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ORIGINAL RESEARCH

Continuous Vancomycin Infusion versus Intermittent Infusion in Critically Ill Patients

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Background: Vancomycin is the best-choice medication for methicillin-resistant staphylococcal and enterococcal infections, which are major problems in intensive care units (ICUs). Intermittent infusion is standard for vancomycin, although delayed therapeutic target achievement and supra- and subtherapeutic levels are concerns. A recently proposed alternative with superior therapeutic target achievement is continuous infusion.

Objective: To compare the benefits of continuous (CVI) and intermittent (IVI) vancomycin infusion.

Methods: This quasi-experimental study used propensity score-matched historical controls and adult patients in medical and surgical ICUs for whom vancomycin was indicated. The experimental group received CVI for $\geq$ 48 hours. Data on patients receiving IVI between January 2018 and October 2020 were reviewed. Capability to achieve serum vancomycin therapeutic targets (48 and 96 hours), episodes of supra- and subtherapeutic levels, treatment success, mortality, and incidence of acute kidney injury (AKI) were analyzed before and after one-to-two propensity score matching.

Results: The CVI group had 31 patients, while the unmatched IVI group had 125. More CVI patients achieved the therapeutic target within 48 hours (54.8% vs 25.6%; P=0.002). CVI patients had a higher median number of supratherapeutic episodes (2 vs 1; P=0.007) but a lower median for subtherapeutic episodes (0 vs 1; P=0.003). Other outcomes demonstrated no differences. After propensity score matching, target achievement within 48 hours (54.8% vs 22.6%; P=0.002) and fewer subtherapeutic episodes (0 vs 1; P=0.014) remained significant.

Conclusion: CVI's rapid therapeutic target achievement and fewer subtherapeutic episodes make it superior to IVI. No differences in treatment success, mortality, or AKI are evident.

Keywords: continuous infusion, intensive care units, pharmacokinetics, therapeutic drug monitoring, vancomycin

Plain Language Summary

One of the key success factors in treating sepsis is rapidly achieving the antibiotic therapeutic target. We conducted a study comparing the continuous vancomycin infusion to the conventional intermittent infusion in critically ill intensive care unit patients and found that the continuous infusion provided better target attainment with lower episodes of subtherapeutic level. These findings give clinicians more confidence in using this method and may lead to a better outcome.

Introduction

The nosocomial Gram-positive pathogens, methicillin-resistant *Staphylococcus aureus* (MRSA) and Enterococci, cause severe hospital-acquired infections. Vancomycin has long been considered the first-line agent despite the availability of many new antibiotics. Administration of this agent requires a thorough understanding of pharmacokinetics and pharmacodynamics so that appropriate dose adjustments can be made to achieve the therapeutic index.

The antimicrobial activity of vancomycin varies directly with the area under a concentration curve divided by the minimal inhibitory concentration (AUC/MIC).[1–4] In human pharmacodynamic studies, values of more than 400 measured during 24 hours (AUC_{24}/MIC) are associated with successful treatment outcomes.[4–6] As a resistant organism might develop if the drug level is constantly low,[1,6] vancomycin therapeutic drug monitoring (TDM) is crucial to treatment success.

The 2009 guidelines of the Infectious Disease Society of America (IDSA) recommended that vancomycin TDM use a "trough level" between 15 and 20 mg/L before the fourth dose in cases of severe MRSA infection. Within this range, the AUC_{24}/MIC was believed to achieve a level >400 in most MRSA-infected patients, giving a minimum inhibitory concentration (MIC) of ≤1 mg/L. For nonsevere MRSA infections, the vancomycin trough level range could be lower, between 10 and 15 mg/L.[6]

Subsequently, evidence emerged that the trough level was not an acceptable therapeutic target. Even though the trough level might imply an AUC_{24}/MIC of >400, it cannot express the exact value of AUC_{24}/MIC, thereby risking an overdose. Therefore, the recent IDSA 2020 guidelines suggest using an AUC_{24}/MIC of 400 to 600 as the TDM target for MRSA infections.[7] In practice, however, using the AUC for TDM is problematic. This is because multiple vancomycin levels are needed for calculations or for use with Bayesian-derived AUC monitoring. Thus, TDM with trough level measurement remains the standard method.

