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Research Article

Comparing Two Equations for Estimation of Kidney Function (Cockcroft-Gault and Glomerular Filtration Rate Assessment in Liver Disease) for Vancomycin Dosing in Adult Liver Transplant Recipients: A Pilot, Randomized Clinical Trial

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Abstract

Background: In the setting of impaired liver function, estimation of glomerular filtration rate (GFR) using common creatinine-based equations is inaccurate. Recently, the Glomerular filtration Rate Assessment In Liver disease (GRAIL) model has been introduced to estimate GFR in liver transplantation. This study was conducted to compare vancomycin dose adjustment in liver transplant patients using Cockcroft-Gault (C-G) versus the GRAIL method.

Methods: In this pilot, randomized clinical trial, adult liver transplant recipients who were a candidate to receive intravenous vancomycin were enrolled. The level of kidney function was estimated using the GRAIL model and C-G equation in the intervention and control arms, respectively. Then, vancomycin maintenance doses were accordingly adjusted. At the steady state, peak and trough serum concentrations of vancomycin were collected for area under the concentration-time curve (AUC) calculation and pharmacokinetic comparisons.

Results: Fifteen patients were enrolled in each arm of study. The mean daily dose of vancomycin was estimated insignificantly lower for individuals in the GRAIL arm than the C-G group (1550.00±544.45 mg versus 1750.00± 389.60 mg). Compared with the C-G group, a higher rate of patients in the GRAIL arm experienced below-target vancomycin trough concentrations (40.0% versus 13.3%), and a lower rate showed above target trough concentration (40.0% versus 66.7%). These differences did not reach statistical significance.

Individuals in the GRAIL arm represented a significantly higher rate of below target vancomycin AUC/MIC than patients in the C-G arm (46.7% versus 6.7%) (P=0.049). No differences in clinical outcomes were observed between the two groups.

Conclusion: Using the GRAIL model for vancomycin dosing may result in less percent of patients with at target AUC/MIC compared to the C-G method and expose more patients at risk for vancomycin under dosing.

Introduction

Liver transplantation is the only life-saving and durable treatment option for patients with advanced liver disease.[1] Many liver transplant recipients have pre-existing impaired kidney function either independent of liver disease or as a sequel of advanced liver disease.[2] Besides, in the early or late phase post-transplantation, liver transplant recipients are at high risk of developing acute kidney injury (AKI) or chronic kidney disease.[3,4] Precise determination of kidney function is essential in liver transplant candidates because it affects the decision on combined kidney and liver transplantation, the estimate of medication dose adjustment, and modification of immunosuppression regimen.[5,6]

Although measurement of glomerular filtration rate (GFR) by the clearance of exogenous markers such as inulin is considered the best way to assess kidney function, it is not routinely used in the clinical setting due to its cost and burden.[7] Serum creatinine (sCr) is a readily available test which is widely used as an endogenous biomarker for estimating GFR(eGFR). The renal function could be easily estimated by sCr-based equations such as Cockcroft-Gault (C-G), Modification of Diet in Renal Disease (MDRD-4, MDRD-6), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). These formulas were not specifically obtained from studies in the liver transplant

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population or individuals with impaired liver function.[8-10]

In the setting of impaired liver function, sCr could be detected falsely low or normal; therefore, estimating renal function using laboratory data such as sCr or blood urea nitrogen (BUN) by formulas not specifically derived in this population is not precise.[11]

Recently, the Glomerular filtration Rate Assessment In Liver disease (GRAIL) model was introduced to estimate GFR, classify kidney function and organ allocation in the patients with liver diseases pre and post-liver transplantation. GRAIL model consists of various equations based on time points relative to transplant surgery and the prediction of kidney function. It was reported that GRAIL model had better performance to assess kidney function compared to MDRD-4, MDRD-6 and CKD-EPI formulas even in the patients with ascites.[12]

To the best of our knowledge, no data were published regarding the clinical use of the GRAIL method for drug dosing. This pharmacokinetic study was conducted to compare the medication dose adjustment in liver transplant patients using the C-G versus GRAIL method.

Materials and Methods

Study population

This pilot study was a single-blinded, randomized, two parallel groups clinical trial. Adult liver transplant recipients with stable kidney function (*i.e.*, less than 0.3 mg/dL variations in sCr levels within 48 hours) who were the candidate to receive intravenous vancomycin were evaluated for enrollment.

The exclusion criteria were as follows: patients with eGFR of less than 15mL/min/1.73m^2,[13,14] re-transplantation or simultaneous kidney and liver transplantation,[12] co-administration of oral vancomycin,[15] change in vancomycin dose before obtaining drug levels,[16] need for albumin administration within past two days,[17] receiving medications which interact with sCr assay (such as cephalosporins, cimetidine, high dose vitamin C and catecholamines),[18-21] pregnant and lactating women.[22]

The study was conducted in the liver transplantation ward of Imam Khomeini Hospital Complex, affiliated with Tehran University of Medical Sciences, Tehran, Iran, from September 2019 to February 2021. All patients in this study received their organs from deceased donors.

