

Original Article**Successful prevention of tunneled, central catheter infection by antibiotic lock therapy using cefotaxime**

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**Abstract**

**BACKGROUND:** Chronic hemodialysis patients frequently require vascular access through central venous catheters (CVCs). The most significant complication of these catheters is infection. This risk can be lowered by the use of an antibiotic-Heparin lock. This study focuses on hemodialysis patients using Tunneled-cuffed catheters (TCC), to assess the rate of catheter-related infections (CRI) in catheter-restricted filling with Cefotaxime and Heparin in end stage renal disease patients.

**METHODS:** A double-blind randomized study was conducted to compare 5000 U/ml Heparin plus 10 mg/ml cefotaxime (CE/HS) as catheter-lock solutions, with Heparin (5000 U/ml) alone. A total of 30 patients with end-stage renal disease and different etiologies, were enrolled for chronic hemodialysis with permanent catheters from December 2009 to March 2010. These patients were randomly assigned to two groups of 15 members. Blood samples were collected for culture, sensitivity, and colony count, from the catheter lumen and the peripheral vein. CRI was considered as the end point.

**RESULTS:** The rate of CRI was significantly lower in the cefotaxime group versus control group ( $p < 0.001$ ). No exit site infection was occurred in both groups. Infection-free survival rates at 180 days were 100% for the CE/HS group, and 56% for the HS group.

**CONCLUSIONS:** Antibiotic lock therapy using cefotaxime reduces the risk of CRI in hemodialysis patients.

**KEYWORDS:** Catheter, Hemodialysis, Lock Solution Infection, Cefotaxime, Heparin.

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A native arteriovenous fistula is the gold-standard vascular access for haemodialysis (HD), but venous catheter use is also widespread.<sup>1</sup> Catheter-related infection (CRI) is a significant complication of chronic hemodialysis. CRI is associated with high morbidity and mortality and the prevention of CRI has remained a significant challenge.<sup>1</sup> CRI constitutes a substantial component of hospital-acquired infections. Hospital admissions for vascular access infection has

doubled in the last decade<sup>2,3</sup> resulting not only in substantial patient morbidity, but also in consumption of hospital resources. Furthermore, this is also associated with increased all-cause infection-related mortality.<sup>4,6</sup>

An incidence of two to three CRI episodes per 1000 catheter-days is considered relatively low.<sup>7-10</sup> Most studies reporting four to six episodes per 1000 catheter-days.<sup>11-16</sup> The prevalence of Gram-positive organisms (usually *Staphylococcus* species) is about 60% and Gram-

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negative organisms 40%, depending upon local patterns of bacterial flora. The frequency of CRI depends on several factors including criteria for the definition of bacteremia and infection, duration of catheter use, type of catheter (temporary vs. permanent), frequency of manipulations and exit site care, history of bacteremia, and infection-control procedures.<sup>11,17</sup>

Although the use of tunneled cuffed hemodialysis catheters (TCC) has increased in past years, but yet the appropriate strategy for TCC management is controversial. Typically, initial treatment of CRI is administration of a systemic antibiotic.<sup>11</sup> However, the reported efficacy of systemic antibiotics alone is only 25-32%.<sup>18,19</sup>

In order to prevent intraluminal colonization and the development of a biofilm, an approach has been used to instill an antimicrobial solution into the lumen(s) of the catheter (lock solution) at the end of each hemodialysis session. Fong suggested that antibiotic infusion followed by Vancomycin or Ciprofloxacin antibiotic-lock successfully eradicated catheter-related sepsis without catheter removal.<sup>20</sup> To further investigate intraluminal antibiotics in the prevention of CRI in patients requiring hemodialysis, we determined the rate of catheter-related infection (CRI) of Cefotaxime and Heparin in end-stage renal disease patients.

## Methods

### Study Design

A hundred and fifty patients with end-stage renal disease were assessed for eligibility. The study was a prospective, randomized, controlled clinical trial (Iranian Clinical Registration Number 13881182370N6), and conducted at two tertiary-care urban medical center. Patients with end-stage renal disease from December 2009 to March 2010 were included in the study. The catheters were dual-lumen, 200-mm, and silicone based.

