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A Clinical Study on the Impact of Tigecycline on Coagulation Function in Critically Ill Patients with Severe Infections

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Abstract: Objective: A Clinical Study on the Effect of Tigecycline on Coagulation Function in Severe Infected Patients. Methods: A total of 90 patients with severe infections, selected from October 2022 to October 2023, were divided into control and observation groups of 45 cases each using a computer-generated random number table. The control group received monotherapy with an antibacterial agent, while the observation group underwent combined therapy with cefoperazone-sulbactam and tigecycline. The clinical efficacy of the two groups was compared. Results: Prior to treatment, there were no statistically significant differences in coagulation indices between the two groups ($P > 0.05$). Post-treatment, the Fib, APTT, and PT values, as well as clinical efficacy, were higher in the observation group compared to the control group. Conversely, adverse reactions, hs-CRP, PCT, IL-6, and TNF-α values were lower in the observation group, with statistically significant differences ($P < 0.05$). Conclusion: The observation group experienced fewer adverse reactions, with a statistically significant difference ($P < 0.05$). Conclusion: Although cefoperazone sulbactam combined with tigecycline has an impact on the coagulation function of patients, its therapeutic effect is superior to other single-drug regimens, and other adverse reactions are relatively mild. Therefore, it is worth considering the combination of tigecycline in the treatment of severe infections, and actively monitoring the coagulation function.

Keywords: Tigecycline; Severe Infection; Coagulation Function; Inflammatory Cytokines.

1. Introduction

With the continuous advancement of modern medicine, the treatment of severe infections has remained a focal and challenging aspect of clinical practice. Tigecycline, as a novel broad-spectrum antibiotic, plays a pivotal role in the realm of severe infection management. It exhibits potent antimicrobial activity against a myriad of pathogens, including anaerobes, Gram-positive cocci, Gram-negative bacilli, and multidrug-resistant pathogens, with a relatively low rate of resistance. Consequently, tigecycline is widely employed in the treatment of multidrug-resistant bacterial infections, complicated intra-abdominal infections, and community-acquired pneumonia [1]. However, an increasing number of studies in recent years have indicated that tigecycline may exert an impact on the coagulation function of patients during its administration. Given that patients with severe infections are predisposed to coagulation dysfunction, which occurs with a prevalence ranging from 10% to 40%, this issue warrants closer scrutiny. Coagulation dysfunction typically manifests as an initial hypercoagulable state followed by a hypocoagulable state, with common clinical symptoms including bleeding, such as mucocutaneous hemorrhage, internal organ bleeding, and gastrointestinal bleeding [2]. In severe cases, this can lead to shock, multiple organ dysfunction, and hemolytic anemia. In light of this, a thorough investigation into the effects of tigecycline on the coagulation function of patients with severe infections holds significant clinical importance, as detailed below:

2. Information and Methods

2.1. General Information

A cohort of 90 critically infected patients from October 2022 to October 2023 was selected and randomly divided into a control group and an observation group, each comprising 45 cases. In the control group, the gender ratio was 20 males to 25 females, with ages ranging from 58 to 80 years, averaging 69.00 ± 12.55 years [3]. Comorbidities included 15 cases of diabetes, 22 cases of coronary heart disease, and 8 cases of other conditions. The observation group consisted of 30 males and 25 females, aged from 59 to 81 years, with an average age of 70.00 ± 13.00 years. Comorbidities in this group comprised 26 cases of diabetes, 13 cases of coronary heart disease, and 6 cases of other conditions. No significant differences were observed in the general characteristics between the two groups ($P > 0.05$).

2.2. Inclusion and Exclusion Criteria

Inclusion Criteria: (1) Confirmed as severe infection based on rigorous verification, meeting the disease-specific criteria for diagnosis. (2) The experimental drug has undergone sensitivity testing and has been proven not to induce allergic reactions. (3) The patient has not previously received treatment with the same medication and demonstrates excellent adherence to the therapeutic regimen. (4) The patient possesses robust communication skills and the ability to express themselves clearly [4].

Exclusion Criteria: (1) Patients who are currently utilizing antiplatelet or anticoagulant medications. (2) Individuals with a history of drug allergies. (3) Patients with severe conditions

affecting critical organs such as the heart or kidneys. (4) Those with co-existing infections of different types [5].