This project was approved by the local ethics committee of the Institute of Pharmaceutical Sciences, Tehran University of Medical Sciences (ID# IR.TUMS.TIPS.REC.1398.003). It was also registered in the Iranian registry of clinical trials (IRCT20100111003043N14) on 24/09/2019. All methods in this study were performed in accordance with the relevant guidelines and regulations, including the declaration of Helsinki. Participants signed an informed consent form before recruitment.

Intervention and data collection

Patients' demographic, laboratory and clinical data and information about microbial cultures were recorded during the study period.

In the presence of suspected or documented resistant gram-positive cocci infection, the loading dose of vancomycin was administered by an infectious disease specialist. Then, a specified clinical pharmacist was consulted to determine the maintenance dose of vancomycin to reach the serum trough level of 15-20 mg/L. The clinical pharmacist assessed the patient's eligibility for enrollment in the trial. A blocked randomization list with block size of 4 was created online by sealed envelope method. According to randomization list, patients were equally allocated into intervention group (GRAIL) or control group (C-G). Participants were blind to groups' assignment. sCr was measured by Jaffe method in the steady-state condition. Renal function was estimated using the GRAIL model (mL/min/1.73 m^2) in the intervention arm and by the C-G equation (mL/min) using total body weight in the control arm. C-G calculated creatinine clearance was corrected for body surface area (BSA) (1.73× CG (ml/min)/BSA (m^2)) and expressed by mL/min/1.73 m^2 unit. Equations are presented in Table 1. The clinical pharmacist adjusted proper vancomycin maintenance dose and interval according to estimated GFR and total body weight as recommended by Golighty.[23]

At the steady-state condition after the third maintenance dose of vancomycin, two blood samples as peak and trough concentrations of the fourth dose were collected. Peak level samples were obtained after the distribution phase, *i.e.*, 1 hour or 1.5-2.5 hours after completing a 2-hour infusion or a 1-hour infusion of vancomycin, respectively. Trough level samples were drawn 30 minutes prior to the fifth dose of vancomycin.[16] Chemiluminescent microparticle immunoassay technique was used for quantitative measurement of vancomycin concentration via an Architect i1000SR analyzer (Abbott®; USA). Measurement range of this instrument was 0.24 mg/L to 100.00 mg/L.[24]

A one-compartment model was assumed for the vancomycin distribution phase to describe pharmacokinetic parameters. Participants' elimination rate constant (k) was computed using observed steady-state vancomycin peak and trough levels of the same fourth dose. Then, the area under the concentration-time curve from 0 to 24 hours (AUC_{0-24}) was calculated. Pharmacokinetic formulas are presented in Table 1.

Considering the local antimicrobial susceptibility patterns of *Staphylococcus aureus*,[25] minimum inhibitory concentration (MIC) of vancomycin was assumed 1 mg/dL and AUC/MIC was calculated. Vancomycin trough level and AUC/MIC were categorized as follows: at target range at trough level of 15-20 mg/L and AUC/MIC of 400-600, below target at trough level<15 mg/L and AUC/MIC<400 and above target at trough level >20 mg/L and AUC/MIC>600.[26] In either arm of the study, vancomycin new dose was calculated for patients whose fourth dose trough concentration was not in the target range by the formula presented in Table 1.[16]

The primary outcome of this trial was the comparison

Table 1. Equations for GFR estimation and pharmacokinetic parameters.

Equation	Formula	Ref.
C-G (mL/min)	$\frac{[140-\text{age(year)}]\times\text{total body weight(kg)}\times[0.85\text{ if female}]}{\text{sCr(mg/dL)}\times 72}$	8
GRAIL (mL/min/1.73m^2)	1.GRAIL model[a] $\text{constant(ij)}\times\text{gender(ij)[if female]}\times\text{black(ij)[if black]}\times[\text{age(year)}]^{\text{age}-\exp(\text{ij})}\times[\text{sCr(mg/dL)}]^{\text{cr}-\exp(\text{ij})}\times[\text{BUN(mg/dL)}]^{\text{BUN}-\exp(\text{ij})}\times[\text{Alb(mg/dL)}]^{\text{Alb}-\exp(\text{ij})}$ 2.Trigger to estimate low GFR $\text{logit}=-7.281+0.793\times(\text{if female})-0.730\times(\text{if black})+0.526\times\log(\text{age})+3.706\times\log(\text{Cr})+1.263\times\log(\text{BUN})-2.662\times\log(\text{Alb})$ $p=1/(1+\exp(-\text{logit}))$ If 0≤p≤0.05 then trigger=0 else if p>0.05 then trigger=1 3. Coefficients for GRAIL model are selected based on timing of measurement and degree of renal dysfunction using trigger above.	12
K (1/h)	$\frac{\ln(\frac{\text{C peak}}{\text{C trough}})}{\Delta t}$	27
AUC_{0-24} (mg.L/h)	$\left[t'\times\frac{(\text{C peak}+\text{C trough})}{2}+\frac{(\text{C peak}-\text{C trough})}{k}\right]\times 24\text{hr}/T$	16
New dose (mg/day)	$\frac{\text{target concentration}}{\text{measured concentration}}\times\text{current dose(mg/day)}$	16