In current medical practice, a loading dose, followed by intermittent vancomycin infusion (IVI), is the standard method of administering vancomycin. Delayed achievement and the risk of supratherapeutic or subtherapeutic levels are the major concerns of the IVI method, especially in critically ill patients with sepsis and alternating renal function. Recently, continuous vancomycin infusion (CVI) was introduced. It has been proposed as an alternative method that can more rapidly achieve the therapeutic target,[8–11] provide a steadier drug level,[8] and reduce renal toxicity.[12,13] Additionally, TDM is less complicated, serum concentration measurements can be performed at any time in the steady state, and the AUC can be easily calculated with fewer samples and without complex statistics. However, there are concerns regarding phlebitis and compatibility with other drugs.[14]

Rapid achievement and regular maintenance of the therapeutic target are needed in critically ill patients while avoiding adverse drug reactions. Hence, we conducted a study that aimed to compare the capabilities of CVI and IVI in achieving the therapeutic target.

Materials and Methods
Study Setting and Population
This was a quasi-experimental study with a propensity score-matched historical control design. It enrolled adult patients admitted to medical and surgical intensive care units (ICUs) at Siriraj Hospital, Bangkok, Thailand, who were indicated for vancomycin. The inclusion criteria were as follows:

- an age of at least 18 years,
- creatinine clearance of more than 30 mL/min/1.73 m²,[15]
- had or was suspected of having a staphylococcal or enterococcal infection, and
- vancomycin was indicated and was anticipated for at least 48 hours.

The historical control group subjects were selected by reviewing medical records to identify patients who met the inclusion criteria and received IVI between January 2018 and October 2020. Regarding the prospective experimental CVI group, patients meeting the inclusion criteria between January 2021 and December 2021 were screened for enrollment.

Ethics Approval and Informed Consent
Written informed consent was obtained from every CVI patient prior to study participation. Before this research began, the Institutional Review Board of the Faculty of Medicine, Siriraj Hospital, Mahidol University, approved its protocol (Si027/2021). The study was conducted per the Code of Ethics of the World Medical Association (Declaration of Helsinki). It was registered with the Thai Clinical Trials Registry (TCTR20210122005).

Study Design and Definitions

Immediately after the CVI patients were enrolled and their informed consent was obtained, a loading dose of 25 to 30 mg/kg (actual body weight) of vancomycin was administered at a maximum loading dose of 3000 mg. The maintenance dose of vancomycin was continuously infused per the study protocol (Figure 1). Other treatments (eg, other antibiotics, vasoactive agents, ventilatory management, or nutritional support) were decided by attending physicians according to the standard of care.

Continuous Vancomycin Infusion Protocol

Drug Preparation and Administration

In normal saline, vancomycin was diluted to a 10 mg/mL concentration. The drug was continuously infused over the next 24 hours with an infusion pump. The daily dose of CVI (mg/day) was calculated with the formula ($17 \times$ creatinine clearance) + 100.[16] Creatinine clearance was determined using the Cockcroft-Gault equation.[15]

Vancomycin TDM, Adjustment, and Discharge

The serum vancomycin concentration was measured 24 hours after the commencement of the CVI. The therapeutic target was a concentration of 15 to 20 mg/L. The infusion dose remained unchanged if the measured serum concentration was within this range. However, the dose was adjusted by an increase or decrease of 480 mg/day if the concentration was < 15 mg/L or > 20 mg/L, respectively. The maximum daily infused dose was 3000 mg/day.

The serum vancomycin concentration was measured every additional 24 hours, with the daily dose adjusted similarly. Once the concentration was within the target range on 2 successive days, we deemed that it had reached a steady-state concentration. Repeat measurements were subsequently made every 5 days. Nevertheless, additional tests were still possible, depending on the attending physicians' judgment. After 48 hours of CVI, attending physicians were encouraged to continue CVI, but the decision depended on them. Vancomycin was discharged once there were no longer any indications supporting its continued use or for other appropriate reasons.

