The Value of Chemoprophylaxis Against Enterococcus Species in Elective Cholecystectomy

A Randomized Study of Cefuroxime vs Ampicillin-Sulbactam

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Hypothesis: Cephalosporins are widely used and considered to be effective as prophylaxis in biliary surgery. Nevertheless, they lack activity against enterococci. We conducted a study to compare the efficacy of ampicillin-sulbactam vs cefuroxime in preventing surgical site infections following elective cholecystectomy.

Design: A prospective randomized controlled trial.

Setting: A major tertiary care hospital.

Patients: Four hundred eighteen randomized patients (of 549 total), who from July 2002 to August 2004 underwent elective open or laparoscopic cholecystectomy with prospective assessment for development of surgical site infections for 1 month postoperatively.

Intervention: A single intravenous dose of 1.5 g of cefuroxime (group A, n=207) or 3 g of ampicillin-sulbactam (group B, n=211) was administered during induction of anesthesia. Bile and gallbladder mucosal cultures were taken intraoperatively from all patients.

Main Outcome Measure: Number of postoperative surgical site infections.

Results: A postoperative surgical site infection was noted in 19 (4.5%) of 418 patients, 18 from group A and 1 from group B ($P < .001$). In the group that received cefuroxime, 15 (83.3%) of 18 surgical site infections were due to Enterococcus species. Intraoperative bactibilia as well as intraoperative gallbladder rupture were associated with surgical site infections ($P < .001$).

Conclusions: A single dose of ampicillin-sulbactam favored better compared with cefuroxime for prevention of postoperative surgical site infections due to Enterococcus species after elective cholecystectomy. Ampicillin-sulbactam may be a better agent for antimicrobial prophylaxis in high-risk patients undergoing elective cholecystectomy, especially in a setting where the incidence of enterococcal infections is higher.

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The use of antimicrobial agents as a means of preventing surgical site infections (SSIs) is still controversial in elective cholecystectomy. Many authors believe that antibiotic prophylaxis may not be necessary in low-risk patients undergoing elective cholecystectomy.1-4 On the contrary, other randomized controlled trials, as well as a large meta-analysis, found significantly reduced rates of SSI with prophylactic antimicrobials and strongly recommend the use of prophylactic antimicrobials in patients undergoing elective biliary tract surgery.5-11 The bacteria most often implicated in SSI following a cholecystectomy include Escherichia coli, Klebsiella species, and Enterococcus species.8-12-16 Cefazolin as well as other cephalosporins, such as cefuroxime, have been used for prophylaxis in biliary surgery. Despite the wide use of cephalosporins as prophylaxis in elective biliary surgery, they lack activity against Enterococcus species.17-19 Ampicillin-sulbactam, on the other hand, has a broader spectrum, including enterococci. Thus, a prospective randomized study was designed to compare the use of cefuroxime vs ampicillin-sulbactam as single-dose prophylaxis in elective cholecystectomy. The main hypothesis was that fewer postoperative infections would be observed.

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Methods

A prospective randomized controlled study comparing the prophylactic use of cefuroxime vs ampicillin-sulbactam was performed from July 2002 to August 2004 in a major ter-
Data are reported as mean (SD), rates, or odds ratio (OR) with 95% confidence interval (CI). We used a paired-sample t test for normally distributed data and a Wilcoxon signed rank test otherwise. Baseline characteristics were compared between the 2 groups for each of the study medications using nonparametric, independent-sample tests (Kruskal-Wallis and Wilcoxon rank) for continuous data and χ² Fisher exact tests for categorical data. Relationships between surgical risk, specific coexisting diseases, ASA score, and antimicrobials administered intraoperatively; type and duration of operation; iatrogenic gallbladder perforation; bactibilia; and postoperative SSI were examined between the 2 groups. Backward stepwise logistic regression analysis was then conducted to determine independent correlates of SSI. Variables with P < .10 in the univariate analysis were considered for inclusion in the multivariate analysis. Significance was set at P < .05. It was estimated that for an expected reduction from 6% to 0.6% between patients exposed and unexposed to ampicillin-sulbactam, a power of 80%, and a 2-tailed α of .05, 206 patients would be required for each arm of the study. All statistical tests used were 2-sided. SPSS version 10.0 for Windows software (SPSS, Inc, Chicago, Ill) was used for data analysis.

