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Original Article

Efficacy and Safety of Intravenous Single-agent Antibiotics - Cefoperazone/Sulbactam in Non-critically Ill Surgical Patients with Intra-abdominal and Soft Tissue Bacterial Infection

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Abstract

Purpose: **To evaluate the efficacy and safety of intravenous single-agent antibiotic Cefoperazone/Sulbactam for the treatment of bacterial infection among surgical patients.**

Methods: **This prospective opened non-comparative clinical trial was conducted in the Department of Surgery, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand from 1October 2008 to 30 September 2009. Therapeutic Cefoperazone/Sulbactam (Sulcef®) at the dose of 1.5 grams was given intravenously every 12 hours to patients with bacterial infection who needed emergency or elective surgical interventions, and the APACHE II score was equal or less than 15. All patients were scheduled for follow-up visits at 7, 14 and 30 days after the first dose of intravenous Cefoperazone/Sulbactam for monitoring the clinical outcomes.**

Results: **Thirty-five patients were enrolled and 31 patients had completed the follow up. There were 17 males and 14 females with the mean age of 53 years (range 20-85 years). The clinical efficacy of Cefoperazone/Sulbactam to improve or cure patients was 87%, whereas the bacterial eradication rate was 84%. Neither drug-related serious adverse reaction nor drug allergy was observed.**

Conclusions: **Cefoperazone/Sulbactam demonstrated broad-spectrum antibacterial coverage in patients infected with gram-positive, gram-negative and anaerobic bacteria. Intravenous Cefoperazone/Sulbactam is safe and effective for empirical treatment of bacterial infection among surgical patients.**

Keywords: **Antibiotics, monotherapy, surgical infection, intra-abdominal infection, skin and soft tissue infection**

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Introduction

Surgical infection (SI), such as skin and soft tissue infection and intra-abdominal infection, is a common problem in surgical practice. It is significantly associated with high morbidity and mortality. Empirically antimicrobial therapy in conjunction with appropriate surgery is considered the principle of management of SI[1].

Effective empiric antibiotics should have broad-spectrum antibacterial activity against common pathogens specific to each organ. Inappropriate treatment of bacterial infection may lead to high costs and even death. Antimicrobial resistance has been dramatically increasing, especially among gram-negative bacteria, which is commonly resistant to beta-lactam antibiotics.

Briefly, the mechanism of beta-lactam antibiotic resistance could occur through the bacterial production of beta-lactamases that lead to amide bond destruction. Thus, the beta-lactam ring is disrupted and unable to bind with penicillin-binding proteins. This process leads to neutralization of bactericidal effects. To overcome this problem, the beta-lactamase inhibitors are added into beta-lactam antibiotics. The beta-lactamase inhibitors permanently bind to the beta-lactamase at the active site of serine hydroxyl group[1-2].

The combination of beta-lactam antibiotics and beta-lactamase inhibitors, also called beta-lactam/beta-lactamase inhibitors (BLBI) have been used as a single agent or monotherapy for both prophylactic and therapeutic purposes[3-4]. Well-known examples of such agents include amoxicillin/clavulanate and cefoperazone/sulbactam. These combinations also enhance the bactericidal activity against both gram-positive and gram-negative bacteria.

The spectrum of BLBIs may cover gram-positive bacteria such as *Staphylococcus aureus, Staphylococcus epidermidis* and *Staphylococcus pyogenes*, and may cover gram-negative bacteria such as *Haemophilus influenza*, *Escherichia coli*, *Proteus* spp., *Citrobacter* spp., Serratia spp., *Enterobacter* spp., *Neisseria gonorrhoeae*, *Neisseria meningitidis* and *Acinetobacter* spp. In addition, BLBIs also cover anaerobic bacteria such as *Bacteroides fragilis*, *Fusobacterium* spp. and *Eubacterium* spp.[3-8]

BLBIs commonly have a half-life of 1-2 hours on average. They effectively distribute into various organs and body fluids, including the gallbladder, bile, skin, uterus and ovary[9-10].

At present, various regimens of monotherapy and combined therapy of antibiotics have been used as empiric treatment of SI. Combined therapy such as Ceftriaxone and Metronidazole has been commonly used as the first line empiric agents for mixed aerobic and anaerobic bacterial infection. However, in a setting where lack of nursing staff and huge ward workload is a major issue, monotherapy may be more favorable than a combined regimen.

