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Main determinants of tunneled cuffed catheters infection in hemodialysis patients

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ABSTRACT

Introduction: Despite all efforts to prevent tunneled-cuffed catheter (TCC) infection, the incidence of this infection has remained considerably high.

Objectives: The present study aimed to assess risk determinants affecting TCC infection in hemodialysis patients.

Patients and Methods: This case-control study was performed on 165 consecutive patients as known cases of end-stage renal disease on maintenance hemodialysis through double-lumen-TCC. The patients were assigned into two groups as the case group with the clinical evidences of TCC infection and the control group with noninfectious condition.

Results: In the group with TCC infection, the most common microorganisms cultured in the medium included *Staphylococcus aurous* and *Staphylococcus epidermidis* with the overall prevalence of 17.6% and 15.3% in blue lumen and 14.1% and 14.1% in red lumen, respectively. Overall, 75.3% of the lumens were positive for infection, while 52.9% of blood cultures were positive. Multivariable logistic regression modeling showed that female gender, insertion catheter through jugular vein, higher C-reactive protein (CRP) level, lower serum iron level and higher serum ferritin level could predict TCC infection in dialysis patients. According to ROC curve analysis, measuring CRP level, serum iron and serum ferritin could effectively discriminate TCC infection from noninfectious condition. Particularly, serum CRP >16 mg/dL, ferritin > 200 ng/mL and serum iron <40 mg/dL could predict TCC infection.

Conclusion: Around 75% of samples extracted from catheter lumens are positive for TCC infection. The main determinants of TCC infection included female gender, insertion catheter by jugular vein, higher CRP level, lower serum iron level, and higher serum ferritin level.

Implication for health policy/practice/research/medical education:
Given the high prevalence of tunneled-cuffed catheters (TCCs) infection in hemodialysis patients, early diagnosis, prevention and treatment of infection is important. Hence, detecting of high risk population can be helpful. Some risk factors expose patients at greater risk of TCCs infection include female gender, insertion catheter by jugular vein, higher CRP level, lower serum iron level, and higher serum ferritin level.

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Introduction

Providing vascular access has been known as the "Achilles heel" of hemodialysis patients , while it had successfully improved patients' outcome (1). Tunneled-cuffed catheters (TCC) inserted in a central vein are commonly applied in hemodialysis patients as a temporary vascular access until an arteriovenous fistula is provided to use (2). The insertion of tunneled dialysis catheters leads to potential advantages including facility of placement with acceptable duration of function (3). However, some important limitations of the catheters have been also pointed out such as central vein stenosis (4), poor blood flow (5,6), catheter thrombosis (7,8) and infection (9-11). Infection is a major problem of using TCC catheters. The overall reported incidence of TCC catheter infection has been estimated as 0.4 to 4.5 per 1000 catheter days and its bacteremia as 0.2 to 3.9 per 1000 catheter days (12,13). This type of infection leads to some potential complications such as endocarditis, abscess, and septic arthritis. Also, TCC infection is responsible for the catheter failure in 6% to 28% of the patients (14-16). The predominant causative microorganisms of TCC infections include gram positive bacteria in half of the affected patients followed by gram negative bacilli and polymicrobials (17). Two main

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sources have been identified for TCC infections including migration of skin organisms along the external surface of the catheter from the exit site wound. Likewise, low socio-economic state and poor hygiene by health care staffs and patients was other sources for catheter failure. The main modality to treat TTC infection is administrating oral antibiotics for minor infections and by intravenous rout, if there is a discharge from the tunnel or exit site. In case of failure in controlling TTC infection, the catheter should be removed and reinserted through a different track (18-20). Despite all efforts to prevent TTC infection or its treatment appropriately, the incidence of this infection has remained considerably high. Moreover, the main determinants of TCC infection have not been clearly defined.

Objectives

The present study thus aimed to exclusively assess risk determinants which affecting TCC infection in hemodialysis patients.

Patients and Methods

This case-control study was performed on 165 consecutive patients aged more than 18 years as known cases of end-stage renal disease on maintenance hemodialysis three times per week for 4 hours through a double-lumen-TCC at Hasheminejad hospital in Tehran, Iran in 2015. Patients were assigned into two groups as the case group (n = 85) with the clinical symptoms of fever and chill without other local or systemic infectious sources and the control group (n = 80) without any symptoms or signs infections or any episodes of infection or antibiotic administration during the previous three months. The baseline information including demographic data, medical history, catheter-related information (the type and location of catheter placement, the proportion of catheter insertion and embedded date), and laboratory parameters were collected from the patients' recorded files. All patients in the case group were initially assessed for erythema and purulent discharge in catheter site and other possible causes of fever including upper airway infections, pneumonia, gastroenteritis, and urinary tract infection were ruled out. Initially, peripheral blood samples and samples sourced from catheter lumen were extracted for blood culture. Then, patients in case group were treated by intravenous vancomycin 1gram as loading dose followed by 1 gram in every five days for three consecutive weeks plus ceftazidime every 48 hours. In cases with sepsis or prolonged fever (more than 72 hours), catheter was removed and its tip sent to the laboratory for culture. If fever persisted for more than 72 hours or there was a doubt for endocarditis, echocardiography was performed. The response criterion to treatment was based on significant improvement of clinical symptoms and fever relief within 72 hours of antibiotic therapy.

