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Locking of Tunneled Cuffed Hemodialysis Catheters with a Mixture of 45% Ethanol and 4% Trisodium Citrate is Effective in Preventing Catheter-Related Infections and Thrombosis

Tünelli Keçeli Hemodiyaliz Katanterlerinin %45 Etanol ve %4 Trisodyum Sitrattan Oluşan Karışım ile Kapanması Kateter İlişkili Enfeksiyonların ve Trombozun Önlenmesinde Etkindir

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ABSTRACT

OBJECTIVE: In this study, we aimed to investigate the effect of a mixture consisting of 45% ethanol and 4% trisodium citrate (E-TSC) on the development of catheter-related infection (CRI) and catheter thrombosis in hemodialysis patients.

MATERIAL and METHODS: A total of 114 patients were included in the study. Patients were separated into two groups according to the type of catheter lock solution as the E-TSC and classic heparin groups. There were 51 patients in the E-TSC group and 63 patients in the heparin group.

RESULTS: The development of CRI was significantly lower in the E-TSC group compared to the heparin group (p= 0.011). CRI developed in only 1 patient in the E-TSC group whereas it developed in 10 patients in the heparin group. There was no significant difference between the two groups with regard to the development of thrombosis (p > 0.05).

CONCLUSION: E-TSC solution has favorable effects on the prevention of the development of CRI compared to classic heparin. It also is as effective as heparin on the prevention of the development of catheter thrombosis.

KEY WORDS: Catheter-related infection, Catheter thrombosis, Ethanol, Trisodium citrate, Tunneled cuffed hemodialysis catheter

ÖZ

AMAÇ: Çalışmada, hemodiyaliz hastalarında kateter ilişkili enfeksiyon (KİE) ve kateter trombozu gelişimi üzerine %45 etanol ve %4 trisodyum sitrattan (E-TSS) oluşan karışımının etkisini araştırmayı amaçladık.

GEREÇ ve YÖNTEMLER: Çalışmaya toplam 114 hasta dahil edildi. Hastalar kateter kapama solüsyonun tipine göre iki gruba ayrıldı: E-TSS ve klasik heparin grupları. E-TSS grubunda 51 hasta, heparin grubunda 63 hasta mevcuttu.

BULGULAR: KİE gelişimi E-TSS grubunda heparin grubuna kıyasla anlamlı olarak daha düşüktü (p= 0,011). E-TSS grubunda sadece bir hastada KİE gelişirken heparin grubunda 10 hastada KİE gelişti. Tromboz gelişimi açısından 2 grup arasında anlamlı fark yoktu (p > 0,05).

SONUÇ: E-TSS solüsyonu, klasik heparine kıyasla, KİE gelişiminin önlenmesi üzerine olumlu etkilere sahiptir. Bu solüsyon ayrıca kateter trombozu gelişimini önlemede heparin kadar etkindir.

ANAHTAR SÖZCÜKLER: Kateter ilişkili enfeksiyon, Kateter trombozu, Etanol, Trisodyum sitrat, Tünelli keçeli hemodiyaliz kateteri

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INTRODUCTION

Use of tunnelled cuffed hemodialysis (HD) catheters for vascular access in HD patients is increasing. The most important catheter related-complications are catheter-related infections (CRIs) and catheter thrombosis (1). The frequency of tunneled cuffed catheter use for vascular access in HD patients varies from country to country. In the DOPPS study, for example, the frequency was found to be 17% in the USA and 8% in Europe (2). In our country, Turkey, the rate is 10.8% (3). Such widespread use of tunneled cuffed HD catheters is associated with increased catheter-related complications, morbidity, and mortality (4). The risk of bacteremia is more than seven times higher in patients with tunneled cuffed HD catheters than in those with arteriovenous fistula (AVF) (5).

Various methods are used in the prevention of CRIs. Catheter lock solutions with antibiotic have been shown to decrease CRIs and CRI-related mortality (6). On the other hand, some side effects including antibiotic resistance, allergic reactions, ototoxicity, and increased anticoagulant activity (especially with the use of catheter lock solutions with heparin or citrate) may develop with the use of these solutions (7,8).

Another permanent tunneled HD catheter-related complication is catheter thrombosis. The catheter lock solutions containing heparin, citrate, urokinase or various concentrations of sodium chloride have been used to prevent this complication (9-13).

It is well known that trisodium citrate inhibits the clotting cascade by chelating ionized calcium and that ethanol has antibacterial and antifungal effects (14-16). The combined use of these agents can lead to both anticoagulant and antibacterial effect and prevent CRIs and catheter thrombosis. Therefore, we performed this prospective study to investigate the effect of a mixture consisting of 45% ethanol and 4% trisodium citrate (E-TSC) on the development of CRI and catheter thrombosis in patients undergoing HD via a tunneled cuffed catheter.

