

### **Hemodialysis catheter-related infections: incidence in temporary catheters locked with Vancomycin and Heparin vs. Heparin-only**

#### **Abstract**

**Background:** The increasing incidence of end stage renal disease (ESRD) patients initiating hemodialysis (HD) through a temporary HD catheter has caused the rise in catheter related infections and associated morbidity and mortality. An antibiotic lock solution (ALS) for the prevention of catheter-related bacteraemia is a promising strategy. The present randomized control study has evaluated the efficacy and safety of vancomycin as an ALS in 54 patients who required temporary double lumen catheters for HD.

**Methods:** The patients were randomized to receive either (A) an ALS (vancomycin 5 mg/ml + heparin 5000 IU/ml) – group A; or (B) unfractionated heparin (5000 IU/ml) alone as a catheter lock control – group B. The study duration was of three months and was conducted at the Department of Nephrology, PIMS, Islamabad.

**Results:** The primary endpoint of the study was catheter related blood stream infection (CRBSI). The vancomycin group (A) had one episode of infection (CRBSI rate = 1.23/1000 days) compared with six episodes in the heparin-locked control group (B) (CRBSI rate = 8.55/1000 days). Mean catheter survival was significantly ( $p < 0.05$ ) more in group A ( $30.48 \pm 5.7$  days) compared to group B ( $26 \pm 6.5$  days). No thrombotic episodes or side effects were recorded.

**Conclusion:** Vancomycin appeared to be a safe and effective ALS, preventing CRBSI and increasing survival of catheter in HD patients.

**Keywords:** Vancomycin, Heparin, Catheter related blood stream infection (CRBSI), Bacteraemia, Catheters, Renal dialysis

#### **Introduction**

Hemodialysis (HD) is the most common treatment in the management of end-stage kidney disease to compensate the kidney function. HD is achieved by placing a central venous catheter (CVC).<sup>1</sup>

Infections are very common among patients undergoing chronic HD. Insertion of catheters increases the risk of hospitalization up to 2-3 fold due to infections and associated mortality as compared to an arteriovenous fistula or graft.<sup>2</sup> CVC use in HD are associated with catheter-related blood-stream infections (CRBSIs), exit-site infections (ESI), and tunnel infections. CRBSIs are as frequent as 1.1 to 5.5 episodes per 1000 catheter days. CRBSIs are reported to be associated with increased morbidity, hospitalization, and death.<sup>3</sup>

Bacteremia in patients undergoing HD may be caused due to infections originated from the cannula or catheter double lumen (CDL). CRBSI is confirmed in HD patients presenting symptoms of systemic infection when the cultures isolated from catheter tips and peripheral blood are identical in the absence of any other source of infection besides the catheter itself.<sup>4</sup>

The factors influencing the rate of CRBSI are site and duration of catheter placement, catheter material, potency of contamination at the exit site, CVC/CDL insertion technique and patient associated risk factors for infection such as diabetes mellitus, Staph. nasal colonization, etc.<sup>5</sup> *Staphylococcus aureus* and coagulase-negative *Staphylococcus* account for 40% to 80% of the CRBSI.<sup>6</sup> About 20–30% of CRBSIs are caused by gram-negative organisms.<sup>7</sup>

The important clinical manifestations of catheter related bacteraemia are fever with or without chills. These symptoms account for up to 80% of positive blood cultures in HD patients with catheters.<sup>8</sup> Purulence at the exit site is a more specific sign of catheter related bacteraemia. The presence of an exit site infection is associated with an increased risk of a full-blown bacteraemia.<sup>9</sup> Septic shock, acidosis or altered mental status, and catheter dysfunction are other less common clinical manifestations of catheter related bacteraemia. The important complications associated with catheter related bacteraemia are thrombophlebitis, endocarditis, septic arthritis, osteomyelitis, abscesses.<sup>10</sup>

Removal of catheter and use of systemic antibiotics can be used for the treatment of CRBSIs. The use of systemic antibiotics does not eliminate the risk of future CRBSIs as the infections originate in the catheters and are then spread in the systemic circulation and in other organs. Therefore, it is quintessential to have antibiotic solutions that can eliminate the bacteria from the catheters.<sup>11</sup>

In between HD sessions, to avoid catheter thrombosis, the CVCs are sealed with heparin. Though heparin is a very effective anticoagulant, it does not prevent infections. Therefore, sealing solutions that can prevent or reduce catheter related infections should be an effective way of dealing with CRBSIs.