Safety Monitoring

Complete blood count and serum creatinine were obtained on days 2 and 7 to monitor acute kidney injury (AKI) and drug-induced cytopenia. If vancomycin was administered via a peripheral vein, thrombophlebitis was monitored every 8 hours. Each patient was assessed for tinnitus and alteration of hearing upon completion of vancomycin treatment by the attending physician. In the event of these symptoms, an otolaryngologist consultation was made.
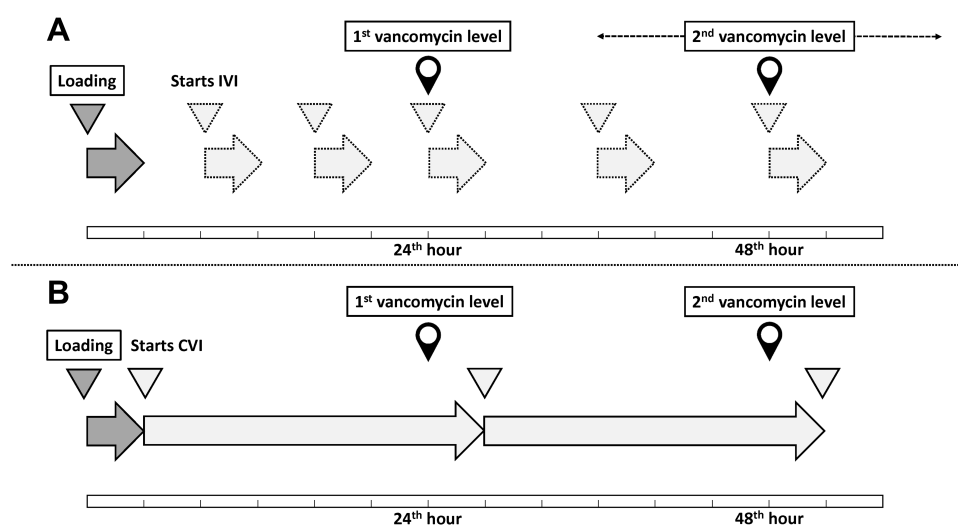

Figure 1 Comparison of intermittent vancomycin infusion and continuous vancomycin infusion protocols. Intermittent vancomycin infusion protocol (**A**); continuous vancomycin infusion protocol (**B**).
Abbreviations: CVI, continuous vancomycin infusion; IVI, intermittent vancomycin infusion.

Intermittent Vancomycin Infusion Protocol (Figure 1)

Our institution's protocol for IVI consisted of a 25 to 30 mg/kg (actual body weight) loading dose and a 15 to 20 mg/kg maintenance dose every 8 to 12 hours. TDM was made by measuring the vancomycin trough level 30 minutes before the fourth dose. The attending physician adjusted the dose to keep the trough level between 15 and 20 mg/L.

The medical records of patients in the medical and surgical ICUs who received vancomycin between January 2018 and October 2020 were reviewed. One of the investigators recorded the serum vancomycin levels intended for trough level measurement.

Measurement of Outcomes

The primary outcome was the capability to achieve a therapeutic target within 48 hours. This was defined as achieving a steady-state concentration of serum vancomycin either at 24 or 48 hours for the CVI group, or as reaching the trough level for the IVI group (15–20 mg/L) within 48 hours. The other outcomes of interest were achieving the vancomycin therapeutic target within 96 hours of the commencement of infusion and the median number of subtherapeutic and supratherapeutic episodes during this period.

