Prophylactic Antibiotics for Elective Laparoscopic Cholecystectomy

Are They Necessary?

Andrew Higgins, MD; Jeremy London, MD; Scott Charland, PharmD; Erick Ratzer, MD; Jeffrey Clark, MD; William Haun, MD; D. Patrick Maher, MD

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.1–3 Tar-garona et al4 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.5

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.

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 cholangiogram, 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 with 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 choledochocholithiasis; 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 χ² 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 χ² 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 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.

COMMENT

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.\textsuperscript{7} 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 study demonstrated no lowering of infection rates with a single dose of prophylactic antibiotics in elective laparoscopic cholecystectomy. Illig et al\textsuperscript{8} 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 5,444 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\textsuperscript{9} 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.

**Table 1.** Demographic Data\textsuperscript{*}

<table>
<thead>
<tr>
<th>Risk class</th>
<th>Age, y</th>
<th>BMI, kg/m²</th>
<th>ASA score</th>
<th>Length of operation, min</th>
<th>Antibiotic administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>48.2 ± 13.6</td>
<td>28.7 ± 6.4</td>
<td>1</td>
<td>68.9 ± 31.2</td>
<td>Cefotetan (n = 137)</td>
</tr>
<tr>
<td></td>
<td>48.1 ± 15.4</td>
<td>28.9 ± 5.9</td>
<td>0</td>
<td>64.0 ± 28.8</td>
<td>Cefazolin (n = 140)</td>
</tr>
<tr>
<td></td>
<td>47.1 ± 12.6</td>
<td>29.0 ± 7.1</td>
<td>2</td>
<td>63.5 ± 25.2</td>
<td>Placebo (n = 135)</td>
</tr>
</tbody>
</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>
<thead>
<tr>
<th>Treatment Group, No. of Patients</th>
<th>Cefotetan</th>
<th>Cefazolin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic administration</td>
<td>10</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>not documented</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operation cancelled</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Missing chart</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

**REFERENCES**

most all wound infections are the result of internal contami-
ation from the patient's own bacteria. Very large series of gal-
bladder 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 concen-
trations roughly equivalent to feces when cultured quantita-
tively. Because there is no internal contamination at uncom-
plicated 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 dif-
ferent situation. Where operating room contamination is a threat,
prophylactic antibiotics may help.

**Dr Clark:** Who do we consider a high-risk patient? Any-
one 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 dia-
abetes and chronic renal failure to be high risk? I do not know
the number of diabetic patients in this series. There were, how-
ever, no patients with chronic renal failure on dialysis, but those
groups have been shown in other studies to be high risk. Dia-
betics 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 tech-
nique 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 with-
out further intervention.

The cost savings were going to be studied prospectively,
but it turned out to be too much of a problem with the logis-
tics 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 antibiot-
ics 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 hos-
pital, 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.