Antibiotic lock therapy (ALT) is mostly used as an adjunctive to systemic antibiotics for tunnelled catheter salvage to eliminate the bacteria from the biofilm formed on the catheters.<sup>12</sup> The antibiotic locks are inserted in each lumen at each dialysis session and are sustained for the whole duration of systemic antibiotic therapy.<sup>12</sup>

The most commonly used antibiotics in combination with heparin are vancomycin (5mg/ml), ceftazidime (10mg/ml) or cefazolin (10mg/ml). The antibiotics in the locks are switched according to culture reports and if the systemic antibiotics are changed.<sup>13</sup>

The success rate of antibiotic locks varies with the type of bacteria involved. The success rate of antibiotic locks is 87 to 100% in gram-negative infections, 84% for Staph. epidermidis, and only 40% with Staph. aureus infections.<sup>14</sup> Gentamicin and vancomycin are most commonly used in the antibiotic locks. Vancomycin has been observed as the most stable antibiotic in combination with heparin. In combination with heparin, vancomycin is reported to be stable at concentrations as high as 10 mg/ml. Vancomycin is the most preferred antibiotic to prevalent Staph. infections. Therefore, vancomycin is ideal to be used to prevent nasal MRSA colonization in the dialysis patients which is as frequent as 60% in the HD patients.<sup>15</sup>

Many randomized controlled trials have reported a reduction in the incidence of CRBSIs with the use of antibiotic lock.<sup>16</sup> However, there are concerns raised by the CDC and the Infectious Diseases Society of America on the development of antibiotic resistance for the agent used. The CDC and the Infectious Diseases Society of America recommend the antibiotic locks to be used in the patients with a history of multiple CRBSIs.

This study evaluated the efficacy of a prophylactic antibiotic lock solution, in the form of vancomycin with heparin, on the incidence of CRBSI in patients undergoing HD with a double-lumen catheter, compared to standard group with heparin-only lock.

## **Materials and Methods**

### ***Study Design***

The randomized control study (RCT) was conducted at the Department of Nephrology, Shaheed Zulfiqar Ali Bhutto Medical University, PIMS Islamabad for a period of 3 months from April to June 2019.

### ***Sample size calculation***

Sample size was calculated using WHO sample size calculator. With a level of significance of 5%, power of test at 80%, anticipated population proportion (rate of infection in heparin group), p1 of 21.7%, and anticipated population proportion (rate of infection in vancomycin-heparin group), p2 of 3.7%, the sample size was calculated to be 27 patients in each group A and B with total number of 54 patients in the study.

### ***Inclusion criteria***

Both male and female patients with end stage renal disease those who had no permanent access and patients with AKI requiring HD support in the age group of 18 to 70 years were included in the study.

### ***Exclusion criteria***

Patients admitted with septicaemia, femoral catheter insertions, history of fever, who had a previous double lumen catheter (DLC) insertion in the past 30 days, who developed infection during study other than DLC, and patients using systemic antibiotics for any cause were excluded from the study.

### ***Randomization and data collection***

Patients were selected by non-probability consecutive sampling on first stage and were divided into two groups alternating, following coin method.

All patients fulfilling inclusion criteria were divided into two groups by lottery method. Group-A had both lumens of their catheters locked with 1.5 ml per lumen of vancomycin-heparin solution (5mg/ml vancomycin, 5000 IU/ml heparin) at the end of each HD session, and Group-B had their catheters locked with 1.5 ml per lumen of heparin solution only (5000 IU/ml heparin).

All the patients had blood cultures drawn at days 0, 7, 14 and 21 from the catheter lumen hubs. A peripheral blood culture was drawn from the patients at the earliest sign of infection or complains of a fever. Blood complete picture and CRP levels of all patients were sent at days 0, 7, 14, 21 and at sign of infection.

Those patients who remained asymptomatic were observed until either their permanent access was matured or catheter's flow became compromised (flow decrease of 20% or <200ml/min).

All data collection and study procedures were conducted effectively to control the selection bias and maintain the data quality and quantity. Patients were given color-

coded wrist bands (red for group A, yellow for group B) and solutions were prepared, then color-coded, labelled and placed in the refrigerator. All HD staff were advised and trained regarding nature of study with special attention on preventing accidental flushing and systemic exposure to solutions.

The outcome was assessed by comparing the mean duration of catheter *in-situ*, development of obvious bacteraemia, exit site infection and flow compromise in the two groups of patients whose catheters had been locked with different solutions between sessions of HD.

