ORIGINAL RESEARCH

Related Factors of CRKP Infection in Neurosurgery and Comparison of Therapeutic Effects of Tigecycline Versus Polymyxin B for CRKP Infection

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ABSTRACT

Objective • This paper aimed to identify the factors related to *Carbapenem-resistant Klebsiella pneumoniae* (CRKP) infection in neurosurgical patients, and to compare the therapeutic effects of tigecycline versus polymyxin B against CRKP infection, so as to provide a reliable reference for neurosurgery in future prevention and treatment of CRKP infection.

Methods • One hundred and fifty cases of KPN treated in the neurosurgery department of our hospital from January 1, 2019 to December 31, 2021 were selected, 50 of which were found to be infected with CRKP and the other 100 were detected with *carbapenem-sensitive Klebsiella pneumoniae* (CSKP) by culture, analysis of factors associated with infection with CRKP. Subsequently, CRKP-infected patients were randomized into a group treated with Ti (group Ti) and a group treated with PB (group PB). The clinical efficacy, bacterial clearance, adverse reactions, and pre- and post-treatment hepatorenal function were comparatively analyzed.

Results • Based on the Logistic regression analysis, tracheal intubation (or mechanical ventilation), combination of multiple underlying diseases, presence of impaired consciousness, and use of carbapenem antibiotics are independent risk factors for CRKP infection ($P < .05$). Ti and PB groups had no evident differences in clinical efficacy and bacterial clearance ($P > .05$); however, Ti group presented a worse hepatorenal function and a higher incidence of adverse reactions than PB group ($P < .05$).

Conclusions • Tracheal intubation (or mechanical ventilation), multiple underlying diseases, consciousness disturbance, and use of carbapenem antibiotics are related factors affecting CRKP infection in neurosurgical patients. Both Ti and PB have excellent therapeutic efficacy, but the former has more obvious toxicity and side effects. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Klebsiella pneumoniae (KPN) is one of the most important pathogens in clinical isolation and nosocomial infections, which bears responsibility for more than 95% of *Klebsiella* infections.[1] KPN pneumonia caused by KPN is one of the world's high-incidence diseases, with more than 600 000 new cases worldwide every year and an increasing trend year by year.[2] Carbapenems are often used as the first-line anti-infective agents for severe KPN infection in clinical patients.[3] However, with the evolution of pathogenic bacteria and the development of drug resistance, *carbapenem-resistant Klebsiella pneumoniae* (CRKP) was first discovered in clinical trials in 2001.[4] In contrast to conventional KPN, CRKP not only exhibits strong resistance to carbapenem antibiotics, but may be insensitive to all commonly used anti-infective drugs due to the drug-resistant gene-cassette carried by the drug-resistant plasmid. In addition, the emergence of highly virulent CRKP reported in recent years has brought greater challenges to clinical anti-infective treatment.[5] Hence, clinical efforts are ongoing to explore and find new anti-CRKP schemes, but no significant results have been achieved so far.

Tigecycline (Ti) has ultra-broad-spectrum antimicrobial activity and is now often used for the treatment of abdominal

infections, skin infections, soft-tissue infections and pneumonia.[4] Its excellent therapeutic efficacy on CRKP has also been reported.[6] Polymyxin B (PB) is a kind of antibacterial peptide with positive charge, whose mechanism of action is to achieve bactericidal effect by destroying the integrity of bacterial outer membrane. Despite its great toxic and side effects, PB has regained its clinical role as a means of combating CRKP and become the current "last resort" treatment for CRKP, a pathogenic bacteria resistant to the vast majority of antibiotics.[7] Both antibiotics are currently used to treat CRKP, but the optimal course of treatment has not yet been determined.[8] Therefore, the purpose of this study is to compare the effects of Ti and PB in the treatment of CRKP, and to analyze the related factors of CRKP infection, so as to provide valid reference and guidance for future clinical treatment.