[a]On line GRAIL model calculator is accessible.[28]
Abbreviations: GFR: glomerular filtration rate; C-G: Cockcroft-Gault; sCr: serum creatinine; BUN: blood urea nitrogen; Alb: albumin; GRAIL: glomerular filtration rate assessment in liver disease; AUC: the area under the concentration-time curve.
Symbols: i= 0-1 (low GFR trigger: 0=predicted mGFR30+, 1=predicted mGFR<30); j= 1-6 (timing: 1=pre liver transplant on waiting list, post liver transplant: 2=day 1-30, 3=day 31-90, 4=day 91-1 year, 5=1-5 years, 6=5-25 years); k: elimination rate constant; C peak: vancomycin peak concentration at steady-state; C trough: vancomycin trough concentration at steady-state; Δt: time interval between sampling peak and trough concentrations of a same dose; *t'*: infusion time; τ: dose interval.

of percentages of patients reaching therapeutic pharmacokinetic targets after initial vancomycin dose selection in either arm. Another primary endpoint was the comparison of the initial daily vancomycin dose between the two groups. Secondary objectives were comparisons of the following items between study arms: duration of treatment with vancomycin, days of hospital stay, one-month mortality, resolution of fever or hypothermia, C-reactive protein (CRP) reduction, improvement in leukocytosis or leukopenia, and AKI due to vancomycin. Vancomycin induced AKI was defined using Acute Kidney Injury Network classification.[29]

Statistical analysis

The thumb rules for pilot studies were applied for determining the sample size. By assuming the medium effect size (standardized difference) and 90 percent powered the main trial, 15 patients in each study arm were considered for the current study.[30]

Quantitative variables were described by mean±standard deviation (SD) or median (interquartile range (IQR)) which is appropriate. Categorical variables were described using frequency and percentage. The normality of continuous variables was assessed by the Kolmogorov-Smirnov test. Univariate endpoints among arms were compared using Pearson chi-square test or Fisher exact test for categorical variables and t-test or Mann-Whitney test for continuous data. Vancomycin trough concentrations and AUC/MIC variability among treatment arms were compared with Levene's test. A log-rank test was used to compare patients' hospital length of stay among groups, accounting for the competing risk for death. For individuals with C-G<60mL/min and ≥60mL/min at baseline, a stratified analysis was performed. For this analysis, Breslow-Day's test was used to assess the homogeneity of the relationship among treatment arms and outcomes, including vancomycin trough concentrations and AUC/MIC categories (below versus at or above target) across baseline C-G categories. Clinical outcomes based on vancomycin trough concentrations and AUC/MIC categories were compared using Fisher exact test for categorical outcomes and Kruskal-Wallis test for continuous outcomes. Statistical analyses were conducted

by SPSS, version 23 statistical software. P values less than 0.05 were considered statistically significant.

Results

Fifteen patients in each arm completed the study (Figure 1). As seen in Table 2, patients' characteristics and demographic data were comparable between the two study groups at baseline. Ninety percent of the patients were presented during the first year after transplantation.

Information about infectious diseases, microbial cultures, and vancomycin dosages are presented in Table 3. Patients in both groups had comparable estimated kidney function based on C-G method. While considering applied eGFR formula based on group allocation, kidney function estimation based on GRAIL model in the intervention group was lower than kidney function estimation based on C-G equation in the control group. This finding was not statistically significant. The mean daily dose of vancomycin was lower for individuals in the GRAIL arm than the C-G arm, although this difference did not reach statistical significance.

The number (percent) of patients who achieved the target vancomycin trough concentration was similar between the two study arms. Compared with C-G group, the higher number of patients in the GRAIL arm experienced below-target vancomycin concentrations, and lower showed above target trough concentration. These differences did not reach statistical significance.

The higher number of patients with at target and above target vancomycin AUC/MIC were seen in the C-G group

Table 2. Patient characteristics and demographic data at baseline.