One of the most widely used monotherapy regimen for the treatment of SI includes BLBI such as Cefoperazone/Sulbactam. Excellent efficacy and safety of intravenous Cefoperazone/Sulbactam for the treatment of SI has been reported in the literature[11-12]. However, these studies were mainly conducted in the western population, whose pharmacokinetics and pharmacodynamics could be different from those of Thai patients. Also, bacterial susceptibility to various antibiotics could be different in different settings as well. The aim of the present study was to evaluate the efficacy and safety of intravenous Cefoperazone/Sulbactam for the treatment of SI in Thai patients.

Material and Methods

After obtaining ethical approval from the Institutional Review Board, a prospective opened non-comparative clinical trail was conducted in the Department of Surgery, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand from 1 October 2008 to 30 September 2009. Patients were enrolled with the following inclusion criteria: age over 18 years, having intra-abdominal infection or skin and soft tissue infection which required intravenous antibiotics with or without surgical interventions, and the APACHE II score was at most 15. Patients were excluded by any one of the following criteria: previous history of hypersensitivity or allergy to penicillin, cephalosporins or their derivatives; pregnancy; lactation; renal insufficiency; hepatic impairment; and refusal to participate.

All patients received empiric intravenous Cefoperazone/Sulbactam (Sulcef®, Siam Pharmaceutical, Thailand) at the dose of 1.5 grams administered every 12 hours for at least 5 days with therapeutic intention. Collection of blood, pus, discharge and

Table 1 Demographic data, diagnosis, and treatment

Data	Number (%); n = 31
Sex	
Male	17 (54.8)
Female	14 (45.2)
Age (mean ± SD)	52.9 ± 19.1
APACHE II Score (mean ± SD)	6.3 ± 3.9
Co-morbidity	17 (54.8)
Diabetes mellitus	8(25.8)
Hypertension	10 (32.3)
Dyslipidemia	2 (6.5)
Gouty arthritis	1 (3.2)
Hepatitis	1 (3.2)
Parkinsonism	1 (3.2)
Cerebrovascular disease	1 (3.2)
Ischemic heart disease	1 (3.2)
Diagnosis	
Skin and soft tissue infection	6 (19.4)
Necrotizing fasciitis	4 (12.9)
Ischiorectal abscess	2 (6.5)
Intra-abdominal infection	25 (80.6)
Bowel gangrene or perforation	9 (29.0)
Ruptured appendicitis and appendiceal abscess	6 (19.4)
Acute cholangitis	4 (12.9)
Acute colonic diverticulitis	3 (9.7)
Others	3 (9.7)
Treatment modalities	
Operations	26 (83.9)
Celiotomy and bowel resection	7 (22.6)
Appendectomy	4 (12.9)
Percutaneous drainage	4 (12.9)
Soft tissue debridement	3 (9.7)
Biliary drainage / ERCP	3 (9.7)
Colectomy	2 (6.5)
Cholecystectomy	1 (3.2)
Ileostomy	1 (3.2)
No operation	5 (16.1)

SD: standard deviation; ERCP: endoscopic retrograde cholangiopancreatography

necrotic tissue were carried out for bacterial culture and susceptibility test as needed. Patients underwent surgical intervention such as incision and drainage or intra-abdominal operations as appropriate. The choice of operative procedures depended on the diagnosis and intraoperative findings. Additional oral antibiotics such as oral BLBIs or oral cephalosporin plus metronidazole were prescribed to patients as switched therapy if indicated. Patients were discharged from the hospital if they had no fever, normal bowel function, good ambulation and no signs of infection. All patients were scheduled for follow-up examinations at 7, 14 and 30 days postoperatively for monitoring the outcomes.

Results

This prospective opened non-comparative clinical study was conducted on a series of 35 patients with American Society of Anesthesiology (ASA) status I-III. Of the 35 patients, 31 completed the study. Four patients were excluded from the study by the exclusion criteria. There were 17 males (55%) and 14 females (45%) aged between 20 to 85 years (mean 52.9 years,

Table 2 Outcomes

Data	Number (%) ; n = 31
Clinical improvement	
Cure/Improvement	27 (87.1)
Failure	4 (12.9)
Adverse reactions	11 (35.5)
Anorexia	8 (25.8)
Nausea	8 (25.8)
Vomiting	7 (22.6)
Diarrhea	3 (9.7)
Constipation	3 (9.7)

Table 3 Microbiology

Data	Number (%); n = 31
Microbiology	
Positive culture by site	17 (54.8)
Blood	4 (12.9)
Abdominal pus/ discharge	9 (29)
Skin and soft tissue	2 (6.5)
Central line	1 (3.2)
Intra-articular fluid	1 (3.2)
Positive culture by species	22 (71)
Enterabacter cloacae	1/22 (4.5)
Group C *streptococci*	1/22 (4.5)
Alpha-hemolytic *streptococci*	2/22 (9)
Methicillin-susceptible *S. aureus*	3/22 (13.6)
E. coli ESBL negative	6/22 (27.3)
E. coli ESBL positive	4/22 (18.2)
Salmonella sp.	1/22 (4.5)
Enterococcus faecalis	1/22 (4.5)
Klebsiella pneunoniae	3/22 (13.6)