Treatment success, mortality rate, AKI rate, and other adverse drug reactions were assessed in patients who received vancomycin as a definite treatment, defined by culture positivity for pathogens susceptible to vancomycin and with the drug given for at least 96 hours. Treatment success was defined as the resolution of the infection, indicated by clinical defervescence, improvement in abnormal signs and symptoms related to the infection, or disappearance of the pathogen. Mortality was assessed on day 14 after enrollment and before hospital discharge. If the patient was discharged before day 14, mortality was assessed on the discharge date. AKI was defined as a serum creatinine increase of ≥ 0.3 mg/dL or ≥ 1.5 times from baseline.[17]

Statistical Analysis

The sample size calculation was based on data from clinical trials.[18] A literature review revealed that 41% of patients using the CVI method reached a serum vancomycin level within the therapeutic target range compared with 11% of patients using the IVI method.[18] With a 95% confidence interval (Z=1.96) and a power of 90% (β=0.1), the sample size was calculated using the Z-test for 2 independent proportions (without continuity correction). At least 31 subjects needed to be prospectively enrolled in the CVI group. We planned to use one-to-two propensity score matching for the patients in the IVI group; thus, 62 subjects needed to be retrospectively reviewed in the IVI group.

Continuous variables were compared using the independent samples t-test for data with a normal distribution or the Mann–Whitney U-test for nonnormally distributed data. As appropriate, the categorical variables were compared using Pearson's χ^2 test or Fisher's exact test. Probability (P) values <0.05 were considered statistically significant.

All potential clinical parameters underwent univariate analysis to determine the primary outcome's predictive factors. The clinical parameters showing an association with the primary outcome, indicated by a P value of < 0.1 in the univariate analysis, were entered into a multivariable logistic regression model.

To balance the baseline characteristics that might interfere with the achievement of the primary outcome, propensity score matching was performed using a logistic regression model. Factors that might relate to the primary outcome, together with the method of infusion, were used. One-to-two patient baseline matching was planned using the nearest-neighbor method while balancing the key characters. All analyses were performed using PASW Statistics for Windows, version 18.0 (SPSS Inc, Chicago, IL, USA).

Results

In all, 156 patients were enrolled (experimental CVI group, 31 patients; historical IVI group, 125 patients; Figure 2). Almost half of the patients in both groups were female (48.4% vs 47.2%; P=0.906), with a non significantly higher mean age in the CVI group (62 ± 12 vs 52 ± 20 years; P=0.190). The CVI patients also had a higher mean weight (67.4 ± 17.4 vs 57.7 ± 12.4 kg; P<0.001), body mass index (26.26 ± 6.52 vs 22.24 ± 4.71 kg/m^2; P<0.001), and proportion with diabetes mellitus (58.1% vs 20.0%; P<0.001). Vancomycin was prescribed as the definite treatment for a higher
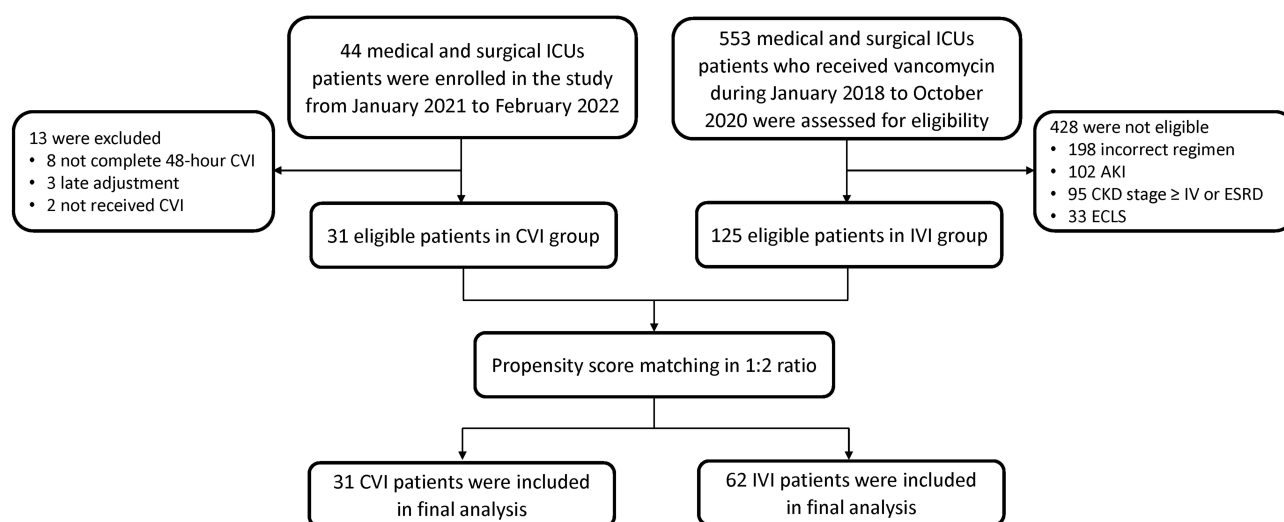
Figure 2 Study flow diagram.
Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; CVI, continuous vancomycin infusion; ECLS, extracorporeal life support; ESRD, end-stage renal disease; ICUs, intensive care units; IVI, intermittent vancomycin infusion.

