Earlier Targeted Vancomycin Troughs Concentration with Loading Dose: A Retrospective Study

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Research

Keywords: Vancomycin, Troughs concentration, Loading dose, Infection, Serum creatinine

Posted Date: March 1st, 2021

DOI: https://doi.org/10.21203/rs.3.rs-226665/v1

Abstract

Background: Studies have shown the failure of vancomycin treatment against vancomycin-sensitive gram-positive bacteria is common, possibly because the drug concentration did not reach the target serum concentration in time. In this study, we conducted a retrospective analysis to determine whether the target serum concentration could be reached earlier with the first loading dose of vancomycin.

Methods: A retrospective single-center study was conducted in the Department of Critical Care Medicine, Ruijin Hospital North Affiliated to Shanghai Jiao Tong University School of Medicine between June 2018 and June 2020. The study enrolled patients who were suspected or confirmed with gram-positive bacterial infection and had been treated with vancomycin. According to whether the first loading dose of vancomycin was given, the patients were divided into the loading dose and the control groups. The serum concentration of vancomycin before the second dose and that before the fifth dose were compared to determine whether the target serum concentration was reached earlier with the first loading dose. And renal functions were monitored for a week to analyze whether the loading dose caused any acute kidney injury.

Results: 55 patients were finally included in the study. Of these patients, 29 received first-loading dose of vancomycin, while the remaining 26 patients underwent the traditional dose regimen of vancomycin. The concentration of vancomycin before the second dose was 10.3±6.1 mg/L in the loading group, and 5.7±4.4 mg/L in the control group, significantly higher in the former group (P=0.002). The concentration of vancomycin before the fifth dose was 12.4±7.3 mg/L in the loading group, and 10.3±6.3 mg/L in the control group, where there was no inter-group difference (P=0.251). The 28-day motality of loading dose group is significantly lower (6.7% vs 34%, P=0.026) than the control group. There were no significant changes in serum creatinine levels in both groups, and there was no statistical difference in serum creatinine levels between the two groups.

Conclusions: With the loading dose of vancomycin, the target serum concentration of vancomycin could be reached earlier without causing acute kidney injuries, also the mortality might be reduced.

Introduction

Infections in critically ill patients may lead to sepsis or septic shock. Infections caused by multidrug-resistant Gram-positive pathogens always result in high medical cost and high mortality. MRSA strains with intermediate susceptibility to vancomycin and high-level resistance occur but are relatively infrequent. Vancomycin is still the first-line parenteral antibacterial for the treatment of invasive MRSA infections, especially MRSA bacteremia. Nevertheless, several observational studies reported a frequent correlation between vancomycin treatment failures and in vitro MICs at the upper end of the official range of “susceptibility”. One of the reasons for the failure of vancomycin treatment is inadequate dosing.

One study showed that 63% of doctors would change antibiotics from vancomycin to others when patients still have fever on day 2[1]. Frequent changing of antibiotics was associated with doctors’ lack of

pharmacokinetic knowledge on antibiotic dosing[2]. It is well known that the trough serum concentration of vancomycin should be measured before the fourth or fifth dosing in order to ensure that the targeted vancomycin trough levels are reached on the second day. However, at the same time, many doctors opt to change to other antibiotics. In such cases, vancomycin may actually have worked; it's just that the doctors are not aware of that. If the target trough serum concentration of vancomycin can be reached earlier, the patient outcome may be improved.

In this study, the serum concentration of vancomycin before the second dose was compared between the loading-dose group and the control group to verify the hypothesis that the targeted trough levels of vancomycin can be reached sooner with the loading dose, and to investigate the safety of the loading dose of vancomycin.

Methods

This retrospective single-center study was conducted in the Department of Critical Care Medicine, Ruijin Hospital North Affiliated to Shanghai Jiao Tong University School of Medicine between June 2018 and June 2020.

Inclusion criteria:

1) Patients who were treated in the Department of Critical Care Medicine, Ruijin Hospital North Affiliated to Shanghai Jiao Tong University School of Medicine between June 2018 and June 2020.

