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Original Article

Efficacy of imipenem/cilastatin in the treatment of patients with severe infection in the emergency department and its effect on PCT and CRP

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Abstract: Objective: To investigate the efficacy of imipenem/cilastatin on severe infection in the emergency department and its impact on procalcitonin (PCT) and C-reactive protein (CRP). Methods: A total of 108 cases of severe infection in the emergency department were randomly divided into the research group (n = 54) and the control group (n = 54). Patients in the control group were treated with ceftriaxone, and patients in the research group were treated with imipenem/cilastatin. The clinical efficacy, infection control time, bacterial clearance rate, changes in serum PCT (procalcitonin) and CRP (C-reactive protein) levels before and after treatment, and the incidence of adverse reactions were compared between the two groups. Results: The total effective rate of the research group was significantly higher than that of the control group ($P < 0.05$). The infection control time of the research group was significantly shorter than that of the control group, and the bacterial clearance rate of the research group was significantly higher than that of the control group (all $P < 0.05$). After treatment, the serum PCT and CRP levels were significantly lower in both groups than those before treatment, and were lower in the research group than in the control group (all $P < 0.001$); there was no significant difference in the incidence rate of adverse reactions between the two groups during treatment ($P > 0.05$). Conclusion: Imipenem/cilastatin can significantly improve bacterial clearance rate, reduce inflammatory reaction, improve the symptoms of infection, and produce less adverse reactions in patients with severe infection in the emergency department, which is of great value for clinical application.

Keywords: Imipenem/cilastatin, severe infection, bacterial clearance rate, procalcitonin, C-reactive protein

Introduction

Severe infection refers to the massive reproduction of various invading pathogenic microorganisms in the body, further causing systemic inflammatory response syndrome, sepsis, septic shock, septicemia, and even multiple organ dysfunction syndrome. It is a common disease in the emergency department, and develops rapidly. Most of the patients developing such disease are critically ill, thus it is relatively difficult to treat [1, 2]. In recent years, more and more bacteria have developed drug resistance due to the irrational use of antibiotics, increasing the difficulty in the treatment of severe infections [3]. Third-generation cephalosporins are the first choice for the treatment of severe infections in clinics. However, with the emergence of bacterial mutation and resistance, their clinical anti-infective effect is usually affected to some extent [4].

Imipenem/cilastatin is a carbapenem antibacterial compound composed of imipenem and cilastatin in a ratio of 1:1, which releases bacterial endotoxins that can bind to penicillin-binding proteins (PBPs), and in turn hinder the synthesis of mucopeptides of bacterial cell walls to exert an antibacterial effect [5]. It has a broad spectrum of antimicrobial activity, and is a potent antibiotic with long-lasting post-antibiotic effect [6]. However, many pathogenic bacteria can cause severe infections, and relevant results are not consistent. Therefore, we analyzed common pathogenic bacteria causing severe infection in the emergency department, and measured the bacterial clearance rate of imipenem/cilastatin. In addition, we also observed the effect of imipenem/cilastatin on serum procalcitonin (PCT) and C-reactive protein (CRP) levels in the patients. The results are reported as follows.

Materials and methods

General data

A prospective study was conducted on 108 patients with severe infection in the emergency department who received treatment in Weihai Municipal Hospital from January 2019 to February 2020. The patients were randomly divided into the research group and the control group, with 54 cases in each group. This study was reviewed and approved by the Medical Ethics Committee of Weihai Municipal Hospital.

Inclusion criteria: Patients aged between 18-75 years old; patients met the diagnostic criteria for severe infection in the *Internal Medicine* (8th Edition), which is defined as body temperature >38°C, white blood cells (WBC) count >12*10^9/L or WBC count <4*10^9/L, and blood pressure <90/60 mmHg [7]; patients had complete clinical data and signed informed consent.

Exclusion criteria: Patients with acquired immune deficiency syndrome (AIDS), severe mental illness, and malignant tumor; patients with organic lesions or impairment of the heart, liver, kidney and other important organs; patients allergic to penicillin or cephalosporins; patients during pregnancy or lactation; patients involved in other research projects at the same time.