DATA AND METHODS

Study participants

One hundred and fifty cases of KPN treated in the neurosurgery department of our hospital from January 1, 2019 to December 31, 2021 were selected, 50 of which were found to be infected with CRKP and the other 100 were detected with *carbapenem-sensitive Klebsiella pneumoniae* (CSKP) by culture. The data of CRKP patients and CSKP patients were analyzed to obtain the relevant factors affecting CRKP. Subsequently, CRKP-infected patients (n=100) were randomized into a group treated with Ti (group Ti) and a group treated with PB (group PB). This study was approved by the Medical Ethics Committee, and all patients were informed and signed the informed consent form.

Criteria for patient enrollment and exclusion

The eligible patients, all aged ≥18 (adults), were confirmed as CRKP or CSKP by bacterial culture, of which CRKP patients were all sensitive to Ti and PB as indicated by the results of the drug susceptibility test and received corresponding anti-infection treatment for more than 7 days. In contrast, patients with severe infectious diseases, incomplete treatment for various reasons, pregnancy or lactation, immunodeficiency and/or neutrophil < 2×10^9/L were excluded.

Treatment methods

Ti group: Ti + carbapenems were used for treatment. First dose of 100mg, followed by one dose of 50mg every 1 time/12h. Intravenous drip, each drip for 30-60min, followed by the administration of imipenem/cilastatin or meropenem. PB group: The PB + carbapenems scheme was used. PB was administered intravenously at a first dose of 2.5 mg/kg and a maintenance dose of 1.25 mg/kg, and carbapenems were administered in the same way as in the Ti group. Patients in both groups were treated for 14d.

Clinical response evaluation

Clinical response assessment was performed with reference to the "Guidelines for Clinical Research of Antibacterials".[9] A cure means the basic disappearance of clinical symptoms and signs and normal laboratory examination indicators. A marked response corresponds to obviously relieved clinical symptoms and signs and normal laboratory examination indexes, but the failure of the recovery of one of the above four items. Alleviated clinical symptoms and signs and improved laboratory examination indicators are considered to be a response. Non-response is indicated by no change or aggravation of clinical symptoms and signs, and no obvious change or aggravation of laboratory examination indexes. Overall response rate (ORR) = (cure cases + marked response cases) / total cacses×100%. According to the bacterial culture results of sputum or bronchoscope lavage fluid samples re-examined after treatment,[10] CRKP is cleared if it is not detected in the culture medium after treatment; otherwise, it is not cleared. Replacement is indicated if a new pathogen, rather than CRKP, is detected. Bacterial clearance rate = number of cases with clearance / total number of cases ×100%. Finally, adverse reactions, such as nausea, vomiting, and loss of appetite, were counted during treatment.

Blood sampling and testing

After treatment, fasting venous blood was collected in coagulant tubes and centrifuged for 30 min at room temperature to obtain serum for the determination of hepatorenal function by measuring alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBil), and serum creatinine (Scr) levels with an automatic biochemical analyzer.

Statistical methods

This study used SPSS24.0 for statistical analysis and a minimum significance level of $P < .05$. The chi-square test was adopted to identify difference in counting data that were expressed as percentages (%). Measurement data were statistically described as ($\bar{x} \pm s$) and compared using the t test and paired t test. Logistic regression analysis was used to analyze the related factors.

RESULTS

Univariate analysis of CRKP infection

First, the basic data of CRKP and CSKP patients were compared. No statistical difference was identified in gender composition and age between groups ($P > .05$), indicating that the above indicators are not potential factors influencing CRKP infection. But compared with CSKP patients, the duration of ICU stay in CRKP group was significantly longer, and the number of patients with posterior fossa lesions, tracheal intubation (or mechanical ventilation [MV]), consciousness disturbance, multiple underlying diseases, and use of carbapenem antibiotics was greater ($P < .05$). It can be seen that the above indicators are potential single factors affecting CRKP infection. Table 1