### **Statistical analysis**

All the selected data was entered and analyzed with SPSS version 25. Mean and standard deviation were calculated for quantitative variables like age, serum albumin, day of removal of the DLC. Cross tabulation was done with CRBSI as one variable and Diabetes, Insertion Site, Age in group, Gender, and Albumin in group as the other. T-test was also applied to those who developed CRBSI and had diabetes and hypoalbuminemia in their history to assess their association with development of infection. P value of <0.05 was considered to be statistically significant.

### **Results**

A total of 54 non-tunnelled double lumen catheters were inserted and randomized among 54 patients between April and June 2019. Twenty seven catheters (50%) were randomized to group A (Vancomycin+Heparin) and 27 DLCs (50%) to group B (Heparin only). In group A, one patient lost follow-up, two patients had their catheters removed with good flow as their AV-fistula had matured, one patient's DLC got out while he was changing clothes, and another died during HD after presenting to the ER with pulmonary edema. In group B, one patient lost follow-up, while the rest were followed till their catheter was removed.

The mean age of patients in group A was  $42 \pm 12.5$ , and in group B was  $39.9 \pm 13$  years ( $p > 0.05$ ). In group A there were 17 (63%) males and 10 (37%) females, while in group B there were 18 (67%) males and 9 (33%) females.

The mean serum albumin was  $3.28 \pm 0.25$  mg/dl in group A and  $3.27 \pm 0.28$  mg/dl in group B ( $p > 0.05$ ).

### **Site of catheter placement**

Eighteen (67%) catheters were placed in the internal jugular vein and 9 were placed in the subclavian vein in group A and 24 (88%) catheters were placed in the internal jugular vein and 3 were placed in the subclavian vein in group B.

### **Incidence of CRBSI**

A total of 7 CRBSI were recorded during the study (four males and three females). One episode of blood stream infection was recorded in the vancomycin-locked group A while 6 episodes were recorded in the heparin-locked group B. The CRBSI incidence in the heparin-only group B (8.55/1000 catheter days) was significantly ( $p < 0.05$ ) higher as compared to the vancomycin-locked group A (1.23/1000 catheter days). Five of the seven observed CRBSI occurred in jugular catheters, and two in subclavian catheters. The most common age group for developing CRBSI was 41-50 years (5 cases).

Twelve patients (44%) in group A and 10 (37%) in group B had diabetes. The only patient in group A who developed a CRBSI had diabetes, while four out of the six

CRBSI from group B had diabetes. This difference was statistically significant ( $p < 0.05$ ).

### ***Culture reports: Pathogens identified***

Four peripheral and catheter lumen cultures from group B (heparin-only) grew staph. aureus and two grew staph. epidermidis; while the only patient who developed CRBSI in study group A locked with vancomycin grew staph. epidermidis in the culture of both lumen and peripheral blood sample.

### ***Exit site infection***

ESI occurred in one patient from group A and grew staph. epidermidis, corresponding to the growth from the lumen and peripheral blood cultures. From group B, two patients developed an ESI prior to developing a bacteremia and the growth from the exit site swab revealed staph. aureus in one and staph. epidermidis in the other. No statistically significant difference among the two groups was recorded. All ESI's preceded the catheter bacterial colonization by an average of 5.3 days.

The CRBSI recorded in the single patient from the vancomycin group (A) occurred 19 days after catheter insertion and was preceded by the ESI by 5 days. The six episodes of CRBSI in group B occurred at an average of 16.2 days after catheter insertion.

### ***Causes of catheter removal***

The most common cause of catheter removal was poor flow in both groups (Figure 1). Twenty one patients (78%) in group A and 20 patients (83%) in group B had their catheters removed because of inadequate flow. None of them had been taking systemic (oral/subcutaneous) anticoagulants apart from the heparin lock to the catheters.

### ***Catheter survival***

There was a statistically significant difference in catheter survival among the two groups (Figure 2). Mean number of catheter days was greater in group A ( $30.48 \pm 5.7$ ) compared to group B ( $26 \pm 6.5$ ) ( $p < 0.05$ ). The mean cumulative infection-free catheter survival in the vancomycin group was significantly higher than that in the heparin group ( $p = 0.006$ ).

### ***Discussion***

The increasing incidence of ESRD patients initiating hemodialysis through a temporary hemodialysis catheter has led to the rise in catheter related infections and associated morbidity and mortality. Antibiotic lock solutions (ALS) holds great potential for the prevention of these catheter related infections in HD patients.

