ORIGINAL ARTICLE

NOBLE METAL COATED CENTRAL VENOUS CATHETERS ARE NOT SUPERIOR TO UNCOATED CATHETERS IN PREVENTING INFECTIOUS AND NON-INFECTIOUS COMPLICATIONS IN IMMUNOCOMPROMISED PATIENTS

Raheel Iftikhar, Qamar Un Nisa Chaudhry, Tariq Mehmood Satti, Syed Kamran Mahmood, Humayun Shafique Satti, Tariq Ghafoor, Mehreen Ali Khan

Stem Cell Transplant, Armed Forces Bone Marrow Transplant Centre, Rawalpindi-Pakistan

Background: Patients with haematological malignancies and stem cell transplant recipients are at high risk of opportunistic infections. Little international and no national data is available comparing noble metal coated versus uncoated central venous catheters (CVC) in this special population of severely immunocompromised patients. Objective of the study is to compare infectious and non-infectious complications of noble metal coated versus uncoated central venous catheters in patients undergoing stem cell transplantation and receiving chemotherapy for acute myeloid leukaemia. **Methods:** This is a prospective, cross-sectional, randomized study (January to December 2016), enrolling 45 consecutive patients undergoing stem cell transplantation or chemotherapy for acute myeloid leukaemia. Patients were randomized in 2 groups. Twenty 23 patients received standard CVC and 22 patients received CVC catheters coated with three noble metals (Gold, Silver, Palladium). Patients were observed for catheter related infectious and non-infectious complications. Data was analysed using SPSS. **Results:** Mean age was 24.3 (±4.91) in uncoated and 25.09 (±5.22) in coated CVL group. CRBSI infection was detected in 2 (8.6%) and 3 (13.6%) patients in uncoated and coated group respectively with *p*-value of .279. There was no statistically significant difference in febrile episodes between coated (95.4%) and uncoated (91.3%) group. While we considered non-infectious complications, 2 patients in coated (8.6%) and 1 in uncoated CVCs group (4.3%) had CVC thrombosis which was not significant statistically. **Conclusion:** There was no efficacy of BG-thin noble metal coated CVCs in reducing infectious and non-infectious complications (thrombosis) in our study

Keywords: Central Venous Catheters; Infection; Thrombosis

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INTRODUCTION

Central venous catheters (CVCs) insertion is an important component of management of patients receiving high dose chemotherapy for haematological malignancies and undergoing stem cell transplantation.[1] All these patients are severely immunocompromised and have prolonged neutropenia. CVCs facilitate fluid and electrolyte management, chemotherapy and antibiotics administration and monitoring central venous pressures in this special group of patients. However, these indwelling catheters require continuous monitoring and special nursing care to prevent and reduce various infectious and non-infectious complications.[2]

Febrile neutropenia is seen invariably in all of these patients and common sources of infection include oral flora, gut flora and indwelling catheters. CVC are associated with infectious and non-infectious complications, representing an important cause of morbidity and mortality in hospitalized patients. Use of CVC is associated with bacterial colonization and increased risk of catheter related blood stream infection (CRBSI).[3] CRBSIs poses a serious problem in developing countries with infection rates 5 times higher than developed countries as per 2014 review by international nosocomial infection control consortium (INICC).[4] CRBSIs are associated with increased morbidity and mortality, economic burden and increased risk of emergence of resistant organisms.[5] one of the methods proposed to reduce catheter related infections is coating or impregnating them with antibacterial, anti-metabolites or noble metals.[6]

Noble metals are metals that are resistant to chemical actions, does not corrode and resist oxidation in moist environment. Silver, Gold and Palladium are examples of noble metals used for catheter coating. Data regarding efficacy of catheter impregnation with noble metals is conflicting.[7] Only a limited data is available about use and efficacy of impregnated or coated catheters in haemoncology and

stem cell transplantation. An initial study by Ellis *et al*. did not recommend impregnated CVCs for prolonged use in severely immunocompromised patients. However, Ostendorf, documented reduction in risk of colonization of catheters, although there was no difference in incidence of catheter related bacteraemia as compared to a control group.[8] immunocompromised patients are at increased risk of CVC complications and can result in life threatening complications. There is data to suggest that use of coated CVC can reduce its complications. This study was conducted to compare efficacy of noble metal coated versus uncoated CVC in preventing infectious and non-infectious complications in patients with haematological malignancies and those undergoing HSCT.

MATERIAL AND METHODS

This is a single centre, randomized, cross sectional, prospective study carried out in Armed forces bone marrow transplant centre (AFBMTC) Rawalpindi, Pakistan. Study duration was one year, from January to December 2016. Study was approved by hospital ethical committee and informed written consent was taken from the patients. In this study we enrolled 45 consecutive patients undergoing allogeneic hematopoietic stem cell transplant or those of acute myeloid leukaemia admitted for chemotherapy between January to December 2016. Sample size was calculated using WHO sample size calculated with 95% confidence interval.