The main characteristics of the patients who participated in the study with respect to the prophylaxis group assigned are presented in Table 1. In total, 549 patients were evaluated and 418 patients were eligible and entered the protocol (Figure 1). The reasons for exclusion were emergency cholecystectomy (n = 44); patients who received antimicrobials 2 weeks prior to the operation, mainly because of cholecystitis (n = 37); cholecystectomy performed as a part of any other major operation (n = 26); prior allergy to cefuroxime or ampicillin-sulbactam (n = 19); colostomy (n = 2); inflammatory bowel disease (n = 2); and colonic diverticulosis (n = 1). All 418 eligible patients underwent elective cholecystectomy for cholelithiasis: 228 (54.5%) with the conventional and 190 (45.5%) with the laparoscopic method. The mean (SD) age of the entire group was 56.6 (13.7) years, 161 (38.5%) of 418 were male, and 217 (51.9%) were deemed high-risk patients (Table 1).

### RESULTS

**Table 1. Demographic Data of Patients Participating in the Study According to Randomization Group and Risk**

<table>
<thead>
<tr>
<th>Caracteristic</th>
<th>Whole Group (N = 418)</th>
<th>Cefuroxime (n = 207)</th>
<th>Ampicillin-Sulbactam (n = 211)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>56.6 (13.7)</td>
<td>57.5 (13.7)</td>
<td>55.8 (14.4)</td>
<td>.20</td>
</tr>
<tr>
<td>Soft tissue surgical site</td>
<td>19</td>
<td>18 (8.7)</td>
<td>1 (0.47)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Deep incisional SSI, No.</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>High risk (all with ASA score &gt;1)</td>
<td>217 (51.9)</td>
<td>114 (55.1)</td>
<td>103 (48.8)</td>
<td>.20</td>
</tr>
<tr>
<td>Age ≥70 y</td>
<td>124 (29.7)</td>
<td>64 (30.9)</td>
<td>60 (28.4)</td>
<td>.60</td>
</tr>
<tr>
<td>Obesity</td>
<td>106 (25.4)</td>
<td>58 (28)</td>
<td>48 (22.7)</td>
<td>.20</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>97 (23.2)</td>
<td>48 (23.2)</td>
<td>49 (23.2)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Acute cholecystitis within last 6 mo</td>
<td>26 (6.2)</td>
<td>13 (6.3)</td>
<td>13 (6.2)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Obstructive jaundice</td>
<td>20 (4.8)</td>
<td>12 (5.8)</td>
<td>8 (3.8)</td>
<td>.40</td>
</tr>
<tr>
<td>Open procedure</td>
<td>228 (54.5)</td>
<td>110 (53.1)</td>
<td>118 (55.9)</td>
<td>.60</td>
</tr>
<tr>
<td>Positive intraoperative culture results</td>
<td>116 (27.8)</td>
<td>60 (29)</td>
<td>56 (26.5)</td>
<td>.60</td>
</tr>
</tbody>
</table>

Abbreviations: ASA, American Society of Anesthesiologists; SSI, surgical site infection.

*Values are expressed as number (percentage) unless otherwise indicated.

†For between-group comparisons.
High-risk cases were homogeneously distributed between the 2 antimicrobial groups ($P = .20$). Examining the distribution of high-risk patients according to the procedure performed, it was found that 133 (58.3%) of 228 who underwent conventional cholecystectomy presented a high operative risk. Also, 84 (44.2%) of 190 who underwent laparoscopic cholecystectomy were deemed high risk ($P < .01$). The mean (SD) hospitalization was 6.7 (3.1) and 3 (0.7) days for conventional and laparoscopic cholecystectomy, respectively.

Cefuroxime was administered to 207 (49.5%) [ie, group A] of 418 patients, and 211 (50.5%) of 418 patients received ampicillin-sulbactam (ie, group B). A schematic diagram of the main findings of the study is depicted in Figure 2. Two patients developed a sterile wound collection and were not included in the analysis. Overall, 19 (4.5%) of 418 patients developed an SSI in both prophylaxis groups. Infection developed in 18 of 207 patients from group A and 1 of 211 from group B ($P < .001$). More specifically, 17 (97.3%) of 19 patients developed a soft tissue SSI, and 2 (1.7%) of 19 had a postoperative subhepatic abscess. Enterococcus species was the predominant organism and it was isolated in 15 (78.9%) of 19 patients, while E. coli and Klebsiella species followed. All 15 SSIs that were attributed to an Enterococcus species occurred in the cefuroxime prophylaxis group.

