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ORIGINAL RESEARCH

External Validation of a Pharmacokinetic Model Developed for Vancomycin Administration via Target-Controlled Infusion

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Purpose: Target-controlled infusion (TCI) could provide a patient-tailored approach for vancomycin dosing. This study aimed to externally evaluate the predictive performance of a previously constructed pharmacokinetic model of vancomycin (Choi model) specifically optimized for TCI administration of vancomycin differing from the existing model, and to assess the feasibility of administering vancomycin via TCI in clinical practice. Additionally, clinical outcomes were exploratively compared between the TCI and intermittent infusion (standard) methods for vancomycin administration.

Patients and Methods: Clinically ill patients were randomly assigned in a 1:1 ratio to either the TCI or standard group. In the TCI group, vancomycin was administered using the Choi model, targeting an initial concentration of 25 mg/L, adjusted to maintain therapeutic levels (20–30 mg/L). The standard group received a loading dose of 25 mg/kg, then 15 mg/kg every 12 hours. Vancomycin concentrations for analysis were obtained from three blood samples per patient at set times, along with routine therapeutic drug monitoring data. Predictive performance was assessed using four parameters: inaccuracy, divergence, bias, and wobble. The occurrence of acute kidney injury (AKI) during and up to 7 days after vancomycin was investigated.

Results: The study was terminated early due to challenges in enrolling subjects (TCI: n=12, standard: n=13). Thirty-seven serum concentration measurements from the TCI group were analyzed. Pooled median bias and inaccuracy (95% confidence interval) were −2.7 (−7.3 to 1.9) and 17.0 (13.9 to 20.2), respectively. AKI incidence was similar between groups (TCI: n=0, standard: n=1) in this exploratory analysis, but caution is warranted in interpreting these outcomes as the planned sample size was not met.

Conclusion: The predictive performance of the TCI system integrated with the Choi model was suitable for clinical use. Further studies with a large cohort should be performed to determine the clinical effectiveness of vancomycin administered via the TCI method.

Trial Registration: This study was registered at the Clinical Research Information Service of the Korean National Institute of Health (CRIS, http://cris.nih.go.kr), with registration number KCT0003462, on January 31, 2019).

Keywords: vancomycin, concentration, pharmacokinetics, model, target-concentration controlled infusion, predictive performance

Introduction

Vancomycin is a critical antibiotic for treating infections caused by Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA).[1] Although widely used in clinical settings, conventional administration methods, such as intermittent infusion and continuous infusion, present significant limitations.[2] Intermittent infusion often causes substantial fluctuations in drug concentration between doses, making it challenging to maintain the therapeutic range (20–30 mg/L), and increasing the risk of nephrotoxicity,[3] thus necessitating continuous monitoring of peak and trough blood levels.[4] In contrast, continuous infusion maintains stable drug concentrations, reducing the risk of nephrotoxicity but necessitating an initial loading dose to promptly achieve therapeutic levels.

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To address these limitations, target-controlled infusion (TCI) has emerged as a more advanced and personalized dosing strategy.[5] TCI systems dynamically adjust the drug infusion rates in real time based on an incorporated pharmacokinetic model, maintaining drug concentration within the desired target range.[6] In addition, this approach accounts for patient-specific characteristics such as age, weight, and renal function, offering tailored therapy. A simulation study demonstrated that administering vancomycin through the TCI approach resulted in a significantly higher probability of achieving efficacious concentrations compared with conventional rule-based dosing methods, highlighting the potential of using TCI for individualized vancomycin administration.[7]

Numerous pharmacokinetic models for vancomycin administration have been developed. However, most of these models are constructed using therapeutic drug monitoring (TDM) data collected during routine clinical practice and are not specifically optimized for TCI administration of vancomycin.[8–10] Although numerous pharmacokinetic models have been developed for vancomycin, most of these models were built using therapeutic drug monitoring (TDM) data. Such models face challenges in accurately capturing the phase of rapid concentration changes that occur during or immediately after vancomycin administration, often resulting in the use of one or two-compartment mammillary models. Consequently, these existing models have limitations in accurately reflecting the pharmacokinetic properties of vancomycin, rendering them unsuitable for application in the TCI of vancomycin. In order to address these limitations, our group previously developed a three-compartment pharmacokinetic model (Choi model) for vancomycin administration through TCI in critically ill patients, utilizing vancomycin concentration data measured at predefined time points for research purposes apart from routine TDM data.[11] To implement this model in clinical practice, it is essential to evaluate its predictive performance in patient populations not involved in the original model development process.[12,13] Furthermore, comparing the clinical effectiveness of administering vancomycin via the TCI approach with that of standard administration methods would be meaningful.

Therefore, the objectives of this study were twofold: (1) to externally validate the formerly developed Choi model for TCI-based vancomycin administration, and (2) to compare the clinical effectiveness, including the acute kidney injury (AKI) incidence associated with administering vancomycin via the TCI method, with that of the conventional intermittent infusion method in critically ill patients.