proportion of patients in the IVI group than in the CVI group (41.6% vs 22.6%, respectively; *P*<0.001). The other baseline demographic and clinical characteristics of the 2 groups were similar (Table 1). For definite treatment, the leading sources of infection were catheter-related (CVI group, 28.6%; IVI group, 25.0%; *P*=1.000) and the bloodstream

Table 1 Baseline Demographic and Clinical Characteristics

Parameters	Overall Comparison			Matched Comparison		
	IVI (125)	CVI (31)	*P* value	IVI (62)	CVI (31)	*P* value
Female, n(%)	59 (47.2)	15 (48.4)	0.906	31 (50)	15 (48.4%)	0.883
Age, mean ± SD, years	52 ± 20	62 ± 12	0.190	62 ± 19	62 ± 12	0.945
Weight, mean ± SD, kg	57.7 ± 12.4	67.4 ± 17.4	<0.001*	61.3 ± 12.5	67.4 ± 17.4	0.059
BMI, mean ± SD, kg/m^2	22.24 ± 4.71	26.26 ± 6.52	<0.001*	23.98 ± 4.89	26.26 ± 6.52	0.061
Comorbidities, n(%)	118 (94.4)	28 (90.3)	0.417	60 (96.8)	28 (90.3)	0.329
Diabetes mellitus	25 (20.0)	18 (58.1)	<0.001*	23 (37.1)	18 (58.1)	0.055
ICUs admission, n(%)	117 (93.6)	28 (90.3)	0.458	56 (90.3)	28 (90.3)	1.000
Admission service, n(%)						
Internal medicine	90 (72.0)	21 (67.7)	0.639	45 (72.6)	21 (67.7)	0.628
Surgery	35 (28.0)	10 (33.3)	0.639	17 (27.4)	10 (33.3)	0.628
APACHE II, mean ± SD	18 ± 5	18 ± 4	0.808	18 ± 5	18 ± 4	0.865
SOFA score, mean ± SD	5 ± 3	5 ± 3	0.878	5 ± 3	5 ± 3	0.997
Definite treatment, n(%)	52 (41.6)	7 (22.6)	0.051	14 (22.6)	7 (22.6)	1.000
Creatinine, median (IQR), mg/dL	0.78 (0.55–1.11)	0.79 (0.63–1.10)	0.712	0.87 (0.63–1.15)	0.79 (0.63–1.10)	0.651
Creatinine clearance, median (IQR), mL/min/1.73m^2	75.1 (47.62–101.45)	95.09 (47.83–114.78)	0.312	72.45 (47.53–98.61)	95.09 (47.83–114.78)	0.176

Note: *Statistically significant.
Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; CVI, continuous vancomycin infusion; ICUs, intensive care units; IQR, interquartile range; IVI, intermittent vancomycin infusion; SD, standard deviation; SOFA, Sequential Organ Failure Assessment.

(CVI group, 28.6; IVI group, 21.2%; *P*=0.643). Most infections were caused by enterococci (CVI group, 42.9%; IVI group, 26.9%; *P*=0.399) and coagulase-negative staphylococci (CVI group, 28.6%; IVI group, 15.4%; *P*=0.338; Table 2).