To the best of our knowledge, the present study is the first to demonstrate the clinical efficacy of vancomycin as an antibiotic lock solution for the prevention of CRBSI at our institute. The study highlights the use of vancomycin in combination with heparin as an antibiotic lock solution in non-tunnelled catheters in HD patients for reducing the incidence of CRBSI as well as increasing the catheter survival. It was observed that the vancomycin/heparin solution was not only effective but also was safe, and had no side effects. The application of ALS resulted in a significant reduction in the episodes of CRBSI compared to the use of heparin lock only.

Consistent with the findings of the present study, a similar study on 131 HD patients reported a CRBSI rate of 6.7/1000 days in the heparin only group and a significantly lower CRBSI rate of 1.21/1000 catheter days in the vancomycin group (and  $p = 0.006$ ).<sup>17</sup>

Similarly, another study on 120 patients on HD with temporary dialysis catheters found a reduction in CRBSI with the use of ALS. However, they had used an ALS containing cefazolin, gentamicin and heparin. The CRBSI rate was significantly lower (0.44/1000 catheter days) when compared to 3.12 in the heparin only group.<sup>18</sup> Two meta-analyses of randomized controlled trials reported the effectiveness of ALSs in reducing CRBSI rate in HD patients without any significant side effects. Also, it was shown that the addition of antibiotic to the anticoagulant would increase the rates of thrombosis.<sup>19</sup> ALS in combination with heparin increased the catheter survival time significantly.

The American Society of Diagnostic and Interventional Nephrology recommends the use low heparin concentration or a 4% citrate solution as a locking solution in non-tunnelled catheters used for HD.<sup>20</sup> The antibiotics in ALS can affect the anticoagulant properties of heparin, especially if precipitation occurs.<sup>21</sup> Therefore, the preferred dose of vancomycin (5 mg/ml) and heparin (5000 IU/ml) was chosen at which the solution is shown to not precipitate and be effective at eliminating the growth of any microorganisms embedded in the biofilm.<sup>22</sup> This study also addressed the logistical challenges, compatibility of vancomycin with heparin and its stability for prolonged periods of time.

It has been reported that a significant proportion of HD patients (up to 60%) and the attendants of these patients are nasal carriers of MSSA and MRSA.<sup>15,23</sup> Since vancomycin is the antibiotic of choice for the treatment of MSSA and MRSA, it was selected as an antibiotic for the ALS used in the present study.

Moreover, vancomycin is effective against staphylococci and enterococci and no reports are available about the vancomycin-resistant enterococci (VRE) in HD patients receiving a vancomycin lock for the prevention of CRBSI.<sup>24</sup> These reasons make vancomycin an ideal antibiotic to be used in ALS in HD patients with catheters. Development of gentamicin resistance has been seen in HD patients with tunnelled catheters after 6 months of using combination of heparin and gentamicin as an antibiotic lock. This highlights the evaluation of non-antibiotic agents with antimicrobial properties in lock solutions in HD patients with catheters.<sup>25</sup> There are chances of possible leakage and accidental flushing of the antibiotic locks in the use of tunnelled catheters exposing the patient to inappropriately suboptimal concentrations of the antibiotic for prolonged periods of time resulting in antibiotic resistance. However, because of the relatively shorter period of time it is used for, antibiotic resistance associated with the use of ALS has not been observed in non-tunnelled catheters.<sup>26</sup>

Furthermore, using the ALS with temporary catheter is low cost and also decreases the rate of a CRBSI, thereby decreasing morbidity, mortality and cost of treatment. Also, the use of ALS negates the use of intravenous antibiotics, thereby reducing the emergence of antibiotic resistance.<sup>22</sup>

Diabetes has been shown to be a risk factor for CRBSI.<sup>27</sup> Similarly, in this study, diabetes has been found to be significantly associated with the development of bacteraemia in both groups ( $p < 0.05$ ). The only patient to develop a CRBSI in the vancomycin lock group had diabetes. Furthermore, an ESI was observed five days before the development of CRBSI. It is suggestive of the microorganism migrating from the skin surface along the outside of the catheter to invade the blood stream.

Further studies are required for comparing the use of an antibiotic lock solution in patients with and without concomitant use of an antibiotic ointment on the exit site.

### **Limitations**

Drug level monitoring to identify systemic exposure to vancomycin was not carried out, the single-centre nature of the study, and small sample size. These limitations may limit the generalization of these results to the general population. The observations are restricted to non-tunnelled catheters for a shorter period of time as the study was performed only for an average duration of one month.

