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Effect of dynamic monitoring based on renal function indexes on the efficacy and safety of vancomycin in the treatment of MRSA pneumonia in elderly patients

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Abstract

Objective: To explore the feasibility of dynamic monitoring based on renal function indexes to evaluate the efficacy and safety indexes of vancomycin in the treatment of methicillin-resistant Staphylococcus aureus (MRSA) pneumonia in elderly patients, and to provide reference for the evaluation of the feasibility of vancomycin pharmaceutical care. **Methods:** 118 elderly patients with MRSA pneumonia treated from March 2017 to February 2020 were divided into routine treatment group (n=56) and intervention group (n=62). Patients in the routine treatment group were treated with routine vancomycin, while patients in the intervention group flexibly adjusted the dosage of vancomycin according to the dynamic monitoring of endogenous creatinine clearance (CCR), blood creatinine (SCR) and urea nitrogen (BUN). The changes of CCR, SCR and BUN and the difference of vancomycin serum. Valley concentration were compared between the two groups before and after vancomycin treatment, and the correlation between the changes of CCR, SCR and BUN and vancomycin serum. Valley concentration was analyzed to explore the difference of clinical efficacy and adverse reaction rate between the two groups after treatment. **Results**: Two factor analysis of variance showed that the serum trough concentrations of SCR, bun and vancomycin in the intervention group were significantly lower than those in the routine treatment group, but the CCR value was significantly higher than that in the routine treatment group (P<0.05). Pearson correlation analysis showed that the serum. Valley concentration of vancomycin was negatively correlated with CCR (r=-0.473), but positively correlated with SCR (r=0.537) and bun (r=0.619) (P < 0.05) more.

Keywords: renal function; vancomycin; methicillin resistant staphylococcus aureus; pneumonia patients

1.Introduction

Methicillin resistant *Staphylococcus aureus* (hereinafter referred to as MRSA) is a kind of Staphylococcus aureus resistant to isoxazole penicillin and Cefradine or positive for MEC gene[1]. Due to the non-standard use of antibiotics, MRSA infection is increasing day by day, which mainly occurs in newborns and elderly patients[2], which seriously threatens people's life safety and physical and mental health. As a macromolecular glycopeptide antibacterial drug, vancomycin is the first-line treatment for MRSA pneumonia[3,4]. However, vancomycin is mainly metabolized by the kidney in the human body and has strong nephrotoxicity. If the dosage of vancomycin cannot be controlled in real time, it is easy to lead to renal function injury and even renal failure[5]. Referring to the guidelines of MRSA treatment guidelines (2012) formulated by the American Infection Society, China has also issued the Chinese expert consensus on the clinical application dose of vancomycin, which suggests that the concentration of vancomycin should be maintained at 15~20mg/L[6]. However, considering the individual situation of elderly patients, the dosage is often reduced according to clinical experience, which leads to the inability to balance the relationship between low drug concentration and renal toxicity. Therefore, finding a sensitive method that can reflect the concentration of vancomycin and the level of renal function is of far-reaching significance to evaluate the clinical efficacy and safety of vancomycin in elderly patients with MRSA pneumonia. Endogenous creatinine clearance (CCR), serum creatinine (SCR) and urea nitrogen (BUN) can effectively reflect the level of renal function. They are also one of the important indexes to evaluate renal function. In addition, it is reported that CCR, SCR and bun are correlated with the blood concentration and efficacy of antibiotics[7]. Based on this, based on the dynamic monitoring of renal function indexes (CCR, SCR and BUN), the author explored the relationship between them and the blood concentration, clinical efficacy and safety of vancomycin in the treatment of MRSA pneumonia in elderly patients, so as to provide a theoretical basis for the clinical use of vancomycin. The report is as follows.

2. Data and methods

2.1. Data sources

118 elderly patients with MRSA pneumonia diagnosed in the hospital from March 2017 to February 2020 were selected, and the clinical medical records were complete. The patients (72 males and 46 females) were aged from 38 to 69 years, with an average age of (55 ± 6.04) years. According to different treatment methods, they were divided into 56 cases in the routine treatment group and 62 cases in the intervention group. There was no significant difference in the general data between the two groups (P>0.05). See **Table 1** for details.