2) Patients who were suspected or confirmed with gram-positive bacterial infection and who had been treated with vancomycin.

3) Patients whose serum concentration of vancomycin before the second dose and the fifth dose were measured.

4) Patients of age > 18 years.

Exclusion criteria:

1) Patients on renal replacement therapy during the treatment.

2) Treatment duration of vancomycin ≤ 3 days.

3) Missing data such as vancomycin concentrations, follow-up data.

4) Patients who have been administered vancomycin within 3 days before admission to the ICU.

5) Changed the administration route of vancomycin from bolus injection to continuous infusion before the fifth dose.

6) Pregnancy.

All patients who met the inclusion criteria but not the exclusion criteria were included. According to the first dosage, patients were divided into two groups:

Group 1: the loading group. Patients received intermittent bolus doses as ordered by attending physicians based on their creatinine clearance rates. The first dose was 1.5 times of the conventional dose.

Group 2: the control group. Patients received intermittent bolus doses as ordered by attending physicians based on their creatinine clearance rates.

The target trough serum concentration of vancomycin was 10–20 mg/L.

Patients' blood samples were collected and stored at − 80°C until analysis. The serum concentrations of vancomycin before the second dose and before the fifth dose were measured. Serum concentrations of vancomycin were quantified by high-performance liquid chromatography (HPLC). The lower limit of quantification for plasma samples was 0.2 mg/L. Serum creatinine levels were tested daily.

A standard case report form was used to collect data including demographic characteristics, (*e.g.* age, gender, body weight, height), APACHE II score, SOFA score, diagnosis, infection position, type of pathogens, MIC of vancomycin for MRSA, creatinine, creatinine clearance, dosage and frequency of vancomycin, treatment duration, total dose of vancomycin, and outcome.

Statistical analysis

All statistical analyses were performed using Statistical Package for Social Sciences 23.0 (SPSS, Inc, Chicago, IL, USA). Results were expressed as mean ± SD, and categorical variables as the number of cases (*n*) and percentage of occurrence (%). Statistical analyses were performed using unpaired Student's *t* test and unpaired Wilcoxon rank-sum test to evaluate the continuous variables. The Chi-squared (χ^2) test was used to compare categorical data. The P value 0.05 was used to define statistical significance.

Ethics

For this retrospective study, the requirement for informed consent from each patient was waived in nature and because of the use of anonymized patient and hospital data. The study was approved by the appropriate ethics committee. This study was registered in the Clinical Trial Website (ChiCTR2000035369).

Results

55 patients were finally included in the study (Fig. 1), of which 29 received the loading dose of vancomycin, while the other 26 received the traditional dose of vancomycin.

General patient characteristics were presented in Table 1. There were no significant differences in age, sex, height, weight, SOFA score, and APACHEII score. Among the 55 patients, the sources of infections were lung, blood, skin and soft tissue, intracranial, abdominal, and urinary tract. There were no significant differences between the two groups in terms of the source of infections. The incidence of sepsis was similar. Pathogens were detected in 81% of the patients in the control group and 34% in the loading groups. Gram–positive pathogens detected include *S. aureus*, *Staphylococcus epidermidis*, *Staphylococcus cephalis*, *Staphylococcus hemolyticus*, *Streptococcus*, *Corynebacterium striatum*, *Enterococcus faecalis*, and *Enterococcus Faecium*. Among the aforementioned gram-positive bacteria, only Staphylococcus hemolyticus was different between the two groups in terms of detection percentage, with 5 cases in the control group, but no cases in the loading group. Among all the pathogens that were cultured, the minimum inhibitory concentration (MIC) of 24%, 36%, and 40% pathogens was 0.5, 1, and 2 mg/L respectively (Table 2).

The baseline body temperature and biochemical parameters were shown in Table 3. The body temperature and γ-GT levels in the loading group were higher than those in the control group. There were no differences in white blood cell (WBC), neutrophil ratio, C-reactive protein (CRP), procalcitonin (PCT), arterial oxygen partial pressure, arterial carbon dioxide partial pressure, sodium, potassium, albumin, prealbumin, transaminase, bilirubin, urea nitrogen, and lactate levels. Creatinine clearance was calculated by the following formula: Ccr = (140-age)*weight*88.4/72/Cr. In this study, there was no difference in serum creatinine, body weight, or creatinine clearance.

