



CORONARY ARTERY BYPASS GRAFTING; VANCOMYCIN INDUCED NEPHROTOXICITY AND OXIDATIVE STRESS IN PATIENTS

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Article received on:

14/07/2017

Accepted for publication:

20/09/2017

Received after proof reading:

03/11/2017

ABSTRACT... Objectives: To evaluate effect of vancomycin in producing nephrotoxicity and oxidative stress in patients undergoing coronary artery bypass grafting. **Study design and technique:** Cross-sectional study, convenient sampling. **Setting:** Faisalabad institute of cardiology, Faisalabad, Pakistan. **Period:** 09 months. **Material and Methods:** Total 50 patients who were undergoing coronary artery bypass grafting were enrolled in the study based on convenience sampling after taking consent. Participants received a single dose of vancomycin (15mg/kg) before coronary artery bypass grafting and then twice a day after surgery for five days. Blood was collected at day 0, 4 and 7 and checked for serum creatinine, blood urea, blood urea nitrogen, catalase, melondialdehyde, total oxidant status and total antioxidant capacity in order to determine vancomycin induced nephrotoxicity and oxidative stress. **Results:** The levels of serum creatinine, blood urea and blood urea nitrogen were significantly high at day 4 and 7 as compare to day 0 with p-value 0.001. Serum catalase was significantly decreased at day 4 and 7 as compare to day 0 with p-value 0.001 while the level of serum melondialdehyde was increased significantly at day 4 and 7 in comparison with day 0 with p-value 0.01. Total antioxidant capacity was significantly decreased while total oxidant status was increased at day 4 and 7 in comparison with day 0 with p-value 0.001 each.

Key words:

Vancomycin, Nephrotoxicity, Oxidative Stress, Coronary Artery Bypass Grafting, Reactive Oxygen Species, Antioxidants, Staphylococcus Aureus, Malondialdehyde, Catalase.

Article Citation: Faisal R, Anwar A, Sharif A. Coronary artery bypass grafting; Vancomycin induced nephrotoxicity and oxidative stress in patients. Professional Med J 2017;24(11):1593-1597. DOI:10.17957/TPMJ/17.4163

INTRODUCTION

Nephrotoxicity is a state in which kidney is unable to perform its normal functions of detoxification and excretion due to toxic effects of a substance either exogenous or endogenous.¹ Along with other factors, drug related nephrotoxicity is also very common.² Various drugs like vancomycin, aminoglycosides, amphotericin-B, cisplatin, and aspirin are significantly nephrotoxic. The American Society of Health-System Pharmacists, the Society of Infectious Diseases Pharmacists and the Infectious Diseases Society of America define nephrotoxicity of vancomycin on the basis of the following criteria: at least two or three consecutive elevations in serum creatinine by 0.5 mg/dl or at least 50% increase from the baseline, whichever is greater; the increase must be documented after several days of vancomycin therapy; and no alternative explanation for the impairment in

glomerular filtration rate.³ Vancomycin may induce nephrotoxicity in 10-20% patients at conventional doses and 30-40% at higher doses (10-20 mg/l).⁴ Vancomycin induced nephrotoxicity (VIN) mostly occurs after 5-7 days of starting treatment. Vancomycin is also thought to stimulate oxidative phosphorylation and formation of free radicals that damage all components of the cell, including proteins, lipids, and DNA leading to various disorders including nephrotoxicity.⁵

Post-operative infections with Staphylococcus aureus are very much common in patients undergoing coronary artery bypass grafting (CABG). Cardiac surgical site infections (SSI) especially sternal infections have significant participation in increasing morbidity and mortality rate. SSI in cardiac surgery occurs in 0.4% to 5.1% of total procedures and Staphylococcus aureus

the most commonly involved pathogen.^{6,7} Staphylococcus aureus infections can be treated with penicillins, first generation cephalosporins, clindamycin and erythromycin.⁸ Penicillin was considered the most important drug in this regard but resistance is shown by most strains of staphylococcus aureus to penicillin (methicillin), such strains are known as Methicillin-resistant strains of staphylococcus aureus (MRSA). MRSA is now becoming very common in hospitals and communities.⁹

Vancomycin (VCM) is used as a first-line therapy for serious infections caused by MRSA now a days.¹⁰ CABG patients who are allergic to beta lactam antibiotics or show resistance to other antibiotics or have suspected colonization of Staphylococcus aureus must be given VCM as surgical prophylaxis.⁴ Only one or two doses of VCM are recommended for prophylaxis but due to increasing rate of MRSA in CABG patients, aggressive use of VCM has been observed. Similarly treatment failures following VCM therapy in patients with MRSA have led to utilization of higher doses of this antibiotic. However, many questions remain on the safety of such high doses of VCM specifically the effects related to nephrotoxicity and oxidative stress.

