the following: a χ^2 value of 2.35, an α error of .05 (2-tailed), a power of 0.80, and an overall wound infection rate of 6.5% in low-risk patients receiving no prophylactic antibiotics. Data were analyzed using the Power and Precision statistical computer program. The 6.5% wound infection rate is historical data from patients undergoing open cholecystectomy without prophylactic antibiotics. It was believed that the infection rate would be lower in patients undergoing elective laparoscopic cholecystectomy; therefore, a poststudy power analysis was planned.

STATISTICAL ANALYSIS

Continuous data were compared using 1-way analysis of variance with a Duncan post hoc test. All frequency data were compared using χ^2 analysis by means of the Stat Most statistical package. Correlation was determined by calculating the Spearman rank correlation. An interim analysis was performed after 225 patients (75 per arm) had completed the protocol and no significant difference had been obtained, so the study continued. P < .05 was considered significant.

wound infection rate. The cefazolin group (140 patients) had 2 superficial surgical site infections and 2 distant infections for a wound infection site rate of 1.4% and an overall infection rate of 2.9%. The placebo group (135 patients) had 2 superficial surgical site infections and 1 distant infection for a wound infection rate of 1.5% and an overall infection rate of 2.2%. There was no correlation between pathologic findings, bile spillage, and wound infection rate. None of the 22% of patients who received their study medication more than 60 minutes prior to surgery had an infectious complication.

Ten patients underwent conversions to open cholecystectomy: 2 from the cefotetan group, 6 from the cefazolin group, and 2 from the placebo group. All patients remained in the study because of “intention to treat.” One patient from the cefazolin group who underwent conversion to an open procedure had both a superficial surgical site infection and pneumonia. Nine of the 10 patients who were converted to open cholecystectomy received intraoperative and/or postoperative antibiotics, including the patients with the infectious complications. Another 10 patients without evidence of infection received antibiotics postoperatively: 7 from the cefotetan group, 2 from the cefazolin group, and 1 from the placebo group. All of these patients were included in the statistical analysis.

Several reviews have demonstrated a significant decrease in wound infections in open cholecystectomy with the use of prophylactic antibiotics. These data cannot
be extrapolated to elective laparoscopic cholecystectomy.

Some antibiotics that are used are very expensive and are no more effective than less expensive antibiotics. We selected cefotetan and cefazolin as they were widely used by surgeons at our institution. However, there is a marked cost difference, with cefazolin costing $2.41 per gram vs cefotetan at $8.80 per gram. This translates to a charge of $9.25 per gram of cefazolin and $24.40 per gram of cefotetan. Cefotetan was most commonly given in a 2-g dose, which doubled this amount. It was estimated that use of cefazolin only could result in a $24,362 savings per year. If no antibiotic is needed, this results in a savings of $30,060 per year. These estimates are for our institution.

Our data demonstrated no lowering of infection rates with a single dose of prophylactic antibiotics in elective laparoscopic cholecystectomy. Illig et al had similar results in a prospective randomized study. They compared use of 3 perioperative doses of cefazolin with no use of antibiotics in elective laparoscopic cholecystectomy. This study was published in April 1997, well after our study started. It should be noted that in their study, patient enrollment was halted at 250 patients “because of the paucity of major infectious complications, the primary end point.” The authors concluded that their study suffered from “relative small sample in relation to a relatively rare event.” We continued our study out to a sample size that was predicted to detect a significant difference in wound infection rates between the 3 arms. Using a power analysis, we now estimate that a sample size of 5444 patients would be necessary to detect significant differences between the 3 arms of this study, because of the rarity of wound infection. Illig et al have studied an additional 108 “low-risk” patients undergoing elective laparoscopic cholecystectomy in the 12 months following their study and they have found no infectious complications without the use of prophylactic antibiotics. Frantzides and Sykes had similar results in a prospective nonrandomized study comparing preoperative cefotetan with preoperative chlorhexidine gluconate scrub without preoperative antibiotics. In fact, they reported more infections in the group of patients receiving cefotetan (n = 14) than in the group of patients who received only a scrub (n = 0). Frantzides and Sykes believed that in properly selected, low-risk patients, a well-performed surgical scrub was all that was needed. One question that can be asked is: does the use of prophylactic antibiotics create a false sense of security in the operating team and lead to careless technique? If this is true, we need better technique not more antibiotics.

Our study consisted of a preselected group of patients who had no evidence of acute cholecystitis, cholelithiasis, or gallstone pancreatitis. In these high-risk patients, we support the use of prophylactic antibiotics.

Elective laparoscopic cholecystectomy carries a low risk of wound infection. Use of prophylactic antibiotics is not justified in patients undergoing elective, uncomplicated laparoscopic cholecystectomy.


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## REFERENCES


**Table 1. Demographic Data**

<table>
<thead>
<tr>
<th>Group</th>
<th>Cefotetan Group (n = 137)</th>
<th>Cefazolin Group (n = 140)</th>
<th>Placebo Group (n = 135)</th>
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<tr>
<td>Age, y</td>
<td>48.2 ± 13.6</td>
<td>48.1 ± 15.4</td>
<td>47.1 ± 12.6</td>
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<tr>
<td>BMI, kg/m²</td>
<td>28.7 ± 6.4</td>
<td>28.9 ± 5.9</td>
<td>29.0 ± 7.1</td>
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<tr>
<td>1</td>
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<tr>
<td>Length of operation, min</td>
<td>68.9 ± 31.2</td>
<td>64.0 ± 28.8</td>
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<td>Risk class</td>
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<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Antibiotic administration prior to incision, min</td>
<td>52.9 ± 52.6</td>
<td>49.7 ± 32.7</td>
<td>44.9 ± 30.5</td>
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</table>

*Data are given as mean ± SD or number of patients. BMI indicates body mass index; ASA, American Society of Anesthesiologists; and NR, not recorded.