Fifteen (78.9%) of 19 patients who developed SSI were high risk. The main coexisting disease was diabetes mellitus in 14 (93.3%) of 15. Operative candidates with any condition carrying a higher operative risk developed postoperative SSI significantly more often ($P = .02$). This increased risk for SSI was particularly seen in patients with diabetes ($P < .001$) and obesity ($P < .01$). None of the 49 patients with diabetes from the ampicillin-sulbactam group vs 14 (29.2%) of 48 from the cefuroxime group had an infection ($P < .001$). In an analysis using ASA score of 3 or higher, such a score was found in 81 of 207 patients in the cefuroxime group vs 73 of 211 patients in the ampicillin-sulbactam group ($P = .36$) and in 13 of 19 patients with an SSI ($P = .006$). The presence of obstructive jaundice or an episode of acute cholecystitis within 2 months prior to operation was not associated with the development of an SSI postoperatively ($P = .20$ and $P = .60$, respectively). In a multivariate model that included age, diabetes, surgical technique, and type of antibiotic used, the use of ampicillin-sulbactam was significantly associated with protection against infection (OR, 0.04 [95% CI, 0.006-0.336]; $P = .003$), whereas the presence of diabetes was a significant predictor for the development of infection (OR, 12.9 [95% CI, 3.9-42.8]; $P < .001$).

The intraoperative culture samples showed a total of 192 positive results (either in the bile, the gallbladder mucosal wall, or in both) in 116 (27.8%) of 418 patients, mainly in the high-risk group ($n = 77$; $P < .01$). All 19 noted infections occurred in patients with bactibilia, while none occurred in patients without bactibilia ($P < .001$).
operative bactibilia was strongly associated with the development of an enterococcal SSI (P<.001). More than 1 isolate was seen in 17 (14.7%) of 116 patients, 13 of whom were of high surgical risk. The patients with positive intraoperative culture results were equally spread between the 2 groups (P=.60) (Table 1). Enterococcus species was isolated in 46 (39.7%) of 116 patients having positive intraoperative culture results. Among the latter, 23 of 46 received cefuroxime (group A) as prophylaxis and 15 (65.2%) of these 23 went on to develop an enterococcal SSI, while 23 (50%) of 46 patients received ampicillin-sulbactam (group B) and none developed a postoperative SSI. Two isolates from patients with bactibilia were identified as Enterococcus faecium, and 1 of them was vancomycin resistant. Nevertheless, these isolates were not associated with an SSI. The microorganisms isolated from the bile and mucosal wall intraoperative cultures were exactly the same as the ones recovered from wound or pus cultures in all patients who developed SSI.

Results of the study according to operative risk (high vs low), type of surgery performed, and development of SSI are presented in Figure 2. No statistical association between type of procedure performed and development of SSI was observed. As evident from Figure 2, open surgery was more frequently performed in high-risk patients compared with low-risk patients. In subgroup analyses, open surgery in high-risk patients who received cefuroxime was associated with development of an SSI (P=.01). Postoperative SSI after cefuroxime administration was found in 13 (72.2%) of 18 and 5 (27.7%) of 18 patients who underwent an open or a laparoscopic cholecystectomy, respectively. Among 190 patients who were operated on laparoscopically, 0 of 93 had an infection in the ampicillin-sulbactam group and 5 of 97, in the cefuroxime group. Three of these 5 patients had a soft tissue SSI and 2 of 5, a subhepatic abscess.