Materials and Methods

Study Population

The Institutional Review Board of Asan Medical Center (Seoul, Korea) approved this study (approval no. 2018–1448; approval date: December 3, 2018), which was conducted in accordance with the Declaration of Helsinki. The study was also registered on an international clinical trials registry platform (http://cris.nih.go.kr; KCT0003462; registration date: January 31, 2019) before enrolling the first study participant. Written informed consent was obtained from the legal representatives of all patients involved in the study. The inclusion criteria included being ≥ 20 years old, weighing ≥ 40 kg, being hospitalized in the surgical intensive care unit, requiring vancomycin for clinical use as outlined by the Hospital Infection Control Practices Advisory Committee (HICPAC) guidelines, and having an estimated glomerular filtration rate (eGFR) of ≥ 60 mL/min/1.73 m², calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. The exclusion criteria included a history of allergic reactions to vancomycin, hemoglobin levels < 8 g/dL, pregnancy, or having received vancomycin within the past week.

Early Termination of Study Due to Difficulty in Recruiting Subjects

Patients were enrolled between June 18, 2020, and August 09, 2024. However, an increase in vancomycin-resistant enterococcus has led to a decrease in the number of patients receiving vancomycin in the intensive care unit.[14] Consequently, alternative antibiotics, such as teicoplanin—which offers similar efficacy to vancomycin, allows for once-daily dosing, and has fewer side effects—are being prescribed more frequently.[15] The difficulties in patient recruitment stemming from this change led to the premature discontinuation of the study. This shift in antibiotic use, along with specific protocol changes in the ICU regarding the administration of vancomycin, contributed significantly to the difficulties in patient recruitment, ultimately leading to the premature discontinuation of the study. A total of 25 patients (12 in the TCI group and 13 in the standard dosing group) were enrolled in the study. As a result, the interpretation of

these clinical outcomes should be approached with caution, as the failure to achieve the planned sample size impacts statistical power and the validity of the interpretation.

Patient Allocation and Study Drug Administration

Patients were randomly assigned in a 1:1 ratio to either the standard group (intermittent infusion) or the TCI group using computer-generated random numbers. Our institution uses the intermittent infusion method as the standard approach for administering vancomycin, so it was employed as a comparator to the TCI method. An independent coordinator, who was not involved in the study, handled patient randomization. In the standard group, patients were administered an initial dose of 25 mg/kg vancomycin via intermittent intravenous infusion. This dose was given over 1 h if the total dose was < 1.5 g or over 1.5 h if the total dose was ≥ 1.5 g. Subsequent doses of 15 mg/kg were administered every 12 h after initiating the first infusion over 1 h.

In the TCI group, 1 g vancomycin was diluted in 50 mL of 5% dextrose water to achieve a final concentration of 20 mg/L. Vancomycin was administered every 12 h using a TCI syringe pump (Pilot Anaesthesia 2, Fresenius Vial) connected to a personal computer via an RS232 cable and managed by the TCI software (Asan pump, version 2.1.5; Bionet Co. Ltd., Seoul, Korea). In the TCI method, once the specified dose set in the standard dosing group was fully administered, the target concentration was adjusted to zero, and the infusion was discontinued. The pharmacokinetic parameters of the Choi model, derived from a previous pharmacokinetic analysis study, were configured into the Asan pump.[11] The initial target serum concentration was set to 25 mg/L, with subsequent adjustments made based on measured vancomycin levels to ensure that the therapeutic drug concentrations were maintained within the range of 20–30 mg/L. The dosage and infusion rate were recorded in a "csv" file at 10-s intervals.

In both groups, vancomycin was administered until the attending physician determined that treatment for infection control was no longer necessary. Additionally, if AKI occurrence was suspected during treatment, the attending physician discontinued vancomycin administration in either group.

Blood Sampling and Measurement of Vancomycin Concentrations for Predictive Performance Analysis

In the TCI group, three arterial blood samples of 5 mL each were collected per patient for research purposes at predetermined intervals: 1 and 2 h after the first administration and 2 h after the second administration. Serum concentrations were analyzed at the clinical laboratory of Asan Medical Center, accredited by the College of American Pathologists and the Korean Society for Laboratory Medicine. Additionally, vancomycin concentration data were included in the predictive performance analysis if TDM was conducted throughout the administration of vancomycin via the TCI method.

Performance Analysis

The predictive performance of the TCI system, incorporating the previously developed Choi model, was assessed by calculating four standard parameters: inaccuracy, divergence, bias, and wobble.[16] The performance error (PE) concept was used to evaluate how close the measured value was to the predicted value, as follows:

$$PE_{ij} = \frac{measured_{ij} - predicted_{ij}}{predicted_{ij}} \quad (1)$$

where $predicted_{ij}$ is the j^{th} prediction of the serum vancomycin concentration in the i^{th} individual and $measured_{ij}$ is the measured serum vancomycin concentration.

The inaccuracy of a TCI system for the i^{th} individual was calculated as the median absolute PE ($MDAPE_i$) as follows:

$$MDAPE_i = \text{median}\left\{ \left|PE_{ij}\right|, j = 1, \ldots\ldots N_i \right\} \quad (2)$$

where N_i is the number of PE in the i^{th} individual.