Table 1. Univariate analysis of CRKP infection

		CSKP patients (n=100)	CRKP patients (n=50)	χ^2 (or t)	P value
Gender composition	Male / female	68(68.00)/32(32.00)	32(64.00)/18(36.00)	0.689	.407
Age		68.00±4.98	67.70±4.75	0.319	.750
Tracheal intubation (or MV)	Yes / no	56(56.00)/44(44.00)	41(82.00)/9(18.00)	10.820	.001
Consciousness disturbance	Yes / no	34(34.00)/66(66.00)	38(76.00)/12(24.00)	26.780	<.001
Duration of ICU stay		6.13±1.01	10.30±3.25	13.520	<.001
Site of surgery (cranial fossa)	Front / middle / rear	30(30.00)/36(36.00)/34(34.00)	12(24.00)/10(20.00)/28(56.00)	9.083	.011
Multiple underlying diseases (more than two kinds)	Yes / no	42(42.00)/58(58.00)	38(76.00)/12(24.00)	16.670	<.001
Use of carbapenem antibiotics	Yes / no	17(17.00)/83(83.00)	42(84.00)/8(16.00)	74.270	<.001
Long-term smoking	Yes / no	36(36.00)/64(64.00)	20(40.00)/30(60.00)	0.257	.612
Past medical history	Yes / no	29(29.00)/71(71.00)	18(36.00)/32(64.00)	0.779	.377

Multivariate analysis of CRKP infection

Logistic regression analysis was carried out after assigning values to THE above-mentioned single factor indexes with differences between CRKP and CSKP patients. The output results of multivariate analysis using patient type as dependent variable and other single factors as covariables showed that the surgical site and duration of ICU stay are not independent factors affecting CRKP ($P > .05$), but tracheal intubation (or MV), multiple underlying diseases, consciousness disturbance, and use of carbapenem antibiotics were independent risk factors for CRKP infection ($P < .05$). Table 2 and 3

Comparison of therapeutic effects between Ti and PB

Statistical analysis of the clinical response of Ti and PB groups showed 7 cured cases in Ti group with an ORR of 88.00%; in the PB group, 6 patients were cured, and ORR was 92.00%. The above data revealed no statistical difference between groups ($P > 0.05$). Table 4

Comparison of bacterial clearance between Ti and PB

After treatment, the CRKP clearance rate in Ti group was 72.00%, and carbapenem-resistant Pseudomonas aeruginosa was detected in sputum culture in 1 patient after the negative conversion of CRKP. In PB group, the CRKP clearance rate was 76.00%, and no patient had strain replacement. The two cohorts also differed insignificantly in CRKP clearance ($P > .05$). Table 5

Comparison of hepatorenal function before and after treatment

Before treatment, there was no significant difference in the results of liver and kidney function tests between Ti and PB groups ($P > .05$). After treatment, ALT, AST, TBil and Scr in both groups increased ($P < .05$), with even higher levels in Ti group versus PB group ($P < .05$). Figure 1

Adverse reactions during treatment

The total incidence of adverse reactions in Ti group was 36.00%, with obvious gastrointestinal reactions reported in 5 patients, versus an overall incidence of 12.00% in PB group with only one patient developed gastrointestinal reactions. The inter-group comparison determined a higher overall incidence of adverse reactions in Ti group as compared to PB group ($P < .05$). Table 6

Table 2. Assignment Table

Indicators	Assignment
Tracheal intubation (or MV)	Yes=1 / no=0
Consciousness disturbance	Yes=1 / no=0
Duration of ICU stay	-
Site of surgery	Front=2 / middle=1 / rear=0
Multiple underlying diseases	Yes=1 / no=0
Use of carbapenem antibiotics	Yes=1 / no=0