MATERIAL and METHODS

We prospectively enrolled incident HD patients who needed a tunneled cuffed catheter for vascular access, from a single HD unit at the Department of Nephrology, Erciyes University, Kayseri, Turkey. The patients were followed at the satellite HD units after discharge from the hospital. The study was approved by the Ethics Committee of Erciyes University Faculty of Medicine. Patients were notified about the study and the subjects who gave written informed consent were recruited for the protocol.

A total of 114 patients were included in the study. Patients were separated into two groups according to the type of the catheter lock solution including E-TSC (in a 2 mL syringe) and unfractionated sodium heparin (5000 U/mL heparin in a 2 mL syringe). There were 51 patients in the E-TSC group and 63 patients in the heparin group.

After the HD session was completed, each lumen of the tunneled cuffed catheter was flushed with 10 mL of 0.9% sodium chloride and locked with either of the catheter lock solutions.

The syringe was filled with the amount of the locking solution exactly equivalent to lock one internal lumen of the tunneled cuffed catheter. The solution containing a mixture of E-TCS was prepared at the Department of Analytical Chemistry, Faculty of Science, Erciyes University, Kayseri. The solution was filtered through a 0.22 μm filter and 100 mL packages were prepared. The solutions were exposed to 2 Gy gamma sterilization at the Department of Radiation Oncology, Faculty of Medicine, Erciyes University, Kayseri.

The tunneled cuffed 14.5 F polyurethane catheters (19-23 cm Covidien, Mahurkar Maxid™ dual lumen or 24-28 cm Medcomp, Hemoflow™ dual lumen) were used for HD according to the diameter of the vein. Experienced radiologists inserted the catheters under direct image guidance by the Seldinger method at the Department of Interventional Radiology, Faculty of Medicine, Erciyes University, Kayseri. The tunneled cuffed catheter was implanted in the vein under sterile conditions. After the catheter was placed, we routinely examined the chest X-ray for early complications of catheter insertion. All necessary procedures were used and all precautions were taken before HD.

Patients were excluded if they were less than 18 years old or were pregnant. The patients' demographic data including age, gender, etiology of renal disease, use of warfarin therapy, and history of other diseases were recorded.

We noted the time of the insertion of the tunneled cuffed catheter and the vein that the catheter was inserted in.

The primary outcome measure was the development of catheter thrombosis or CRI.

After the catheter had been placed in the vein, the patients were followed for any occurrence of CRIs or thrombosis. The catheters and the exit sides were inspected before every HD session. If CRIs or thrombosis occurred, the day of the complication was recorded. If a patient was transferred from HD or died, we recorded the total catheter days and excluded the patient from the study.

We prepared two different experimental models to test the antimicrobial properties of E-TSC. In the first experimental model, 900 μL tryptic soy broth was added to 3 different tubes containing 1 mL of catheter lock solution. In the second experiment model, 450 μL tryptic soy broth and 450 μL defibrinated sheep blood were added separately to each of the 3 tubes to simulate the catheter. Three standardized reference strains from the American Type Culture Collection (ATCC): Gram- positive strains of *S. aureus* (ATCC 29213), and Gram-negative strains of *P. aeruginosa* (ATCC 27853) and *E. coli* (ATCC 25922) were used for bacterial quality control strains. From each type of bacterium, a final bacterial concentration of

10^8 colony-forming units per mL (CFU/mL) was prepared. 100 μL of each microbial suspension was put separately into each of the 3 tubes of the two experimental models (*E.coli* to the first tube, *P. aeruginosa* to the second, and *S. aureus* to the third).

All tubes were subsequently incubated overnight at 35°C. Also, to check the sterility, the catheter lock solution was put in a tube by itself, and tryptic soy broth was placed in another tube. After the incubation, 100 μL of the suspension was taken from the tubes and placed on 5% sheep blood agar and afterward incubated overnight at 35°C. Bacterial growth was then evaluated, and the colonies were counted and recorded. We examined all samples by Gram staining.

Assessment of Infection

CRI was defined according to the criteria of the Centers for Disease Control (17-20). The diagnostic criteria were as follows: (1) positive blood culture taken from the catheter hub, tip of the catheter or the subcutaneous part of the catheter with no other obvious source of infection, (2) the development of redness or tenderness and/or induration within 2 cm of the exit site without a purulent exudate around the site not resulting from residual stitches or microbiologic exit-site infection where the exudate yields a microorganism in blood culture, (3) redness, tenderness and/or induration 2 cm away from the entrance of a tunneled catheter, and along the tunnel, (4) redness, tenderness and/or induration or purulent exudate on the skin over the reservoir with no other obvious source of infection, (5) the growth of the same organism in the infusion fluid and blood culture with no other obvious source of infection, (6) manifestations of blood stream infection (fever (temperature >38°C)) and one positive blood culture result with no other obvious source of infection.