Divergence, a measure of the expected systematic time-related changes in performance, was calculated for the i^{th} individual through the slope obtained from the linear regression of the $|PE_{ij}|$ values of that individual against time:

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$$Divergence_i\ (\% \cdot h^{-1}) = 60 \times \frac{\sum_{j=1}^{N_i} |PE_{ij}| \times t_{ij} - \left(\sum_{j=1}^{N_i} |PE_{ij}|\right) \times \left(\sum_{j=1}^{N_i} t_{ij}\right)/N_i}{\sum_{j=1}^{N_i} (t_{ij})^2 - \left(\sum_{j=1}^{N_i} t_{ij}\right)^2/N_i} \quad (3)$$

where t_{ij} is the time (in min) at which the corresponding PE_{ij} was determined.

Bias for the i^{th} individual was calculated as the median PE ($MDPE_i$):

$$MDPE_i = \text{median}\{\ PE_{ij}, j = 1, \ldots\ldots N_i\} \quad (4)$$

$Wobble_i$ for the i^{th} individual was a measure of the variability of the PE_{ij} in that individual:

$$Wobble_i = \text{median absolute deviation of}\{\ PE_{ij}, j = 1, \ldots\ldots N_i\} \text{ from } MDPE_i \quad (5)$$

Population estimates for inaccuracy, divergence, bias, and wobble were obtained using a pooled data approach considering the dependency between concentration measurements within each patient[16] and utilizing the software *fit4NM* 3.3.3 (Eun-Kyung Lee and Gyu-Jeong Noh, available at https://cran.r-project.org/src/contrib/Archive/fit4NM/, last accessed October 29, 2012).[17]

Comparison of Clinical Outcomes Between the TCI and Conventional Intermittent Infusion Methods

To compare the clinical outcomes of vancomycin administration via the TCI method with those using the conventional intermittent infusion method, we assessed the incidence of AKI during vancomycin treatment and up to 7 d after its cessation. AKI incidence was evaluated based on the Kidney Disease Improving Global Outcomes (KDIGO) guidelines.[18] Additionally, we recorded the total amount and duration of vancomycin administered, along with the changes in urine output and laboratory test results, including serum creatinine (Scr), eGFR, and creatinine clearance (CrCL) following administration.

Simulation

The simulated vancomycin dosage over 7 d was evaluated for both the TCI and intermittent infusion methods using stochastic simulation, considering inter-individual and intra-individual random variabilities. A hypothetical 70-year-old male patient with a weight of 60 kg and a height of 163 cm was assumed for the simulation. In the intermittent infusion method, a loading dose of 25 mg/kg (1.5 g) was administered, followed by a maintenance dose of 15 mg/kg (0.9 g) every 12 h for 7 d. Each dose was infused over 1 h. For the TCI method, the target concentration was set at 25 mg/L, with the same dosing interval used in the intermittent infusion method. Once the target dose was reached, the target concentration was adjusted to zero (0). Stochastic simulation was performed 1000 times for each administration method using *fit4NM* (version 3.3.3, Eun-Kyung Lee and Gyu-Jeong Noh, available at https://cran.r-project.org/src/contrib/Archive/fit4NM/, last accessed October 29, 2012). The infusion rate for the TCI method was also simulated using the TCI software (Asan pump, version 2.1.5; Bionet Co. Ltd., Seoul, Korea) in the same hypothetical patient.

Sample Size

As this is an exploratory study focusing on the predictive performance analysis of the Choi model, a specific calculation for sample size was not performed. In contrast, we aimed to recruit an adequate number of patients to obtain sufficient vancomycin concentration data for conducting a predictive performance analysis. To compare AKI incidence, the sample size was calculated as follows: according to a previous study, the average incidence of AKI in the intermittent infusion method was 26.2%, whereas continuous infusion method was associated with a reduced odds ratio of 0.5 for AKI occurrence.[3] We assumed that the TCI method would yield effects similar to those of continuous infusion in reducing AKI incidence. Accounting for a dropout rate of 10% and a 1:1 random allocation ratio, we calculated a total sample size of 354 patients, with 177 patients per group, to achieve a statistical power of 80% at a type I error rate of 0.05.

Statistical Analysis

Statistical analyses were performed using the *SigmaStat* software version 3.5 for Windows (Systat Software, Inc., Chicago, IL, USA). The *Shapiro–Wilk* test was used to assess the assumption of normality. Normally distributed continuous variables were compared using Student's *t*-test, while the Mann–Whitney *U*-test was employed for those continuous variables that were not normally distributed and for ordinal variables. Categorical variables were compared using either chi-square test or Fisher's exact test. Data are expressed as mean ± standard deviation (SD) for continuous variables with a normal distribution, median (25–75%) for non-normally distributed continuous variables, or as counts for categorical variables. A p value < 0.05 was regarded as statistically significant.