Table 3. Multivariate analysis of CRKP infection

Indicators	β-value	S.E.-value	*Wald* χ^2	P value	OR-value	95%CI
Tracheal intubation (or MV)	0.04	0.16	14.85	<.001	2.63	1.62-4.63
Consciousness disturbance	0.11	0.24	6.84	<.001	3.06	2.06-5.11
Duration of ICU stay	0.61	0.55	2.63	.074	2.06	1.94-6.60
Site of surgery	0.16	0.73	0.43	.128	0.84	0.24-3.94
Multiple underlying diseases	0.15	0.36	17.26	<.001	5.06	2.84-10.15
Use of carbapenem antibiotics	0.09	0.47	15.10	<.001	3.71	1.84-6.03

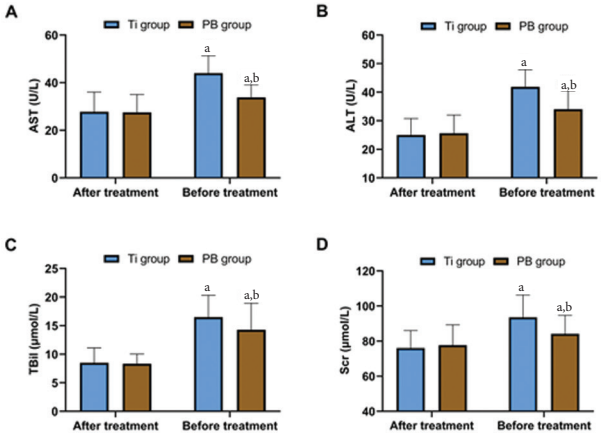
Table 4. Comparison of therapeutic effects

Group	Cure	Marked response	Response	Non-response	ORR
Ti group (n=25)	7(28.00)	10(40.00)	5(20.00)	3(12.00)	88.00%
PB group (n=25)	6(24.00)	13(52.00)	4(16.00)	2(8.00)	92.00%
χ^2					0.222
P value					.637

Table 5. Comparison of bacterial clearance

Group	Clearance	Not cleared	Replacement	Bacterial clearance rate
Ti group (n=25)	18(72.00)	6(24.00)	1(4.00)	72.00%
PB group (n=25)	19(76.00)	6(24.00)	0(0.0)	76.00%
χ^2				0.104
P value				.747

Figure 1. Comparison of liver and kidney function. A: Comparison of AST before and after treatment, B: Comparison of ALT before and after treatment, C: Comparison of TBil before and after treatment, D: Comparison of Scr before and after treatment.



[a]*vs.* before treatment, $P < .05$
[b]*vs.* Ti group, $P < .05$

Table 6. Adverse reactions during treatment

Group	Gastrointestinal reactions (nausea, vomiting, etc.)	Allergic skin rash	Insomnia	Total incidence
Ti group (n=25)	5(20.00)	2(8.00)	2(8.00)	36.00%
PB group (n=25)	1(4.00)	1(4.00)	1(4.00)	12.00%
χ^2				3.947
P value				.047

DISCUSSION

As a new multidrug-resistant strain in KPN, CRKP not only poses a greater threat to patients, but also increases the treatment difficulty.[11] Therefore, an in-depth understanding of the factors related to CRKP infection and drug resistance is conducive to effective prevention and treatment of CRKP infection, thus providing patients with more reliable safety protection. Although there have been clinical studies on the related factors of CRKP infection in recent years,[12-14] their conclusions are not completely consistent with controversies. At present, few reports have clearly indicated the difference in efficacy between Ti and PB for CRKP infection, and there is a lack of reliable drug guidance in clinical practice. Thus, this study has important implications for the future prevention and treatment of CRKP infection.