Assessment of Thrombosis

Thrombosis was defined as persistence of flow problems, despite positional changes of the patient and/or additional flushing of the catheter, defined as a blood flow rate of <200 mL/min for three consecutive dialysis sessions or inability to dialyze the patient leading to removal of the tunneled cuffed catheter or using thrombolytic therapy (13).

Statistical Analysis

Statistical analysis was performed using the SPSS 15.0 software (SPSSFW; SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to determine normality of distributions of variables. Continuous variables with normal distribution were presented as mean ± SD. Statistical analysis for the parametric variables was performed using Student's t-test between two groups. The qualitative variables were given as percent and the correlation between categorical variables was investigated by the Chi-square (χ^2) test and Fisher's Exact test. Risk of development of the primary end point was analyzed using logistic regression analysis. The log rank test was used to compare catheter stay times between the two groups. *P*-values of <0.05 were considered statistically significant.

RESULTS

Table I shows comparison of demographic and clinical parameters of the patients in the two groups. The development of infection was significantly lower in the E-TSC group compared to the standard heparin group (p: 0.011). In contrast, there was no significant difference between the two groups with regard to the development of thrombosis (p > 0.05). Presence of co-morbid disease was significantly higher in the E-TSC group compared to the standard heparin group (p: 0.003). On the other hand, there was no significant difference between the two groups in terms of age, gender, cause of hemodialysis, etiology of chronic kidney failure, catheter insertion location, use of warfarin, and history of previous tunneled-catheter placement (p > 0.05).

Table II shows bacteria causing infections (the results of cultures taken from various places). In E-TSC, infection developed in only 1 patient. *S. epidermidis* grew in blood culture from the catheter lumen. In contrast, other cultures were negative. In the standard heparin group, infection developed in 10 patients. In blood culture from the catheter lumen, *Coagulase-negative staphylococci* grew in 5 patients whereas *K. pneumoniae* grew in 1 patient. In blood culture from the peripheral blood, *Coagulase-negative staphylococci* grew in 6 patients whereas *K. pneumoniae* grew in 1 patient. In addition, *P. aeruginosa* grew in 1 patient. In exit-site culture, *S. epidermidis* grew in 2 patients.

Comparison of patients with and without infection according to albumin level categories is expressed in Table III. There was no significant difference between the two groups in terms of albumin level categories ($p > 0.05$).

Univariate logistic regression analysis was performed to identify predictors considered to be related with the primary end point (catheter-related infection or catheter thrombosis). Table IV shows the results regarding the 5 variables examined in univariate analysis. Only the catheter look solution type was significantly associated with the primary end point (odds ratio: 2.83, confidence interval: 1.27-6.30, *p*: 0.001). Therefore, we did not perform multivariate analysis.

We observed that mixture lock solution of E-TSC showed antibacterial activity against *E. coli, P. aeruginosa*, and *S. aureus* on high concentrations of inoculum (5 x 10^6 CFU/mL) and the effect continued in the simulation environment prepared with blood.

DISCUSSION

In patients with ESRD, HD still continues to be the most widely applied renal replacement therapy. Permanent HD catheters, which are commonly used for vascular access, can result in significant complications such as CRIs and catheter thrombosis, which cause morbidity and mortality in the patients (21). Antibiotic-based catheter lock solutions have been shown to reduce CRIs and infection-related mortality in such patients

Table I: Comparison of demographic and clinical parameters of the patients in the two groups.

	Ethanol and citrate group (n: 51)	Standard heparin group (n: 63)	p value
Age (year)	59.7 ± 14.1	60.9 ± 14.4	0.647
Gender (male/female, %)	26 (51.0)/25 (49.0)	35 (55.6%)/28 (44.4)	0.383
Cause of hemodialysis (%)			0.234
Acute kidney injury	3 (5.9)	1 (1.6)	
Chronic kidney failure	48 (94.1)	62 (98.4)	
Etiology of chronic kidney failure (%)			0.780
Diabetes mellitus	21 (43.8)	22 (35.5)	
Hypertension	12 (25.0)	17 (27.4)	
Glomerulonephritis	2 (4.2)	3 (4.8)	
Obstructive nephropathy	1 (2.1)	1 (1.6)	
Other/unknown	12 (25.0)	19 (30.6)	
Catheter insertion location (%)			0.561
Right jugular	44 (86.3)	51 (81.0)	
Left jugular	7 (13.7)	11 (17.5)	
Right subclavian	-	1 (1.6)	
Presence of co-morbid disease	25 (49.9)	14 (22.2)	0.003
Use of warfarin (%)	-	1 (1.6)	0.553
History of previous catheter placement (%)	17 (34.0)	28 (44.4)	0.176
Development of thrombosis (%)	12 (23.5)	21 (33.3)	0.174
Development of infection (%)	1 (2.0)	10 (15.9)	0.011

Table II: Bacteria causing infections (the results of cultures taken from various sites).