The doses and serum concentrations of vancomycin were shown in Table 4. The concentration of vancomycin before the second dose was 10.3 ± 6.1 mg/L and 5.7 ± 4.4 mg/L in the loading group and the control group, respectively. The concentration of vancomycin before the second dose in the loading group was significantly higher than that in the control group ($P = 0.002$) (Fig. 2). The concentration of vancomycin before the fifth dose was 12.4 ± 7.3 mg/L and 10.3 ± 6.3 mg/L in the loading group and the control group, respectively; there was no inter-group difference ($P = 0.251$). In the loading group, there was no difference in the concentration of vancomycin between before the second dose and before the fifth dose. In the control group, the concentration of vancomycin before the fifth dose was significantly higher than that before the second dose ($P = 0.004$). The mortality in loading group was much lower than that in control group ($P = 0.026$).

Renal functions were continuously monitored for one week after vancomycin administration. The results showed that there were no significant changes in serum creatinine levels in both groups, and no statistical difference in serum creatinine levels between the two groups (Table 5, Fig. 3).

Table 1
General characteristics of the patient population

Variables	Loading group (n = 29)	Control group (n = 26)	P
Age (years)	59 ± 14	57 ± 15	0.613
Female, n (%)	8(27.6)	7 (25.9)	0.889
Height (cm)	166.1 ± 7.4	168.6 ± 5.0	0.162
Weight (kg)	65.7 ± 11.0	67.4 ± 17.2	0.664
Body mass index (kg/m^2)	23.8 ± 3.6	23.6 ± 5.2	0.881
SOFA score	5 ± 3	6 ± 3	0.235
APACHEII score	12 ± 6	15 ± 7	0.061
Source of infection			
Lung	16	16	0.757
Blood	7	7	0.877
Skin and soft tissue	4	3	0.762
Intracranial	5	2	0.266
Abdominal	5	2	0.266
Urinary tract	3	0	0.086
Sepsis, n (%)	8(27.6)	11(40.7)	0.299
Bacteria cultured			
Staphylococci			
S. aureus	1	6	0.102
Staphylococcus epidermidis	2	4	0.650
Staphylococcus cephalis	2	0	0.085
Staphylococcus hemolyticus	0	5	0.042
Streptococcus	2	1	0.359
Corynebacterium striatum	2	1	0.359
Enterococcus faecalis	1	3	0.473
Enterococcus Faecium	0	1	0.391

Table 2
MIC in the two groups

MIC (mg/L)	Loading group	Control group	Total
0.5	0	6	6
1	5	4	9
2	1	9	10

Table 3
Baseline body temperature and biochemical parameters

Variables	Loading group(n = 29)	Control group (n = 26)	P
Temperature (°C)	38.5 ± 0.9	37.9 ± 1.0	0.030
WBC ($\times 10^9$/L)	12.2 ± 4.7	10.2 ± 6.4	0.184
N (%)	84.0 ± 7.4	83.6 ± 7.8	0.886
CRP (mg/L)	69.5[39.0-131.8]	56.0[35.0-88.3]	0.181
PCT (ng/mL)	4.8 ± 15.6	7.0 ± 20.6	0.665
PaO_2 (kPa)	17.9 ± 24.0	16.4 ± 5.5	0.766
$PaCO_2$ (kPa)	5.6 ± 2.8	5.2 ± 1.4	0.623
Na (mmol/L)	143.0 ± 8.6	140.2 ± 7.3	0.201
K (mmol/L)	3.9 ± 0.5	4.1 ± 0.4	0.302
Albumin (g/L)	32.9 ± 4.5	31 ± 6.5	0.231
Prealbumin (mg/L)	149.0 ± 70.3	131.3 ± 61.9	0.336
ALT (IU/L)	36.4 ± 29.5	39.2 ± 38.7	0.759
AST (IU/L)	44.6 ± 39.2	53.6 ± 97.0	0.653
TB (μmol/L)	19.7 ± 16.3	33.3 ± 73.3	0.351
DB (μol/L)	7.5 ± 10.7	16.9 ± 51.7	0.358
ALP (IU/L)	97.0 ± 54.8	76.6 ± 39.8	0.126
γ-GT (IU/L)	53.0[26.0–95.0]	31.5[21-63.5]	0.030
Cr (μmol/L)	85.0 ± 52.7	68.5 ± 22.0	0.146
BUN (mmol/L)	13.5 ± 22.1	16.9 ± 44.1	0.718
Cystatin C (mg/L)	1.4 ± 0.7	1.1 ± 0.5	0.183
Lactate (mmol/L)	2.1 ± 0.9	2.1 ± 1.4	0.997
CCr (ml/min)	90.7 ± 36.2	105.4 ± 34.5	0.134