Characteristic	All (30)	GRAIL arm (15)	C-G arm (15)	P
Age (years)	46.17±12.71	47.73±12.13	44.60±13.49	0.509
Gender				0.065
Female	13(43.3)	9(60.0)	4(26.7)	
Male	17(56.7)	6(40.0)	11(73.3)	
Weight (kg)	63.87±10.54	61.13±9.59	66.60±11.05	0.159
Height (cm)	165.60±8.34	163.20±8.57	168.00±7.64	0.117
BSA (kg/m^2)	1.71±0.17	1.65±0.17	1.77±0.16	0.065
sCr (mg/dL)	1.40±0.61	1.38±0.77	1.41±0.41	0.884
BUN (mg/dL)	33.73±15.97	32.27±15.56	35.20±16.77	0.623
Albumin (g/dL)	2.79±0.71	2.80±0.63	2.78±0.81	0.940
Indication for liver transplantation				0.283
NASH	9(31.0)	3(21.4)	6(40.0)	
AIH	9(31.0)	7(50.0)	2(13.3)	
HBV	1(3.4)	1(7.1)	0	
HCV	1(3.4)	0	1(6.7)	
HBV-HDV	1(3.4)	0	1(6.7)	
PSC	4(13.8)	1(7.1)	3(20.0)	
Cryptogenic	2(6.9)	1(7.1)	1(6.7)	
Acute liver failure	1(3.4)	0	1(6.7)	
Liver metastasis	1(3.4)	1(7.1)	0	
Time post liver transplant				0.327
Day 1-30	16(53.3)	7(46.7)	9(60.0)	
Day 31-90	6(20.0)	5(33.3)	1(6.7)	
Day 91-year 1	5(16.7)	2(13.3)	3(20.0)	
Year 1-5	3(10.0)	1(6.7)	2(13.3)	
Calcineurin inhibitor agent				0.439
Tacrolimus	20(66.7)	9(60.0)	11(73.3)	
Cyclosporine	10(33.3)	6(40.0)	4(26.7)	
Renal function estimation				
C-G (mL/min)	66.10±26.43	68.33±34.88	63.87±14.79	0.652
C-G<60 (mL/min)	10(33.3)	4(26.7)	6(40.0)	0.439
Kidney function assessment according to the patients allocation (mL/min)[a]	-	55.27±26.66	63.87±14.79	0.287

Note: Values for categorical variables are given as count (percentage); values for continuous variables, as mean± standard deviation. P-values come from Chi-square test for categorical variables and independent sample t-test for continues variables.

[a] Kidney function was assessed based on C-G method in the C-G arm (control group) and based on GRAIL method in the GRAIL arm (intervention group). In order to comparison, eGFR values calculated by GRAIL model were converted to mL/min. Therefore, GRAIL value for each person was multiplied by BSA and divided by 1.73m^2.

Abbreviations: BSA: body surface area; sCr: serum creatinine; BUN: blood urea nitrogen; NASH: non-alcoholic steatohepatitis; AIH: autoimmune hepatitis; HBV: hepatitis B virus; HCV: hepatitis C virus; HDV: hepatitis D virus; PSC: primary sclerosing cholangitis; C-G: Cockcroft-Gault; GRAIL: glomerular filtration rate assessment in liver disease.

