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ORIGINAL ARTICLE

The impact of Vancomycin loading dose on the emergency department in Saudi Arabia: a multicenter cohort study

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ABSTRACT

Background: The emergency department (ED) is a crowded area with complex workflow. Broad spectrum antibiotics given within the first hour of recognizing sepsis have proven to lower the mortality rate. Initiating optimal dose of Vancomycin to attain targeted serum level is an important role of emergency physicians and pharmacists.

Objective: To evaluate the efficacy and safety of Vancomycin loading dose (VLD) (25-35 mg/kg) in reaching the targeted Vancomycin serum trough level compared to regular dose (15-20 mg/kg) in ED.

Study design and settings: A multicenter, retrospective, cohort study.

Methods: The study was carried out in four hospitals in Saudi Arabia; patients who received VLD were matched in a 1:1 fashion based on age category and diagnosis suspected in the ED. Inclusion criteria were age ≥14 years, diagnosed with serious infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), and microbiology culture confirmed MRSA. Exclusion criteria were missing weight, SCr, or Vancomycin trough level, patient on dialysis therapy/continuous renal replacement therapies, and concomitant use of nephrotoxic drugs at ED.

Results: Over the 1-year study period, a total of 3,746 patients were prescribed Vancomycin in the ED. 232 patients received VLD matched to 232 patients received regular dose. Mean dose were 25.3 mg/kg (±4.3) and 13.7 mg/kg (±2.6) for VLD and regular dose groups, respectively. The targeted Vancomycin trough level was significantly reached with the VLD group within 24 hours post-initial dose vs regular dose [18.7 (±3.2) *vs.* 11.6 (±4.3), respectively, $p < 0.0001$]. No difference in SCr value was noted post-Vancomycin initial dose between VLD and regular dose groups [1.5 (± 1.5) *vs.* 1.4 (± 1.8), respectively, $p = 0.735$]. Nephrotoxicity incident was higher with VDL (33, 14.2%) compared to regular dose, but the difference was not significant (22, 9.5%, $p = 0.117$).

Conclusion: VLD has a rapid effect in reaching the targeted Vancomycin serum trough level compared to regular dose with a low rate of nephrotoxicity effect. The finding supports the use of VLD in patients admitted to ED who were suspected to have serious infections caused by MRSA.

Keywords: Vancomycin, loading dose, emergency department, nephrotoxicity MRSA.

Introduction

Sepsis is a common cause for hospitalization in the emergency department [1,2]. Broad spectrum antibiotics given within the first hour of recognizing sepsis have proven to lower the mortality rate [3-5].

Vancomycin is a glycopeptide antibiotic used for the treatment of serious Gram-positive infections including methicillin-resistant *Staphylococcus aureus* (MRSA)

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[6]. MRSA is a serious cause of sepsis [7,8]. Guidelines recommend empiric intravenous Vancomycin added to antibiotic regimens, in patients with sepsis or at high risk for infection caused by MRSA [9], although the targeted serum Vancomycin trough level is between 15 and 20 mg/l [10]. Reaching this targeted level is sometimes not attainable duo to the Vancomycin complex pharmacokinetics profile [10]. Different dosing regimens for Vancomycin were used to reach the targeted serum level [10]. Some regimen used Vancomycin loading dose (VLD) to attain a rapid targeted serum level for patient with normal renal function [10].

In a recent meta-analysis study, two RCTs and seven cohort studies with 2,816 participants were included; the study showed that VLD increases the achievement of targeted concentration [11]. Vancomycin 30 mg/kg LD was proven to achieve a higher percentage of targeted concentration at 12 hours compared to 15 mg/kg in RCT enrolled 99 patients [12]. Another interventional study evaluated the efficacy of a standardized 2 g VLD in achieving the targeted levels in critically ill patients [13]. 33% of the post-intervention group has higher achievement of the targeted Vancomycin concentrations (p = 0.08) [13]. A cohort study, evaluating the pharmacokinetic of VLD in critical ill patients, revealed that patients who received VLD at baseline treatment obtained the targeted trough serum concentrations [14]. Patients with maintained Vancomycin trough concentration between 15 and 20 mg/l have a high impact to reach AUC/MIC above 4; and that may have a negative impact on Vancomycin resistance [7,8,10,15].