The mean (SD) operative time in all patients was 45.3 (15.5) minutes. Patients who developed a postoperative SSI had a significantly longer duration of operation (mean [SD], 78.9 [25.9] vs 43.7 [12.8] minutes; P<.01). Concerning technical difficulties during surgery, 52 (12.4%) of 418 patients had intraoperative gallbladder rupture (19 [8.3%] of 228 open procedures vs 33 [17.4%] of 190 laparoscopic procedures), mainly due to intense inflammation and adhesions found at the time of surgery. Bactibilia was noted in 228 open procedures vs 33 [17.4%] of 190 laparoscopic procedures). Among the latter, 23 of 46 received cefuroxime (group A) as prophylaxis and 15 (65.2%) of these 23 went on to develop an enterococcal SSI, while 23 (50%) of 46 patients received ampicillin-sulbactam (group B) and none developed a postoperative SSI. Two isolates from patients with bactibilia were identified as Enterococcus faecium, and 1 of them was vancomycin resistant. Nevertheless, these isolates were not associated with an SSI. The microorganisms isolated from the bile and mucosal wall intraoperative cultures were exactly the same as the ones recovered from wound or pus cultures in all patients who developed SSI.

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Table 2. SSIs According to Prophylaxis Group and Whether Bactibilia Was Present

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Cefuroxime</th>
<th>Ampicillin-Sulbactam</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Isolates in Bile and Mucosa</td>
<td>Isolates in Bile and Mucosa</td>
</tr>
<tr>
<td>Enterococcus species</td>
<td>24</td>
<td>15*</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>Klebsiella species</td>
<td>6</td>
<td>6†</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Citrobacter species</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Streptococcus species</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Staphylococcus species</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Bacteroides fragilis</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Enterobacter aerogenes</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Acinetobacter species</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Haemophilus alvei</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Candida species</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Patients</td>
<td>60</td>
<td>18</td>
</tr>
</tbody>
</table>

Abbreviation: SSI, surgical site infection.

*Two patients had deep incisional SSI (subhepatic) with enterococci.
†One patient had SSI with E coli and Klebsiella species at the same time.
‡One patient had SSI with Enterococcus species and E cloacae at the same time.

The main goal of this study was to present the benefits of using ampicillin-sulbactam instead of cefuroxime as chemoprophylaxis within an elective cholecystectomy setting. As evident from the results, ampicillin-sulbactam prophylaxis fared better compared with cefuroxime for the prevention of SSI after elective cholecystectomy. Not only did the vast majority of infections occur in the cefuroxime group, but also the main pathogen involved was Enterococcus species. Abscess was treated with reoperation, complete evacuation of the intra-abdominal purulence, drainage, and administration of antibiotics. No antibiotics were administered postoperatively in any of the other patients in the study. No postoperative death occurred.

COMMENT

The main goal of this study was to present the benefits of using ampicillin-sulbactam instead of cefuroxime as chemoprophylaxis within an elective cholecystectomy setting. As evident from the results, ampicillin-sulbactam prophylaxis fared better compared with cefuroxime for the prevention of SSI after elective cholecystectomy. Not only did the vast majority of infections occur in the cefuroxime group, but also the main pathogen involved was Enterococcus species. Abscess was treated with reoperation, complete evacuation of the intra-abdominal purulence, drainage, and administration of antibiotics. No antibiotics were administered postoperatively in any of the other patients in the study. No postoperative death occurred.
We were not able to find any similar randomized study analyzing in a systematic fashion the effect of an appropriate prophylactic regimen against enterococci in the development of SSI after elective cholecystectomy. A study that assessed cefazolin sodium vs piperacillin in open cholecystectomy found a better in vivo activity of piperacillin in comparison with cefazolin against bacterial isolates recovered from bile cultures. However, only 5 of 34 isolates from biliary cultures were identified as enterococci, and only 1 mixed infection with Enterococcus species and 3 other gram-negative pathogens were observed in the piperacillin group. One other study of 80 patients found equal efficacy between ampicillin-sulbactam and cefoxitin sodium as prophylaxis in biliary surgery. Our results contradict those of a small study that compared the use of 3 instead of 1 perioperative doses of amoxicillin-clavulenate potassium (a combination similar to the one used in the present study) to 1 dose of cefibuten and found more infections in the group that received amoxicillin-clavulenate potassium. Another study that looked at 205 patients with upper abdominal surgery (including biliary operations) found no statistical differences in wound infections between amoxicillin-clavulenate potassium and cefotaxime sodium, a third-generation cephalosporin. Nevertheless, this study may have been underpowered since fewer wound infections occurred in the amoxicillin-clavulenate potassium group (4.5% vs 7.4%).