Results

External Validation of the Choi Model

The demographic data of the 12 patients included in the predictive performance analysis of the Choi model are detailed in Table 1. This study was initially designed to collect three arterial blood samples per patient for research purposes. However, three samples were not collected due to the omission of sample transportation to the laboratory, and a total of 33 samples for research purposes were obtained from 12 patients. Additionally, four blood samples were obtained for routine TDM data throughout the period of vancomycin administration by the TCI approach. Consequently, a total of 37 samples were available for the measurement of serum vancomycin concentrations. Comparison between measured (Cm) and predicted (Cp) concentrations of vancomycin is depicted in Figure 1. The changes in concentration over time are shown in Figure 2. No noticeable tendency in the measured concentration or the ratio of the measured concentration to the target vancomycin concentrations (Cm/Ct) over time was observed. The pooled bias, inaccuracy, divergence, and wobble of the TCI system equipped with the Choi model are depicted in Table 2. These results demonstrate the feasibility of administering vancomycin using the TCI method based on the Choi model in clinical settings.

Simulation

The simulated vancomycin dosage in a hypothetical 70-year-old male patient with a weight of 60 kg and a height of 163 cm over a 7-d period, using both TCI and intermittent infusion methods, is detailed in Table 3. Presuming that vancomycin was administered via the TCI method for 7 d, the total amount administered was approximately 14.4% less than that of the intermittent infusion method (11.3 g for the TCI method vs 13.2 g for the intermittent infusion method).

Comparison of Clinical Outcomes Between the TCI Method and the Conventional Intermittent Infusion Method

This study initially aimed to recruit 354 patients to evaluate the clinical outcomes of the TCI method compared to the conventional intermittent infusion method. Unfortunately, the study was prematurely terminated due to difficulties in patient recruitment. Ultimately, data were collected from 25 enrolled patients (12 in the TCI group and 13 in the standard group), and their clinical outcomes were compared in an exploratory manner. The characteristics of the patients and

Table 1 Demographic Characteristics of the Patients

	Standard Group (n = 13)	TCI Group (n = 12)	P-value
Age, years	67.8 ± 9.5 (50.0–80.0)	65.3 ± 9.0 (52.0–76.0)	0.517
Weight, kg	65.8 ± 21.3 (45.6–120.7)	64.4 ± 8.2 (48.3–78.8)	0.663
Sex, female	7 (53.8%)	6 (50.0%)	0.848
Height, cm	159.4 ± 10.0 (138.9–175.1)	162.1 ± 9.8 (148.7–182.0)	0.503
BMI, kg/m^2	25.9 ± 6.7 (18.6–39.4)	24.5 ± 2.9 (18.6–28.8)	0.786
IBW, kg	55.0 ± 7.7 (40.0–69.0)	57.7 ± 8.7 (46.5–74.1)	0.541

Note: Data are expressed as mean ± SD (range) or count (percent) as appropriate.
Abbreviations: BMI, body mass index; IBW, ideal body weight (calculated using the Robinson formula).[19]

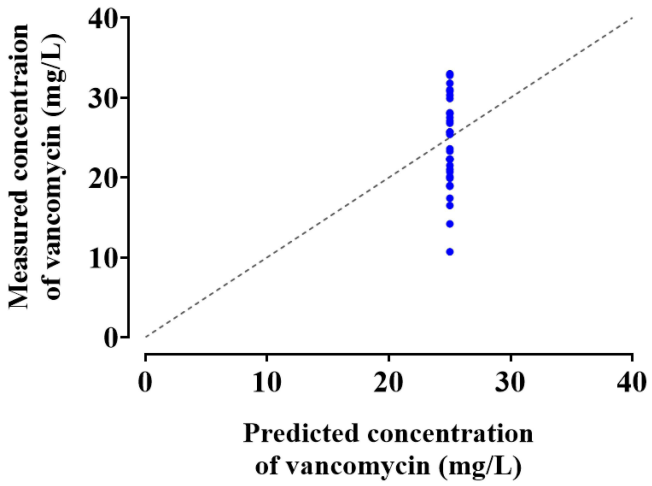

Figure 1 Comparison between measured (Cm) and predicted (Cp) concentration of vancomycin. The dotted line represents the line of identity. The data were obtained from enrolled patients (n = 12) who received vancomycin via the target-controlled infusion (TCI) method using the Choi model, with the target concentration set to 25 mg/L.

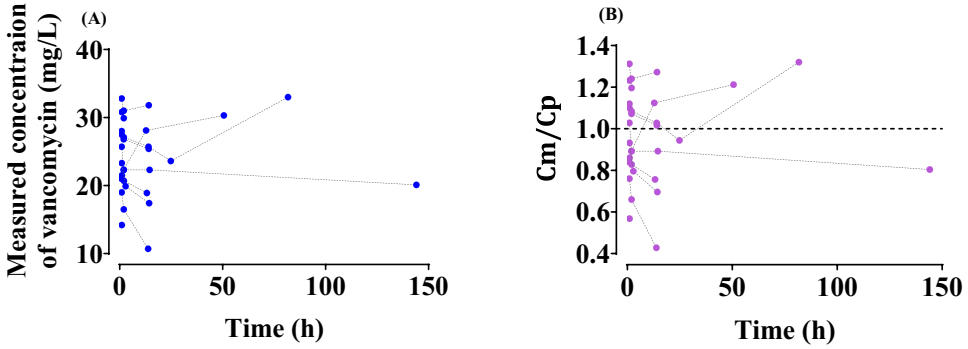

Figure 2 Time course of vancomycin concentration. (**A**) Measured vancomycin concentration (Cm) over time. (**B**) Ratio of measured to predicted (Cm/Cp) vancomycin concentration over time. Thirty-seven blood samples for serum concentration measurements were obtained from 12 patients during the administration of vancomycin via the TCI method.