Inclusion criteria: (1) Those whose diagnosis met the "diagnostic criteria for severe pneumonia" in the guidelines for the diagnosis and treatment of community-acquired pneumonia in Chinese adults[8] formulated by the respiratory branch of the Chinese Medical Association; (2) Those

diagnosed with MRSA pneumonia by microbiological test results (that is, the patient coughed deeply after cleaning the mouth or isolated and cultured MRSA strain from tracheal sputum through sputum suction tube); (3) Age ≥ 60 years old, suitable for elderly patients; (4) There was no indication of renal injury or renal failure before vancomycin use.

Exclusion criteria: (1) Renal disease or renal transplantation, serum creatinine≥130 μmol/L or 24 h urine volume < 20 ml/h; (2) Heart, liver and other important organ dysfunction; (3) Those with pulmonary fungal infection or pulmonary tuberculosis; (4) Patients with mental illness and communication difficulties, unable to cooperate with the tester.

2.2. Administration method of vancomycin

Both groups were given basic treatment according to severe pneumonia, and 0.5g vancomycin hydrochloride for injection (product of Zhejiang Pharmaceutical Co., Ltd.) was added into 100ml of 0.9% sodium chloride injection and intravenous drip. Of which:

The patients in the routine treatment group received vancomycin 0.5g, q8H, intravenous drip for 1h, and the treatment time was 14 days.

In the intervention group, vancomycin 0.5g, q8H, intravenous drip was completed within 1h, and the treatment time was 10~14d, and the attending physician adjusted the administration scheme according to the monitoring of CCR level.

2.3. Monitoring of renal function indexes and blood drug concentration

The CCR and blood concentration were measured one day before the use of vancomycin, and on the first, third, seventh and fourteenth days after the use of vancomycin. CCR was calculated by Cockcroft formula, that is, CCR of male patients = (140-age) × Body mass (kg)/[0.85 × Serum creatinine(μmol/L)] (measured results of female patients in male patients) × 0.81）. The levels of serum creatinine (SCR) and urea nitrogen (BUN) were detected by P800 automatic biochemical instrument (Roche).

Table 1. General clinical data of patients in routine treatment group and intervention group (n/case%)

Group	Number of cases	Number of male/female cases	Age (T/year)	BMI	hypertension	History of COPD	Drinking history	Smoking history
Routine treatment group	56	32/24	70.73±9.14	25.04±4.22	19(33.93)	29(51.78)	39(69.64)	28(50.00)
Intervention group	62	40/22	71.27±9.88	25.83±4.97	25(40.32)	38(61.29)	36(58.06)	27(43.55)
t/ χ^2 value		0.330	1.257	0.914	0.514	1.083	1.703	0.492
P value		＞0.05	>0.05	＞0.05	＞0.05	＞0.05	＞0.05	＞0.05

Detection of blood drug concentration: 4ml fasting venous blood was collected, and the serum concentration of

vancomycin was measured by chemical immunoanalyzer i2000 (Abbott, USA). Because the nephrotoxicity of vancomycin is mainly related to its serum Valley concentration, this study takes the serum. Valley concentration of vancomycin as the research index.

2.4. Efficacy evaluation indicators and adverse reactions

According to the guiding standard for clinical research of antibiotics issued by the Ministry of health, the efficacy of vancomycin in the treatment of elderly patients with MRSA pneumonia is divided into cure, significant effect, improvement and ineffective. Among them: (1) The patients were cured, and the infection symptoms, signs, microbiological examination and laboratory indexes of the patients completely returned to normal after treatment. (2) After treatment, the patient's infection condition was significantly relieved, but only three of the above four indexes returned to normal. (3) After treatment, the symptoms and signs of infection were improved, but the microbiological examination results were still positive, and there were still some indicators that had not been recovered in the laboratory examination. (4) Ineffective, the patient did not appear obvious remission or even aggravation after treatment. The total effective rate is calculated by cure and obvious effect, that is, the total effective rate = (number of cured cases + number of obvious effect cases)/total number of cases in the group × 100%.