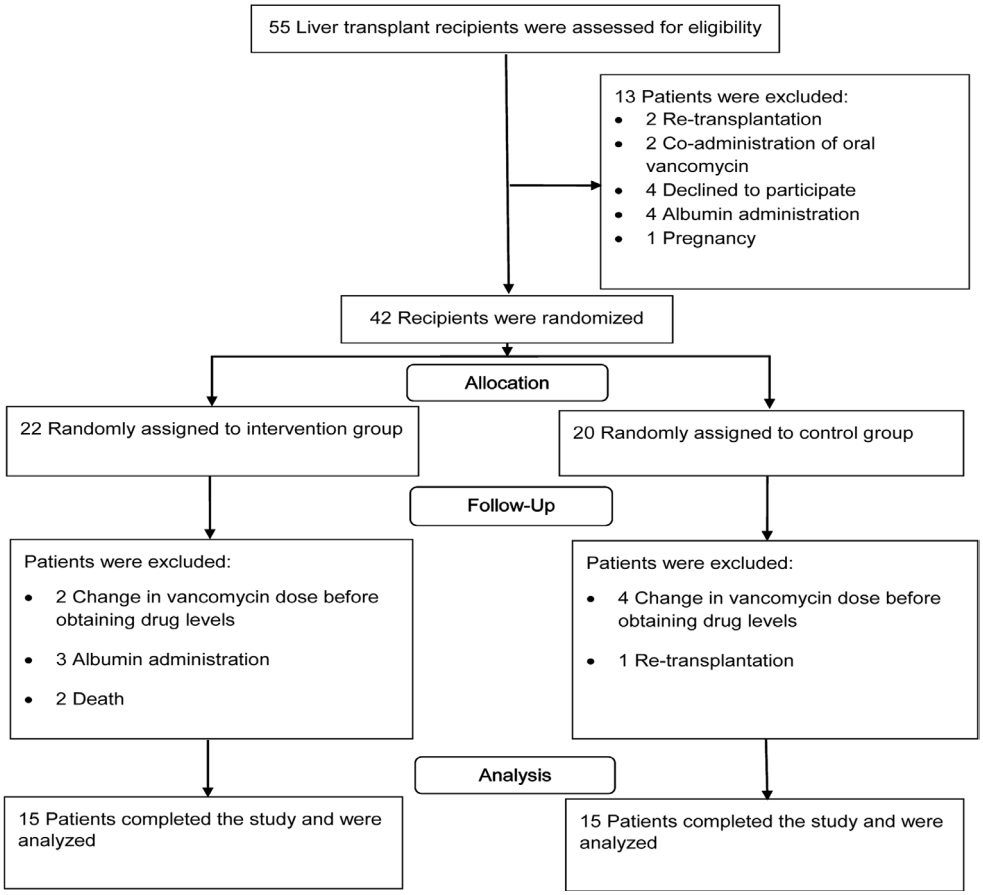

Figure 1. Patients' enrollment flow chart.

Table 3. Infectious disease and antimicrobial information.

Characteristic	All(n=30)	GRAIL arm(n=15)	C-G arm(n=15)	P
Suspected source of infection				
Pulmonary	13(43.3)	6(40.0)	7(46.7)	0.713
Abdomen	15(50.0)	6(40.0)	9(60.0)	0.273
Skin and soft tissue	4(13.3)	4(26.7)	0(0.0)	0.100[a]
Unknown	3(10.0)	1(6.7)	2(13.3)	1.000[a]
Microbiology				
Positive culture	12(40.0)	5(33.3)	7(46.7)	0.456
Gram + culture	5(16.7)	3(20.0)	2(13.3)	1.0[a]
MRSA	0(0.0)	0(0.0)	0(0.0)	-
VSE faecium	1(3.3)	1(6.7)	0(0.0)	1.0[a]
VSE faecalis	1(3.3)	0(0.0)	1(6.7)	1.0[a]
VRE	2(6.7)	1(6.7)	1(6.7)	1.0[a]
Vancomycin resistant streptococcus viridans	1(3.3)	1(6.7)	0(0.0)	1.0[a]
Vancomycin daily dose (mg)	1650.00±476.16	1550.00±544.45	1750.00±389.60	0.367
Concomitant antibiotic				
Meropenem	27(90.0)	13(86.7)	14(93.3)	1.0 [a]
Ciprofloxacin	10(33.3)	4(26.7)	6(40.0)	0.439
Cefepime	2(6.7)	2(13.3)	0(0.0)	0.483[a]
Colistin	4(13.3)	3(20.0)	1(6.7)	0.598
Levofloxacin	1(3.3)	0(0.0)	1(6.7)	1.0[a]

Note: Values for categorical variables are given as count (percentage); values for continuous variables, as mean± standard deviation. P-values come from Chi-square test for categorical variables and independent sample t-test for continues variables.

[a] Fisher's exact test.

Abbreviations: BSA: body surface area; sCr: serum creatinine; BUN: blood urea nitrogen; NASH: non-alcoholic steatohepatitis; AIH: autoimmune hepatitis; HBV: hepatitis B virus; HCV: hepatitis C virus; HDV: hepatitis D virus; PSC: primary sclerosing cholangitis; C-G: Cockcroft-Gault; GRAIL: glomerular filtration rate assessment in liver disease.

compared with the GRAIL group. Individuals in the GRAIL arm represented significant higher rate of below target vancomycin AUC/MIC than C-G arm (Table 4). Vancomycin trough concentration and AUC/MIC showed lower variabilities in the C-G arm than the GRAIL arm, although the differences were not significant (Figure 2).

When all patients were stratified according to the estimation of their baseline kidney function using the C-G formula (<60 mL/min versus ≥60 mL/min), the effect of study group (GRAIL versus C-G arm) on the distribution of vancomycin trough concentration was not modified by kidney function estimation (Figure 3; P= 0.080), but the effect of study group on vancomycin AUC/MIC distribution was modified (Figure 3; P=0.011). Among individuals with baseline C-G≥60 mL/min (n=20), the patients in the GRAIL arm showed a higher rate of below target (7 versus 0 patients), lower rate of at target (3 versus 4 patients), and a lower rate of the above target (1 versus 5 patients) AUC/MIC.

Clinical and laboratory outcomes, including 4-week mortality, vancomycin treatment duration, time to fever resolution, and CRP or leukocytosis improvement were similar between the study arms (P>0.05). Three patients (10%) experienced vancomycin-induced AKI. They were in the GRAIL arm and had AUC_{0-24} of more than 880 mg×h/L. Only hospital stay duration did significantly differ between patients who attained the target pharmacokinetic indices and those who did not (P<0.001) (Table 4).