All patients more than 15 years of age admitted for treatment of acute leukaemia and those undergoing stem cell transplants were included in the study. Those having damaged skin at site of CVC insertion, fever at time of CVC insertion or thrombosis were excluded from the study. Detailed medical history, clinical examination, complete blood counts, PT, PTTK, urea, creatinine, quantitative C-reactive protein was done for all patients. Those meeting inclusion and exclusion criteria were randomized into 2 main groups, Group 1 receiving uncoated CVC and group 2 receiving noble metal coated CVC. All the patients in each group were randomized by stratification to receive noble metal coated or uncoated CVC based on their age group, gender, diagnosis, indication of CVC insertion, baseline platelet count, previous documented infections.

Twin lumen uncoated central venous catheter with blue flex catheter tip (Arrow) and thin noble metal (Gold, Silver, Palladium) coated CVC with Bactiguard infection protection technology (BIP), Sweden were inserted from January 2016 to December 2016. All the catheters were inserted by intensive care trained physicians with at least 2-year experience in ultrasound guided CVC insertion. CVC were inserted in internal jugular vein (right or left) under ultrasound guidance ensuring strict asepsis. Skin preparation was done in two steps, first alcohol-based skin cleanser was used followed by poviodone-iodine solution. All the patients received inj ceftazidime and inj teicoplanin half hour before procedure as per our institutional policy. CVC were inserted using saldinger technique. After CVC insertion, occlusive sterile dressing was done which was changed once weekly or if required in case of loose or soiled dressing, insertion site discharge or local skin reaction. CVC handling institutional protocols were carried out during management of patients. Removal of CVC was done under strict aseptic technique as per clinical indication. Catheter monitoring and assessment of infectious and non-infectious complications was carried out daily from the time of CVC insertion.

Blood cultures were sent for all the patients having febrile neutropenia, insertion site erythema or purulent discharge. Blood cultures were obtained under strict aseptic measures. Paired blood culture from peripheral vain and CVC were obtained before starting antibiotics and inoculated at bedside into Bactec culture bottles (Becton Dickinson Europe). The samples were then analysed in Bactec Becton Dickinson automated analyser. Any positive sample was assessed and identified by means of standard microbial procedures and sensitivity detected. Diagnosis of catheter related blood stream infection (CRBSI) was made if same organism was grown from catheter tip/ catheter lumen and peripheral vein. Sample from CVC should become positive at least 2 hours before peripheral vein blood culture. Positive cultures from both CVC and blood were labelled as CRBSI.

Positive cultures from catheter alone were repeated for confirmation and if positive were considered CVC colonization. Positive blood culture alone with negative CVC culture was also repeated for confirmation prior to initiating anti-microbial therapy. Skin swabs from insertion site were taken in case of erythema or purulent discharge. Clinical examination was done for assessing CVC thrombosis and if suspected, Doppler USG was done to confirm the diagnosis. SPSS version 20 was used for statistical analysis. Results were expressed as mean, standard deviation (±SD) for all continuous variables and frequency and percentage for categorical data. We used t-test and chi-square test as appropriate to the nature and distribution of the variables. A p-value < 0.05 was considered statistically significant

RESULTS

Demographic characteristics of study group are summarized in table-1. Uncoated CVL catheters were inserted in 23 patients and coated CVL catheters in 22 patients. All the coated and uncoated catheters were Twin lumen. There was no statistically significant difference found between coated and uncoated CVCs recipients for median age, gender, disease, number of CVL dressings, mean days of neutropenia and number of days CVCs were kept inserted, as summarized in the table. Both the groups of coated and uncoated CVCs were further randomized to receive near equal patients of each disease category as summarized in table and there was no statistically significant difference.

Table-1: Demographic characteristics of study group

Variable	Uncoated	Coated	*p*-value
Number	n=23	n=22	
Disease			
Aplastic anaemia	12	11	.95
AML	7	7	
ALL	1	2	
CML	2	1	
MDS	1	1	
Age (year) mean	24.3 (±4.91)	25.09 (±5.22)	.337
Male : female	14/9	15/7	.432
Duration of neutropenia (ANC < 1x 10^9/l) days	23.39 (5.07)	24.32 (4.71)	.688
Mean Platelet count	24 (±32)	21 (±37)	.571
Total days of CVL insertion (mean)	25.91 (5.03)	24.27 (5.37)	.648
Number of CVL dressings changes	4.96 (1.022)	5 (1.69)	.06
CRBSI (culture positive)	2 (8.6%)	3 (13.6%)	.279
CRBSI (probable)	4 (17.3%)	3 (13.6%)	.326
Febrile episode	21 (91.3 %)	21 (95.4%)	.577
Catheter related Thrombosis	1 (4.34%)	2 (8.6%)	.524