Ethical issues

The research followed the tenets of the Declaration of Helsinki; informed consent was obtained; and the research was approved by the ethical committee of Iran University of Medical Sciences. All patients' information remained confidential. This study was conducted as a nephrology fellowship thesis at this university.

Statistical analysis

The study endpoint was to determine the main risk factors for occurring TCC infection by multivariate comparing patients' and catheter-related variables. For statistical analysis, results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Normality of data was analyzed using the Kolmogorov-Smirnoff test. Categorical variables were compared using chi-square test or Fisher's exact test when more than 20% of cells with expected count of less than 5 were observed. Quantitative variables were also compared with *t* test or Mann-Whitney U test. The multivariable logistic regression analysis was applied to assess the main correlates of TCC infection with the presence of the potential confounders. The ROC curve analysis was used to assess the value of baseline parameters to discriminate TCC infection from non-infection status. For the statistical analysis, the statistical software SPSS version 16.0 for windows (SPSS Inc., Chicago, IL) was used. *P* values of 0.05 or less were considered statistically significant.

Results

The baseline characteristics and clinical data in the case and control groups were initially compared. As shown in Table 1, the two groups were similar in gender, mean age, duration of dialysis, use of TauroLock, as well as some laboratory indices including serum hemoglobin and serum calcium levels. However, regarding catheter insertion site, the catheter in case group were mostly inserted in jugular vein, while the catheters inserted in subclavian vein was revealed more, in control group. Also, the mean duration of catheter administration in the case group was significantly shorter in case group than in control group ($P<0.05$). Women more affected by TCC infection compared to men ($P<0.05$). Moreover, we found, lower mean levels of serum albumin, iron, TIBC, and PTH in case group ($P<0.05$). Furthermore, we detected higher levels of CRP and serum ferritin in case group when compared to control group ($P<0.05$). Out of 82 cultures from blue lumen, in group with TCC infection, we found 75.3% were positive mostly by staphylococcus aurous and *S. epidermidis* with the overall prevalence of 17.6% and 15.3%, respectively (Figure 1). Regarding culture provided from red lumen, 75.3% of which were positive for infection mostly by *Staphylococcus aurous* and *S. epidermidis* with the prevalence rates of 14.1% and 14.1%, respectively (Figure 2). Overall, 52.9% of blood cultures were positive. Multivariable logistic regression modeling (Table 2) showed that among all baseline variables, female gender (odds ratio [OR] = 10.095, $P = 0.044$), insertion catheter through jugular vein (OR = 0.140, $P = 0.021$),

Table 1. The baseline characteristics and clinical data in groups with and without TCC infection

Characteristics	Group with TCC infection (n = 85)	Group without TCC infection (n = 80)	*P* value
Age, year	57.98 ± 15.12	57.99 ± 17.07	0.99
Male gender, No. (%)	26 (30.5)	48 (60)	< 0.001
History of diabetes, No. (%)	47 (55.3)	46 (57.5)	0.80
Catheter location, No. (%)			<0.001
Subclavian	63 (76.8)	75 (94.9)	
Jugular	13 (15.9)	1 (1.3)	
Femoral	6 (7.3)	3 (3.8)	
Use of TauroLock, No. (%)	29 (34.1)	36 (45)	0.20
Catheter duration, month	7.55±7.14	8.80 ±6.30	0.01
Duration of dialysis, year	4.18±3.63	5.16±6.23	0.35
Laboratory parameters			
Calcium (mg/dL)	8.8 ± 0.85	9.03 ± 0.75	0.24
Hemoglobin (g/dL)	9.96 ± 1.96	10.48 ± 1.68	0.07
Albumin (g/dL)	3.88 ± 0.51	3.63 ± 0.93	0.04
Phosphate (mg/dL)	4.36 ± 1.81	5.57 ± 1.48	< 0.001
CRP	53.54 ± 29.36	20.24 ± 21.90	< 0.001
Iron (mg/dL)	38.81 ± 59.04	227.8 ± 212.56	< 0.001
TIBC	248.71 ± 88.41	208.92 ± 99.83	0.03
Ferritin (mg/dL)	582.52 ± 396.87	277.08 ± 253.44	< 0.001
Parathyroid hormone (mg/dL)	173.20 ± 167.0	314.53 ± 301.86	< 0.001