MRSA clearance rate calculation: If MRSA is negative in two consecutive sputum cultures and still negative after two weeks, it is determined that MRSA is cleared, that is, MRSA clearance rate = number of patients with MRSA clearance/total number of patients in the group × 100%.

After the patients were treated with vancomycin, the early morning venous blood was collected to detect liver function, renal function and blood routine, and the auditory evoked potential was measured to evaluate the effect of vancomycin on the index values of hearing, liver, kidney and platelet. The adverse reaction rate was calculated, that is, the incidence rate = the number of adverse reactions/the total number of cases in the group × 100%.

2.5. Evaluation index

(1) Comparison of blood drug. Valley concentration and CCR, SCR and BUN measured values at different time points before and after vancomycin treatment between the two groups; (2) The correlation between the concentration of vancomycin blood Valley and the measured values of CCR, SCR and bun; (3) The clinical efficacy and adverse reactions of the two groups after vancomycin treatment.

2.6. Statistical methods

Spss17. The data were analyzed by statistical software version 0. The data were expressed as mean ± standard error ($x - \pm s$), number of cases (n) and percentage (%). The differences of each index between the two groups at different times were compared by two-way ANOVA. Pearman correlation was used to analyze the correlation between serum trough concentration and CCR, SCR and BUN after vancomycin treatment. If the difference between the two groups is involved, F test or Z test is used for

comparison, and $P<0.05$ indicates that the difference is statistically significant.

3. Results

3.1. Effect of trough concentration on renal function before and after treatment in the two groups

After the serum. Valley concentration and the measured values of CCR, SCR and BUN in the two groups on the first day before treatment, the first day, the third day, the seventh day and the 14th day after treatment with vancomycin, it was found that with the extension of the time of vancomycin, the serum. Valley concentration of SCR, bun and vancomycin in the conventional treatment group gradually increased, while the CCR value gradually decreased. The changes of these four indexes in the intervention group tended to be gentle after the 7th day of vancomycin administration. Two factors analysis of variance showed that there was significant difference between the changes of serum. Valley concentration of vancomycin and the measured values of CCR, SCR and BUN between the two groups ($P<0.05$). See **Table 2** for details.

3.2. Correlation analysis between serum trough concentration and CCR, SCR and BUN

Pearson correlation analysis showed that the serum Valley concentration of vancomycin was negatively correlated with CCR ($r=-0.473$, $P<0.05$), and positively correlated with SCR ($r=0.537$, $P<0.05$) and bun ($r=0.619$, $P<0.05$).

Table 2. Correlation between serum trough concentration and measured values of CCR, SCR and BUN at different time points after vancomycin treatment in the two groups ($\bar{x} \pm s$)

Detection index	group	Different time points after vancomycin treatment					F value	P value
		Before administration	1D after administration	3 days after administration	7 days after administration	14 days after administration		
CCR (v/mL·min^{-1})	Routine treatment group	108.96±10.13	100.97±9.57	93.86±13.75	75.57±11.57	60.92±12.75,	17.853	<0.001
	Intervention group	106.42±10.97	102.64±9.97	90.85±11.74	84.94±17.63	78.46±9.25		
Scr (e/μmol·L^{-1})	Routine treatment group	58.94±28.41	66.37±31.63	96.04±41.64	136.35±53.27	186.98±72.83*	16.924	<0.001
	Intervention group	61.62±23.86	67.95±29.85	88.84±39.62	114.74±52.73	121.52±68.59		
BUN (c/nmol· L^{-1})	Routine treatment group	5.24±2.19	5.88±2.08	7.35±3.01	8.68±4.07	10.94±4.85*	10.241	<0.001
	Intervention group	5.52±2.73	5.83±2.61	6.48±2.65	7.23±3.29	6.96±2.81		
Serum trough concentration (ρ/ng·L^{-1})	Routine treatment group		8.47±2.35	14.36±5.46	22.64±9.57	31.73±8.95	14 857	<0.001
	Intervention		8.96±3.01	13.98±4.88	20.85±5.74	17.53±8.04*		

group								

Note: compared with routine treatment group (* $P < 0.05$).