Methods

Patients in the control group were treated with ceftriaxone sodium for injection (Sichuan Pharmaceutical Preparation Co., Ltd., China, specification: calculated based on C18H18N8O7S3, 2.0 g) by intravenous drip, 2.0 g/time, twice daily.

Patients in the research group were treated with imipenem/cilastatin sodium for injection (Shenzhen Haibin Pharmaceutical Co., Ltd., China, specification: 2.0 g, 1.0 g of C12H17N3O4S and C16H26N2O5S each) by intravenous drip, 2.0 g/time, 3 times/day. Both groups were continuously treated for 7 days.

Outcome measures

Primary outcome measures: Clinical efficacy was evaluated according to the *Guidelines for the Clinical Application of Antimicrobial Drugs*: cured: fever and other clinical symptoms and signs completely disappeared, and laboratory biochemical indicators and pathogen testing were normal; markedly effective: 2 of the above 4 examination items did not return to normal; effective: 1 of the above 4 examination items did not return to normal; ineffective: the patients' condition did not improve, or even aggravated [8]. Total effective rate = (number of cured + markedly effective + effective)/total case number * 100%.

Before and after treatment, about 5 mL of venous blood was drawn from the patients, and centrifuged after coagulation. Then the serum was separated to detect PCT (procalcitonin) and CRP (C-reactive protein) levels using enzyme-linked immunosorbent assay. The test kits were provided by Shanghai Enzyme-linked Biotechnology Co., Ltd., (China, cat. nos. ml2-25323 and ml057570).

Secondary outcome measures: The infection control time, starting from fever subsidence to the time without recurrence of the disease, was recorded in both groups.

The bacterial clearance rate of the two groups was calculated according to bacterial culture results before and after treatment, and the microbiological evaluation criteria were divided into five grades: complete clearance, partial clearance, no clearance, replacement, and reinfection [9]. Bacterial clearance rate = (number of complete clearance + partial clearance)/total strains before treatment * 100%.

During treatment, adverse reactions of the patients were recorded in the two groups, such as nausea, diarrhea, vomiting, pain at the injection site, headache or dizziness.

Statistical analysis

SPSS 20.0 software was used for statistical analysis of the data. Enumeration data were expressed as the number of cases or percentages (n, %), and examined using χ^2 test. Measurement data were expressed as mean ± standard deviation (x ± sd). A paired t-test was used to compare data before and after treatment between the same group. An independent sample t-test was used for comparison between the two groups. $P < 0.05$ was considered statistically significant.

Table 1. Comparison of baseline data (n, x ± sd)

Characteristics	Research group (n = 54)	Control group (n = 54)	t	P
Gender (n)			0.926	0.336
Male	30	25		
Female	24	29		
Age (years)	55.5±6.2	57.1±7.6	1.199	0.233
BMI (kg/m^2)	23.22±2.10	23.50±2.33	0.656	0.513
APACHE II score (points)	20.02±3.20	20.33±2.56	0.556	0.579
Disease type (n)			0.775	0.410
Lower respiratory tract infection	10	8		
Upper respiratory tract infection	10	12		
Intra-abdominal infection	11	9		
Peritoneal infection	8	10		
Gynecological infections	4	5		
Urinary tract infection	5	6		
Others	6	4		

Note: APACHE II: Acute Physiology and Chronic Health Evaluation II.

Table 2. Comparison of clinical efficacy after treatment (n, %)

Group	Cured	Markedly effective	Effective	Ineffective	Total effective rate
Research group (n = 54)	20 (37.04)	27 (50.00)	5 (9.26)	2 (3.70)	52 (96.30)
Control group (n = 54)	17 (31.48)	21 (38.89)	8 (14.81)	8 (14.81)	46 (85.19)
t	0.370	1.350	2.641	3.967	3.967
P	0.543	0.245	0.104	0.046	0.046

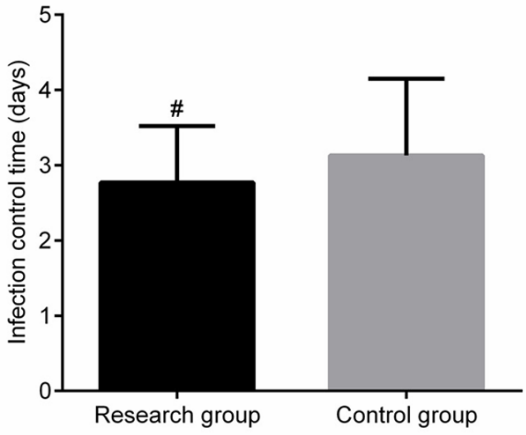

Figure 1. Comparison of infection control time. Compared with the control group, #P < 0.05.