variables related to clinical outcomes showed no significant differences between the groups (Table 4). The total amount, daily amount, and duration of vancomycin administered during the ICU admission were as follows:

1. Standard method: 5.5 (4.6–12.2) g, 2.2 ± 0.5 g and 3.0 (2.0–6.5) d
2. TCI method: 7.1 (5.8–11.6) g, 2.0 ± 0.3 g and 4.0 (3.0–6.0) d

There were no statistically significant differences observed ($P > 0.05$, for all). The proportion of patients who developed AKI during vancomycin administration and up to 7 d post-therapy was comparable between the two methods (1 patient [7.7%] for the standard method vs 0 patients [0.0%] for the TCI method, $P = 1.000$). Furthermore, there were no significant differences between the two groups in laboratory findings, urine output, and the number of patients requiring dialysis during vancomycin treatment and up to 7 d post-administration ($P > 0.05$ for all). However, the total number of enrolled patients for comparing clinical outcomes was 25, and the number of patients who experienced AKI was too low, making it inadequate for assessing AKI occurrence. Therefore, clinical outcomes could only be compared in an exploratory fashion, requiring caution in interpretation due to the small sample size and the study's exploratory nature, which limit the robustness of the findings.

Table 2 Pooled Bias (Median Performance Error, MDPE), Inaccuracy (Median Absolute Performance Error, MDAPE), Divergence, and Wobble of the Vancomycin Model

Parameters	Values
Bias (%)	–2.72 (–7.29 to 1.85)
Inaccuracy (%)	17.04 (13.87 to 20.20)
Divergence (% h^{-1})	–0.17 (–0.33 to –0.01)
Wobble (%)	5.86 (2.90 to 8.82)

Notes: Values are median (95% confidence interval). Bias: the median performance error (MDPE); inaccuracy: the median absolute performance error (MDAPE); divergence: the measurement of the expected systematic time-related changes in performance; wobble: the variability of the performance error.

Table 3 Simulated Amount of Vancomycin Over a 7-d Period When Vancomycin Is Administered via the Intermittent Infusion and TCI Methods

Period	Intermittent Infusion Method	TCI Method
Day 1	2.4	2.4
Day 2	1.8	1.8
Day 3	1.8	1.5
Day 4	1.8	1.4
Day 5	1.8	1.4
Day 6	1.8	1.4
Day 7	1.8	1.4
A total of 7 days	13.2	11.3

Notes: This is the result of stochastic simulations performed on a hypothetical 70-year-old male with a weight of 60 kg and a height of 163 cm. For the intermittent infusion approach, it was assumed that a loading dose of vancomycin was administered at 25 mg/kg (totaling 1.5 g), followed by maintenance doses of 15 mg/kg (0.9 g) at 12-h intervals over 7 d. The administration duration for vancomycin was assumed to be 1 h. For the TCI method, a target concentration of 25 mg/L was established. The dosing regimen mirrored that of the intermittent infusion method, maintaining the same administration intervals. Upon reaching the target dose, the target concentration was subsequently adjusted to 0.
Abbreviation: TCI, target-controlled infusion.

Discussion

This study demonstrates that the predictive performance of the TCI system incorporating pharmacokinetic parameters from the Choi model is clinically acceptable, considering the model's bias and inaccuracy. To successfully implement the TCI system with a pharmacokinetic model in clinical settings, it is essential to externally evaluate its predictive performance, which requires testing the model with data independent of its development dataset.[13] The predictive performance of a TCI system is typically assessed using bias (MDPE) and inaccuracy (MDAPE) parameters, as outlined by Varvel et al.[16] For a TCI system to be clinically acceptable, it has been suggested that the MDPE should be < 20% and the MDAPE < 30%.[13,24,25] In this study, we assessed the predictive performance of the Choi model based on these parameters in a distinct population separate from the original development cohort. Our results showed that the model's predictive performance fell within the clinically acceptable range: −2.7% (−7.3 to 1.9%) for bias and 17.04 (13.87 to

Table 4 Characteristics of the Patients and Variables Related to Clinical Outcomes