Table 4
Results of serum concentrations of vancomycin and dosages of vancomycin

Variables	Loading group (n = 29)	Control group (n = 26)	P
Serum concentration of vancomycin before the second dose (mg/L)	10.3 ± 6.1	5.7 ± 4.4	0.002
Serum concentration of vancomycin before the fifth dose(mg/L)	12.4 ± 7.3	10.3 ± 6.3*	0.251
Ratio of serum concentration of vancomycin between that before the second and before the fifth dose	1.0 ± 0.7	0.9 ± 1.4	0.706
Total dosage of vancomycin (g)	14.3 ± 8.9	15.1 ± 11.4	0.771
Days of using vancomycin (days)	7 ± 8	8 ± 6	0.791
28-day mortality no. /total no. (%)	2/29 (6.7%)	9/26 (34.6%)	0.026

*compared with the serum concentration of vancomycin before the second dose in the same group, P = 0.004.

Table 5
Renal function after vancomycin used in the two groups.

	Variables	Loading group	Control group	*P*
Day2	Cr(μmol/L)	83.9 ± 54.5	66.1 ± 19.7	0.138
	BUN(mmol/L)	17.3 ± 39.9	18.7 ± 52.2	0.912
	Cystatin C(mg/L)	1.1[0.8–1.7]	1.0[0.8–1.3]	0.163
	CCr(ml/min)	92.0 ± 39.4	109.3 ± 41.2	0.134
Day3	Cr(μmol/L)	85.6 ± 57.2	65.0 ± 20.6	0.103
	BUN(mmol/L)	8.7[4.8–14.2]	7.6[4.8–11.4]	0.105
	Cystatin C(mg/L)	1.1[0.9-2.0]	1.0[0.9–1.5]	0.026
	CCr(ml/min)	88.8 ± 37.1	109.5 ± 32.8	0.043
Day4	Cr(μmol/L)	81.4 ± 54.7	66.4 ± 26.8	0.253
	BUN(mmol/L)	9.8 ± 4.4	8.4 ± 6.5	0.412
	Cystatin C(mg/L)	1.3 ± 0.5	1.1 ± 0.5	0.192
	CCr(ml/min)	88.7 ± 35.7	114.5 ± 38.7	0.027
Day5	Cr(μmol/L)	78.2 ± 41.7	65.8 ± 27.7	0.268
	BUN(mmol/L)	9.0 ± 4.2	9.0 ± 7.5	0.983
	Cystatin C(mg/L)	1.3 ± 0.5	1.1 ± 0.5	0.182
	CCr(ml/min)	93.7 ± 38.7	117.4 ± 45.0	0.067
Day6	Cr(μmol/L)	67.6 ± 19.9	65.4 ± 26.6	0.785
	BUN(mmol/L)	9.4 ± 3.6	8.6 ± 7.4	0.709
	Cystatin C(mg/L)	1.2 ± 0.3	1.1 ± 0.4	0.291
	CCr(ml/min)	96.7 ± 38.0	112.3 ± 43.6	0.277
Day7	Cr(μmol/L)	73.0 ± 33.9	70.3 ± 49.2	0.834
	BUN(mmol/L)	24.1 ± 70.4	14.8 ± 28.5	0.568
	Cystatin C(mg/L)	1.3 ± 0.5	1.2 ± 0.8	0.564
	CCr(ml/min)	100.2 ± 39.6	109.6 ± 37.8	0.428