Emergency department (ED) is a crowded area with complex workflow. Initiating optimal dose of Vancomycin to attain targeted serum level is an important role of emergency physicians and pharmacists.

A cohort study showed that 70.7% of the patients who visited ED received Vancomycin for MRSA treatment and were determined to underdose Vancomycin [16], while another study assessed the dose of Vancomycin in orthopedics patients also revealed that 69% of them received underdose Vancomycin [17]. Another study showed that Vancomycin supra-therapeutic dosing has been document in 7.2% of the patients who received Vancomycin in the ED [16]. Incidence of nephrotoxicity induced by Vancomycin was increased in critical care wards [18-20], while previous studies showed that incident of nephrotoxicity induced by Vancomycin was at a range between 5% and 7% [21-23]. Nephrotoxicity was confirmed in patients with Vancomycin trough concentration above 15 mg/l [18-20].

The use of VLDs in Saudi population was lacking in the literatures. The efficacy and safety of VLD assessment in Saudi population is needed to optimize Vancomycin effectiveness, especially in patients with sepsis. Evaluating the role of Vancomycin loading in ED will help to standardize the use of Vancomycin doses; thus, it will improve the ED workflow in managing severe infection.

The aim of our study is to evaluate the efficacy and safety of VLD (25-35 mg/kg) in reaching the targeted Vancomycin serum trough level compared to the regular dose (15-20 mg/kg) in the ED.

Methods

This is a multicenter, retrospective, cohort study. The study was carried out at four hospitals in Saudi Arabia between January 1 and December 31, 2019: two hospitals in Riyadh (King Saud University Medical City and Prince Mohammed Bin Abdulaziz Hospital), one hospital at Taif (Armed Forces Hospital), and one hospital at Wadi Aldawasir (Armed Forces Hospital).

The study included all patients who received Vancomycin intravenously and who matched the study inclusion and exclusion criteria in ED at the four hospitals. The institutional review board's (IRB) approval was taken from the four hospitals. All research activities were carried out in compliance with fundamental ethical principles and policies of IRB-Confidentiality of the patient's identifiers and the collected data were kept under strictly privacy throughout the study period. A written consent form from the participants was not obtained due to the nature of study.

Inclusion criteria

(1) Patient treated in the ED; (2) patient aged 14 years or older; (3) patient diagnosed with serious infections suspected to be caused by MRSA, including sepsis, bacteremia, endocarditis, osteomyelitis, cellulitis, meningitis, and healthcare-associated pneumonia; and (4) microbiology culture confirmed MRSA.

Exclusion Criteria

(1) Patient younger than 14 years; (2) concomitant use of nephrotoxic drugs in the ED; (3) patients on dialysis therapy; (4) patients recommended to start continuous renal replacement therapies for acute kidney injury; and (5) pregnant or breastfeeding patients.

Study procedure

All patients who received VLD (initial dose > 20 mg/kg, actual body weight) who fit the inclusion and exclusion criteria were matched to control group (initial dose ≤ 20 mg/kg, actual body weight) in a 1:1 fashion based on age category and diagnosis suspected in the ED. The age categories were 14-34 years, 35-64 years, and ≥65 years, while the diagnosis was based on the suspected infection source: bacteremia, endocarditis, meningitis, pneumonia, skin and soft tissue, and sepsis.

All detailed information was extracted from the electronic databases from each institution and then it was documented in an excel sheet to study the different variables. The data collected include demographic details (age, gender, weight, and height), indication of Vancomycin order, Vancomycin details (dose in mg, date, and time of Vancomycin administration, trough level at 24 hours post-infusion, and date and time Vancomycin serum sample withdrawn), and clinical characteristics for renal function pre- and post-Vancomycin administration (Serum creatinine value).