2.3. Methods

In the treatment protocol, the control group is administered a monotherapy approach using a single antibacterial drug. Specifically: Meropenem for Injection (Approval Number: H20010249, Manufacturer: Shenzhen Haibin Pharmaceutical Co., Ltd.), administered at a dose of 250 milligrams, which is mixed with 5 milliliters of saline solution for intravenous infusion. The infusion duration is controlled to be between 15 and 30 minutes, with an intravenous infusion conducted every 8 hours, each infusion amounting to 500 milligrams [6].

In the observation group, a combined therapy of cefoperazone-sulbactam and tigecycline was administered. Initially, 2 grams of cefoperazone-sulbactam (National Drug Approval Number: H20020597, manufacturer: Pfizer Pharmaceuticals Limited) were dissolved in 100 milliliters of normal saline for intravenous infusion, with an infusion frequency of every 12 hours. For tigecycline (National Drug Approval Number: H20123394, manufacturer: Jiangsu Hansoh Pharmaceutical Group Co., Ltd.), an initial dose of 100 milligrams was dissolved in 100 milliliters of normal saline for intravenous infusion [7]. Thereafter, the dosage was adjusted to 50 milligrams dissolved in 100 milliliters of normal saline for intravenous infusion, administered every 12 hours. Both groups of patients underwent treatment according to their respective protocols for a continuous period of two weeks.

2.4. Observational Metrics

(1) Coagulation indicators. Using the STA-type coagulation analyzer, a precise analysis of the venous blood sample from the patient is conducted. A disposable venipuncture needle is used, adhering to aseptic operating norms, to collect venous blood from the patient's elbow. The blood is collected into a vacuum tube containing an appropriate anticoagulant, with a volume based on the testing requirements, typically 2-3ml. The tube is gently inverted several times to ensure thorough mixing of the blood with the anticoagulant, preventing clotting. Post-collection, the blood sample should be promptly submitted for testing [8]. The sample tubes are centrifuged at 1500-2000g for 10-15 minutes to separate plasma from blood cells. Plasma is then aspirated into dedicated coagulation analysis cups, taking care to avoid contamination with blood cells or debris, ensuring sample purity. Subsequently, three indicators—Fib (fibrinogen; Fibrinogen), PT (prothrombin time; Prothrombin Time), and APTT (activated partial thromboplastin time; Activated Partial Thromboplastin Time)—are measured according to testing requirements, with real-time monitoring of the coagulation process to accurately determine the coagulation parameters [9].

(2) Adverse Effects. Following the administration of treatment, a spectrum of adverse effects may be triggered. Hemopoietic disturbances manifest as a reduction in red blood cell count, potentially compromising the body's oxygen transport capabilities; a decrease in platelet count may disrupt coagulation, elevating the risk of hemorrhage. In the digestive system, gastrointestinal reactions such as nausea, vomiting, abdominal pain, and diarrhea may occur, causing discomfort. Neurological manifestations may include headaches, inflicting physical distress and discomfort upon the patient.

(3) Inflammatory Mediators. Prepare appropriate blood collection instruments. While the patient is in a fasting state, choose an appropriate venipuncture site, and accurately draw 4ml of venous blood using a disposable blood collection needle. Carefully transfer the collected blood sample into a sterile anticoagulant tube [10]. Subsequently, place the anticoagulant tube into a professional centrifuge, set to an appropriate speed and duration, and centrifuge at a relative centrifugal force of 3000-3500g for 10-15 minutes to separate the blood into distinct layers, isolating the serum. Following this, strictly adhere to the standard procedures of the enzyme-linked immunosorbent assay for the measurement of levels of high-sensitivity C-reactive protein (hs-CRP), procalcitonin (PCT), interleukin (IL)-6, and tumor necrosis factor (TNF)-α.

(4) Clinical efficacy. A comparative analysis of the clinical outcomes after treatment for both groups was conducted, following the guidelines outlined in the 'Principles of Clinical Application of Antibacterial Drugs.' A comprehensive evaluation was performed based on the following specific efficacy criteria: Recovery—after 5 days of medication, all symptoms and signs completely disappeared, body temperature returned to normal, and inflammatory indicators decreased to normal levels; Significant improvement—after 5 to 7 days of medication, symptoms and signs significantly improved, body temperature dropped below 38°C, and inflammatory indicators decreased by more than 50% compared to before treatment; Improvement—after 7 to 14 days of medication, symptoms and signs showed some improvement, body temperature dropped below 38°C, and inflammatory indicators decreased by 50% compared to before treatment; Ineffective—none of the above criteria were met [11].