Results

Baseline data

There was no significant difference in the general baseline data between the two groups (P > 0.05), suggesting that the two groups were comparable. See **Table 1**.

Clinical efficacy

The results showed that the total effective rate in the research group was significantly higher than that in the control group (96.30% vs 85.19%, P < 0.05). See **Table 2**.

Infection control time

After treatment, the infection control time was (2.77±0.75) d in the research group and (3.13±1.02) d in the control group. Statistical analysis showed that the infection control time in the research group was significantly shorter than that in the control group (t = 2.090, P = 0.039). See **Figure 1**.

Bacterial clearance rate

After treatment, the bacterial clearance rate in the research group was significantly higher than that in the control group (81.43% vs 66.22%, P < 0.05). See **Table 3**.

PCT and CRP levels

After treatment, the serum PCT and CRP levels were significantly lower in both groups than

Table 3. Comparison of bacterial clearance rate (n, %)

Bacteria	Acinetobacter baumannii	Escherichia coli	Pseudomonas aeruginosa	Klebsiella pneumoniae	Staphylococcus aureus	Chryseobacterium meningosepticum	Others	Total
Research group (n = 54)								
Before treatment (strain)	21	17	12	7	4	3	6	70
Clearance (strain)	14	10	8	5	2	2	3	44
Partial clearance (strain)	5	4	2	1	0	0	1	13
Clearance rate (%)	19 (90.48)	14 (82.35)	10 (83.33)	6 (85.71)	2 (50.00)	2 (66.67)	4 (66.67)	57 (81.43)
Control group (n = 54)								
Before treatment (strain)	24	14	13	9	5	5	4	74
Clearance (strain)	13	8	5	4	3	2	3	38
Partial clearance (strain)	4	3	2	1	1	0	0	11
Clearance rate (%)	17 (70.83)	11 (78.57)	7 (53.85)	5 (55.56)	4 (80.00)	2 (40.00)	3 (75.00)	49 (66.22)
t	2.701	0.070	2.493	1.667	0.900	0.533	0.079	4.285
P	0.100	0.791	0.114	0.197	0.343	0.465	0.778	0.038

Table 4. Comparison of PCT and CRP levels before and after treatment (x ± sd)

Group	PCT (μg/L)	CRP (mg/L)
Research group (n = 54)		
Before treatment	15.57±3.66	20.58±3.95
After treatment	4.48±2.22***,###	4.30±2.05***,###
Control group (n = 54)		
Before treatment	15.29±3.20	21.10±3.22
After treatment	7.47±2.10***	8.14±2.40***

Notes: Compared with that before treatment, ***P < 0.001; compared with the control group after treatment ###P < 0.001. PCT: procalcitonin; CRP: C-reactive protein.

those before treatment, and were lower in the research group than in the control group (all P < 0.001). See **Table 4**.

Adverse reactions

The results showed that there was no significant difference in the incidence of adverse reactions between the two groups during treatment (P > 0.05). See **Table 5**.

Discussion

Various pathogenic bacteria can cause severe infection in the emergency department, including gram-negative bacteria, gram-positive bacteria and some fungi. It is precisely due to the complexity and diversity of pathogenic bacteria causing severe infection that antibiotics with broad-spectrum and strong bactericidal effect should be used to control the infection [10, 11].

