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ORIGINAL ARTICLE

CLINICAL ASSESSMENT OF NEPHROTOXICITY ASSOCIATED WITH VANCOMYCIN TROUGH CONCENTRATIONS DURING TREATMENT OF DEEP-SEATED INFECTIONS: A RETROSPECTIVE ANALYSIS

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ABSTRACT:
Background: Ever since of its introduction in early 1950s, one of the common associated features observed with vancomycin is nephrotoxicity. Use of vancomycin was limited in early years due to lingering safety concerns and availability of methicillin and cephalothin. It was after 1961 that the use of Vancomycin began to increase after the emergence of methicillin-resistant Staphylococcus aureus (MRSA). Hence; we aim to evaluate whether elevated serum vancomycin trough concentrations (≥15 mg/l) are required for the treatment of pneumonia, endocarditis or osteomyelitis caused by MRSA. **Materials & methods:** The present retrospective was conducted in the department of physiology of the medical institution and included all those patients who had a minimum history of 20 years old pneumonia, endocarditis osteomyelitis caused by MRSA, who received treatment with vancomycin for at least 5 days and had at least one vancomycin trough concentration obtained during therapy. Evaluation of the data regarding the potential confounding factors for acute renal failure was done which included assessment of concomitant nephrotoxins, hypotension, sepsis, cardiac arrest and radiographic contrast exposure. Worsening, recurrent, or new signs and symptoms of infection; or the need for additional antibiotic therapy; or when a change in antibiotic therapy was needed; or positive culture of MRSA at the end of vancomycin therapy; or infection-related readmission within 90 days; or death included the category of failure. **Results:** Mean age of the patients in the two study groups was 61.5 and 58.2 years respectively. Male percentage in patients with high trough and low trough group was 52 and 64 percent respectively. Pneumonia was the most prevalent among the two study group (52% and 53 % respectively). Non-significant correlation was obtained while comparing the clinical and demographic parameters of the patients. 26 percent of the cases of pneumonia in high trough group showed completely cure following the treatment while in low trough group 62 percent of the cases showed completely cure result. Statistically non-significant results were obtained while comparing the clinical outcome in between patients of the two study groups. **Conclusion:** No significant correlation exist in the clinical outcome of the patients although an increased risk of nephrotoxicity is associated with patients with vancomycin trough concentrations of more than 15 mg/l.
Key words: Nephrotoxicity, Vancomycin

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INTRODUCTION

Ever since of its introduction in early 1950s, one of the common associated features observed with vancomycin is nephrotoxicity. Manufacturing processes attributed to the initial reports of the vancomycin-associated nephrotoxicity. Successful treatment of 13 out of 15 patients formed the basis on which Vancomycin's approval was done by the FDA.[1]

Use of vancomycin was limited in early years due to lingering safety concerns and availability of methicillin and cephalothin. It was after 1961 that the use of Vancomycin began to increase after the emergence of methicillin-resistant Staphylococcus aureus (MRSA).[1, 2] In 1980s, the nephrotoxicity associated with vancomycin was reported in 0 to 5 percent of the patients. Due to the presence of concomitant nephrotoxic agents, an increase in the rates of vancomycin associated toxicity was observed to be as high as in 35 percent of cases.[3, 4] Hence; we aim to evaluate whether elevated serum vancomycin trough concentrations (≥15 mg/l) are required for the treatment of pneumonia, endocarditis or osteomyelitis caused by MRSA.