2.5. Statistical Processing

SPSS 27.0 statistical software was used to analyze the data in depth, and the measurement data were presented in the form of (mean ± standard deviation), and the t-test was used for intra-group comparisons; for the count data, the chi-square test was used and expressed as a percentage. The statistical significance was scientifically assessed by accurately calculating the P-value to ensure that the results reached the significance level ($P < 0.05$).

3. Results

3.1. Comparison of Coagulation Indices Between the Two Groups

Table 1. Comparison of coagulation indices between the two groups $\{\bar{x} \pm s\}$

Group	Fib (g/L)		APTT (s)		PT (S)	
	Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment
Observation group (n=45)	5.40±0.43	4.12±0.31	44.12±3.99	36.70±3.26	22.01±2.15	14.09±1.15
Control group (n=45)	5.22±0.51	3.22±0.45	43.08±3.70	34.15±3.01	21.05±2.16	10.12±1.37
T	1.810	11.049	1.282	3.855	2.113	14.889
P	0.074	＜0.001	0.203	＜0.001	0.037	＜0.001

There was no statistically significant difference in the comparison of blood coagulation indexes between the 2 groups before treatment, P＞0.05. After treatment, Fib, APTT, PT data of the observation group was higher than that of the control group, and the difference was statistically significant, P<0.05.

3.2. Adverse Reaction

In terms of adverse reactions, the observation group experienced fewer adverse reactions, with a statistically significant difference (P < 0.05).

Table 2. Adverse reactions [cases (%)]

Group	Red blood cell counts decreased	Platelet count decreased	Gastrointestinal reactions	Headache	Incidence
Observation group (n=45)	1	0	3	1	5(11.11)
Control group (n=45)	4	1	6	2	13(33.33)
$\chi 2$	-	-	-	-	4.444
P	-	-	-	-	0.035

3.3. Inflammatory Factor

The comparison of inflammatory factors between the 2 groups of patients before treatment was not significant (P > 0.05). After treatment, the data of hs-CRP, PCT, IL-6, and TNF-α of patients in the observation group were lower than those of the control group, and the difference was statistically significant, P < 0.05 [12].

Table 3. Comparison of inflammatory factors between the two groups $\{\bar{x} \pm s\}$

Group	hs-CRP (mg/L)		PCT(μg/L)	
	Before Treatment	After Treatment	Before Treatment	After Treatment
Observation group (n=45)	39.25±10.61	14.52±6.41	6.23±1.40	0.90±0.57
Control group (n=45)	40.75±10.66	22.03±8.58	6.25±1.29	1.81±0.64
T	0.669	4.735	0.070	7.123
P	0.505	<0.001	0.944	<0.001
Group	IL-6 (pg/ml)		TNF-α(nmol/L)	
	Before Treatment	After Treatment	Before Treatment	After Treatment
Observation group (n=45)	141.20±30.00	61.50±15.28	52.49±12.99	24.72±10.39
Control group (n=45)	139.88±28.91	84.06±17.31	53.00±14.35	35.39±11.27
T	0.213	6.554	0.177	4.656
P	0.832	<0.001	0.860	<0.001

3.4. Clinical Effects

The clinical effectiveness rate of the observation group was significantly higher than that of the control group, with statistical significance, P < 0.05.

Table 4. Clinical Efficacy [Cases (%)]

Group	Cure	Effective	Efficient	Ineffective	Productive
Observation group (n=45)	26	15	2	2	43(95.56)
Control group (n=45)	20	12	4	9	36(80.00)
χ^2	-	-	-	-	5.075
P	-	-	-	-	0.024

4. Discussion

In critically ill patients receiving radiotherapy and chemotherapy, bodily functions are prone to adverse effects, notably manifesting in a marked decline in immune function, which inevitably fosters an environment conducive to the proliferation of multiple and multi-site infections. In the clinical treatment domain, the extensive use of broad-spectrum antibiotics, while contributing positively to infection control to a certain extent, concurrently exacerbates the issue of bacterial resistance, which can escalate to a degree that jeopardizes patient lives. Consequently, the selection of scientific methodologies in the treatment of severe infections emerges as a critical component, as it not only impacts the enhancement of therapeutic outcomes but also plays a pivotal role in mitigating the incidence of adverse reactions [13].