3.3. Comparison of clinical efficacy between the two groups after vancomycin treatment

The study found that the total effective rate of vancomycin treatment in the intervention group was slightly lower than that in the conventional treatment group (72.60% *vs* 75.00%), but there was no significant difference by F test ($P > 0.05$). See Table 3 for details.

3.4. Comparison of MRSA clearance rate between the two groups after vancomycin treatment

The study found that MRSA was detected in the two groups before treatment, but the clearance rate of MRSA after vancomycin treatment in the intervention group was slightly higher than that in the conventional treatment group (64.28% *vs* 66.13%), but there was no significant difference between the two groups by Z-test ($P>0.05$). See T**able 3** for details.

3.5. Comparison of adverse reactions caused by vancomycin between the two groups

The total incidence of adverse reactions (liver function, renal function, hearing impairment and thrombocytopenia) after vancomycin treatment in the intervention group was lower than that in the conventional treatment group (4.84% *vs* 17.86%, $P < 0.05$). See Table 4 for details.

Table 3 Comparison of clinical efficacy and MRSA clearance after vancomycin treatment between the two groups

group	Number of cases (*n* cases,%)	Clinical efficacy (*n*/case,%)					MRSA clearance rate (*n*/strain,%)	
		Number of cured cases	Number of effective cases	Number of improvement cases	Number of invalid cases	Total effective rate	Number of clear cases	Clearance rate
Routine treatment group	56	22(39.29)	20(35.71)	12(21.43)	2(3.57)	42(75.00)	36	64.28
Intervention group	62	20(32.26)	25(40.32)	14(22.58)	3(4.84)	45(72.58)	41	66.13
F/Z value						0.089		0.091
P value						>0.05		>0.05

Note: the total effective rate was calculated by cure and significant effect, and there was no significant difference between the groups ($P > 0.05$).

Table 4. Comparison of adverse reactions after vancomycin treatment between the two groups (n/case%)

group	Number of cases	Number of cases of liver function injury	Number of cases of renal function injury	Number of hearing impairment cases	Number of thrombocytopenia cases	Total incidence
Routine treatment	56	2(3.57)	5(8.93)	1(1.79)	(2 3.57)	10(17.86)

group						
Intervention group	62	0((0.00)	2(3.23)	0(0.00)	(1 1.61)	3(4.84)*
Z value						5.087
P value						<0.05

Note: compared with routine treatment group (* $P < 0.05$).

4. Discussion

In recent years, the infection rate of MRSA has increased year by year all over the world. According to epidemiological studies, premature infants and the elderly are susceptible to MRSA[9]. Some studies have also found that in the age distribution of patients with MRSA infection, the isolation rate of MRSA in elderly patients is significantly higher than that in children, and their lung infection is also a common site of MRSA infection[10]. Vancomycin is still the first-line drug for the treatment of MRSA. Generally speaking, the blood concentration of vancomycin 10mg/l can play an anti infective role, but because vancomycin often accumulates in body fluid and has poor penetration, it is better to maintain the blood concentration of vancomycin at 15~20mg/L in the treatment of MRSA pneumonia[11]. If sufficient vancomycin blood concentration cannot be maintained, it is easy to induce MRSA and other pathogens to develop drug resistance, which is counterproductive[12]. If the blood concentration of vancomycin is too high, it can lead to serious adverse reactions, such as hearing loss, liver function damage, platelet abnormalities, etc., of which renal function damage is the most common[13]. Therefore, vancomycin, as a time-dependent antibacterial drug, effectively maintaining the blood concentration is the key factor affecting the success of its antibacterial and anti infective effect. However, the detection of its blood drug concentration and the early method of adjusting the dose of vancomycin through the blood drug concentration have not been popularized. Many grass-roots hospitals cannot monitor the blood drug concentration of MRSA infected patients in real time and make adjustments in time. Therefore, a simple and feasible method with guiding value of vancomycin dynamic detection is needed. The kidney is the main metabolic site of vancomycin, and the drug clearance rate and blood drug concentration are closely related to it. Therefore, taking the indicators reflecting renal function and renal clearance rate as the method to monitor the blood drug concentration of vancomycin may have guiding significance for patients with MRSA pneumonia.