First, we conducted a preliminary analysis of the factors associated with neurosurgical CRKP infection. The results showed that tracheal intubation (or MV), multiple underlying diseases, consciousness disturbance, and use of carbapenem antibiotics were all independent risk factors for CRKP infection, which is consistent with the previous research results,[15,16] supporting our research findings. As we all know, tracheal intubation (or MV) can easily lead to airway dryness and affect lung cilia movement, leading to the inability to discharge lung sputum in time and increasing the possibility of aggravating lung infection.[17] In addition, patients generally have relatively serious functional disorders and low immunity,[18] so inflammatory mediators may be further activated to destroy the original barrier during tracheal intubation or MV, increasing the risk of infection.[19] The combination of multiple underlying diseases will inevitably lead to more serious deterioration of the patient's condition and dysfunction of the body, resulting in reduced resistance to pathogenic bacteria.[20] When patients suffer from consciousness disturbance, their immunity and compensatory ability are poor, which makes them less resistant to pathogenic invasion, thus rising the incidence of nosocomial infection of CRKP.[21] Patients with impaired consciousness are often accompanied by decreased cough and swallowing reflex function, making it difficult to discharge sputum, which is also an important factor causing infection.[22] Moreover, the associated sensitive pathogenic bacteria are killed by the application of carbapenem antibiotics, while the resistant strains survive in large numbers, eventually leading to the occurrence of CRKP. Based on the above analysis, neurosurgery should pay strict attention to patients in the future. And according to the above experimental results, we believe that in the future clinical treatment of ICU patients, attention should be paid to hygiene, isolation of patients, prevention of cross infection, and strict grasp of the indications for the use of carbapenems antibiotics. Besides, local or hospital bacterial distribution characteristics should be understood, and initial empirical antibiotic therapy should be given correctly to avoid excessive use of carbapenem antibiotics. Furthermore, MV and invasive mechanical procedures should be avoided as far as possible, and the principle of aseptic operation should be strictly followed for patients who do require invasive procedures to reduce the possibility of CRKP infection. For those with multiple underlying diseases, while attaching importance to the treatment of basic diseases, it is necessary to improve the basic functions of patients as much as possible, alleviate the progression of basic diseases, and enhance the anti-infection ability of patients.

When comparing the therapeutic effects of Ti versus PB in the treatment of CRKP infection, we found no significant difference in the clinical efficacy and bacterial clearance between groups, suggesting stable and reliable efficacy of both drugs for the treatment of CRKP infection. This result can be expected as Ti and PB, the most commonly used drugs for CRKP, have been validated to be effective.[7,23] The slightly lower bacterial clearance and clinical efficacy in both patient cohorts may be due to the changes in airway structure caused by chronic lung disease in some patients. On the other hand, it may be because some neurosurgical patients are bed-ridden for a long time, leading to easy colonization of bacteria and their difficult removal. In the comparison of hepatorenal function and adverse reactions, we found significantly worse hepatorenal function and more serious gastrointestinal reactions in Ti group after treatment, indicating that high-dose Ti has greater toxic and side effects on CRKP-infected patients. It can be seen that in the future, we should be more cautious when choosing therapeutic agents for the treatment of CRPK infection.

However, the possibility of chance in statistical calculations cannot be ruled out due to the small number of cases included in this study. Besides, the dosage and frequency of Ti and PB, as well as the underlying diseases of patients, may all affect the final treatment outcome. Therefore, in the follow-up research, larger samples and more scientifically designed studies are needed to confirm the above views.

CONCLUSION

Tracheal intubation (or MV), multiple underlying diseases, consciousness disturbance, and use of carbapenem antibiotics are all independent risk factors for CRKP infection in neurosurgical patients, so we should pay attention to these conditions in the future to prevent CRKP from happening. In addition, both Ti and PB have excellent therapeutic effects on CRKP. But considering that high-dose Ti is easy to cause obvious liver and kidney damage and gastrointestinal reactions in patients, the treatment drugs should be carefully selected according to the actual situation of patients during the clinical treatment of CRKP infection, thus providing a more reliable guarantee for the prognosis of patients.

ETHICAL APPROVAL

The study protocol was approved by the Ethics Committee of The First Affiliated Hospital of Jinan University (No:JN2021524).

AUTHORS CONTRIBUTION

Ning Li and Huixuan Chen contributed equally to the work.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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