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Research Paper

Therapeutic Neonatal Vancomycin Trough Level: Attainment and Need in Clinical Practice

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ABSTRACT:

BACKGROUND:

Due to the increasing resistance of staphylococcal strains, vancomycin is often used as empiric therapy in neonatal late-onset sepsis. The Infectious Disease Society of America 2011 methicillin-resistant *Staphylococcus aureus* guidelines recommended that the goal serum trough level concentration for vancomycin to be increased from 5-10 mg/L to 10 to 20 mg/L in children and adults. Neonatal references have also recommended these target levels but dosing recommendations remained the same as previous.

OBJECTIVE:

This study aimed to assess the percentage of neonates attaining a serum trough level between 10 and 20 mg/L with empiric vancomycin dosing in a neonatal care unit patients and the evaluation of clinical outcomes in relation to initial trough level.

PATIENTS AND METHODS:

A prospective cohort study conducted in the neonatal care unit of Children Welfare Teaching hospital of Medical City on 43 neonates during the period from 27th of January 2020 through 15th of December 2020. Neonates included were treated with vancomycin with a minimum of three doses.

RESULTS:

Of the 43 vancomycin serum trough levels included in the primary outcome, only 14 (32.6%) achieved a goal trough of 10 to 20 mg/L with empiric dosing. Overall, vancomycin trough values below 10 mg/L were significantly associated with lower gestational age (<37 weeks) (P value 0.0394). No statistically significant difference between the group of patients who achieved a trough of greater than 10 mg/L and those who did not in terms of hospital stay and mortality

CONCLUSION:

The initial vancomycin dosing regimens result in low attainment of vancomycin target trough levels in neonates. However the trough level does not predict mortality or clinical outcomes in patient with culture confirmed late-onset sepsis.

KEYWORDS: Vancomycin, Neonates, Trough, Sepsis.

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INTRODUCTION:

Gram-positive bacteria make up 70% of the isolated pathogens responsible for late onset sepsis (LOS) in neonates, while coagulase-negative staphylococci (CoNS) make up 48% of the isolates [(1)]. Vancomycin, a glycopeptide antibiotic, is still the recommended course of treatment because the majority, if not all, of CoNS isolates are resistant to β-lactam antibiotics, including penicillinase-resistant penicillins [(2)]. Vancomycin is commonly used as an empirical treatment since staphylococcal isolates are becoming increasingly resistant to other antimicrobials [(3)]. The Infectious Disease Society of America 2011 methicillin-resistant *Staphylococcus aureus* guidelines recommended that the goal serum trough level concentration for vancomycin to be increased to 10–20 mg/L, with a higher range of 15–20 mg/L for methicillin-resistant *Staphylococcus aureus* (MRSA) infections in adults and children. The dose guidelines for neonates remain unchanged, despite the fact that neonatal sources have also suggested these higher target values [(4)]. There is no ideal regimen for administering vancomycin to neonates for a variety of reasons, including the

narrow therapeutic index, the substantial pharmacokinetic heterogeneity among the neonates, and the absence of consensus standards regarding precise dose and therapeutic drug monitoring (TDM) [5,6].

Neonates have different vancomycin pharmacokinetic characteristics than adults [7]. In both term and preterm neonates, these discrepancies are mainly caused by changes in body water content and renal function maturation throughout the first few weeks of life (7-10). Neonates also differ more between individuals than adults do as a result of these alterations [7]. Application of TDM enables correlation between the drug concentration and bactericidal efficacy (Pharmacokinetic/ Pharmacodynamic) of antibiotics with the minimum inhibitory concentration (MIC) in conjunction with microbiological results [11]. Trough concentration (Ctrough) or level is the lowest plasma concentration during a regimen's dosing interval. Typically, it is the value just before the next dose is administered (normally measured within 30–60 minutes of the next dosage) [9,12]. Because vancomycin follows time-dependent bacterial elimination [9] trough levels are typically correlated with therapeutic efficacy. Target nadir levels are 10-15 mg/L for the majority of infections, while 15-20 mg/L may be required for meningitis, pneumonia, and other severe infections [8]. Vancomycin trough levels should be measured just prior to the third or fourth dose, when steady-state levels are likely to be reached [11]. The ideal vancomycin delivery schedule or target trough levels linked to better clinical outcomes in newborns are still up for debate in the scientific literature [13].