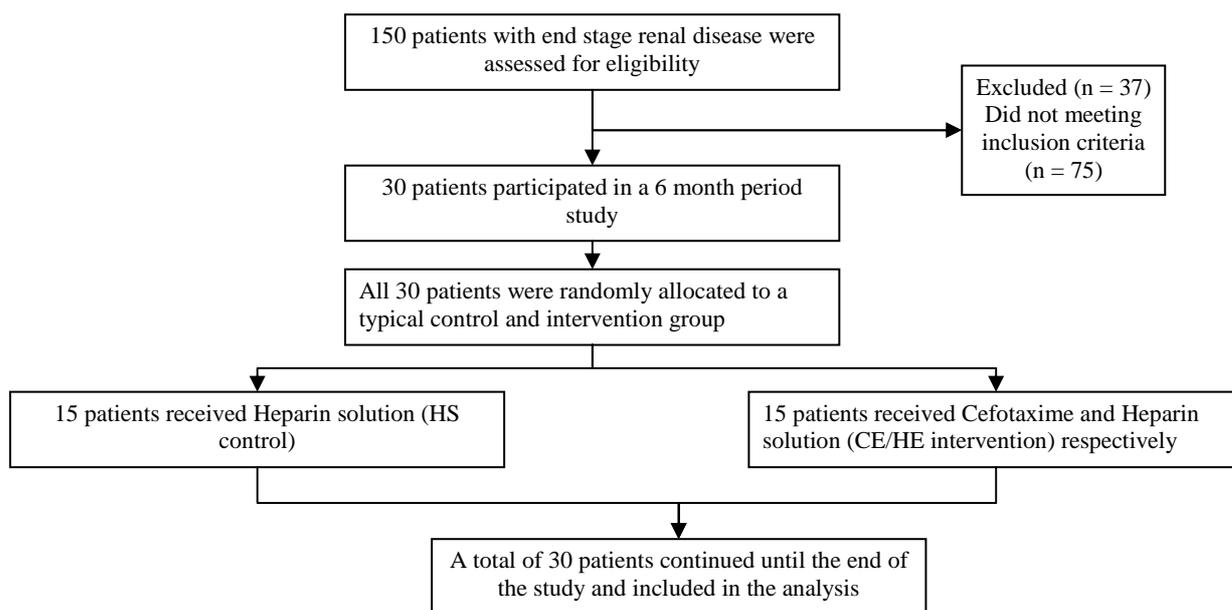
Inclusion criteria included age more than 18, being dialyzed with central tunneled catheter, Med Comp (only if placed in the internal jugular vein), with a maximum time of one month post catheterization, dialysis 3 times a week and having accepted to participate in the

study. Exclusion criteria were allergy to Cefotaxime, antibiotic treatment within 2 weeks prior to enrollment, patients requiring a surrogate decision maker, catheters with blood flow rates less than 300 ml/min, or requiring frequent thrombolytic solution dwells in the catheter lumen because of malfunction.

At the beginning of the study, 150 patients were dialyzed with tunneled catheters. According to the inclusion criteria, 38 patients were eligible to participate in the study, but 30 of them were consented (20.6%). Study profile is shown in (Figure 1).

Enrolled patients were randomly assigned by using a block computerized randomization protocol into two groups of 15 patients. In intervention group, we used Cefotaxime, at a concentration of 10 mg/ml as the experimental antibiotic lock solution.

Cefotaxime-Heparin "lock" solutions were prepared by dissolving sterile Cefotaxime sodium powder in normal saline for injection to reach a concentration of 10 mg/mL for Cefotaxime. Then mixture of 1.5 cc Cefotaxime (10 mg/ml) and 1.5 cc Heparin solution (5,000 U/ml) (CE/HS), was prepared in a syringe using aseptic precautions to fill 1.6 mL in the venous and 1.4 ml in the arterial lumen of the catheter at the end of each dialysis session (exact volume of each venous and arterial port so that Cefotaxime would not enter the blood stream, preventing its systemic effect and microbial resistance). In control group we just filled 1.6 ml and 1.4 ml of standard Heparin solution (HS; 5,000 U/ml) in the venous and arterial lumens respectively. In both groups, the catheter exit-site was washed with antiseptic solution at the initiation and termination of each session, and covered by topical mupirocin and dry sterile gauze during dialysis intervals. Antibiotic solutions were stored in the refrigerator and Nurses were trained to instill the solution into each of the two ports of the HD catheter at the end of each dialysis session, and withdraw it immediately before the next dialysis session. TCCs were inserted by experienced vascular access surgeons. In this study all the included patients received dialysis three times



**Figure 1.** Study profile

a week with the same catheter and the same exit site care, and they all had the same duration of catheter insertion.

