Original article

Cefepime for prophylaxis of infections in the surgery of cholelithiasis. Results of a multicentric comparative trial

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Abstract. A multicenter, open labelled, randomized study was carried out to compare the prophylactic efficacy of Cefepime and Ceftriaxone in patients undergoing biliary tract surgery. Two hundred and nine patients were included in the study and randomized to receive preoperative infusion of 2 g Cefepime (n=107) or 2 g Ceftriaxone (n=102) both in a single i.v. administration. Antimicrobial prophylaxis was successful in preventing infections in 98.9% of patients in the Cefepime group and 97.7% in the Ceftriaxone group (p=0.3871). Both regimens were well tolerated without any adverse drug-related reactions. A single dose of Cefepime seems to be a very useful alternative to other regimens for antibiotic prophylaxis of postoperative infectious complications in the elective surgical treatment of cholelithiasis. (www.actabiomedica.it)

Key words: Antimicrobial prophylaxis, biliary tract surgery, cholecystectomy, Cefepime, Ceftriaxone

Introduction

Among the clinical manifestations of symptomatic cholelithiasis, biliary colic is by far the most frequent. This is caused by chronic inflammation of the gallbladder, associated with and caused by the presence of gallstones. Surgery represents the elective treatment of cholecystitis due to gallstones. In recent years, this is performed through laparoscopic or minilaparotomic techniques whenever possible, although surgeons may still need to choose open cholecystectomy for patients with complicated gallstone disease, such as cases of delayed treatment of acute cholecystitis or chronic recurrent cholecystitis (1-5).

A substantial reduction of morbidity and mortality associated with surgical treatment of gallstone disease is routinely obtained through the use of elective antibiotic prophylaxis of surgical infections (6). Prophylaxis also contributes to reduce costs related to the length of hospitalisation. Appropriate regimens of antibiotic prophylaxis should offer a good protection against the most common pathogens causing surgical wound infections, while preserving the resident bowel flora. Drugs of choice should therefore be able to reach active concentration at the site of surgery for a sufficient length of time. Ceftriaxone has been long considered the drug of reference for prophylaxis of infections in biliary surgery, because of its wide antibacterial spectrum, its long half-life (8 hours), its favourable tissue distribution and its biliary metabolism (7-9). Cefepime is a fourth generation cephalosporin, with a modified zwitterionic structure which allows for a more favourable penetration in the bacterial wall, a higher affinity for its molecular target (PBP3), and a reduced susceptibility to beta-lactamases. Previous studies compared its efficacy with that of gentamicin and mezlocillin in the treatment of acute cholecystitis associated with gallstones; the

overall profile of this agent turned out to be favourable in terms of treatment, duration, costs, and renal toxicity (10-14).

This study was carried out to compare single preoperative infusions of a fourth-generation cephalosporin, Cefepime, and Ceftriaxone, as prophylactic agents in patients undergoing elective biliary tract surgery.

Materials and methods

We carried out a randomized, comparative, multi-center study designed to compare the efficacy and safety of a prophylactic treatment of Cefepime and Ceftriaxone in patients undergoing biliary tract surgery. Two hundred and nine patients (>18 yrs. old) were enrolled in the study, with indication of surgical treatment of symptomatic cholelithiasis. All patients provided informed consent the after approval of the local ethical committees.

Primary endpoint of this study was the evaluation of the efficacy of antibiotic prophylaxis for infections related to biliary tract surgery as assessed by a clinical evaluation at the "test-of-cure" visit, 4 to 6 weeks after surgery.

Secondary endpoints were evaluation of safety of the prophylactic regimens under comparison, as well as microbiological evaluation of possible failures, through identification of causative pathogens.

Patients were not considered for enrollment (Exclusion criteria - Table 1) if they showed an acute cholecystitis (as indicated by biliary colic, fever and WBC > 12.000/mmc), emergency surgery, co-existence of gastrointestinal, biliary or other neoplasia, jaundice, liver abscesses, chronic inflammatory bowel diseases, renal insufficiency, cystic fibrosis, immune disorders, HIV infection, pregnancy, known history of hypersensitivity to beta-lactams, or administration of any other antibiotic within the 15 days preceding surgery and/or at the time of surgery.