Discussion

Due to the inaccuracy of conventional eGFR formulas for assessment of kidney function in liver transplant recipients and subsequent effects on medication dosing in the presence of impaired renal function, we designed this pilot study to evaluate the competence of the GRAIL model for drug dosing.

This study exhibited that kidney function estimation and vancomycin daily dose was insignificantly lower in the GRAIL group in comparison to C-G group. Nevertheless, a significantly higher percentage of patients in the GRAIL group had lower at target AUC/MIC in comparison to C-G group. In fact, a small change in vancomycin daily dose caused a large effect in the pharmacokinetic parameter associated with drug efficacy. However, vancomycin trough concentration was statistically comparable between the two study groups. AUC/MIC is the best pharmacokinetic/pharmacodynamics index for therapeutic drug monitoring (TDM) of vancomycin, while implementation of vancomycin trough level alone to predict the pharmacokinetic properties is associated with less accuracy.[26] Therefore, using GRAIL model for estimating kidney function and vancomycin dosing may put patients at the risk of under-dosing and perhaps treatment failure.

The results of the stratified analysis revealed that among individuals with baseline C-G≥60 mL/min, the patients in the GRAIL arm showed lower target AUC/MIC attainment. According to this finding, it seems the GRAIL model had less accuracy for estimation of GFR and subsequently less accuracy for vancomycin dosing in this subgroup. This finding can be justified by the results of the GRAIL study. Based on the GRAIL study, this model is more accurate in

Table 4. Vancomycin pharmacokinetic targets attainment and clinical outcomes based on study arms.

Characteristic	All (30)	GRAIL arm (15)	C-G arm (15)	P
Frequency of vancomycin target trough concentration attainment				0.276[a]
Below target	8 (26.7)	6 (40.0)	2 (13.3)	
At target	6 (20.0)	3 (20.0)	3 (20.0)	
Above target	16 (53.3)	6 (40.0)	10 (66.7)	
Frequency of vancomycin target AUC/MIC attainment				0.049[a]
Below target	8 (26.7)	7 (46.7)	1 (6.7)	
At target	10 (33.3)	4 (26.7)	6 (40.0)	
Above target	12 (40.0)	4 (26.7)	8 (53.3)	
Clinical outcomes				
AKI due to vancomycin	3(10.0)	3 (20.0)	0 (0.0)	0.224[a]
Mortality	2(6.7)	2 (13.3)	0 (0.0)	0.483[a]
Hospital duration stay (days)	24 [16.75-72.75]	21 [16-102]	24 [19-63]	0.728[b]
Vancomycin treatment duration (days)	10 [7-20.5]	9 [7-22]	10 [7-14]	0.838[c]
CRP improvement[e]	16 (59.3)	8 (61.5)	8 (57.1)	0.816[d]
Leukocytosis improvement[f]	10 (47.6)	3 (33.3)	7 (58.3)	0.387[a]
Fever resolution[g]	19 (100.0)	9 (100.0)	10 (100.0)	-

Note: Values for categorical variables are given as count (percentage); values for continuous variables, as median [interquartile range].
[a] Fisher's exact test.
[b] Log-rank test for comparing length of stay, accounting for death as a competing risk.
[c] Mann-Whitney test.
[d] Pearson chi-square test
[e] Patients who achieved ≥50% reduction in amount of CRP at the end of the vancomycin treatment duration.
[f] Patients who achieved resolution or improvement in leukocytosis within 48 to 72 hours after initiation of vancomycin treatment.
[g] Patients who achieved resolution of fever within 48 to 72 hours after initiation of vancomycin treatment.
Abbreviations: AKI; acute kidney injury, CRP; C reactive protein.