Discussion

Vancomycin, a glycopeptide antibiotic, is often used in infections caused by Gram-positive micro-organisms. After 3–5 doses or at least 24 hours of continuous infusion (in order to reach steady state), the serum vancomycin level is routinely determined (therapeutic drug monitoring, TDM). The target levels are a trough concentration of 10–15 mg/L or 15–20 mg/L [3, 5]. Some studies reported that the trough concentration of vancomycin should be maintained at 20 mg/L or higher to reach a target value of the AUC/MIC ratio of 400 or higher [4]. The problem is that vancomycin can't be further used due to its toxicity. In the most recent guideline of IDSA (Infectious Diseases Society of America), a higher trough concentration of 15–20 mg/L has been suggested, which is related to an expected reduced susceptibility of the micro-organisms for vancomycin (MIC > 1 mg/L) [6]. Elevated vancomycin levels are correlated with the risk of nephrotoxicity, especially with prolonged therapy (> 7–14 days). A recent meta-analysis showed an odds ratio of 2.7 for nephrotoxicity in patients treated with vancomycin doses leading to troughs > 15 mg/L compared to patients treated with doses leading to troughs ≤ 15 mg/L [7]. Therefore, implementing new guidelines aiming at higher vancomycin serum concentrations should be carefully considered. In pediatric patients, the trough range of vancomycin of 8–15 mg/dL is considered to be therapeutic [8]. In the present study, the trough concentration was 10–20 mg/L. Serum creatinine levels were monitored daily. We found that the first loading dose did not cause kidney injuries.

We had to test the serum concentration of vancomycin before the fifth dose in the traditional regimen of vancomycin infusion, meaning that we had to wait for the result of serum concentrations of vancomycin for more than two days. This was a long waiting time, and patients might still have a fever. At this point, most doctors will choose to switch antibiotics [1]. The target concentration of vancomycin was reached earlier with the first loading dose. Some studies focused on the application of continuous infusion of vancomycin in order to reach target trough serum concentration [9–12]. Bly et al. [10] found that continuous infusion of vancomycin resulted in more sustained drug levels in blood. Akers et al. had similar observations [11]. However, therapeutic vancomycin levels were achieved infrequently in this study, with the target drug concentration achieved in only 22.6–30.7% of the no-CVVH patients. Wysoki et al. [12] found that, with continuous infusion of vancomycin, the target concentration could be reached faster with low variability. However, they found no difference in clinical outcomes and treatment failure between two groups. At the same time, there was a moderate increase in creatinine levels in both groups. In 2013, Eldemiry et al. [9] reported the opposite result. They found that there was a significant decline in serum creatinine levels after vancomycin treatment, but they did not provide any explanation. Continuous infusion always requires more efforts by the nurses, of whom there is a shortage in most intensive care units. This problem can be solved by the first-loading dose.

Vancomycin is mainly excreted from the kidney, thus its dose has to be adjusted by renal function. In our study, the dosage of vancomycin was adjusted according to renal function individualization. The first-loading dose is 1.5 times of the adjusted single dose. In this study, we found that there was no difference in creatinine levels between the loading group and the control group, suggesting that the first-loading dose of vancomycin was safe for ICU patients.

In our study, we observed a lower mortality rate in the load-dose group. This may be related to vancomycin reaching target concentration faster. Therefore, the loading dose may be beneficial to improve the prognosis of crtical care patients. However, our study sample size was small, and this finding needs to be confirmed in larger prospective studies.

Bacterial drug resistance is becoming more and more serious. The MIC of vancomycin against MRSA has been recently observed to be gradually increasing. Some experts worried about that vancomycin is no longer effective. The sample size of the present study was low, which led to the inadequacy of data for the analyses of the susceptibility and resistance of pathogenic bacteria to vancomycin. However, it was observed that the pathogenic bacteria with MIC = 2 were relatively increased.