Eleven parameters potentially affected the achievement of the vancomycin therapeutic level within 48 hours. The univariate analysis identified 3 of these factors as having a *P* value <0.1, and they were enrolled in our multivariate analysis model. Only CVI was determined to be an independent factor associated with achieving the therapeutic level within 48 hours (Table 3).

Regarding the primary outcome, 17 of the 31 patients (54.8%) in the CVI group achieved the therapeutic target within 48 hours, whereas 32 of the 125 IVI patients (25.6%) did, with a significant difference (odds ratio [OR]: 3.53; 95% CI: 1.56–7.96; *P*=0.002). However, the achievement of the vancomycin therapeutic level within 96 hours by the 2 groups was not significantly different (18/31 [58.1%] vs 62/125 [49.6%] patients; OR: 1.14; 95% CI: 0.64–3.12; *P*=0.399). During the study period, the median incidence of subtherapeutic episodes in the CVI group was significantly lower than that in the IVI group (median 0 [IQR 0–1] vs 1 [0–1]; *P*=0.003). Conversely, the median for supratherapeutic episodes was higher in the CVI group than in the IVI group (2 [IQR 1–2] vs 1 [0–2]; *P*=0.007). The therapeutic success rate, the 14-day mortality rate, and the in-hospital mortality rate of the 2 groups did not differ (Table 4).

Interestingly, although the vancomycin loading doses of the CVI and IVI groups were not different (25.91 ± 1.29 vs 26.12 ± 3.31 mg/kg; *P*=0.573), the maintenance dose for the CVI group was significantly lower (24.20 ± 9.96 vs 34.89 ± 8.37 mg/kg/day; *P*<0.001). The AKI rate was lower for the CVI patients (3/31 [9.7%] vs 26/125 [20.8%]; OR: 0.41; 95% CI: 0.12–1.45; *P*=0.154), but without significance.

For the matched cohort, propensity score matching resulted in 31 patients in the CVI group and 62 in the IVI group. There was no significant difference in any baseline clinical parameter (Table 1). The matching model revealed that a significantly higher proportion of CVI patients achieved the therapeutic target within 48 hours than IVI patients (17/31

Table 2 Definite Sources of Infection and Causative Organisms

	Unmatched			Matched		
	IVI (52)	**CVI (7)**	*P* value	**IVI (14)**	**CVI (7)**	*P* value
Sources of infection						
Bloodstream	11 (21.2)	2 (28.6)	0.643	3 (21.4)	2 (28.6)	1.000
Intraabdominal	9 (17.3)	2 (28.6)	0.604	1 (7.1)	2 (28.6)	0.247
Pulmonary	9 (17.3)	1 (14.3)	1.000	2 (14.3)	1 (14.3)	1.000
Genitourinary	2 (3.8)	0 (0.0)	1.000	1 (7.1)	0 (0.0)	1.000
Skin and soft tissue	3 (5.8)	0 (0.0)	1.000	1 (7.1)	0 (0.0)	1.000
Catheter-related	13 (25.0)	2 (28.6)	1.000	6 (42.9)	2 (28.6)	0.656
Endocarditis	2 (3.8)	0 (0.0)	1.000	0 (0.0)	0 (0.0)	–
Bone and joint	3 (5.8)	0 (0.0)	1.000	0 (0.0)	0 (0.0)	–
Causative organisms						
MSSA	10 (19.2)	1 (14.3)	1.000	1 (7.1)	1 (14.3)	1.000
MRSA	4 (7.7)	0 (0.0)	1.000	2 (14.3)	0 (0.0)	0.533
CoNS	8 (15.4)	2 (28.6)	0.338	2 (14.3)	2 (28.6)	0.574
MRCoNS	11 (21.2)	1 (14.3)	1.000	5 (35.7)	1 (14.3)	0.613
Enterococci	14 (26.9)	3 (42.9)	0.399	2 (14.3)	3 (42.9)	0.280
Others	5 (9.6)	0 (0.0)	1.000	2 (14.3)	0 (0.0)	0.533

Abbreviations: CoNS, coagulase-negative staphylococci; CVI, continuous vancomycin infusion; IVI, intermittent vancomycin infusion; MRCoNS, methicillin-resistant coagulase negative staphylococci; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*.