AIM OF THE STUDY:

This study aims to determine the percentage of neonates attaining a serum trough level between 10 and 20 mg/L with empiric vancomycin dosing in neonatal care unit patients and the evaluation of clinical outcomes in relation to the initial trough level.

METHODS:

Study design & settings:

This study is a clinical prospective cohort study conducted in a tertiary neonatal care unit at the Children Welfare Teaching Hospital of Medical City during the period from the 27th of January 2020 through the 15th of December 2020.

Study population:

All neonates admitted to the neonatal care unit (NCU) of the Children's Welfare Teaching Hospital in need of specialized care for medical or surgical problems and who were started on vancomycin primarily for LOS (i.e. >72 hours after birth) during the study period and were reviewed for inclusion. Patients were included if they had received at least three doses of vancomycin and had an adequately drawn initial trough level at steady state (serum sample taken 60 minutes before the third or fourth dose in order to measure the trough level). Excluded patients were those with no vancomycin level (during the first month of the coronavirus lockdown period and on weekends); troughs that were drawn inappropriately; neonates with vancomycin started at another hospital before being transferred to Children Welfare Teaching Hospital for completion of treatment; and neonates with renal impairment or oliguria (i.e., serum creatinine (SCr) > 1.5 mg/dL or urine output less 1 mL/kg/h over the preceding 24 hours (4).

Sampling for vancomycin trough level:

Convenient samples of 43 patients treated with vancomycin were collected and analyzed after eligibility to inclusion and exclusion criteria. Vancomycin serum levels were quantified with ARCHITECT iVancomycin Reagent Kit (1P30) (Abbott Laboratories Abbott Park, IL 60064 USA) (lot: 01019K000) using a chemiluminescent microparticle immunoassay (CMIA) on an Abbott Architect System platform, The ARCHITECT i1000SR immunoassay analyzer (Abbott Laboratories, Abbott Park, IL, USA), the tests were performed at a Nursing home private hospital laboratory. The data were collected from the patients' medical records in a prepared questionnaire. The questionnaire included basic demographics of the patient and data about clinical outcomes. To compare with data gathered during the course of the vancomycin course, baseline information on the patients was gathered from the day before the start of the treatment with the medication.

Vancomycin dosing and adminstration in neonatal care unit:

Vancomycin (Hospira, Inc., Lake Forest, IL 60045 US ® lot 011253A) is used when indicated. The published dosing regimens (14-17) advise beginning patients on 10 or 15 mg/kg/dose, with a frequency determined by the patient's blood creatinine, gestational age (GA), and postnatal age (PNA). The attending physician has the final say

over whether to start vancomycin at 10 or 15 mg/kg/dose. Given the mounting data supporting the maintenance of higher serum trough levels of 15–20 mg/L, the department's neonatologists typically start their patients on 15 mg/kg/dose for severe infections including sepsis. The administration of vancomycin in the NCU occurs as an intermittent intravenous infusion over 60 minutes after reconstitution by adding 20 milliliter of the diluting solution to the 1gram vial of dry vancomycin powder to obtain a concentration of 50 mg/ml and further dilution with compatible intravenous fluid (mainly normal saline) to a final concentration of not more than 5-10 mg/ml (as mentioned in the product information) is done before administration.

Data collection and Patients' assessment for the outcome:

The primary outcome was the percentage of NCU patients achieving a trough level between 10 and 20 mg/L with published vancomycin dosing regimens used in the NCU. The determination of trough levels did not involve pharmacokinetic calculations. In addition, patients were followed up until discharge for secondary outcomes which included: Length of vancomycin therapy and hospital stay with overall NCU survival. To evaluate the aforementioned secondary clinical outcomes, according to Ctrough level, the patients with culture-proven sepsis were divided into those with initial vancomycin Ctrough <10 mg/L and ≥10 mg/L, respectively. The Percentage of patients treated for culture-proven sepsis and types of implicated microorganisms were also evaluated using results of blood culture and sensitivity test. The data were collected from the patients' medical records in a prepared questionnaire. The questionnaire included the following: **basic demographics** including GA, gender, birth weight, weight when vancomycin was started, age when vancomycin was started, vancomycin dosing regimen used, vancomycin trough level at steady state, and duration of therapy. For **clinical outcomes**, the following data were collected: clinical status at the time of antibiotic introduction, including the need for feeding assistance, the need for breathing support, urine production, any imaging findings, and the care team's stated clinical justifications for starting antibiotics, complete blood counts, serum biomarkers for sepsis like C- reactive protein, culture results with susceptibility data including blood, urine, and cerebrospinal fluid (if obtained), and patient's final clinical outcome as death or discharge to home. To compare with data gathered during the course of the vancomycin course, baseline information on the patients was gathered the day before to the start of the medication.

Ethical approval:

The study was approved by the Iraqi board for medical Specializations and The Scientific Committee of Children Welfare Teaching Hospital / Medical City. Verbal consent was obtained from the patients' guardians before participation in the Study

Statistical analysis:

The Statistical Package for Social Sciences (SPSS) version 24 computerized statistical software was used to enter all patient data. Frequencies are expressed as percentages and descriptive data are shown as mean ± standard deviation. A number of contingency tables were created, and relevant statistical analyses were carried out. For categorical data, the Chi square test was employed, and the independent sample t-test was utilized to compare two means. The level of significance (p value) in all statistical analyses is set at ≤ 0.05, and the results are displayed as tables.

RESULTS:

A total of 611 neonates admitted to NCU of the Children Welfare Teaching hospital during the study period were screened and evaluated for inclusion and exclusion criteria. Only 43 patients met the inclusion criteria and were included in this study. **Table 1** shows characteristics of the 43 participants expressed as mean ± standard deviation (SD) and/or percentage. The mean ± SD (GA) of patients was 35.05 ± 3.95 weeks. Patients were admitted to the NCU at mean ± SD age of 9.16 ± 8.37 days, started vancomycin at mean ± SD (PNA) of 9.16 ± 8.37 days, and mean ± SD weight of 2627.93 ± 968.2 grams. They received vancomycin for mean ± SD of 11.26 ± 3.63 days. Male patients were more common than female patients with a male-to-female ratio of 1.4:1. **Table 2** demonstrates that of the patients included, 29 (67.4%) obtained levels below 10 mg/L with statistical significance (*p* value.0000001), while 14 (32.6%) of the patients achieved target therapeutic serum trough levels of 10–20 mg/L. **Table 3** shows demographics and Clinical characteristics utilized to compare between the group of patients who achieved therapeutic vancomycin trough levels between 10-20 mg/L and the group of patients who achieved levels

below 10 mg/L, to explore the influence of the mean of different variables on achieving vancomycin trough levels. Only GA was significantly associated with suboptimal trough levels, the mean was 34.21 weeks in the patients who did not achieve a trough of greater than 10 mg/L, compared with 36.79 weeks in the patients who did (P = 0.043). **Table 4** shows the analysis of different Patient factors or dosing regimens in relation to therapeutic (10-20 mg/L) and subtherapeutic (<10mg/L) trough level attainment. Of all examined variables, only GA was a significant factor that affected trough attainment. GA below 37 weeks was significantly associated with subtherapeutic trough levels (<10 mg/L) (X2 4.24, p = 0.0394).

31 patients identified to have pathogen in their blood culture and Polymerase chain reaction (PCR) results, the most commonly implicated type was gram positive bacteria in 20 patients (64.5%) followed by gram negatives in 7 patients (22.6%), the remainders were viral and fungal causative agents for LOS representing (9.7%) and (3.2%) of total isolates respectively as shown in **Table 5.** The resultant 20 patients with culture proven sepsis caused by gram positive bacteria , 9 patients in the target therapeutic trough level (10-20) mg/L group and 11 patients in the subtherapeutic < 10 mg/L trough level group, were evaluated for the impact of the initial trough level on the clinical outcomes. There were no statistically significant differences between the two groups with initial vancomycin trough level below 10 mg/L and those with initial trough level between 10-20 mg/L, in terms of clinical outcome including duration of vancomycin therapy, total length of stay, and NCU survival as shown in **Table 6.**

Table 1: Characteristics of patients (n =43).