Study outcomes

The primary outcome of this study is to obtain the percentages of patients who reach the targeted Vancomycin level (15-20 mg/l) within 24 hours post-VLD infusion. The secondary outcome is to study the incidence of nephrotoxicity related to VLD within 5 days per consensus criteria (at least two serial serum creatinine values greater than the initial measurement by at least 0.5 mg/dl or an increase of at least 50% from baseline).

Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS)® statistical package, Version 20.0 (SPSS Inc., Chicago, IL) for Windows®. A *p*-value of <0.05 was considered statistically significant. Descriptive statistics are reported mean and medians ± standard deviation or as frequencies and percentages, as appropriate. Chi-squared test was used to determine association between qualitative variables.

Results

Over the 1-year study period, a total of 3,746 patients were prescribed Vancomycin in the ED. 3,079 were excluded and only 667 patients fit the inclusion and exclusion criteria (Figure 1). 232 patients received VLD matched to 232 patients who received regular dose. There was no difference in demographic and clinical characteristic between the two groups (Tables 1 and 2).

Primary outcome

Targeted Vancomycin trough level was significantly reached with the VLD group within 24 hours post-initial dose versus regular dose [18.7 (±3.2) versus 11.6 (±4.3), respectively, *p*-value < 0.0001]. Mean dose was 25.3 mg/kg (±4.3) and 13.7 mg/kg (±2.6) for VLD and the regular dose group, respectively, while Vancomycin average doses per mg was 1,881.5 (±239.4) in the VLD group compared to 983 (±66.9) in the regular dose group (Table 3). The doses were rounded to the nearest 250 mg to save the vial cost. Overweight patients or obese patients' doses were maximized to 2 g.

Secondary outcome

No difference in serum creatinine (Scr) value post-Vancomycin initial dose between VLD and regular dose groups [1.5 (± 1.5) *vs.* 1.4 (± 1.8), respectively, *p*-value = 0.735]. Nephrotoxicity was higher with VDL (33, 14.2%) compared to regular dose (22, 9.5%) ($p = 0.117$) (Table 3).

Discussion

Vancomycin weight-base dose was recommended by the infectious disease guidelines [24]. ED is a crowded area with a complex workflow. Studies have shown that 1 g fixed dose of Vancomycin was given to all patients who visited ED, regardless of the actual body weight. About 69%-70.7% of the patients were determined to be under-dosed [16,17]. In our study, the mean weight was 77.5 kg (±21.1) in VLD and 73.7 (±18.0) in the control group with a body mass index (BMI) of 29.2 (±7.8) and 27.9 (± 10.2) for VLD and control group, respectively, which showed that our population had a majority of overweight BMI. Our result confirms that 1 g fixed dose of Vancomycin would not be a proper dose for our population.