**Table 2. Protocol Violations**

<table>
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<th>Treatment Group, No. of Patients</th>
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<tbody>
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<td>Cefotetan</td>
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<td></td>
</tr>
<tr>
<td>Antibiotic administration not documented</td>
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<tr>
<td>Operation cancelled</td>
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<tr>
<td>Missing chart</td>
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<tr>
<td>Other</td>
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</table>
DISCUSSION

Mitchel P. Byrne, MD, Evanston, Ill: This is the authors’ second prospective study from St Joseph’s Hospital in Denver presented to the Western Surgical Association over the last few years. It questions the value of antibiotics in low-risk patients undergoing elective laparoscopic cholecystectomy. Their study is a blinded perspective one, done with hospital institutional review board review and involvement of the clinical pharmacy staff. The study compared 3 equal groups: cefazolin, cefotetan, and a placebo group. Excluded were patients younger than 18, older than 80, and those with evidence of acute cholecystitis, common bile duct stones, or gallstone pancreatitis, and those considered at increased risk of infection secondary to medical condition. Results confirm as one other paper in the literature in the last year that in these low-risk gallbladder patients antibiotics are not needed. Obviously, if all low-risk patients undergoing laparoscopic cholecystectomy stop getting antibiotics, there is a big potential reduction in cost as well as avoidance of a variety of antibiotic problems. I have 3 questions. Who do you consider a high-risk patient, and could you comment on some of these such as diabetics, renal failure patients, and others? What about common bile duct procedures that are necessary that are found based on intraoperative cholangiogram? Do you begin antibiotics at that point? Do you consider doing that? Have you at St Joseph’s Hospital stopped using antibiotics for these routine cases of laparoscopic cholecystectomy? What are your estimates of cost savings in this group?

Hiram C. Polk, Jr, MD, Louisville, Ky: I rise to endorse this meticulous paper and hope that you will take it home and practice it. It has been generally gratifying about the appropriate use of prophylactic antibiotics. It is the most common use of antibiotics in the world today, but it is also the most common misuse. This study puts that in very good perspective. Many surgeons, thinking that drugs are totally safe, use antibiotics when the chance of an adverse effect from the drug is greater than the chance for infection in the patient. This report did not address drug complications, but they are numerous. I wanted to suggest one other thing that I thought the authors did especially well and that was to include the principles of Elliott and Chetlin in this study in which patients who get the best advantage from antibiotic prophylaxis are those who have their common bile duct manipulated, are elderly, or have subsiding acute cholecystitis. All of the rest of the biliary patients do not. This is just an exceptional study. It is a big challenge to the membership to see whether you have the courage of their convictions to begin to implement this practice. The gain for your individual patients is probably going to be small, but in the long run, it will be substantial. This is a first-class paper.

Daniel Elliott, MD, Dayton, Ill: In the 1960s the infection rate in a clean operating room environment was exactly the same as reported here, 1.5%. In a clean environment, almost all wound infections are the result of internal contamination from the patient’s own bacteria. Very large series of gallbladder cultures taken at routine cholecystectomies are almost uniformly negative. Less than 1% grow bacteria. In contrast, in acute cholecystitis the incidence of bacteria is 40%, and with common bile duct stones, 60%. These bacteria are in concentrations roughly equivalent to feces when cultured quantitatively. Because there is no internal contamination at uncomplicated cholecystectomies, prophylactic antibiotics are of no value. On the other hand, if you are operating in the third world, or in some of the older hospitals in Europe, from which many statistics on infection rates have been published, there is a different situation. Where operating room contamination is a threat, prophylactic antibiotics may help.

Dr Clark: Who do we consider a high-risk patient? Anyone who had any evidence of common duct stones, presented in an acute fashion with an elevated white cell count, fever, or tenderness in the right upper quadrant would be a high-risk patient and were excluded from our study. Do we consider diabetes and chronic renal failure to be high risk? I do not know the number of diabetic patients in this series. There were, however, no patients with chronic renal failure on dialysis, but those groups have been shown in other studies to be high risk. Diabetics were not excluded in our study. I suspect that it would be a surgeon’s discretion whether or not to use antibiotics in these situations. We do not perform routine cholangiography for elective cholecystectomy; most of our surgeons use that technique selectively. Twenty-four surgeons contributed cases to the study. No common bile duct injuries occurred in the study. If we do have an intraoperative cholangiogram that is positive and we do explore the duct, then I think most surgeons would use antibiotics in that situation as that throws the patient out of this low-risk elective situation that we studied.

Our definition of infection was very liberal. In fact, only 1 patient required opening of the incision; the rest were given oral antibiotics only for localized cellulitis and resolved without further intervention.

The cost savings were going to be studied prospectively, but it turned out to be too much of a problem with the logistics of getting the costs and charges on all of these patients. We estimate retrospectively that we could save between $24 000 and $30 000 a year at our institution by not using antibiotics in this group. That cost savings is based on approximately 600 laparoscopic cholecystectomies that are electively done at our institution per year.

As a result of this study, have we stopped using antibiotics on these low-risk elective laparoscopic cholecystectomies? We finished the study just a few months ago and actually we would like to know that information as well. Since we have done about 3 prospective randomized controlled studies at our hospital, we want to do a retrospective analysis of whether or not the surgeons believe the very studies that were done at their own institution. So, we are actually going to do a retrospective analysis of that data to see if practice patterns were changed.