The discovery of bactibilia in the present study was associated with subsequent development of SSI. When SSI occurred, it was caused mainly by exactly the same pathogen(s) found in intraoperative cultures. This is an issue for further research as our findings concur with previous findings but exactly the opposite has been reported by others. Bactibilia was noted in a significant fraction of the patient population, mainly in those with a high risk for infection. A large percentage of patients had positive intraoperative culture results for Enterococcus species. This finding confirms the role of enterococci on biliary tract infections and provides further rationale for administering antimicrobials with antienterococcal activity in cholecystectomies. Enterococcus faecium, a species that frequently exhibits resistance to β-lactams, was very rarely isolated in our series and was not associated with any SSI.

Contaminated bile can lead to pyogenic fluid collection if the gallbladder ruptures during the operation. Survival depends on the ultimate management of such a collection. Perforation during gallbladder surgery is attributed to traction, grasping, dissection, and removal of the gallbladder and occurs in 10% to 15% of conventional and 15% to 25% of laparoscopic cholecystectomies. The vast majority of SSI occurred in patients who experienced intraoperative gallbladder rupture. The rest occurred in high-risk patients with diabetes mellitus. This is likely not attributed to poor surgical technique, since it was exclusively noted in patients who received cefuroxime. On top of appropriate surgical technique, perioperative prophylactic antimicrobials seem to play a significant role, and if administered, fewer SSIs occur. In contrast, some authors support that the incidence of SSI is not altered by gallbladder rupture, if thereafter a clean surgical technique is applied. Several studies performed so far examining antimicrobial prophylaxis in elective cholecystectomy have given conflicting results. Antibiotic prophylaxis may not be warranted in low-risk patients undergoing laparoscopic cholecystectomy. Nevertheless, large studies seem to suggest that neither laparoscopic nor open cholecystectomy should be performed without adequate perioperative antimicrobial prophylaxis. The role of prophylaxis may be more important in high-risk patients. Approximately half of the population that participated in the present study was classified as high risk and carried a higher risk for infection. Postoperative SSI in the majority occurred in such high-risk patients. The large percentage of high-risk patients included in the study facilitated documenting a differential effect of therapy and could have biased our results toward a beneficial effect of prophylaxis. On the other hand, both patients who developed a subhepatic abscess and required reoperation were of low operative risk, emphasizing that SSI may occur in low-risk patients too.

The current study is strengthened by an unusually high percentage of follow-up. In fact, all patients were contacted about the follow-up appointment in the surgical department to avoid follow-up loss. During this conversation, the patients were specifically asked for symptoms or signs of SSI in order not to miss such an event. On the other hand, the study is limited by its lack of stratification of patients according to type of operation and risk at the beginning of the study and the high incidence of enterococci noted in this cohort. This could be attributed to (1) the large increase in the incidence of enterococcal infections in general (now the third most common cause for bacteremia in the United States), (2) a rising incidence of enterococcal infections in Greece, especially in the nosocomial setting, and (3) the fact that about a quarter of the patients underwent an open procedure and were high risk, and thus, they were more prone to colonization with enterococcus. The current results only confirm the protective role of ampicillin-sulbactam in a setting where there is a high prevalence of enterococcus. The biliary tract can serve as a “leverage-point” environment for such a study. However, in a prophylactic setting, the most important parameter may be the detailed knowledge regarding the microbiological characteristics of the area of concern and the institution’s antibiogram. The use of prophylaxis should be based on these results. In addition, several other regimens containing agents with antienterococcal activity (eg, piperacillin-tazobactam) may provide similar results.

The high rates of open procedures observed have to do with the individual surgeon’s choices after obtaining the written informed consent of the patient. The procedure followed (ie, open or laparoscopic surgery) was the one that the participating surgeon chose and not one enforced by the research team. Nevertheless, it is exactly this population that would benefit the most from the prophylactic regimen proposed, especially if the incidence of enterococcal infections is higher. Moreover, we believe that the inclusion of open procedures is an additional strength of this article.

In conclusion, evidence that ampicillin-sulbactam may be a better regimen than cefuroxime for antimicrobial prophylaxis during routine elective—either conventional or...


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