MIC creep was observed not only with vancomycin, but also with linezolid and daptomycin[13]. New antibiotics are being developed. The combination effects of antibiotics have been studied and it turned out that certain combinations could enhance therapeutic effects [14]. Other important aspects, including hand hygiene, antibiotic management, and single isolation, should be considered to reduce the production of resistant bacteria.

Due to the critical conditions of ICU patients, clinicians often have little chance to adjust antibiotics. It is possible that some patients might die before the doses of antibiotics were increased. Therefore, ICU physicians tend to give patients strong antibiotics, such as carbapenems, vancomycin and linezolid. Both vancomycin and linezolid were first-line antibiotics for MRSA. It has been proved that systemic treatment with linezolid produces more beneficial effects than vancomycin in limiting the MRSA burden in endotracheal tube cuff. However, the effect of these two antibiotics to the outcomes of patients remains unknown [15].

Strengths and limitations

The present study is the first to report the effects of first-loading dose of vancomycin on the time of trough serum concentration. Serum creatinine levels were measured daily and there was no acute kidney injuries. Our study showed that the first-loading dose is safe. Trough concentration of vancomycin could be achieved earlier by the first-loading dose.

There are some limitations in our study: First, it is a retrospective study with many confounding factors such as the use of other antibiotics that may cause nephrotoxicity. Second, the small sample size of our study may lead to selection bias. Third, serum creatinine levels were tested in one week. Information on the long-term nephrotoxicity of vancomycin was not obtained. Fourth, our study did not include patients who had received renal replacement therapies, therefore the effect of first-loading dose on those patients were unknown. Further studies on these patients are warranted.

Conclusion

The present retrospective study suggests that, compared with standard doses, the first-loading dose of vancomycin is effective in achieving the target trough concentration earlier and has no deleterious acute effects on renal functions. The results can be corroborated in a future study with a higher sample size.

Declarations

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Ethical approval and consent to participate

The trial was conducted in accordance with the guiding principles of the Declaration of Helsinki and was approved by the appropriate ethics committee. This study was registered in the Clinical Trial Website (ChiCTR2000035369).

Consent for publication

Not applicable.

Availability of supporting data

It will be available from the corresponding author on reasonable request.

Conflict of interest

All authors report no conflicts of interest to declare.

Funding

Not applicable.

Authors' contributions

YH and LH were involved in the study design, protocol development and wrote this manuscript. YH and LH contributed equally to this work. YH, YD and RZ were responsible for clinical data collection. MM revised the raw manuscript. DC guided this study. All authors reviewed, revised, and approved the final version of the manuscript.

Acknowledgements

Not applicable.