Coronary artery diseases (CAD) are very much common all over the world and especially the population of Indo–Pakistan are at highest risk for it.^{11,12} Most of the patients with CAD ultimately undergo CABG, therefore, Indo–Pakistani population also contribute a significant number in the percentage of patients undergoing CABG.¹³ VCM is preferably given mostly for surgical prophylaxis in CABG patients to avoid SSI. Some researchers also believe that clearance of VCM is also altered in CABG patients, hence increasing its toxicity. Very limited data is available on VIN and oxidative stress in CABG patients globally and almost no data is available locally. Keeping in view the preceding lines, the present study has been designed to evaluate VIN and its effect on oxidative stress in patients undergoing CABG.

METHODS

This cross sectional study was conducted

in Faisalabad Institute of Cardiology (FIC), Faisalabad from February, 2014 to October, 2014. Total 50 patients based on convenience sampling were enrolled in the study after providing them complete information both in verbal and in black and white. Names of the patients were kept confidential. Participants received a single dose of VCM (15mg/kg) before CABG and then twice a day after surgery for five days. All the possible adverse effects and risk factors associated with the study were told to the participants. All those patients who were admitted in the intensive care unit of FIC during the study period and agreed to be a part of this study were included in the study. Patients who were found to have already deranged renal functions were excluded from the study in order to minimize the bias.

Collection of blood samples

An initial blood sample was taken before starting VCM i.e day 0, then blood samples were collected at day 4 and 7. The blood samples were centrifuged at 1107xg for 15 minutes. Serum was separated and stored at -20°C for analysis.

a. Renal function tests

Renal function tests were determined by serum creatinine, blood urea and blood urea nitrogen (BUN).¹⁴ All these parameters were measured by commercially available analytical kits.

b. Oxidant and Antioxidant status

i. Catalase (mU/L)

Catalase (CAT) is a protective (antioxidant) intracellular enzyme and is of great importance for its protective ability against the reactive oxygen species. Catalase renders the accumulation of hydrogen peroxide (H_2O_2) which is potentially harmful oxidizing agent in body and convert it to water (H_2O) and molecular oxygen.¹⁵ A serum level of the enzyme catalase, was determined by method established by Goth.¹⁶

ii. Malondialdehyde (nmol/ml)

Malondialdehyde (MDA) which is an indicator of oxidative stress and is responsible for the production of free radicals in DNA or cell membrane. Serum MDA level is measured as

described by Ohkawa et al., (1979).¹⁷

iii. Total Oxidant Status (umol/L)

Total oxidant status is the measure of oxidative stress in the body. In kidney damage the oxidative stress is increased due to increased production of different reactive oxygen species.

The total oxidant status in the serum was determined using method as described by Erel (2005).¹⁸

iv. Total Antioxidant Capacity (mmol/L)

Damage caused by the reactive oxygen species may be hindered by protective action of antioxidants present in the body by scavenging the free radicals and inhibiting the lipid peroxidation or oxidative stress. TAC measures the free radicals scavenging ability of body. The total antioxidant capacity was determined by the method as described by Erel (2004).¹⁹

Statistical Analysis

After collection data was entered and analyzed by using SPSS 16.0 software. Mean \pm SE for each concentration and parameters was calculated. Comparison between different days was done by ANOVA and Tukey's test was used for post

hoc analysis. P-value $<$ 0.05 was considered statistically significant.

RESULTS

The levels of serum creatinine, blood urea and BUN were increased after VCM therapy. They were found significantly high at day 4 and 7 as compare to day 0 with p-value 0.001. A significant difference was also found between day 4 and day 7 readings with p-value 0.001 (Table-I).

The level of serum catalase was significantly decreased at day 4 and 7 as compare to day 0 with p-value 0.001 while the level of serum malondialdehyde was increased significantly at day 4 and 7 in comparison with day 0. A significant difference was also found for both enzymes between day 4 and day 7 readings with p-value 0.01 each (Table-I).