CRBSI infection was detected in 2 (8.6%) and 3 (13.6%) patients in uncoated and coated group respectively with p value of .279. All the positive cultures yielded gram negative organisms *Actinobacter baumanii* (n=2), *Pseudomonas aeroginosa* (n=1), *Klebsiella pneumonia* (n=1), *Serratia marcescens* (n=1). Probable CRBSI which responded to line lock therapy was also not statistically different in 2 groups 17.3% uncoated versus 13.7% coated (*p* value= .326). There was no statistically significant difference in febrile episodes between coated (95.4%) and uncoated (91.3%) group. While we considered non-infectious complications, 2 patients in coated (8.6%) and 1 in uncoated CVCs group (4.3%) had CVC thrombosis which was not significant statistically.

DISCUSSION

Our study is first study from Pakistan to compare noble metal coated versus uncoated CVC in immunocompromised patients. International data is also sparse with only few randomized trials done in this subset of population and results are conflicting.[9,10]

To reduce the risk of CRBSI, hand hygiene and CVL bundles are widely practiced resulting in reduction of incidence of CRBSI. To further reduce the risk of CRBSI, researchers resorted to trials of CVCs impregnation with antimicrobials. Over last two decades, this has been studied in different trials in critically ill patients admitted to intensive care units with variable documented efficacy. Studies by Schuerer and McConnells failed to demonstrate any significant clinical benefit of antimicrobial impregnation of CVCs[11-12.] Bonne et al demonstrates efficacy and cost effectiveness of CVCs impregnated with chlorhexidine and silver sulfadiazine.[13] Only a little data is available with regard to use of antimicrobial coated catheters in haem-oncology and transplant patients and available data is again contradictory with regards to their benefit. Ostendorf documented reduction in catheter colonization[14], while Ellis *et al* documented no benefit.[15] At least two different meta-analysis failed to demonstrate efficacy of antimicrobial impregnated CVC. Metanalysis by Y.Shi and Z-J Liu concluded that silver impregnated catheters are not associated with reduced catheter colonization or CRBSI.[16] Once antibiotic coated CVCs proved ineffective in reducing CRBSI in large number of trials, researchers focussed on new innovative methods to reduce catheter colonization and bacteraemia.

One of the novel products proposed was catheter coating with thin noble metals. Bactiguard coating of CVCs represented one of major development in this field. Bactiguard coating (Bactiguard AB, Stockholm, Sweden) is comprised of nanosized deposits of Silver, Gold and Pallidium.

First used in urinary catheters, it proved highly effective in reducing catheter related urinary tract infections. The Bactiguard Infection Protection (BIP) technology is based on applying a very thin noble metal coating, consisting of gold, palladium and silver, to medical devices.[17]

The postulated mechanism of action for preventing bacterial adhesion on Bactiguard medical device surface is a galvanic effect in combination with a fine topography in the submicron range which disturbs and prevents microbial surface adhesion and colonization.[18,19]

Another challenge with today's standard catheters is the increased risk of thrombosis. Initial Clinical trials indicated that BG-coated CVCs resulted in reduced risk of infection and lower incidence of thrombosis (0.8%) as compared to uncoated CVC (2.7%); however, the difference was not statistically significant. BG further modified their technology and introduced Bactiguard Infection Protection (BIP) CVC, aim was to further enhance antimicrobial properties without compromising blood compatibility. After their introduction an initial study by Vafa *et al* demonstrated markedly reduced bacterial adhesion and biofilm formation in BIP-CVCs.[20]

Our study was the first study employing use of BIP-CVCs in stem cell transplant recipient and recipient of chemotherapy for acute myeloid leukaemia. Considering the unique population, sample size of our study was small. We had initially planned to enrol 100 patients but considering high rate of CVC associated thrombosis (8.6% vs 4.3%) and no effect in reducing CRBSI (proven and probable) (27.3% vs 25.9%) we terminated the study prematurely. It is emphasized that our target group was a unique group of highly immunocompromised patients who have not benefitted from BG-coated CVCs, these results should not be generalized to all patients.

In developing countries and resource limited countries, muti-disclipnary approach is the key in reducing CVCs related complications. This involves central line care bundle, staff education and training, out comes surveillance, feedback on CRBSI rate and prevention strategies.

In conclusion there was no efficacy of BG-thin noble metal coated CVCs in reducing infectious and non-infectious complications (thrombosis) in our study. More studies are required employing larger number of patients to validate or refute these results.

AUTHORS' CONTRIBUTION

RI: Data collection, study design. QUNC: Study design. TMS: Study design. SKM**:** Data analysis. HSS: Data analysis. TG: Data collection and analysis. MAK: Data collection.

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Address for Correspondence:
Raheel Iftikhar, Stem Cell Transplant, Armed Forces Bone Marrow Transplant Centre, Rawalpindi-Pakistan
Email: drraheeliftikhar@gmail.com