MATERIALS & METHODS

The present retrospective was conducted in the department of physiology of the medical institution and included all those patients who had a minimum history of 20 years old pneumonia, endocarditis osteomyelitis caused by MRSA, who received treatment with vancomycin for at least 5 days and had at least one vancomycin trough concentration obtained during therapy. All the patients who were admitted from 2012 to 2014 were included in the present study. All the patients with history of any other systemic illness, any known drug allergy or any history of any major or minor surgical procedure apart from related to present disease were excluded from the present study. If their neutrophil count was less than 500 cells/mm^3, creatinine clearance was 30 ml/min or less or medical record contained insufficient data for evaluation, the patients were excluded from the present study. Ethical approval was taken from the institutional ethical committee and written consent was obtained after explaining them in written the entire research protocol. Using a randomized and standardized search protocol, patient's medical records, admit and discharge related grouping (DRG), demographic details, primary diagnosis, microbial culture reports, antibiotic susceptibility results, antimicrobial regimens, vancomycin trough concentrations, concomitant nephrotoxic drug regimens, daily vital signs and lab values. Evaluation of the data regarding the potential confounding factors for acute renal failure was done which included assessment of concomitant nephrotoxins, hypotension, sepsis, cardiac arrest and radiographic contrast exposure. Concomitant nephrotoxins, other than radiographic contrast, evaluated were NSAIDs, aminoglycosides, amphotericin B, cisplatin, pentamidine, ribavirin, ACE inhibitors, angiotensin receptor blockers and diuretics. Medical record review included evaluation of the outcomes and included clinical response (cure, improvement, and failure), nephrotoxicity according to three definitions, in-hospital mortality and length of stay (LOS). Worsening, recurrent, or new signs and symptoms of infection; or the need for additional antibiotic therapy; or when a change in antibiotic therapy was needed; or positive culture of MRSA at the end of vancomycin therapy; or infection-related readmission within 90 days; or death included the category of failure. Nephrotoxcity included three main definitions;

1. For a minimum of two consecutive days, rise in serum creatinine (SC) ≥ 0.5 mg/dl above baseline.
2. 50% increase in SC above baseline for at least two consecutive days; and
3. For atleast two consecutive days, a 25% decrease in estimated creatinine clearance from baseline.

All the results were analyzed by SPSS software. Chi-square test was used for the assessment of level of significance.

RESULTS

Graph 1 shows the demographic and clinic-microbiological details of the patients in the two study groups. Mean age of the patients in the two study groups was 61.5 and 58.2 years respectively. Male percentage in patients with high trough and low trough group was 52 and 64 percent respectively. Pneumonia was the most prevalent among the two study group (52% and 53 % respectively). **Table 1** shows the p-value for the demographic and clinic-microbiological details of the patients in between the two study groups. Non-significant correlation was obtained while comparing the clinical and demographic parameters of the patients. **Graph 2** highlights the clinical outcome of the patients in between the two study groups. 26 percent of the cases of pneumonia in high trough group showed completely cure following the treatment while in low trough group 62 percent of the cases showed completely cure result. **Table 2** shows the p-value for the comparison of clinical outcome in between the two study groups. Statistically non-significant results were obtained while comparing the clinical outcome in between patients of the two study groups.

Graph 1: Demographic and clinic-microbiological details of the patients

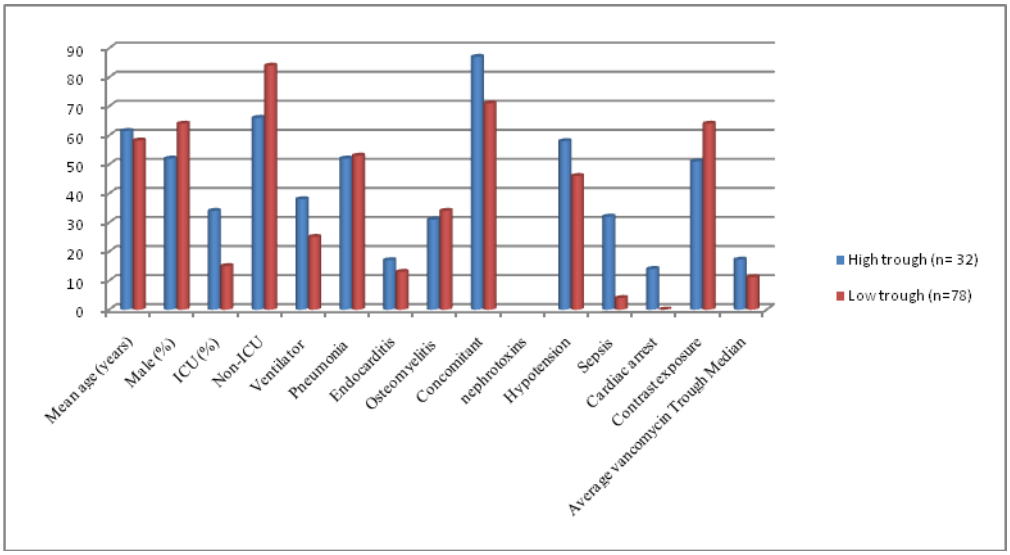


Table 1: p-value for the demographic and clinic-microbiological details of the patients in between the two study groups