ESBL: extended spectrum beta-lactamase

standard deviation (sd), 19.1 years). Seventeen patients (54.8%) had any of the following underlying diseases: diabetes mellitus, hypertension, dyslipidemia, gouty arthritis, hepatitis, Parkinsonism, cerebrovascular disease and ischemic heart disease. The mean APACHE II score was 6.3 (sd 3.9). Diagnosis, treatment, and surgical procedures in these patients are shown in Table 1. The clinical efficacy of Cefoperazone/Sulbactam to improve or cure patients was 87% (27/31), whereas bacterial eradication rate was 84% (26/31). All four patients who failed to be treated by Cefoperazone/Sulbactam had at least one of the comorbidities. No specific disease, surgical intervention, or type of bacteria was clearly responsible for treatment failure. The majority of positive bacterial culture was found from abdominal pus or discharge (9/31, 29%). *Escherichia coli* was the predominant bacteria among positive cultures (10/22, 45.5%). Interestingly, Escherichia coli with positive extended spectrum beta-lactamase (ESBL) was found in 18.2% (4/22) of specimens. Neither drug-related serious adverse reaction nor drug allergy was observed.

Discussion

Li Jia-tai et al. (1997) has studied the efficacy and safety of Cefoperazone/Sulbactam in the treatment of bacterial infection in 235 patients compared with cefotaxime[13]. The efficacy rate of Cefoperazone/Sulbactam was 95% compared with 90% of cefotaxime ($p = 0.186$). The bacterial eradication rate of Cefoperazone/Sulbactam and cefotaxime was 85% and 81% respectively ($p = 0.467$). Both regimens showed no significant difference in terms of adverse events (7.8% vs 8.7%, $p = 0.813$). These adverse reactions included skin rash, nausea, vomiting, thrombophlebitis, rising liver enzymes including alanine aminotransferase, alkaline phosphatase and aspartate aminotransferase. Engin and colleagues (1991) also demonstrated the efficacy and safety of cefoperzone/sulbactam in surgical infection and found the clinical cure rate to be 91% even though they reported a case of drug intolerance with rising glutamic oxaloacetic transaminase, glutamic pyruvic transa-minase, alkaline phosphatase, as well as prolonged bleeding time[14]. Jauregui and colleagues (1990) reported the efficacy of Cefoperazone/Sulbactam compared with that of gentamicin plus clindamycin in 152 patients with intra-abdominal infection[15]. Cefoperazone/Sulbactam had 86.8% cure rate whereas gentamicin plus clindamycin had only 61.8% cure rate ($p < 0.006$). This study, therefore, confirmed the better efficacy of Cefoperazone/Sulbactam in the treatment of intra-abdominal infection.

In the present study, the bacterial eradication rate of 84%, with clinical efficacy of 87% supported the effectiveness of this antimicrobial regimen. This result seemed to be comparable to those of previous studies. In the present study, a high incidence of postoperative anorexia, nausea and vomiting was found (25.8%, 25.8% and 22.6% respectively) within the first 24 hours. These events could have been side effects of general anesthesia as well as those of narcotics used for postoperative pain control. However, these events

were only temporary, and were dramatically improved after 24 hours. Symptomatic treatment using antiemetic agents such as intravenous metoclopramide or ondansetron was sufficient for most patients. Diarrhea and constipation both occurred in 14.3% of patients within the first 48 hours, and could be either true adverse drug reactions or normal early postoperative events. They also disappeared after 72 hours. No drug-induced hypersensitivity syndrome or serious adverse reaction was seen in the present study.

Intravenous Cefoperazone/Sulbactam as a single antimicrobial agent is more convenient to use compared to the commonly used combination of ceftriaxone and metronidazole. However, the surgeon should be aware of adverse drug reactions. Careful medical history should be taken to determine if the patient has had any previous allergy symptoms such as urticaria, pruritus, angioedema, bronchospasm, hypotension or arrhythmia, especially previous serious adverse drug reaction (e.g., drug-induced hypersensitivity syndrome, drug fever, or toxic epidermal necrolysis)[8].

Conclusion

The present study demonstrated the broad-spectrum antibacterial coverage of Cefoperazone/Sulbactam in Thai patients infected with gram-positive, gram-negative and anaerobic bacteria. Parenteral Cefoperazone/Sulbactam is a safe and effective single agent antibiotic for the treatment surgical infection in Thai patients.

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