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Figures

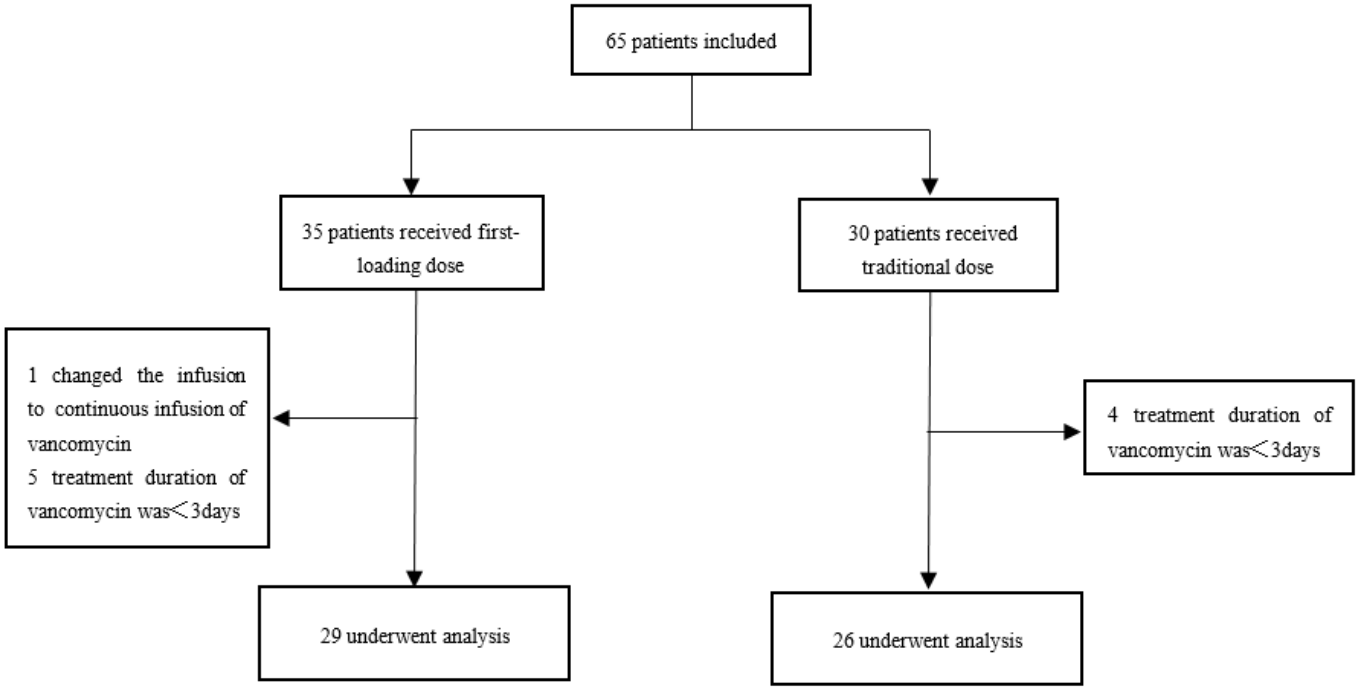

Figure 1

Flowchart of patient screening

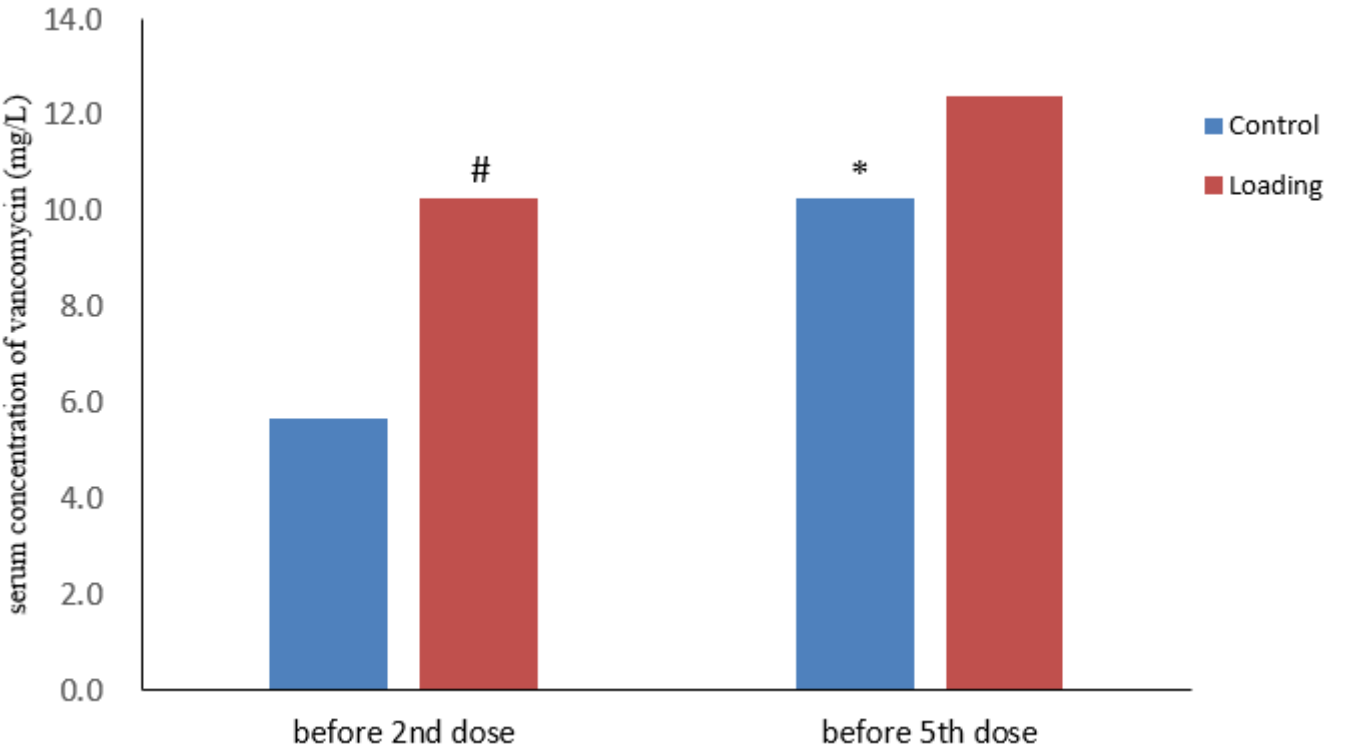

Figure 2

Serum concentrations of vancomycin. # Compared with control group at the same time, P0.05. * Compared with the serum concentration