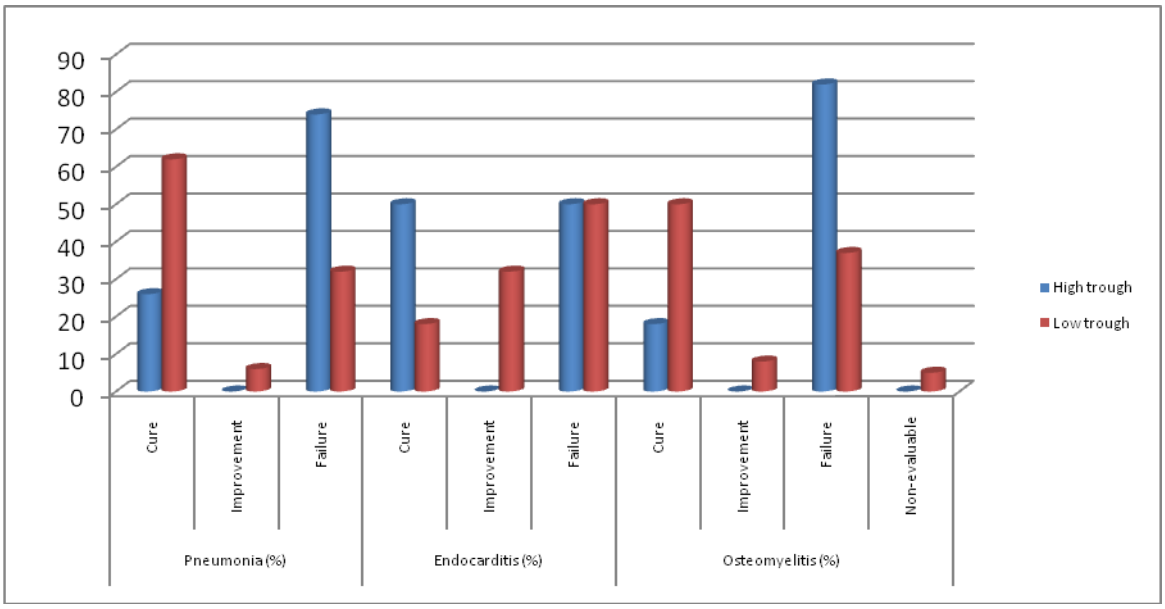
Parameter		High trough (n= 32)	Low trough (n=78)	p-value
Mean age (years)		61.5	58.2	0.550
Male (%)		52	64	0.450
ICU (%)		34	15	0.230
Non-ICU		66	84	
Ventilator		38	25	0.395
Infections	Pneumonia	52	53	0.712
	Endocarditis	17	13	
	Osteomyelitis	31	34	
Confounders of renal function	Concomitant nephrotoxins	87	71	0.112
	Hypotension	58	46	0.419
	Sepsis	32	4	0.001*
	Cardiac arrest	14	0	0.210
	Contrast exposure	51	64	0.530
Average vancomycin Trough Median		17.2	11.2	0.001*

*: Significant

Table 2: p-value for the comparison of clinical outcome in between the two study groups

Parameter		High trough	Low trough	p-value
Pneumonia (%)	Cure	26	62	0.152
	Improvement	0	6	
	Failure	74	32	
Endocarditis (%)	Cure	50	18	0.312
	Improvement	0	32	
	Failure	50	50	
Osteomyelitis (%)	Cure	18	50	0.512
	Improvement	0	8	
	Failure	82	37	
	Non-evaluable	0	5	

Graph 2: Clinical outcome of the patients in between the two study groups



DISCUSSION

Vancomycin is still regarded as the gold-standard antibiotic for the treatment of MRSA infections, despite of the availability of newer antimicrobials mainly because of its cost effectiveness and good clinical response. In particular among the patients with MRSA, there has been an increase in the reported failure cases of treatment with vancomycin in particular with an MIC of 1 – 2 mg/l.[5-7] According to a recent published data on the therapeutic use of vancomycin, recommended concentration of vancomycin trough concentration between 15 and 20 mg/l for bacteremia, endocarditis, osteomyelitis, meningitis and pneumonia, as opposed to the traditional target trough range of 5 – 15 mg/l.[8, 9] Hence; we aim to evaluate whether elevated serum vancomycin trough concentrations (≥15 mg/l) are required for the treatment of pneumonia, endocarditis or osteomyelitis caused by MRSA.