	Standard Group (n = 13)	TCI Group (n = 12)	P-value
Comorbidities (multiple answers allowed)			
Hypertension	9 (69.2%)	6 (50.0%)	0.428
Diabetes mellitus	4 (30.7%)	3 (25.0%)	0.667
Atrial fibrillation	0 (0.0%)	1 (8.3%)	0.480
Cerebral infarct	1 (7.7%)	3 (25.0%)	0.322
Myocardial infarct	1 (7.7%)	1 (8.3%)	1.000
Parkinson's disease	0 (0.0%)	1 (8.3%)	0.480
Asthma	0 (0.0%)	1 (8.3%)	0.480
Bronchiectasis	0 (0.0%)	1 (8.3%)	0.480
Reason for ICU hospitalization			
Postoperative care	11 (84.6%)	9 (75.0%)	0.645
Multiple trauma	0 (0.0%)	2 (16.7%)	0.220
Sepsis	1 (7.7%)	1 (8.3%)	1.000
Pneumonia	1 (7.7%)	0 (0.0%)	1.000
Laboratory tests before vancomycin administration			
Albumin, g/dL	2.2 ± 0.4	2.1 ± 0.4	0.452
Scr, mg/dL	0.8 ± 0.3	0.6 ± 0.2	0.119
eGFR, mL/min/1.73^2	85.0 (74.0–105.0)	95.1 (72.6–104.4)	0.041
CrCl, mL/min	75.5 (57.2–111.8)	112.5 (71.2–132.9)	0.174
APACHE II before vancomycin administration	17.0 (13.0–19.0)	15.0 (13.0–19.0)	0.826
Variables related to vancomycin administration			
Amount of vancomycin administered during ICU stay, g	5.5 (4.6–12.2)	7.1 (5.8–11.6)	0.339
Duration of vancomycin administered during ICU stay, day	3.0 (2.0–6.5)	4.0 (3.0–6.0)	0.253
Amount of vancomycin administered per day during ICU stay, g	2.2 ± 0.5	2.0 ± 0.3	0.158
Laboratory tests after vancomycin administration*			
Scr, mg/dL	0.7 (0.5–0.9)	0.6 (0.5–0.7)	0.073
eGFR, mL/min/1.73^2	95.1 (72.6–104.4)	117.1 (77.4–142.3)	0.128
CrCl, mL/min	90.5 (62.9–99.8)	117.1 (77.4–142.3)	0.157
Total urine output per day after vancomycin administration, L*	2.1 ± 0.6	1.9 ± 0.5	0.451
APACHE II on the date of vancomycin discontinuation	17.0 (14.0–18.5)	13.0 (12.3–17.0)	0.188
Incidence of AKI until 7 d after the end of vancomycin administration, n	1 (7.7%)	0 (0.0%)	1.000
Number of patients who underwent dialysis until 7 d after the end of vancomycin administration, n	1 (7.7%)	0 (0.0%)	1.000

Notes: Data are expressed as mean ± SD, median (25–75%), or count (percent) as appropriate. Data were compared using the two-sample *t*-test, Mann–Whitney rank-sum test, χ^2 test, or Fisher's exact test as appropriate. *Represented the mean value from the start of vancomycin administration to 7 d after the discontinuation of treatment. **Abbreviations**: TCI, target-controlled infusion; BMI, body mass index; IBW, ideal body weight (calculated using the Robinson formula);[19] Scr: serum creatinine; eGFR, estimated glomerular filtration rate (calculated using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] creatinine equation);[20] CrCl, creatinine clearance (calculated by the Cockcroft-Gault formula).[21] APACHE II, Acute Physiology And Chronic Health Evaluation II;[22] ICU: intensive care unit; AKI: acute kidney injury evaluated by KDIGO (Kidney Disease Improving Global Outcomes) guideline.[23]

20.20) for inaccuracy. This confirms the feasibility of administering vancomycin via the TCI method using the Choi model in a clinical setting. The primary objective of assessing the predictive performance of a TCI system is to determine how effectively the target concentration is maintained, which is particularly important when administering vancomycin, a drug with a narrow therapeutic range. Given that the TCI system does not account for inter-individual and intra-individual variability, even with a set target concentration, it is theoretically possible to have measured vancomycin concentrations maintain the predefined target in approximately 50% of patients. Therefore, the predictive performance evaluation of the Choi model conducted to confirm whether MDPE and MDAPE are at acceptable levels in the present

study can not only ensure the model's reliability but also may have significant clinical implications in minimizing toxicity risks and enhancing the therapeutic efficacy of vancomycin therapy.

However, our findings do not completely rule out the possibility that the predictive performance of the Choi model may not align well with patient populations that exhibit different physical characteristics than those used in the evaluation of external validity. Additionally, the MDAPE of 17% indicates that 50% of vancomycin serum concentrations will be within 17% of the target, while the remaining 50% may lie outside this range. This observed degree of inaccuracy in the TCI system incorporating the Choi model indicates that variability persists, requiring ongoing monitoring. This suggests that TDM blood sampling cannot be wholly omitted from routine clinical care. Nevertheless, integrating TCI into routine clinical practice can potentially decrease the frequency of TDM assessments for several reasons. First, TCI allows for real-time adjustments based on patient-specific parameters, which can tailor therapy more closely to individual needs.[5] As TCI continuously calculates and adjusts drug infusion rates based on ongoing input regarding patient characteristics, clinicians may find that less frequent checks are necessary to maintain therapeutic levels within the desired range. Additionally, the use of TCI can lead to more stable drug concentrations over time, minimizing the peaks and troughs often seen with intermittent dosing methods.[6] This stability can reduce the likelihood of subtherapeutic or toxic levels,[7] potentially allowing clinicians to extend the intervals between TDM assessments without compromising patient safety.