After comparing the differences of serum trough concentrations of CCR, SCR, bun and vancomycin between the intervention group evaluated by renal function indexes and the routine treatment group, it was found that CCR, SCR and BUN in the routine treatment group tended to deteriorate after 7 days of vancomycin use, and the patients may have different degrees of renal function damage in terms of laboratory indexes on the 14th day. However, for the intervention group, due to the timely adjustment of the

dosage by the attending physician, the renal function of the patients on the 14th day was significantly better than that of the conventional treatment group, suggesting that real-time adjustment of the dosage of vancomycin is very important for the treatment of elderly patients with MRSA pneumonia, and suggesting that CCR, SCR and BUN may become indicators for monitoring the dosage of vancomycin. Therefore, after analyzing the correlation between the monitoring changes of CCR, SCR and BUN and the serum Valley concentration of vancomycin, the author found that CCR, SCR and BUN were correlated with the serum Valley concentration.

It is reported that CCR can directly reflect the renal clearance rate. If the CCR value is lower than 70ml/min, it often means that the renal clearance capacity decreases. It is found that the decrease of CCR value is related to the blood concentration of vancomycin and is an independent predictor of adverse reactions of vancomycin[14], which is consistent with the results of this study. However, Zhou Qingtao et al.[15] reported that there may be an increase in renal clearance rate in the early stage of vancomycin treatment of severe pneumonia, especially in the administration scheme of 0.5g/12h, suggesting that there may be insufficient administration in the early stage of clinical treatment, but the valley concentration will be too high from the use to the late stage of treatment. Therefore, it also shows the importance of adjusting its dosage scheme in real time. According to Xie et al.[16], it is believed that using CCR alone as the monitoring index of vancomycin can not fully grasp the patient's blood drug concentration, and it needs to be evaluated together with other indexes.

SCR is an important index reflecting early renal injury[17], bun can reflect the index of renal protein metabolism[18], and the two groups of indicators are highly sensitive to renal function damage. This study also believes that there is a correlation between the two and the blood concentration of vancomycin, which can be used as an evaluation index of auxiliary CCR. Through the changes of CCR, SCR and BUN values, the efficacy and safety of real-time intervention of vancomycin dosage on elderly patients with MRSA pneumonia were evaluated, and the efficacy indexes, MRSA clearance and adverse reactions of the two groups were compared. It was found that there was no significant difference in the efficacy and MRSA clearance between the two groups (P>0.05), but the incidence of adverse reactions in the intervention group decreased significantly. The blood concentration of vancomycin mentioned above is 15~20mg/L, which is the best blood concentration for the treatment of MRSA. Therefore, this study found that it is easy to reach the optimal therapeutic concentration of vancomycin at the third point of treatment, while the blood concentration of vancomycin is often higher than 20mg/L in the course of treatment from 7 to 14 days, resulting in adverse reactions such as renal function damage. This not only explains the consistency of the efficacy and clearance rate of the two groups after medication, as well as the decrease of the incidence of adverse reactions in the intervention group, suggesting the necessity of adjusting the

vancomycin dose through the monitoring of CCR, SCR and BUN values for safe medication, but also explains the importance of real-time adjusting the vancomycin dose for the treatment of MRSA infection. However, it should be noted that this study is a single center study with few enrolled cases, which needs to be further demonstrated by a large sample size multicenter prospective clinical study.

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