Among a myriad of therapeutic strategies, combination drug regimens have garnered significant attention, with the pairing of tigecycline and ceftazidime-avibactam being a commonly employed combination. Ceftazidime-avibactam, as a representative of novel broad-spectrum antibiotics, demonstrates exceptional bactericidal efficacy against a variety of bacteria, including Acinetobacter baumannii. Its distinctive feature lies in its potent inhibition of β-lactamases, a characteristic that effectively enhances cellular permeability, enabling the drug to accumulate in substantial quantities within bacteria, thereby achieving precise bacterial eradication.

Tigecycline belongs to the class of glycylcyclines, which exhibit a remarkable broad-spectrum antibacterial efficacy. Its core mechanism of action lies in the interruption of bacterial protein synthesis pathways, achieved by interfering with the bacterial efflux of antimicrobial components, thereby effectively protecting the efflux pump mechanism and significantly curbing the development of ribosomal resistance in bacteria. Notably, the therapeutic efficacy of tigecycline demonstrates exceptional stability, remaining unaffected by individual variations in patient physiology [14]. Moreover, it possesses formidable tissue penetration capabilities, enabling it to penetrate deeply into the affected areas and thoroughly eradicate pathogenic microorganisms and bacteria hidden within the deeper layers of tissues. Additionally, the drug exhibits minimal organ toxicity, which is practically negligible. On a microscopic level, upon entering the body, tigecycline forms a cationic-tetracycline complex, which actively translocates across the outer membrane and intermembrane space of pathogenic bacteria, successfully reaching the cytoplasm. Here, it tightly binds to ribosomal subunits, disrupting the normal elongation process of bacterial peptide chains, ultimately achieving effective inhibition of pathogenic bacterial protein synthesis [15].

From the present study, it is evident that prior to treatment, there was no statistically significant difference in blood coagulation indicators between the two groups ($P > 0.05$). Post-treatment, the Fib, APTT, and PT values in the observation group were notably higher than those in the control group, with statistically significant differences ($P < 0.05$). The underlying reasons for this are as follows: Tigecycline effectively reduces the levels of inflammatory cytokines, and inflammation is intricately linked to the coagulation system. In inflammatory states, cytokines can activate coagulation factors, leading to thrombus formation. When tigecycline alleviates inflammation, it diminishes the abnormal activation of the coagulation system by inflammation, thereby stabilizing the coagulation state [16]. However, in combination therapy with cefoperazone-sulbactam, it may result in a moderate increase in coagulation indicators. Additionally, tigecycline may exert a regulatory effect on endothelial cell function, potentially reducing endothelial cell damage or improving their secretory function. Under normal conditions, endothelial cells secrete anti-coagulant substances, and when endothelial cell function stabilizes, the balance between coagulation and anti-coagulation may shift, leading to an increase in coagulation indicators such as FIB (fibrinogen), APTT (activated partial thromboplastin time), and PT (prothrombin time). Furthermore, the metabolic process of tigecycline in the body may interfere with certain signaling pathways or material metabolisms related to coagulation [17]. Although the specific mechanisms remain to be fully elucidated, it is possible that tigecycline affects the synthesis, metabolism, or regulatory processes of coagulation factors in organs such as the liver, resulting in the observation group exhibiting higher coagulation indicators than the control group during combined therapy. Within the broader context of treatment, this alteration in coagulation indicators may help maintain the coagulation balance during the process of anti-infection, preventing adverse consequences such as disseminated intravascular coagulation caused by excessive coagulation dysfunction due to infection.

The study found that in terms of adverse reactions, the observation group experienced fewer adverse reactions, with a statistically significant difference ($P < 0.05$). The underlying reason lies in: Tigecycline possesses a unique target and mechanism of action in antibacterial activity. It exhibits high affinity for bacterial ribosomes, thereby inhibiting protein synthesis and precisely targeting pathogenic bacteria, mitigating the dysbiotic consequences typically associated with broad-spectrum antibacterial effects [18]. When combined with cefoperazone-sulbactam, tigecycline compensates for the shortcomings of cefoperazone-sulbactam in treating certain drug-resistant bacterial infections, reducing the total dosage and duration of medication, and consequently lowering the risk of adverse reactions due to drug accumulation in the body. Additionally, tigecycline demonstrates relatively low toxicity to normal human cells. Within the framework of combination therapy, it does not impose additional burdens on vital organs such as the liver and kidneys, ensuring the stability of the internal environment. This results in a significantly reduced incidence of adverse reactions, enhancing both the safety and efficacy of the treatment regimen.Although the combination of tigecycline and cefoperazone sulbactam affects coagulation function, it performs better in terms of efficacy and other adverse reactions. Therefore, when dealing with severe infections, a careful assessment is needed.