Table 3 Independent Variables Related to Primary Outcome (Logistic Regression)

Clinical Parameters	Univariate Analysis			Multivariate Analysis		
	Odds Ratio	(95% Confidence Interval)	*P* value	Adjusted Odds Ratio	(95% Confidence Interval)	*P* value
Female	0.60	(0.30–1.19)	0.143			
Age	1.02	(0.998–1.04)	0.086	1.01	(0.99–1.03)	0.267
Diabetes mellitus	2.52	(1.21–5.24)	0.012*	1.58	(0.68–3.65)	0.284
ICUs admission	0.79	(0.22–2.83)	0.742			
Internal medicine service	0.58	(0.28–1.20)	0.141			
APACHE II	1.02	(0.95–1.10)	0.548			
Vancomycin samples	1.22	(0.73–2.04)	0.453			
Creatinine clearance	1.00	(0.995–1.01)	0.943			
Body mass index	0.99	(0.93–1.05)	0.685			
Definite treatment	1.06	(0.53–2.13)	0.868			
CVI method	3.53	(1.56–7.96)	0.002*	2.93	(1.23–6.95)	0.015*

Note: *Statistically significant.
Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; CVI, continuous vancomycin infusion; ICUs, intensive care units.

[54.8%] vs 14/62 [22.6%]; OR: 4.16; 95% CI: 1.65–10.49; *P*=0.002). In addition, there were significantly fewer subtherapeutic episodes among patients receiving CVI (median 0 [IQR 0–1] vs 1 [0–1]; *P*=0.014). However, the 2 groups had no significant difference in their median numbers of episodes of supratherapeutic concentrations. Additionally, the occurrence of AKI in the groups did not differ significantly (Table 4).

Discussion

In this study, the CVI patients received an initial dose adjustment according to their renal function, followed by daily adjustments. In the IVI group, weight-based dose adjustments were rendered at the attending physicians' discretion to achieve the therapeutic target within 48 hours. The analysis found that CVI was superior to IVI in critically ill patients. A higher proportion of patients in the CVI group achieved the therapeutic target within 48 hours, and there were fewer subtherapeutic episodes among the CVI patients than the IVI patients.

The finding that a higher proportion of CVI patients achieved the therapeutic target at 48 hours with fewer subtherapeutic episodes is paralleled in previous studies. However, these works were retrospective, and uniform intervention in the treatment arm was lacking.[10,11,19] Although a few randomized controlled trials have been conducted, the IVI groups in these studies did not receive loading doses. The absence of a loading dose raises the concern that the better target attainment of the CVI group might be influenced by the initial loading.[8,9] Our propensity-score matching design and adequate loading dose for both groups minimized our concerns about many previous studies.

In our work, the total loading doses of the CVI and IVI groups were similar (25.91 vs 26.12 mg/kg). However, the daily maintenance doses were significantly lower in the CVI group (24.20 vs 33.31 mg/kg/day). Pea and Viale demonstrated this finding using the same loading and daily maintenance dosage, but their maintenance dosage was separated into CVI, IVI twice daily, and IVI 4 times daily. Pea and Viale's pharmacokinetic model revealed that CVI had a lower peak and a higher trough level than IVI.[20] This finding revealed another way the CVI method is superior to the IVI method.

We found no difference in mortality or AKI when focusing on the clinical outcomes. Although the incidence of AKI in the CVI group was half that in the IVI group, it did not reach statistical significance. Many studies have shown less renal toxicity in CVI patients.[11,13,19,21] The absence of a difference in mortality or AKI may have arisen because vancomycin was prescribed for three-quarters of our CVI cases as empirical treatment, with a median duration of 3 days.