### **Catheter-Related Infection**

Enrolled patients were routinely monitored clinically for symptoms and signs of infection, during each session of dialysis. Blood cultures were drawn if patients had fever, chills, rigors, sweats, change in mental status, or exit-site infection (4). Other causes of infection were ruled out. The study protocol required peripheral and catheter blood cultures and an exit site swab to be collected, if clinically indicated. If the catheter was removed, the catheter tip was cultured. Patients with positive blood culture results were treated with systemic antibiotics driven by type of organism and antibiotic susceptibility. Blood stream infections were defined by the CDC (Centers for Disease Control) criteria (21).

Definite blood stream infection was defined as the same organism from a semiquantitative culture of the catheter tip (15 colony-forming units/catheter segments) or catheter blood sample versus peripheral blood sample in a symptomatic patient with no other apparent

source of infection (22). If colony count of catheter were 5 times more than blood sample, blood stream infection were established (7, 20).

### **Statistical Analysis**

Data were analyzed using SPSS software (SPSS Inc., Chicago, IL; ver.18). Results are expressed as mean  $\pm$ SD or Number (percent). Statistical analysis was performed with independent Sample T-test and Chi-square tests. P-value less than 0.05 was considered as statistically significant.

### **Results**

All patients were visited in the HD unit on every other daily basis, and clinical events were closely examined. No patient was lost to follow-up. Baseline demographic and clinical data including, age, male-female ratio, weight, diabetes, hypertension, lab data (complete blood count, Serum Ferritin and Serum albumin) did not have significant difference among two groups ( $p > 0.05$ ) (Table 1). No fatalities occurred during the follow up.

Exit site infection was occurred in neither of groups but eleven patients developed CRI in

**Table 1.** Demographic and basic clinical characteristics of patients at the beginning of study

Parameter	HS (control)	CE/HS(intervention)	p-value
Patient age (y)	56 ± 9.60	52 ± 10.30	NS
Sex (male:female)	6:9	7:8	NS
Weight at base line (kg)*	68.50 ± 5.60	65.40 ± 6.10	NS
Hypertension (yes:no)	11:4	12:3	NS
Diabetes (yes:no)	6:9	8:7	NS
Hematocrit (%)*	31.50 ± 4.50	33.50 ± 5.50	NS
Serum ferritin (ng/mL)*	337.40 ± 90.12	310 ± 84.70	NS
Serum albumin (g/dL)*	3.50 ± 0.90	3.70 ± 0.95	NS

\* Mean ± SD

HS: Heparin Solution (5000 U/ml)

CE/HS: Cefotaxime (10 mg/ml) + Heparin Solution (5000 U/ml)

Hypertension (blood pressure more than 140 / 90 mmHg)

Diabetes (Fasting Blood sugar more than 126 mg/dl)

NS: Not Significant (p &gt; 0.05)

the HS (control) group at the time of the first interim analysis, whereas no patient had CRI in the CE/HS group. Clinical examination and follow-up of the patients with infection did not show any other sources except the catheters. Infection rate per 1000 catheter-days was zero in the CE/HS group versus 6.84 in the HS group ( $p < 0.001$ ). The bacteria isolated from peripheral and catheter blood were gram-negative Bacilli in 64%, while 36% of them were gram-positive Cocci. Among gram-positive Cocci, 75% were Staph Aureus. Infection-free survival rates at 180 days were 100% for the (CE/HS) group, and 56% for the HS group ( $p < 0.001$ , Pearson chi-square value = 17.368).

## Discussion

CRI results from migration of skin organisms along the catheter into the bloodstream or contamination and colonization of catheter lumens.<sup>23</sup> All indwelling vascular catheters develop a biofilm on internal and external surfaces. Subsequent colonization of this biofilm occurs in a high percentage of catheters and precedes bacteremia and septic symptoms.<sup>24</sup> Through reduction in CRI rate, we can reach dramatic reduction in morbidity and mortality of hemodialysis patients. Antibiotic lock is one of the methods which can help to prevent CRI, but according to its importance and financial cost,

prospective randomized clinical trials are necessary to confirm its efficacy. The aim of this study was to determine the efficacy of catheter-restricted filling with Cefotaxime and Heparin in preventing tunneled catheter related infections (CRI) in hemodialysis patients.