However, the Choi model was developed and externally validated in ICU patients with normal or mildly impaired renal function (eGFR range: 69.0–126.0 mL/min/1.73 m² for model development and 79.0–126.0 mL/min/1.73 m^2 for model validation). This raises the possibility that its applicability may be limited for clinically ill patients with more severely compromised renal function. Consequently, there are inherent limitations to the generalizability of the Choi model across the entire patient population in clinical settings. Further studies are needed to develop pharmacokinetic models and validate their predictive performance specifically in renal-impaired patients.

Furthermore, implementing TCI in daily practice necessitates clinicians who are proficient in understanding pharmacokinetic principles and interpreting data outputs to make informed clinical decisions. Essential equipment such as infusion pumps and TCI-specific software are also critical for successful implementation. The availability of personnel and such equipment can vary across hospitals and healthcare facilities, and the significant upfront investment required for TCI equipment and software may limit accessibility. These challenges could act as barriers to the widespread adoption of TCI-based drug delivery.

A three-compartment pharmacokinetic model for administering vancomycin via the TCI method was previously developed utilizing serum concentration data obtained for research purposes in critically ill patients.[11] Furthermore, in this study, the predictive performance of the model was externally validated in populations distinct from those used for its development. Consequently, based on the results of our studies, it can be suggested that there is a theoretical basis for achieving individualized vancomycin therapy by administering it via the TCI method. Particularly, the critically ill population is known for exhibiting significant inter-individual variation in vancomycin pharmacokinetics, underscoring the necessity for individualized dosing.[9,26] The Choi model incorporates covariates (patient-specific factors) such as ideal body weight for the central and slow peripheral volume of distribution, as well as age and body weight for clearance. As a result, vancomycin dosing during TCI using the Choi model may vary for each patient according to their physical characteristics, even when administered at the same concentration over the same infusion duration, thereby enabling tailored antibiotic therapy. Moreover, by using the TCI approach in these populations, clinicians may achieve more precise control over drug concentrations, potentially enhancing therapeutic efficacy and reducing the risk of anticipated adverse effects. However, these remain purely theoretical anticipations; therefore, practical evaluation is necessary to determine whether vancomycin administration via the TCI method in clinical practice actually improves clinical outcomes, such as reducing AKI incidence and decreasing dosage requirements compared to the standard dosing method. For this purpose, the authors also aimed to compare the clinical effectiveness and safety of vancomycin administration via the TCI method against conventional intermittent infusion in this study.[3] However, as noted in the results section, this study was unfortunately discontinued prematurely owing to challenges in patient recruitment. Consequently, our results related to the comparison of clinical outcomes should be interpreted with caution, as the planned appropriate sample size was not achieved. We only analysed the clinical outcomes of 25 enrolled patients to completion (12 in the TCI group and 13 in the standard group) in an exploratory manner without finding differences between the two groups in clinical

outcomes, particularly regarding AKI incidence and total vancomycin amount administered during the ICU admission. Recruitment issues that occurred in the present study may potentially skew the results, such as the low incidence of AKI observed in both groups and hinder the generalizability to a broader patient population. Thus, the small sample size and the exploratory nature of this study limit the robustness of these findings, and further research with an adequate sample size is needed to fully understand the implications of these results in clinical practice.

AKI attributed to vancomycin administration during the study occurred in only one patient in the standard dosing group (Table 3). This patient received vancomycin at a dose of 15 mg/kg twice daily, without an initial loading dose, totaling 2.63 g. The following day, Scr levels increased to more than three times the baseline, with a measured vancomycin trough level of 26 mg/L, resulting in a diagnosis of AKI due to vancomycin administration. Vancomycin was immediately discontinued, and Scr levels returned to normal 10 d later. Meanwhile, AKI occurred on the fifth day after initial discontinuation of vancomycin in one patient in the TCI group; however, this was not related to vancomycin administration via the TCI method. This patient received vancomycin by TCI for 3 d every 12 h before treatment was stopped at the attending physician's discretion. On the fourth day thereafter, due to worsening infective myositis in the thigh, vancomycin treatment was later resumed using a conventional intermittent infusion method, at a dose of 15 mg/kg twice, totaling 2.11 g. The following day after resuming treatment, Scr levels increased by > 0.3 mg/dL above baseline, with vancomycin trough concentrations measuring 34.5 mg/L, indicating the cause of AKI was vancomycin administration via intermittent infusion rather than the TCI method. Notably, the exploratory analysis in the 25 patients enrolled in this study revealed that AKI occurred in two patients who received vancomycin via the standard dosing method, whereas no cases of AKI were observed in patients administered with the TCI method. This may be attributed to the fact that unlike intermittent infusion, the TCI approach does not excessively increase the concentration outside the therapeutic range. However, no definitive conclusions can be drawn owing to the insufficient sample size. Therefore, additional research is warranted to comprehensively investigate whether vancomycin administration via the TCI method in clinical practice reduces the AKI incidence compared to the standard dosing method.