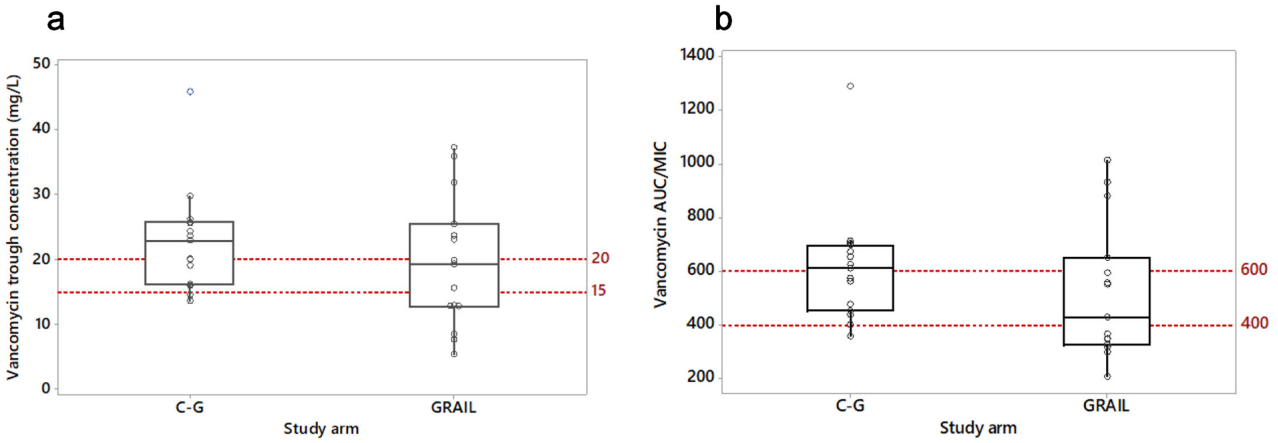

Figure 2. Vancomycin trough concentrations (a) and AUC/MIC (b) distributions according to the study groups.

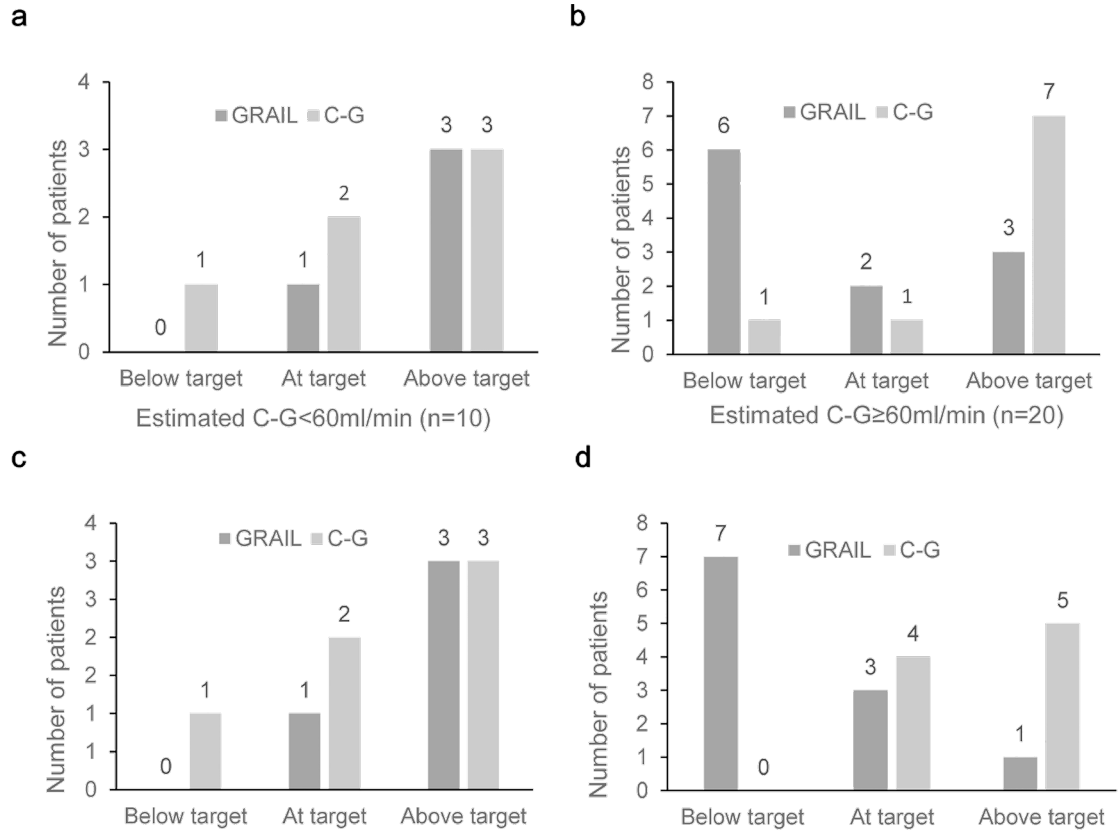

Figure 3. Stratified analysis based on kidney function estimation using C-G. (a) vancomycin trough distribution for patients with C-G<60ml/min. (b) vancomycin trough distribution for patients with C-G≥60ml/min. (c) vancomycin AUC/MIC distribution for patients with C-G<60ml/min. (d) vancomycin AUC/MIC distribution for patients with C-G≥60ml/min. The effect of study group on vancomycin trough concentration distribution was not modified by kidney function estimation using C-G at baseline (< 60 mL/min (a) versus ≥ 60 mL/min (b); P = 0.080). The effect of study group on vancomycin AUC/MIC distribution was modified by kidney function estimation using C-G at baseline (< 60 mL/min (c) versus ≥ 60 mL/min(d); P= 0.011).

the presence of the kidney dysfunction especially in GFR of less than 30mL/min/m^2.[12]

Although the clinical outcomes and adverse effects were comparable between the two study arms, this study was not sufficiently competent to determine these secondary outcomes because various confounding factors influence these endpoints.