Patients with confirmed bacteremia may benefit from administration of intravenous antibiotics and instillation of the antibiotic-Heparin lock between dialysis sessions without catheter removal. Preventing bacteremia and treating without catheter removal would be optimal. A lower concentration of the antibiotic-Heparin lock was investigated for preventing gram-positive central venous catheter related infections in 57 neutropenic patients with cancer.<sup>25</sup> Antiseptic and antibiotic coatings on central venous catheters showed promising results in intensive care populations.<sup>26,27</sup> A 79% reduction in the rate of catheter-related blood stream infections (relative risk [RR] 0.21, 95% CI 0.03-0.95) was reported with use of Chlorhexidine-silver sulfadiazine-coated catheters. Application of these results to patients receiving chronic hemodialysis is limited as catheters used in intensive care unit are in situ for approximately one week, versus hemodialysis catheters which may be in situ for several weeks or even months.<sup>26</sup> Cefotaxime is active against most gram-negative bacilli (except *Pseudomonas*) and

gram-positive cocci (except enterococcus) and is also active against many penicillin-resistant pneumococci. This study suggested that infection rates per 1000 catheter-days were significantly lower in the CE/HS group versus HS (control) group (0.000 vs. 6.84/1000 catheter days). Saxena showed a lower CRI incidence in the CE/HS group versus HS (control) group in non-tunneled HD catheters (1.65 vs. 3.13/1000 catheter days). In tunneled HD catheters, rate of CRI is less than non-tunneled HD catheters.<sup>4</sup> Furthermore, he showed a lower CRI incidence in the CE/HS group versus HS (control) group (1.67 vs. 3.60/1000 catheter days) in TCC.<sup>28</sup> CRI rates were significantly lower with the use of antibiotic locking solution (ALSs). Pooled data from several studies show that CRI is 7.72 (95% confidence interval, 5.1 to 10.3) times less likely with ALS than with Heparin.<sup>29</sup> Six of these studies used Heparin, 5000 U/ml, as the control group, while the study by Kim et al<sup>26</sup> used 1000 U/ml. Antibiotics tested include gentamicin,<sup>22,30,31</sup> gentamicin/citrate combination,<sup>32</sup> cefotaxime,<sup>4</sup> minocycline,<sup>22</sup> ceftazolin/gentamicin combination<sup>26</sup> and chlorhexidine.<sup>33</sup> In this study, the choice of Cefotaxime was based on its broad spectrum effect on gram-negative organisms in addition to being most effective amongst third generation Cephalosporins against *Staphylococcus Aureus*. Cefotaxime was preferred over Gentamicin for locking TCC, which can be potentially ototoxic, especially in elderly patients who often have preexisting hearing disabilities.<sup>28,34,35</sup>

### Conflict of Interests

Authors have no conflict of interests.

### Authors' Contributions

MM, SA, BP, and AA selected and managed patients, FS referred eligible patients after Catheter placement, MA was our statistician, RS, AHDJ, and NS were the major contributors in writing the manuscript. All authors read and approved the final manuscript.

### Conclusions

The present study shows that catheter-restricted filling with a solution containing Cefotaxime and Heparin may significantly reduce the incidence of Catheter-related infection among end stage renal disease patients.

Cefotaxime as an antibiotic lock solution appears to be effective and safe; although there is some concern about the allergy to its leaked solution from lumens. Therefore we excluded the patients who had allergy to Cefotaxime. In order to omit biases in our study, all the patients had the same frequency of manipulation, they all received dialysis three times a week with the same catheter and they all had the same duration of catheter insertion. With the use of antibiotic lock method for reduction in CRI rate, we may reach dramatic reduction in morbidity and mortality of hemodialysis patients.

Since this study was a small sample size and short-term follow-up study, and according to its importance and financial cost associated, there is a need for additional studies with long-term follow-up on larger population to evaluate the efficacy of Cefotaxime lock protocol and its probable adverse effects and its correlation with using topical agents.

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