before the second dose within the same group, P0.05

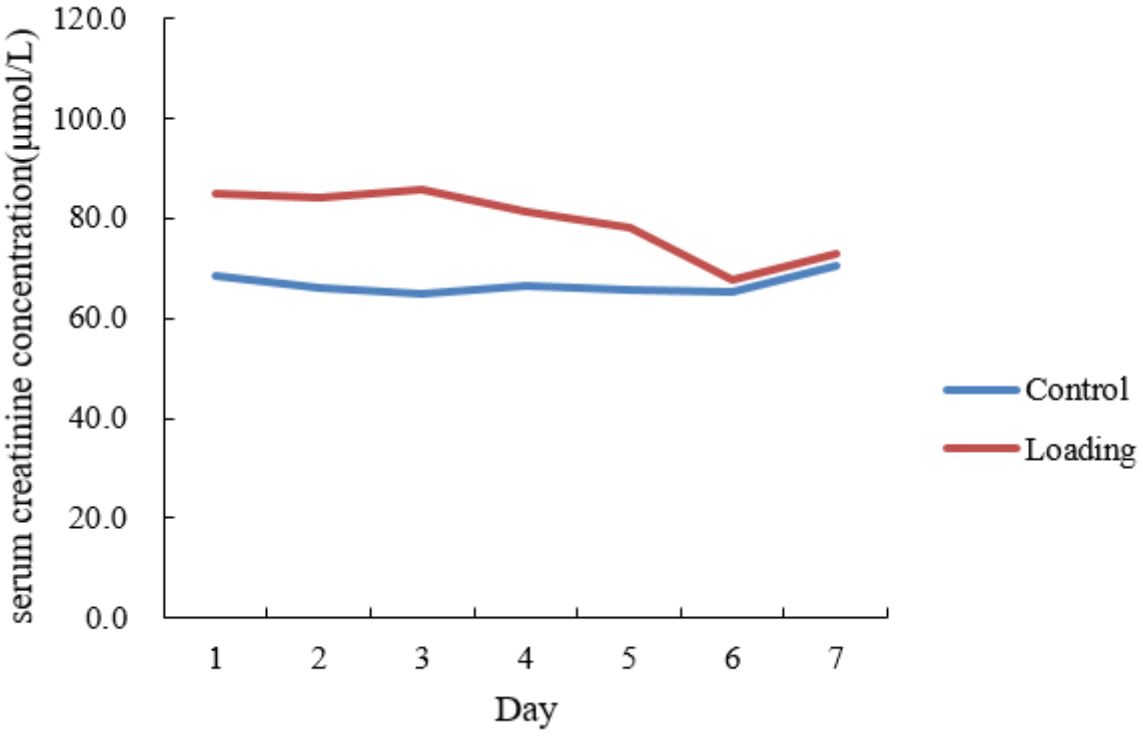

Figure 3

Serum creatinine concentrations. There were no significant changes in serum creatinine leves in 7 days in both groups. There were also no significant differences in serum creatinine levels between the two groups.