In the present study, for treatment of MRSA pneumonia, endocarditis and osteomyelitis, we didn't observe any statistically significant difference in clinical outcomes between patients who achieved high trough concentrations and those with low trough concentrations. In the high trough group, the overall nephrotoxicity was found to be consistently higher. From these findings, it can be suggested that patients with high vancomycin trough concentrations, there is an increased risk for nephrotoxicity. Hermsen et al assessed the relationship of serum vancomycin trough concentration with clinical outcomes and nephrotoxicity for patients with deep-seated MRSA infection. they retrospectively analyzed patients with MRSA pneumonia, endocarditis or osteomyelitis who received vancomycin. They evaluated 55 patients that experienced MRSA pneumonia, endocarditis, osteomyelitis and multiple infections and divided them into two study groups. One group was categorized as low group and other group as high group. They observed nephrotoxicity in the low and high groups, respectively, for 10 and 31%. From the results, they concluded that in trough group, nephrotoxicity is consistently high.[10] Hidayat et al prospectively analyzed adult patients infected with MRSA and determined the distribution of vancomycin MIC and treatment outcomes with vancomycin doses. They observed that out of 95 patients in the study, more than 50% were infected with high-MIC strains and had pneumonia and/or bacteremia. If the target trough was attained irrespective of MIC, an initial response rate of 74% was achieved. From the results, they concluded that an aggressive empirical vancomycin dosing to achieve a trough greater than 15 microg/mL is required for the treatment of clinical MRSA strains with elevated vancomycin MIC (2 microg/mL).[11] Kullar et al compared the clinical outcomes and costs in patients treated with the new vancomycin guidelines recommending goal serum trough concentrations of 15-20 mg/L versus patients treated with vancomycin doses targeting trough concentrations 5-20 mg/L prior to the new guidelines. They retrospectively evaluated 200 patients treated with vancomycin for at least 72 hours for confirmed, complicated methicillin-resistant Staphylococcus aureus (MRSA) bacteremia during one of two study phases relative to the implementation of the vancomycin dosing guidelines targeting serum trough concentrations of 15-20 mg/L: preperiod phase and postperiod phase. They observed significantly lower success rates with

vancomycin in the preperiod as compared to those in postperiod phase. From the results, they concluded that outcomes in patients with complicated MRSA bacteremia is improved by higher vancomycin trough concentrations.[12] Jeffres et al investigated whether more aggressive vancomycin dosing is associated with greater risk for renal toxicity in patients with health care-associated pneumonia (HCAP) attributed to methicillin-resistant Staphylococcus aureus (MRSA). Theyretropsectively analyzed demographic, clinical and microbiological information from all study patients from automated hospital, microbiology, and pharmacy databases and observed that a total of 94 patients with mean age of 59 years were included for analysis. From the results, they concluded that a greater risk for renal toxicity is associated with aggressive vancomycin dosing and prolonged vancomycin administration.[13] Stevens et al conducted a randomized clinical trial and analyzed adults with known or suspected methicillin-resistant Staphylococcus aureus (MRSA) infections who were treated with linezolid (600 mg twice daily; n=240) or vancomycin (1 g twice daily; n=220) for 7-28 days. They observed that in more than 50 percent of the patients, S. aureus was isolated. From the results, they concluded that similar adverse events are associated with both the medicinal regimes.[14]

CONCLUSION

From the above results, the authors conclude that no significant correlation exist in the clinical outcome of the patients although an increased risk of nephrotoxicity is associated with patients with vancomycin trough concentrations of more than 15 mg/l.

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