In our stochastic simulation, when we assumed that vancomycin was administered over a 7-d period via either intermittent infusion or TCI, the TCI method demonstrated a dose reduction of approximately 14.4% compared to intermittent infusion (Table 3). The reason for the reduction in dosage when administering vancomycin via TCI may be attributed to the fact that the dosage is determined based on the drug's disposition during TCI, which leads to a decrease in the infusion rate over time, and consequently, a reduction in the total amount administered.[11,27] However, we observed no difference in the actual total amount of vancomycin administered during the ICU stay between the two groups, which was 5.5 (4.6–12.2) g for intermittent infusion and 7.1 (5.8–11.6) g for the TCI method (Table 4). Unlike in the simulation results, the lack of difference between the two groups in the actual total amount of vancomycin administered in this study may be attributed to the shorter duration of vancomycin administration in the current patient cohort, which was 3.0 (2.0–6.5) d for intermittent infusion and 4.0 (3.0–6.0) d for the TCI method. Consequently, it is plausible that if the duration of ICU stay was extended, leading to a longer administration of vancomycin, the TCI method could potentially reduce the total amount of vancomycin administered compared with the standard dosing method. Therefore, further research is needed to determine whether the TCI method actually offers a reduction in total dosage compared to the standard method in daily clinical practice. In addition, currently available commercial TCI pumps do not incorporate vancomycin models, necessitating that users rely on software such as the Asan Pump to control these pumps for administration using the TCI method.[11] Therefore, to facilitate convenient use in clinical practice, there is a need to develop vancomycin-specific TCI pumps capable of reliably administering medications over extended periods.

Some limitations of this study should be considered. First, the Choi model's predictive performance was assessed in patients with normal or mildly impaired renal function. Previous studies indicate significant variations in vancomycin pharmacokinetics based on the degree of renal function,[28,29] particularly regarding creatinine clearance or eGFR as significant covariates.[7,10] The Choi model was developed using data from ICU patients with similar renal function levels, which may limit its applicability to patients with poorer kidney function. Therefore, validating this model in populations with such renal function would be advisable.

Second, the early termination of the study due to difficulties in patient enrollment meant that the planned sample size for comparing clinical outcomes between the TCI and intermittent infusion methods was not achieved. It remains unclear

whether vancomycin administration via the TCI method demonstrates superior clinical effectiveness and safety compared with conventional infusion methods. Further studies with large-scale studies are essential to provide a more substantial and comprehensive analysis of the practical outcomes of TCI methods. If such these advantages are confirmed, there is a strong likelihood that TCI will find widespread application in daily clinical practice. Future iterations of this study could benefit from a more flexible recruitment approach, such as targeting all ICU patients as well as those in the surgical intensive unit, to mitigate delays arising from changes in clinical practices, ultimately enhancing patient enrolment and ensuring that the study objectives are met. However, the sample size was deemed sufficient for evaluating the predictive performance of the Choi model. Due to its minimal impact on bias and inaccuracy results, the sample size is generally not considered a critical factor in the external validity assessment of pharmacokinetic models;[30] conducting these evaluations with even fewer than 10 patients can be feasible.[24]

Conclusion

In summary, using an external dataset, this prospective evaluation has substantiated the predictive performance of the recently published vancomycin population pharmacokinetic model (Choi model). Consequently, it can be concluded that administering vancomycin via the TCI method based on the Choi model can serve as a viable strategy in clinical practice, providing individualized dosing guidance while effectively maintaining the target therapeutic concentration over the desired duration. In addition, the TCI method for vancomycin administration has the potential to reduce the frequency of TDM in clinical practice although it cannot entirely eliminate the need for TDM blood sampling. However, this study provides exploratory analysis results derived from an insufficiently small cohort of patients regarding clinical outcomes associated with different vancomycin administration methods. Given the limitations of our findings, drawing definitive conclusions about the impact of these methods on clinical outcomes is challenging. Consequently, further research with a larger cohort is needed to comprehensively evaluate the clinical effectiveness and identify any additional clinical implications of vancomycin administration via the TCI method.

Data Sharing Statement

The datasets generated or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

This study was approved by the Institutional Review Board of Asan Medical Center (Seoul, Korea) approved this study (approval no. 2018–1448; approval date: December 3, 2018) and this study was conducted in accordance with the Declaration of Helsinki. The study was also registered on an international clinical trials registry platform (http://cris.nih.go.kr; KCT0003462; registration date: January 31, 2019) before enrolling the first study participant. Written informed consent was obtained from the legal representatives of all patients involved in the study.

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Author Contributions

All authors significantly contributed to the reported work, whether in the conception, literature search, data acquisition, analysis and interpretation, or across all these areas. They participated in drafting and writing, revised the article, reviewed, and approved all versions before submission. They also gave their final approval for the version to be published and agreed to be accountable for all aspects of the work.

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Disclosure

The authors do not have any conflicts of interest to declare in this work.

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