Variable		*n* (%)	Mean±SD
Gestational age (weeks)	< 37	22 (51.2)	35.05±3.95
	≥ 37	21 (48.8)	
Gender	Male	25 (58.2)	
	Female	18 (41.8)	
Weight (g)	<2500	16 (37.2)	2627.93±968.2
	≥ 2500	27 (62.8)	
Postnatal age (days)			9.16±8.37
Age at time of vancomycin initiation (days)			13.05±8.69
Duration of vancomycin therapy (days)			11.26±3.63

Table 2: percentage of patients who achieved a therapeutic vancomycin trough level of greater than 10 mg/L and those who did not (n = 43).

Vancomycin serum trough levels at steadystate	*n* (%)	*P-value*
10-20 mg/L	14 (32.6)	0.0000001
< 10 mg/L	29 (67.4)	
Total	43 (100)	

Table 3: Differences in characteristics of patients who achieved a trough of greater than 10 mg/L and those who did not (n = 43).

Variable	Therapeutic level (10-20 mg/L) (n=14)	Sub-therapeutic level (<10 mg/L) (n=29)	*P*-value
GA (weeks)	36.79±3.59	34.21±3.89	0.043
Age (days)	13.64±8.12	12.76±9.08	0.759
Weight (g)	2946.5±997.2	2474±932.3	0.136
S.Cr (mg/dL)	0.52±0.31	0.51±0.2	0.817
Dose (mg/kg/day)	35.87±12.39	31.8±8.6	0.221
Interval (h)	12.3±3.7	13±4	0.592

Table 4: Trough attainment based on different variables (*n* = 43).

	Total	Target trough (10-20 mg/l)	Trough level (<10 mg/l)	Therapeutic vs. sub-therapeutic	
				Chi²	*P*-value
Gestational age (weeks)	43	14 (32.6)	29 (67.4)	4.24	0.0394
<37		4 (28.6)	18(62.1)		
≥37 weeks		10 (71.4)	11 (37.9)		
Postnatal age (days)	43	14 (32.6)	29 (67.4)	0.406	0.524
≤3		1 (7.1)	4 (13.8)		
>3		13 (92.9)	25 (86.2)		
Weight (g)	43	14 (32.6)	29 (67.4)	2.213	0.137
< 2500		3 (21.43)	13 (44.83)		
≥2500		11 (78.57)	16 (55.17)		
Dosing category	43	14 (32.6)	29 (67.4)	3.322	0.190
10 mg/kg/dose		1 (7.14)	4 (13.8)		
15 mg/kg/dose		7 (50)	20 (69)		
20 mg/kg/dose		6 (42.86)	5 (17.2)		
Dosing regimen	43				
10 mg/kg dosing regimen	5	1 (20)	4 (80)	1.875	0.171
10 mg/kg q8hrs		0(0)	0 (0)		
10 mg/kg q12hrs		0 (0)	3 (75)		
10 mg/kg q24hrs		1 (100)	1 (25)		
15 mg/kg Dosing regimen	27	7 (25.9)	20 (74.1)	1.304	0.521
15 mg/kg q8hrs		1 (14.3)	1 (5)		
15 mg/kg q12hrs		6 (85.7)	17 (85)		
15 mg/kg q24hrs		0 (0)	2 (10)		
20 mg/kg Dosing regimen	11	6 (54.5)	5 (45.5)	0.020	0.887
20 mg/kg q8hrs		1 (16.7)	1 (20)		
20 mg/kg q12hrs		5 (83.3)	4 (80)		
20 mg/kg q24hrs		0 (0)	0 (0)		
S.Cr (mg/dL)	43	14 (32.6)	29 (67.4)	2.193	0.533
< 0.5		7 (50)	15 (51.7)		
0.5-0.79		5 (35.72)	11 (37.9)		
0.8-1.09		1 (7.14)	3 (10.4)		
1.1-1.4		0 (0)	0 (0)		
> 1.4		1 (7.14)	0 (0)		

Table 5: Types of pathogens identified from positive results of blood cultures and PCR in patients treated for LOS.