From the research, it is evident that there was no significant difference in inflammatory factors between the two patient groups prior to treatment ($P > 0.05$). However, post-treatment, the levels of hs-CRP, PCT, IL-6, and TNF-α in the observation group were lower than those in the control group, with statistically significant differences ($P < 0.05$). The reason for this lies in the potent and broad-spectrum antibacterial capabilities of tigecycline, which specifically binds to the 30S subunit of bacterial ribosomes, thereby interrupting protein synthesis and exerting inhibitory or even lethal effects on a variety of drug-resistant bacteria and common pathogens. At the site of infection, it precisely eliminates the pathogens responsible for the inflammatory response, thereby reducing the continuous stimulation of pathogen-associated molecular patterns on immune cells, leading to a decrease in the levels of inflammatory factors such as hs-CRP, PCT, IL-6, and TNF-α. Additionally, during the process of inhibiting bacterial growth and reproduction, tigecycline indirectly prevents the release of endotoxins and other inflammatory-inducing substances resulting from massive bacterial proliferation and lysis. The reduction in endotoxins weakens the activation of immune cells such as monocytes and macrophages, leading to a corresponding decrease in the synthesis and release of pro-inflammatory cytokines. Furthermore, when combined with cefoperazone-sulbactam, the two agents exhibit synergistic antibacterial effects, providing a more comprehensive and efficient control of infection. Tigecycline compensates for potential gaps in antibacterial coverage when used as a single

agent, enhancing overall antibacterial efficacy and thereby allowing the inflammatory response to be curbed more swiftly [19].

The study reveals that the clinical efficacy rate of the observation group is significantly higher than that of the control group, with statistical significance ($P < 0.05$). The underlying reason is that tigecycline exhibits broad-spectrum antibacterial activity, effectively combating a variety of drug-resistant bacteria, including strains that are resistant or insensitive to cefoperazone-sulbactam monotherapy. Through a unique mechanism of action, tigecycline specifically binds to the 30S ribosomal subunit of bacteria, inhibiting protein synthesis and thereby strongly suppressing the growth and proliferation of pathogenic bacteria. In combination therapy, tigecycline synergizes with cefoperazone-sulbactam, broadening the antibacterial spectrum and enhancing the efficacy against diverse bacterial species within complex infections. Simultaneously, tigecycline treatment compensates for the limitations in antibacterial spectrum and activity of cefoperazone-sulbactam, enabling the combined regimen to comprehensively and thoroughly eradicate pathogenic bacteria, mitigate inflammatory responses, and promote the improvement of clinical symptoms. Ultimately, this significantly enhances the clinical efficacy rate, providing robust support for the recovery of patients.

This study may be subject to bias. Despite stringent inclusion and exclusion criteria, the influence of potential confounders cannot be entirely ruled out; the relatively small sample size may compromise the stability and reliability of statistical outcomes; the mechanism linking tigecycline blood concentration with coagulation indicators remains unclear, lacking empirical evidence for support; the study's scope is confined to patients in specific hospital ICUs, thus limiting its generalizability, and further research is required to validate its applicability.

Future research should delve deeper into the association between tigecycline blood concentration and coagulation indicators, exploring its impact on coagulation function through animal and cellular experiments, such as the roles of TFPI and vWF. Additionally, genetic factors influencing tigecycline's effects on coagulation function should be examined, employing genomics and proteomics to identify relevant genetic markers that support personalized therapy. Furthermore, investigations into the combined effects of tigecycline with other medications on coagulation function should be conducted to guide clinical drug use appropriately [20].

Although cefoperazone sulbactam combined with tigecycline has an impact on the coagulation function of patients, its therapeutic effect is superior to other single-drug regimens, and other adverse reactions are relatively mild. Therefore, it is worth considering the combination of tigecycline in the treatment of severe infections, and actively monitoring the coagulation function.

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