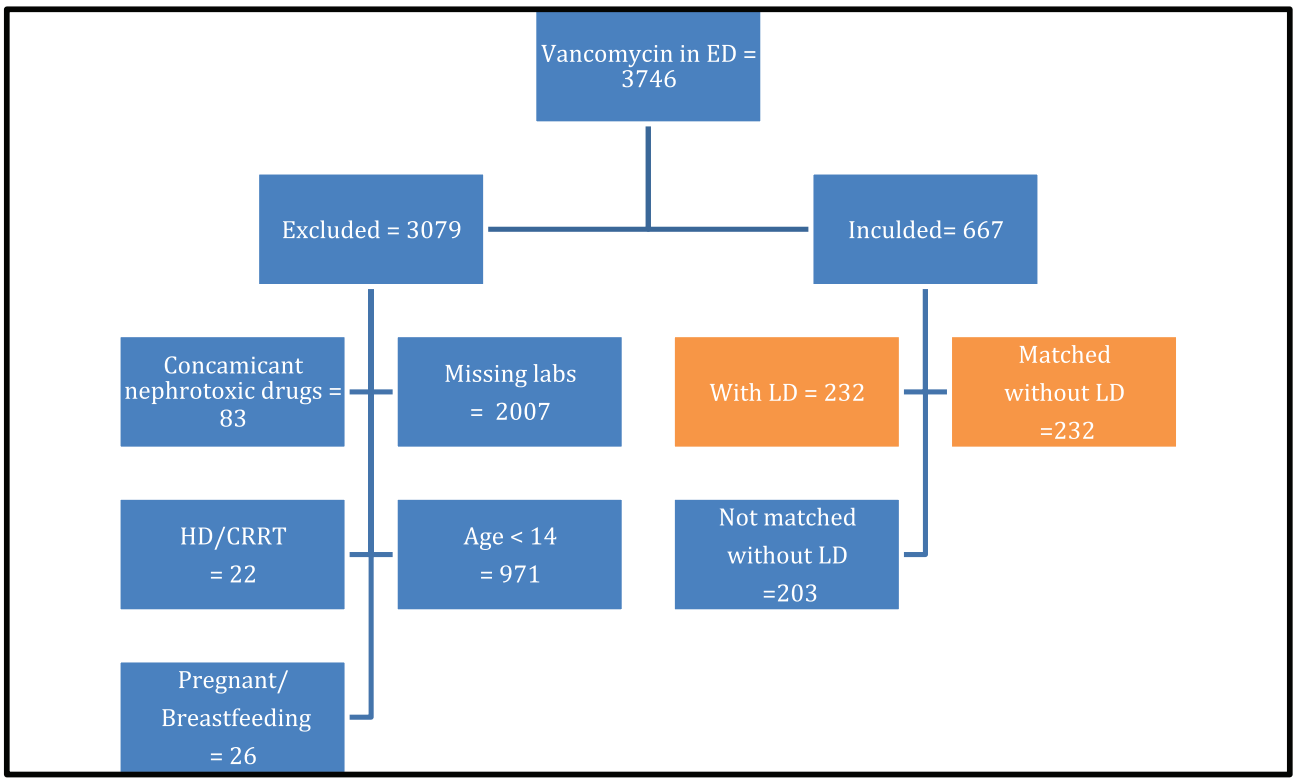

Figure 1. *Sample size allocation.*

Table 1. *Demographic characteristics.*

	VLD	Without LD	*p*-value
	25-35 mg/kg	15-20 mg/kg	
Patients, *n*	232	232	1.000
Institution, *n*			1.000
KSUMC	105	105	
AFH-T	30	30	
PMBAH	70	70	
AFH-WA	27	27	
Age, year mean (±SD)	56 (±23.3)	56 (±18.9)	0.781
Gender, Male (%)	126 (54.3)	136 (58.6)	0.350
wt (kg), mean (±SD)	77.5 (±21.1)	73.7 (±18.0)	0.062
Ht (cm)	163 (±8.9)	(163.2 ± 10.4)	0.727
BMI (kg/m2), mean (±SD)	29.2 (±7.8)	27.9 (± 10.2)	0.103
BMI <30, *n* (%)	150 (64.7)	153 (66)	0.768
BMI ≥30, *n* (%)	82 (35.3)	79 (34)	0.768

VLD = Vancomycin loading dose; Without LD = without loading dose; Ht = Height; wt = weight; BMI = body mass index.

Table 2. *Baseline clinical characteristics.*

	VLD	Without LD	*p*-value
	25-35 mg/kg	15-20 mg/kg	
Serum creatinine (mg/dl)	1.57 (±1.6)	1.91 (±1.6)	0.593
Indication for Vancomycin *n*, (%)			1.000
Bacteremia	7 (3)	7 (3)	
Endocarditis	5 (2.2)	5 (2.2)	
HCAP	37 (15.9)	37 (15.9)	
Meningitis	14 (6)	14 (6)	
Skin and soft tissue	17 (7.3)	17 (7.3)	
Sepsis	152 (65.5)	152 (65.5)	

VLD = Vancomycin loading dose; Without LD = without loading dose.