Table 2. Multivariable logistic regression model to predict TCC infection in hemodialysis patients

Item	B	SE	Wald	*P* value	OR	95.0% CI for OR	
						Lower	Upper
Sex	2.312	1.148	4.053	0.044	10.095	1.063	95.873
Catheter Location	-1.966	0.850	5.352	0.021	0.140	0.026	0.740
Catheter duration	0.198	0.123	2.588	0.108	1.219	0.958	1.552
Alb	-0.995	0.659	2.276	0.131	0.370	0.102	1.347
CRP	0.070	0.024	8.350	0.004	1.073	1.023	1.125
Hb	0.153	0.432	0.126	0.723	1.166	0.500	2.717
Iron	-0.106	0.034	9.784	0.002	0.900	0.842	0.961
Ferritin	0.007	0.003	6.140	0.013	1.007	1.002	1.013
Ca2	0.198	0.666	0.089	0.766	1.219	.330	4.501
Constant	3.986	7.274	0.300	0.584	53.819		

higher CRP level (OR = 1.073, P = 0.004), lower serum iron level (OR = 0.900, P = 0.002), and higher serum ferritin level (OR = 1.007, P = 0.013) could predict TCC infection in dialysis patients. According to ROC curve analysis (Figure 3), measuring CRP level (AUC = 0.830), serum iron (AUC = 0.899) and serum ferritin (AUC = 0.732) could effectively discriminate TCC infection from noninfectious statement. In this regard, CRP > 16 mg/dL (with the sensitivity of 86.6% and the specificity of 70.5%), ferritin > 200 ng/mL (with the sensitivity of 76.1% and the specificity of 60.7%) and serum iron < 40 mg/dL (with the sensitivity of 91.8% and the specificity of 73.1%) could predict TCC infection.

Discussion

The present study had two important points. First, two organisms are responsible for TCC infection include *S. aurous* and *S. epidermidis*. Thus gram positive pathogens are still the most frequent causes for TCC infection in hemodialysis patients. As previously indicated by Blankestijn (21), a clear predominance of skin derived microorganisms especially *S. epidermidis* and *S. aurous* as the main source of TCC infection is now demonstrated. Thus, catheter-related bacteremia with or without severe clinical symptoms should be covered by parenteral antibiotics appropriate for these organisms suspected. In some other studies, gram-positive organisms are the most common cause of catheter-related infections. Both coagulase negative *S. epidermidis* and *S. aurous* accounting for the majority of cases. The remaining infections are due to enterococci, aerobic gram-negative rods, and fungal species (22). There is a strong relation between *S. aurous* bacteremia and dialysis. A total of 14.5% to 66.0% of all bacteremia episodes of this infection happens in individuals with end-stage renal disease (23-26). *S. aurous* is the single important pathogen causing severe infections in dialysis subjects, responsible for 27% to 39% of bacteremia in dialysis individuals (27). The incidence of *S. aurous* bacteremia in individuals who undergo hemodialysis is as high as 1.2 episodes

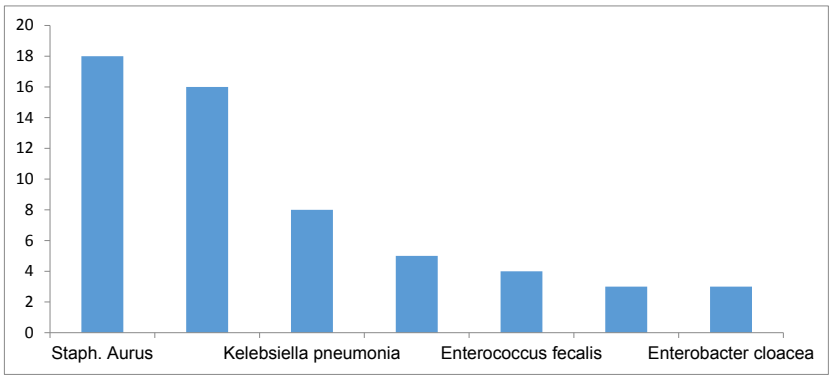

Figure 1. Common microorganisms responsible for infection of blue lumen.