Total antioxidant capacity was significantly decreased at day 4 and 7 as compare to day 0 with p-value 0.001 while total oxidant status was increased significantly at day 4 and 7 as compare to day 0. A significant difference was also found for both total antioxidant capacity and total oxidant status between day 4 and day 7 with p-value 0.001 each (Table-I).

	Blood Urea Nitrogen (mg/dl)	Urea (mg/dl)	Creatinine (mg/dl)	Catalase (KU/L)	Malandialdehyde (nmol/L)	Total Oxidant Status (μ mol/L)	Total Antioxidant Capacity (mmol/L)
Day 0	17.39 \pm 0.74	37.80 \pm 1.62	0.98 \pm 0.025	72.99 \pm 0.86	0.24 \pm 0.15	0.68 \pm 0.008	3.88 \pm 0.019
Day 4	29.16 \pm 1.15**	63.29 \pm 2.53**	1.65 \pm 0.050**	50.08 \pm 0.13**	0.73 \pm 0.19**	0.83 \pm 0.140**	3.36 \pm 0.015**
Day 7	27.82 \pm 0.94**	60.50 \pm 2.02**	1.61 \pm 0.023**	53.45 \pm 1.26**	0.68 \pm 0.18**	0.90 \pm 0.016**	3.34 \pm 0.016**

Table-I. Representation of parameters as mean \pm SE at day 0, 4 & 7

Gender	No.	Age (years)
Males	32	61 \pm 2
Females	18	58 \pm 4

Table-II. Mean age of patients

DISCUSSION

The present study suggested that VCM is capable of producing significant nephrotoxicity and oxidative stress. The parameters like serum creatinine, blood urea, BUN and MDA were significantly increased after VCM therapy while on the other hand the antioxidant enzymes i.e.

CAT and SOD were found to decrease indicating the nephrotoxic and oxidative role of the VCM.

Cetin and his co-workers performed a study to determine nephrotoxicity and oxidative stress produced by VCM. The parameters used were serum creatinine, blood urea, BUN, CAT, MDA

and SOD. Kidneys were also examined for histopathology. The results showed significant rise in serum creatinine, blood urea, BUN and MDA levels. The activity of CAT and SOD was found to be decreased. Histopathological changes were also markedly altered.²⁰ In another study VCM induced renal cortical oxidative stress was evaluated by measuring renal function tests (serum creatinine, blood urea & BUN), MDA, SOD, immunoexpression of antiapoptotic protein (BCL2) and histopathology of kidneys. VCM significantly increased the levels of serum creatinine, blood urea, BUN, MDA and immunoexpression of BCL2 while the level of SOD was found to be reduced. The morphology of the kidneys was also deteriorated.²¹ Similarly Basarslan along with his colleagues also confirmed the association of VCM with nephrotoxicity and oxidative stress. Serum creatinine, blood urea, BUN and MDA were raised after receiving VCM while activities of SOD and glutathione peroxidase were decreased.²²

A study was performed in order to determine the oxidative stress produced by VCM. Oxidative stress was evaluated by measuring the levels of CAT, MDA and SOD. It was found that after VCM therapy the levels of CAT and SOD were decreased while that of MDA were increased.²³ A similar study was conducted by Oktem and his colleagues in which he also evaluated VCM induced oxidative stress and its role in producing nephrotoxicity. Parameters used for oxidative stress were MDA, urinary N-acetyl- β -d-glucosaminidase (NAG), SOD and CAT activities. The levels of MDA and NAG were increased after getting VCM therapy while SOD and CAT were found to be decreased.²⁴

CONCLUSION

The result of the current study strongly supported the role of VCM in producing nephrotoxicity and oxidative stress in patients undergoing coronary artery bypass grafting.

RECOMMENDATION

It is suggested to carry out more studies especially those focusing on the association between the dose and duration of VCM therapy with the development of nephrotoxicity and oxidative

stress in patients undergoing coronary artery bypass grafting.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Rizwan Faisal	Conception and design, important intellectual content and final approval of the version.	
2	Attia Anwar	Conception and design, acquisition of data, important intellectual content and final approval of the version.	
3	Asifa Sharif	Literature search, Analysis and interpretation of data, revising the data critically for important intellectual.	