Implicated pathogen	*n* (%)[a]
Viral	3 (9.7)[b]
Fungal	1 (3.2)[c]
Gram positive bacteria	20 (64.5)
Gram negative bacteria [d]	7 (22.6)
Total	31(100)

[a] all percentages were determined from the total number of isolates (*n*=31). [b] all three viruses identified were HSV. [C] The fungus identified was *candida*. [d] There was a total of 7 Gram-negative organisms, including *Acinetobacter baumannii* (4), *Klebsiella* spp. (2), pseudomonas aeruginosa (1).

Table 6: Clinical outcomes of neonates with culture proven gram positive bacteria according to initial vancomycin trough level.

Variable	Target trough level (10-20 mg/L) (*n*=9)	Trough level (10 < mg/L) (*n*=1)	*P-value*
Total length of hospital stay (days)	22.89±15.75	30.36±19.1	0.360
Duration of vancomycin therapy (days)	11.33±3.77	11.27±4.22	0.974
NCU survival *n* (%)			
Yes (Discharged well)	6 (66.7)	9 (81.8)	0.436
No (Died)	3 (33.3)	2 (18.2)	

DISCUSSION:

With the majority of troughs evaluated being less than 10 mg/L, the performance of empiric vancomycin dosing regimens in neonates in this study was not optimal for attaining the published therapeutic target trough level of 10–20 mg/L. Only 32.5% of the study's patients reached the target trough levels of 10–20 mg/L after starting initial vancomycin dosing regimens for intermittent intravenous vancomycin administration. This performance is similar to previous studies where more than half of the patients achieved sub-therapeutic vancomycin trough levels [(5,18)]. In a retrospective analysis of 171 vancomycin serum trough levels, Ringenberg et al, [(4)] discovered that only 25.1% of patients in a Neonatal intensive care unit population were able to reach a target trough of 10 to 20 mg/L using empirical dosage based on Neofax®. Of 153 children started on the empirical regimen (15 mg/kg/day to 45 mg/kg/day, depending on PNA and weight), only 34.2% of the infants reached the target trough levels between 10 mg/L and 20 mg/L on their first dose (mean 8.7 mg/L), according to Dersch-Mills et al. [(19)] In this study, the only significant covariate linked to elevated vancomycin trough blood levels in newborns was GA; no other risk factors for an elevated vancomycin trough level were found in this investigation. This may be explained by the fact that developmental changes in physiology are particularly noticeable in the early stages of life and affect drug disposition (pharmacokinetics) [(20)]. Due to their elevated water content, the vancomycin trough levels of the most immature (low GA) neonates were below 10 mg/L. Total body water comprises approximately 75% to 80% of a newborn's body weight, and is even higher in a preterm neonate [(8,20)], resulting in a larger volume of distribution for hydrophilic drugs (e.g., vancomycin) than in older neonates, infants, and adults, and this partially explains the lower trough values observed [(21)]. The current study evaluated the clinical significance of trough level in neonates, including the duration of therapy needed, hospital stay, and mortality. Limited previous studies have

examined this topic. In an assessment of 87 newborns treated with vancomycin in the NICU of Surrey Memorial Hospital or Royal Columbian Hospital, Ywaya et al. calculated the proportion of newborns achieving target trough levels of 5 to 15 mg/L, as well as the durations required for negative culture results and clinical resolution [13]. The average duration was 5 days for a negative culture result and 6 days for a clinical remission. The correlation between vancomycin concentration and latency to clinical resolution was not statistically significant (rs = 0.366, p = 0.072). In accordance with the aforementioned study, the vancomycin trough level, clinical resolution, and death did not show any statistically significant association in the current study. These findings may be attributable to the small sample size, but they raise questions regarding whether higher vancomycin levels are required to increase efficacy and whether lower targets would be adequate to minimize the risk of harm while still achieving the desired clinical results.

CONCLUSION:

The findings of this study highlight consistent trends observed across multiple studies, indicating that initial vancomycin dosing regimens in newborns frequently fail to achieve target trough levels. Importantly, despite this, there appears to be little influence of vancomycin trough levels on critical clinical outcomes, including mortality.

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