### **Conclusion**

The study shows the safety and efficacy of vancomycin as an interdialytic ALS for the prevention of CRBSI in HD patients with non-tunnelled catheters. In combination with heparin, it successfully reduced the incidence of CRBSI while concomitantly prolonging the survival of the catheter. Moreover, it does not appear to increase the thrombotic rate, ESI or episodes of bleeding. It is especially recommended to consider using the ALS in patients with a history of repeated episodes of bacteraemia due to indwelling vascular catheters.

### **Declarations**

**Ethical statement:** The study was initiated after approval from the ethical committee.

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### Figure Legends

**Figure 1.** Bar chart showing the reason for catheter removal in each group

**Figure 2.** Grouped distribution of catheter survival in each group

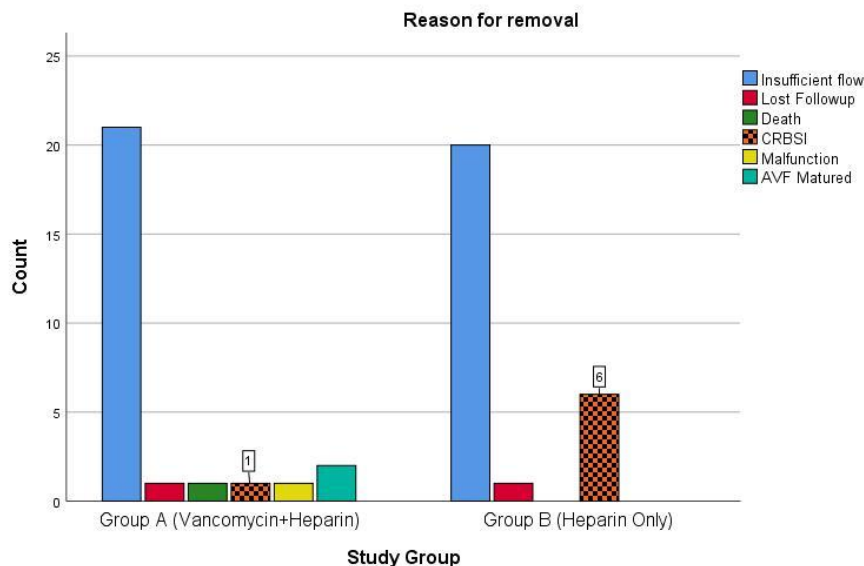


Figure 1. Bar chart showing the reason for catheter removal in each group

225x132mm (96 x 96 DPI)

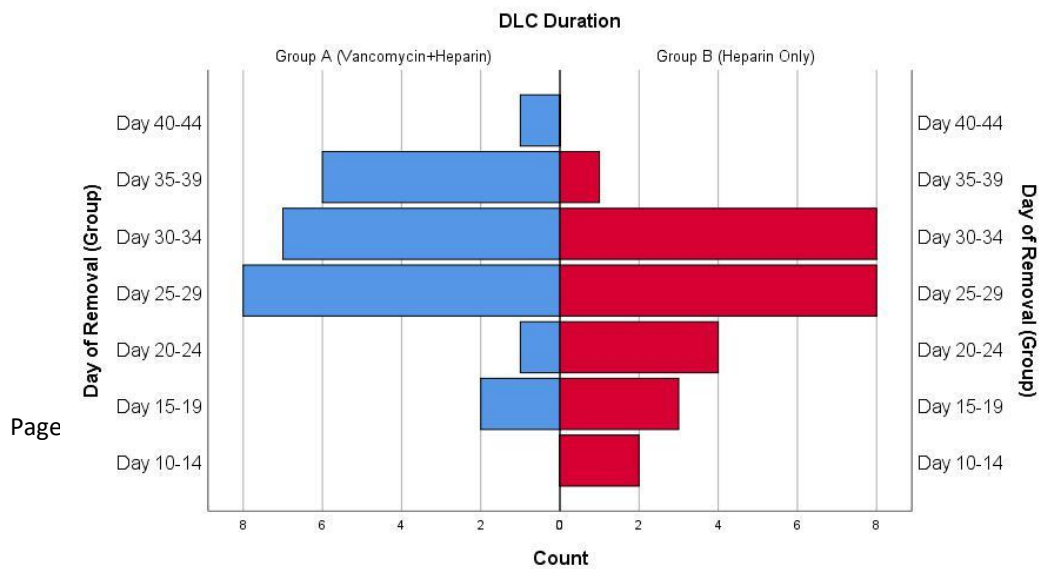


Figure 2. Grouped distribution of catheter survival in each group

225x132mm (96 x 96 DPI)

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