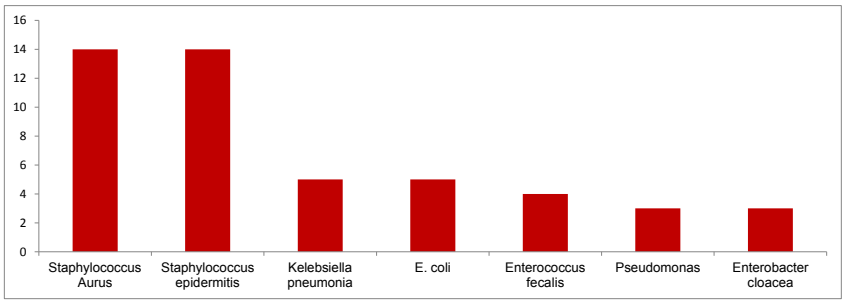

Figure 2. Common microorganisms responsible for infection of red lumen.

per 100 patient-months, with a complication rate of up to 40% to 44% and infective endocarditis in 12% of subjects (28). Hemodialysis patients have an 8.1% to 8.6% chance of developing a *S. aurous* bacteremia during their dialysis career (29,30). Therefore, covering antibiotic treatment of these two pathogens should be considered in all hemodialysis patients who are susceptible for TCC infection.

Various risk factors have been shown in TCC infection in hemodialysis patients. In our observation, female gender, insertion catheter through jugular vein, higher CRP level, lower serum iron level, and higher serum ferritin level could predict TCC infection in dialysis patients. In a study aiming determination of risk factors for long-term TCC infection, significant risk factors for bacteremia episodes in hemodialysis patients with long-term TCC included diabetes mellitus, peripheral atherosclerosis, a previous history of bacteremia, nasal carriage of *S. aurous*, longer catheter duration, more frequent urokinase catheter infusion, higher total intravenous iron dose, and local infection (31). These findings had discrepancy when compared to our results. In other study, site of insertion, duration of use and influence of comorbidity have been reported to impact the risk of developing catheter-related bacteremias (32). The subclavian location has been shown to be associated with the highest risk for developing catheter associated central venous stenosis (33), whereas in our study, the jugular location was prominent to TCC infection. The duration of catheter insertion seems to

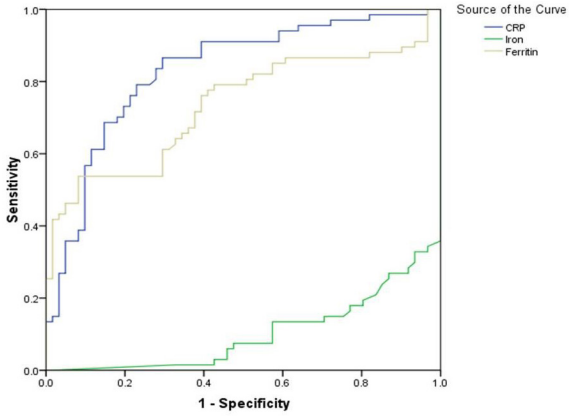

Figure 3. Area under the ROC curve to assess the value of CRP, ferritin and low iron to discriminate TCC infection from noninfectious statement.

be also important while the risk of infection increases linearly with time (34,35), a finding that was not obtained in our study. Higher incidence of TCC infection in women than in men is related to two subjects. First, both early and late complications of TCC more occurred in women than in men. As shown by Tapping et al (36), early and late complications were significantly associated with female gender with odds ratios of 2.9 and 1.9 respectively. As another reason, female gender has been shown as a main factor for increased use of catheter access leading higher catheter-related complications such as infection (37). In

addition, we detected iron deficiency as a risk determinant for TCC infection, while higher total intravenous iron dose has been indicated as a risk profile (38). It can be explainable that our patients with lower serum iron level might receive iron supplements particularly by intravenous rout that led to higher risk for infection. However our study on iron overload or prescribing iron supplements were incomplete at the time of study. Finally, according to the differences between our study and previous studies even after adjusting baseline confounders, more studies are needed to assess the reasons for these discrepancies. In other word, the association between jugular insertion of catheter or low serum level of iron and higher risk for TCC infection should be more assessed.

Conclusion

About 75% of samples extracted from catheter lumens are positive for TCC infection commonly by *S. aurous* and *S. epidermidis*. The main determinants of TCC infection include female gender, insertion catheter via jugular vein, higher CRP level, lower serum iron level, and higher serum ferritin level.

Limitations of the study

This study was conducted on a limited proportion of patients and we suggest larger studies on this feature of hemodialysis patients.

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Authors' contribution

TM conceived the study and analyzed the data and preparing the manuscript, MY collected data and drafted the final manuscript, TS conducted the laboratory tests, YAP contributed to data collection and patient selection. All authors read, revised and approved the final manuscript.

Conflicts of interest

There was no points of conflicts to declare.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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