Based on 2020 FDA guidance for industries, pharmaceutical companies can use any accepted sCr-based formulas for either estimation of GFR (including MDRD and CKD-EPI) or estimation of creatinine clearance (including C-G using total body weight, ideal body weight, or adjusted body weight in over-weight and obese patients) in order to design drugs pharmacokinetic studies in patients with kidney dysfunction. GRAIL model has not yet been introduced by FDA for such studies.[31]

For a large number of medications especially old drugs, the C-G formula has been used for dose adjustment

in pharmacokinetic studies in the presence of kidney dysfunction;[31] Therefor we chose C-G equation for medication dosing in the control group. Although it was shown that the GRAIL model results in a better estimation of kidney function in liver transplantation, it has not yet been examined that if it could provide a better estimation for dosing of renally-eliminated medications.[12] If more precise formulas for estimation of GFR in liver transplant recipients (such as the GRAIL model) replace previously accepted formulas, the FDA may introduce them in the guidance for industries.

No studies were published about medication dosing using the GRAIL model based on our search on Pubmed and Scopus; consequently, we are not able to compare the results of our study to similar ones.

Our project disclosed that more than 50% of patients did not reach the target pharmacokinetic indices in both arms of the study, and it seems that none of these sCr based formulas performed adequately for estimating kidney function and vancomycin dose selection. Similarly, Taber *et al.*[32] showed that sCr is not a suitable marker for estimating creatinine clearance and vancomycin pharmacokinetic properties in liver transplant population. Frazee *et al.*[33] compared C-G and CKD-EPI creatinine-cystatin C for vancomycin dosing in critically ill patients. They found that attainment of target trough concentration was 2 folds higher by implementation of both sCr and cystatin C in CKD-EPI creatinine-cystatin C arm compared to C-G arm. Studies indicated that CKD-EPI creatinine-cystatin C equation had better performance than contemporary sCr-based equations in liver transplant patients as well.[34] The authors of the GRAIL study mentioned that the failure of inclusion cystatin C in addition of sCr is one of the limitations in the GRAIL model design.[12]

The rate of vancomycin-induced AKI was reported to be in the range from 5 to 43%. The small number of studies have revealed that vancomycin trough concentrations of more than 15-20 mg/L and AUC values of more than 650 to 1300 mg×h/L were associated with increased AKI prevalence.[26,35,36] Three patients (10%) who had AUC of more than 880 mg×h/L showed vancomycin-induced AKI in the present study, which is similar to previously mentioned investigations.

The same as former studies, our project represented that the patients had low serum albumin concentration. Low serum albumin is prevalent in post-liver transplant patients and is associated with increased risk of AKI.[37] Using serum albumin for calculating eGFR by GRAIL model may cause limitations to apply this method for all liver transplant patients, especially in the early phase after the surgery that albumin products is needed to be administered in some patients.

This study suffered some limitations. It was a pilot study with the small number of patients. Further studies with a larger sample size is needed to determine if the GRAIL model is a suitable method for dose selection in liver transplant patients. Also, similar pharmacokinetic studies should be performed on other medications to evaluate the competence of the GRAIL model for medication dosing. The lack of measuring GFR as the gold standard method for kidney function evaluation is another limitation of present study.

Conclusion

Although the GRAIL model for assessing kidney function has been specifically derived from liver transplant recipients, using this method compared to the C-G for vancomycin dose selection may result in less percent of patients with at target AUC/MIC attainment. Consequently, using GRAIL model for dose modification may expose more percent of patients at risk of vancomycin under dosing and probable subsequent treatment failure.

Ethical Issues

This project was approved by local ethics committee of Institute of Pharmaceutical Sciences, Tehran University of Medical Sciences (ID# IR.TUMS.TIPS.REC.1398.003) and registered in Iranian registry of clinical trials (IRCT20100111003043N14) on 24/09/2019. All methods in this study were performed in accordance with the relevant guidelines and regulations including declaration of Helsinki. Participants signed informed consent form before recruitment. All authors consent for publication.

Data Sharing

All data has been included in the manuscript. Patients' level data would be available by sending request to corresponding author.

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Author Contributions

YS: Selected the patients, collected clinical and laboratory data, analyzed data, drafted and reviewed the manuscript. SD-K: Conceptualized and designed the study, supervised research process, interpreted the data, drafted and finalized the manuscript. ZA: Clinically assessed the patients, gathered clinical data, reviewed the manuscript. FG: Clinically assessed the patients, gathered clinical data, reviewed the manuscript. All have read and approved the manuscript.

Conflict of Interest

The authors report no conflicts of interest.

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