Table 1. Exclusion criteria

- Clinical and/or laboratory evidence of acute cholecystitis and/or biliary tract infection;
- administration of any other antibiotic within the 15 days preceding surgery and/or at the time of surgery;
- emergency surgery of biliary tract diseases;
- gastrointestinal, biliary or any other neoplasia;
- jaundice and/or liver abscesses;
- known history of hypersensitivity to beta-lactams;
- chronic inflammatory bowel diseases, renal insufficiency, cystic fibrosis, immune disorders, HIV infection, pregnancy.

Randomisation to the 2 study arms was 1:1. Patients assigned to either arm received 2g i.v. of antibiotic 1 hour before surgery.

Patients were evaluated before surgery (visit 1), on the same day as surgery (treatment visit), 3 to 7 days after surgery (visit 2: phone interviewing at this time was accepted in alternative), and 4 to 6 weeks after surgery (visit 3 or "test-of-cure" visit).

The clinical outcome was defined as one of the following:

Success (at visit 3): absence of any sign of infection both in the abdomen and at the surgical wound(s) site;

Failure (at visit 2 or 3): presence of infection(s) of surgical wound(s) and/or abdomen, including abscesses or peritonitis, or use of any antibiotic for any reason in the 4 weeks after surgery, or any drainage procedure performed at surgery site(s);

Not valuable (at visit 2 or 3): whenever clinical outcome could not be clearly defined.

Statistical analysis

The aim of the study was to compare the clinical and bacteriological efficacy of 2 different antibacterial agents, both administered once, 1 hour before surgery, for elective biliary tract surgery (laparoscopic, minilaparotomic or laparotomic cholecystectomy). The expected clinical success rate for ceftriaxone (based on previously published studies) was 95% for valuable patients. Therefore, based on an assumption of equivalence between the 2 drugs under comparison, the clinical success rate for cefepime should not be inferior to 90% (α 2 code = 0.05; β = 0.90). Data were analysed by the Chi-square test.

Results

A total of 209 adult patients who were scheduled to undergo elective biliary tract surgery were enrolled

and randomized to receive cefepime (group A, 107 patients) and ceftriaxone (group B, 102 patients). Mean age at entry was 54 years in group A (range 21-88 years; SD = 15.1), whereas it was 53.1 years in group B (range 22-86 years; SD = 14.1). Seventy-five females (70.1%) were enrolled in group A and 70 (68.6%) were enrolled in group B, and patients of Caucasian descent were 103 (98%) in group A and 100 (98%) in group B. Eighty four patients (41 in group A and 43 in group B) received non-antibiotic concomitant treatments for chronic non-infective diseases (Table 2). Thirty patients underwent laparotomic surgery, while 179 underwent less invasive procedures (149 laparoscopic and 30 minilaparotomic) (Table 3).

At visit 2 one patient presented a wet, non infected wound. At visit 3, 1 failure was observed in group A and 2 were observed in group B. Eight cases were scored as non valuable since they were lost at follow-up. Clinical success rates were 98.9% and 97.7% in group A and B respectively, without any significant difference (p = 0.3871). No adverse drug reaction was observed in both groups.

Table 2. Epidemiological features of patients

	Number (%) of patients	
	Cefepime (group A)	Ceftriaxone (group B)
Age (years)		
Mean	54	53.1
Range	21-88	22-86
Sex		
Males	32 (29.9)	32 (31.4)
Females	75 (70.1)	70 (68.6)
Caucasian descent	103 (98)	100 (98)
Concomitant non antibiotic tx	41 (38.3)	43 (42.2)

Table 3. Surgical techniques

	Number of surgical techniques in all patients
Laparatomic cholecystectomy	30
Miniinvasive cholecystectomy	
Minilaparotomic	30
Laparoscopic	149