In this study, the control group was treated with ceftriaxone and the research group was treated with imipenem/cilastatin. The results showed that compared with those in the control group, the infection control time was significantly shortened, and the bacterial clearance rate was significantly increased in the research group. Furthermore, the total effective rate of the research group was also significantly higher than that of the control group (96.30% vs 85.19%). Such results suggested that imipenem/cilastatin is effective in treating patients with severe infection in the emergency department, can significantly improve bacterial clearance rate, and shorten infection control time. This is because imipenem/cilastatin acts by binding to PBPs and play a bactericidal role by inhibiting the synthesis of the bacterial cell wall. It demonstrates a significant antibacterial effect on most enterobacteria such as Escherichia coli, Klebsiella pneumonia, and most gram-positive bacteria and anaerobic bacteria, and is a broad-spectrum antibiotic [12]. Besides, the penetration ability of imipenem/cilastatin is about 70 times that of ceftriaxone, with the post-antibacterial effect persisting for a long time, so imipenem/cilastatin has a stronger antibacterial effect [13]. Ma et al. found that compared with ceftriaxone, imipenem/cilastatin has a higher clearance rate of Klebsiella pneumonia, Pseudomonas aeruginosa, Acinetobacter baumannii and Escherichia coli, and can better improve various cli-nical symptoms of patients with severe infection, which was consistent with the results of our study [14]. A pharmacokinetic/pharmacodynamic study by Lucasti et al. showed that the clearance rate of carbapenem-resistant bacterial strains was up to 90% when imipenem/cilastatin was administered at a dose of 500 mg/time, 4 times/day [15].

This study found that the serum PCT and CRP levels in the two groups after treatment were lower than those before treatment, and were lower in the study group than in the control group, suggesting that compared with ceftriaxone, imipenem/cilastatin can better control inflammatory response in patients with severe infection in the emergency department, which was consistent with the study results of Salmon-Rousseau et al. [16]. CRP and PCT are usually used as important markers of inflammatory response in clinical practice [17]. CRP is an acute-phase reactive protein. Normally, CRP level is very low in the blood. However, when the body is infected with bacteria or suffers from stress responses such as surgery, the serum CRP level will be dramatically increased [16]. PCT is a highly stable precursor of calcitonin, and is not affected by hormone levels. In normal conditions, it remains low in the blood or even undetectable. However, after the body is under infection of pathogenic microorganisms, the serum level of PCT can be rapidly increased within 4 h. Several studies have confirmed that there is a significant posi-

Table 5. Comparison of adverse reactions (n, %)

Group	Nausea	Diarrhea	Vomiting	Pain at the injection site	Headache or dizziness	Total incidence
Research group (n = 54)	1 (1.85)	2 (3.70)	1 (1.85)	0 (0.00)	2 (3.70)	6 (11.11)
Control group (n = 54)	2 (3.70)	2 (3.70)	1 (1.85)	1 (1.85)	2 (3.70)	8 (14.81)
t	0.343	0.000	0.000	1.009	0.000	0.328
P	0.558	> 0.999	> 0.999	0.315	> 0.999	0.567

tive correlation between serum PCT level and the degree of infection [18-21]. A study in the United Statesfound that in patients with urinary tract infection caused by multidrug-resistant bacteria, the therapeutic effect of imipenem/cilastatin was comparable to that of cefiderocol, and this study has been submitted as evidence to the Food and Drug Administration of the United States for new drug application of cefiderocol [22]. For adverse reactions, we found no serious adverse reactions in both groups of patients, mainly some mild gastrointestinal reactions such as nausea, vomiting, and diarrhea. There was no significant difference in the incidence of adverse reactions between the two groups during treatment, suggesting that ceftriaxone and imipenem/cilastatin are safe in the treatment of patients with severe infection in the emergency department, and can produce few adverse reactions. In short, we found that imipenem/cilastatin had a good effect on the clearance of a variety of pathogenic bacteria causing severe infections. However, we only conducted a single-center study with a small sample size. No significant difference was found in the statistical analysis of less isolated strains, and the effects of imipenem/cilastatin on short-term reinfection of patients after discharge remain unclarified, which needs to be confirmed by more in-depth studies.

To sum up, the administration of imipenem/cilastatin in patients with severe infection in the emergency department can significantly improve bacterial clearance rate, reduce inflammatory response, control the symptoms of infection, and produce less adverse reactions, which is worthy of clinical application.

Disclosure of conflict of interest

None.

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