Table 4 Outcomes

Outcome*	Overall Comparison				Matched Comparison			
	IVI (125)	CVI (31)	OR (95% CI)	*P* value	IVI (62)	CVI (31)	OR (95% CI)	*P* value
Primary outcome								
- Achieve therapeutic target within 48 hours	32 (25.6)	17 (54.8)	3.53 (1.56–7.96)	0.002	14 (22.6)	17 (54.8)	4.16 (1.65–10.49)	0.002
Secondary outcome								
- Achieve therapeutic target within 96 hours	62 (49.6)	18 (58.1)	1.41 (0.64–3.12)	0.399	26 (41.9)	18 (58.1)	1.92 (0.80–4.59)	0.142
- Level below therapeutic range	1 (0–1)	0 (0–1)	–	0.003	1 (0–1)	0 (0–1)	–	0.014
- Level over therapeutic range	1 (0–2)	2 (1–2)	–	0.007	1 (0–2)	2 (1–2)	–	0.242
- Successful treatment	116 (92.8)	31 (100.0)	–	0.206	59 (95.2)	31 (100.0)	–	0.548
- Mortality at 14-day	14 (11.2)	5 (16.1)	1.53 (0.50–4.61)	0.539	5 (8.1)	5 (16.1)	2.19 (0.58–8.24)	0.292
- Mortality in-hospital	58 (46.4)	15 (51.7)	1.24 (0.55–2.78)	0.605	28 (45.2)	15 (51.7)	1.30 (0.54–3.15)	0.559
Vancomycin therapy								
- Vancomycin duration	7 (5–10)	3 (2–5)	–	<0.001	7 (5–8)	3 (2–5)	–	<0.001
- Loading (mg/kg)	26.12 ± 3.31	25.91 ± 1.29	–	0.573	26.12 ± 3.31	25.91 ± 1.29	–	0.654
- Maintenance (mg/kg/day)	34.89 ± 8.37	24.20 ± 9.96	–	<0.001	33.31 ± 8.21	24.20 ± 9.96	–	<0.001
Adverse events								
- Acute kidney injury	26 (20.8)	3 (9.7)	0.41 (0.12–1.45)	0.154	13 (21.0)	3 (9.7)	0.40 (0.11–1.54)	0.174
- Thrombocytopenia	0 (0.0)	1 (3.2)	–	0.199	0 (0.0)	1 (3.2)	–	0.333

Note: *Data are presented as n (%), mean ± standard deviation (SD), or median (interquartile range, IQR), as appropriate.
Abbreviations: 95% CI, 95% confidence interval; CVI, continuous vancomycin infusion; IVI, intermittent vancomycin infusion; OR, odds ratio.

This period might have been too short to assess the effects, making it a limitation of our study. It is also challenging to document that AKI results solely from administering vancomycin. This is because each sepsis patient suffers many renal insults, such as sepsis itself, concomitant nephrotoxic medication, and inappropriate volume status.[8] Interpretations of the causes of AKI must therefore be made very carefully. The only rare adverse event of concern in our study was thrombocytopenia, which developed in 1 of the CVI patients (3%). This very low level is consistent with the literature. Last, most of our patients received CVI via a central vein, with only a few patients infused via a peripheral vein. No phlebitis related to the infusions was observed.

There are some notable limitations of our study. It was a single-center study, was unrandomized, and had a historical control group. Moreover, the investigation was powered for pharmacokinetics and was not intended to measure clinical outcomes. We cannot conclude any clinical benefits since more than half of the patients used vancomycin as an empirical treatment. Last, our study targeted pharmacokinetic outcomes on serum concentration. In contrast, the latest recommendation proposed the use of AUC_{24}/MIC.[7] A multicenter randomized controlled trial targeting AUC_{24} and comparing the CVI and IVI methods is needed to determine CVI's pharmacological and clinical benefits.

Conclusion

In conclusion, the present investigation confirmed that CVI appears beneficial in reaching the therapeutic target faster than IVI. It is also less likely to produce subtherapeutic concentrations without increasing the risk of treatment failure, mortality, and AKI. CVI should be considered an alternative infusion method in critically ill patients.

Data Sharing Statement

The dataset supporting this study's findings will be available from the corresponding author 1 year after publication for a period of 1 year upon a reasonable request.

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Disclosure

The authors have no conflicts of interest to disclose.

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