Discussion

An overall 5 to 20% risk of infections related to laparotomic cholecystectomy has been reported (15-16). Antibiotic prophylaxis is proved to be effective in reducing such a relevant burden, and a more clear-cut benefit has been documented for high-risk patients, such as those with acute cholecystitis, biliary tract obstruction, age > 70 years, or with diabetes (17). In recent years, the advent of less invasive and less infection-prone surgical techniques, such as elective laparoscopic cholecystectomy, raised the issue as to whether systemic antibiotic prophylaxis may still be cost-effective (18). A meta-analysis of recently published series showed that antibiotic prophylaxis was not relevant in reducing surgery-related infections for elective laparoscopic cholecystectomy (19); the authors, however, could not find any factor that were clearly predictive of postoperative complications and/or of the need for intraoperative shifting to more invasive surgical procedures (19). Lippert et al. evaluated 4.477 patients enrolled in a prospective multicentric trial for laparotomic (1.349 pts) or laparoscopic (3.128 pts) cholecystectomy. They observed surgery-related infections in 0.8% of patients undergoing any prophylactic regimen and in 4.6% of patients without prophylaxis, concluding that no cholecystectomy should be performed without antibacterial prophylaxis, in order to optimise length of hospitalisation and overall costs (20).

Our trial was aimed to evaluate the efficacy of a single dose of cefepime for antibiotic prophylaxis, in comparison with the present "gold standard" for biliary tract surgery, which is a single dose of ceftriaxone. Cefepime is the first molecule that ushered the fourth generation of cephalosporins; its advantages in terms of antibacterial spectrum and pharmacokynetics have been clearly elucidated (21). Its chemical structure is characterised by the presence of quaternary nitrogen, whose positive charge in the third position of the beta-lactamic ring is associated with a negative charge in the fourth position. It is therefore a dipolar molecule, with the ability to penetrate more rapidly through the outer membrane of gram negative bacteria, when compared with third generation cephalosporins. This grants a higher level of stability

against type 1 beta-lactamases (21-28). Its high binding affinity to the Penicillin Binding Protein (PBP) 3 and 1 of *Escherichia Coli* and *Pseudomonas Aeruginosa* allows strong inhibition of bacterial growth (21-28). In comparison with other cephalosporins, it also shows a higher binding affinity for PBP2. In vitro its efficacy has been documented on gram positive bacteria, including many strains of *Streptococcus* spp. as well as methicillin sensitive *Staphilococci,* and gram negative bacteria such as *Pseudomonas aeruginosa* and *Escherichia cloacae (*26). Other relevant features of this molecule include dosage linearity, lack of accumulation, renal elimination, and a low grade of binding to seric proteins (21-28). Its seric half life is around 2 hours, allowing two daily doses. Therapeutic concentrations of cefepime have been documented in interstitial and peritoneal fluids, lung tissues, appendix, and bile (28).

In our experience, the incidence of postoperative infections was comparable in both study arms and was overall very low, without significant differences at the statistical analysis of results ($p = 0.38$). Neither serious adverse events nor hypersensitivity reactions were observed.

Our results indicate that a single i.v. 2 gram dose of cefepime, administered one hour before of elective surgery, is as effective as a single 2 gram dose of ceftriaxone in preventing postoperative infections of both biliary tract and surgical wounds, and is also well tolerated. These results also lend support to the view that the use of antibiotic prophylaxis maintains its cost-effectiveness even for less invasive surgical procedures of the biliary tract since of the cost of a single dose of antibiotic administered surgery is lower than that of a long treatment for a post-surgery infection.

A recent article (29) in a once daily cefepime versus ceftriaxone administration for nursing home acquired pneumonia showed that mean antibiotic costs were 117 ± 40 dollars for cefepime and 215 ± 68 dollars for ceftriaxone-treated patients ($p < 0.001$).

In conclusion, cefepime represents a valid option for single dose prophylaxis of postoperative infectious complications of the elective surgical treatment of cholelithiasis.

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