Table 3. *Bivariate comparison between Vancomycin loading and regular doses.*

	VLD	Without LD	*p*-value
	25-35 mg/kg	15-20 mg/kg	
Vancomycin dose			
mg/kg, mean (±SD)	25.3 (±4.3)	13.7 (±2.6)	<0.0001
mg, mean (±SD)	1,881.5 (±239.4)	983 (±66.9)	0.0287
mg, range	1,250-2,000	750-1,000	
Frequency *n*, (%)			
2,000	182 (78.4)		
1,750	4 (1.7)		
1,500	29 (12.5)		
1,250	17 (7.3)		
1,000		214 (92)	
750		18 (8)	
Initial Vancomycin trough level	18.7 (±3.2)	11.6 (±4.3)	<0.0001
Target Vancomycin level, *n* (%)			
<15	0	173 (74.6)	
15-20	181 (78)	55 (23.7)	
>20	51 (22)	4 (1.7)	
Secondary outcome: SCr Post Vancomycin initial dose			
Post Scr, mean (±SD)	1.5 (± 1.5)	1.4 (± 1.8)	0.735
Nephrotoxicity, *n*, (%)	33 (14.2)	22 (9.5)	0.117
SCr increase ≥ 0.5 mg/dl, *n*, (%)	30	19	
SCr increase ≥ 50%	3	4	

SCr = Serum creatinine; VLD = Vancomycin loading dose; Without LD = without loading dose.

In our study, Vancomycin 25 mg/kg loading dose has achieved the targeted Vancomycin trough concentration within 24 hours post-infusion, with a mean value of 25.3 mg/kg (±4.3). The VLD group has a lower mean [25.3 mg/kg (±4.3)] compared to 30 mg/kg in similar studies [11,12]. A lower mean was a result of maximum Vancomycin dose (2 g) and higher percentage of obesity in our population. Based on our result, 2 g Vancomycin has proven to reach a trough Vancomycin of more than 15 mg/l (Table 3).

Our study confirms the efficacy of VLD in achieving the targeted Vancomycin concentration. The trough mean was 18.7 (±3.2) in VLD group compared to 11.6 (±4.3) in control group, which shows a statically significant different between the groups ($p < 0.0001$). Majority of the VLD (78%) reached a trough between 15 and 20 mg/l compared to only 23.7% of the regular dose group. None of the VLD reached a trough less than 15 mg/l, while only 22% of the VLD group reached Vancomycin above 20 mg/l.

Nephrotoxicity incident was reported based on the percentage of serum creatinine which increased equal to or above 0.5 mg/dl from the baseline. Nephrotoxicity was reported in 14.2% of the VLD group compared to 9.5% in the control group. Although there was no significant different between the groups ($p = 0.117$), our population showed a higher nephrotoxicity rate in contrast to previous studies, where nephrotoxicity induced by Vancomycin was ranged between 5% and 7% [18-23].

The study has some limitation. First, the study was retrospective in nature, for which we cannot rule out information bias. Second, 2007 patients were excluded due to incomplete documentation, reflecting a small sample size. Third, patient comorbidity was not considered in the matching criteria between the groups; comorbidity confounders can affect the nephrotoxicity of Vancomycin.

Conclusion

The study showed that the use of VLD has a rapid effect in reaching the targeted Vancomycin serum trough level compared to the regular dose with a low rate of nephrotoxicity effect.

Study centers

- King Saud University Medical City, King Saud University, Riyadh, Saudi Arabia.
- Armed Forces Hospitals, Taif Region, Saudi Arabia.
- Prince Mohammed Bin Abdulaziz Hospital, MoH, Riyadh, Saudi Arabia.
- Armed Forces Hospital, Wadi Aldawasir, Saudi Arabia.

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Conflict of interest

The authors declare that there were no competing interests regarding the content of this article.

Consent to participate

A written consent form from the participants was not obtained due to the nature of study.

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Ethical approval

Ethics approval was sought from IRB, Health Sciences Colleges Research on Human Subjects, King Saud University College of Medicine, dated: 30.11.2020 (15.04.1442H), via Ref. No. 20/0098/IRB.

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