	Ethanol and citrate group (n: 51)			Standard heparin group (n: 63)		
	Catheter lumen	Peripheral blood	Exit-site	Catheter lumen	Peripheral blood	Exit-site
Gram-positive						
CNS	-	-	-	5	6	-
S. epidermidis	1	-	-	-	-	2
S. aureus	-	-	-	-	-	-
Gram-negative						
K. pneumoniae	-	-	-	1	1	-
P. aeruginosa	-	-	-	-	1	-
Culture-negative	-	1	1	4	2	8

CNS: *Coagulase-negative staphylococci*

Table III: Comparison of patients with and without infection according to albumin level categories.

	Patients with infection (n: 11)	Patients without infection (n: 103)	p value
Albumin level category (%)			0.439
<2.5 g/dL	2 (18.2)	22 (21.3)	
2.5 g/dL-3.5 g/dL	9 (81.8)	69 (67.0)	
>3.5 g/dL	-	12 (11.7)	

Table IV: Univariate Logistic Regression Analysis for predictors considered to be related with the primary end point (catheter-related infection or catheter thrombosis).

Variables	Odds ratio	95% CI	p value
Gender (male or female)	1.24	0.58-2.65	0.575
Age group (<65 years or ≥65 years)	1.20	0.56-2.56	0.636
CLS (heparin or ETS-C)	2.83	1.27-6.30	0.011
Hypoalbuminemia (yes or no)	2.02	0.52-7.90	0.314
Diabetes mellitus (no or yes)	1.43	(0.65-3.16)	0.379

CI: Confidential interval, **CLS:** Catheter look solution, **E-TSC:** A mixture solution of 45% ethanol and 4% trisodium citrate.

(8). Heparin, urokinase, citrate, and various concentrations of sodium chloride solution are used to prevent catheter thrombosis (13,22,23). These complications associated with HD catheters cause frequent hospitalizations of patients and an increase in health spending (21,24). According to the United States Renal Data System (USRDS), use of oral or intravenous antibiotics at first six months was 60% and 40% in HD patients dialyzed via catheter or AVF, respectively. It has been also shown that high hospitalization rates due to infection in the first months of treatment relate to high utilization rate of catheters in patients treated for ESRD (25).

Unfortunately, there is no permanent solution for the prevention of catheter thrombosis and CRIs in HD patients with permanent catheter and research on this problem is still ongoing. In the present study, we used mixture of 45% ethanol and 4% trisodium citrate as a different catheter lock solution.

Ethanol is a cheap, broad-spectrum antiseptic and disinfectant agent and has bactericidal effect for both Gram-positive and Gram-negative organisms as well as a fungicidal effect (26). Resistance to the bactericidal effect does not develop because it exerts its effect via nonspecific protein denaturation in the cell wall of the microorganism (27). Thirty percent and higher concentrations of ethanol show a bactericidal effect on *S. aureus* (26).

Trisodium citrate prevents coagulation by chelating ionized calcium in the extracorporeal circulation. It also has an antimicrobial effect (28,29). It has been shown that it is effective as a catheter lock solution in different concentrations (14,30).

We thought that it would be more effective to use these two together because of the properties of ethanol and trisodium citrate. Therefore, we conducted the study to compare the effectiveness of classic heparin and mixture solution of E-TSC, of which there are no studies about *in vivo* use in the literature, as a catheter lock solution. We found that the development of CRIs was significantly lower in the E-TSC group compared to the heparin group. The majority of studies with the E-TSC mixture are *in vitro* and there is no *in vivo* study in which E-TSC and heparin are compared.

In an *in vitro* study, the effectiveness of a 30% ethanol and 4% trisodium citrate lock solution was compared to normal saline to prevent biofilm formation by the most common pathogens causing CRIs. After incubating for 72 hours, this mixture solution prevented the biofilm formation of all isolates of methicillin-resistant *S. aureus* (*MRSA*), methicillin-sensitive *S. aureus* (*MSSA*), methicillin-resistant *S. epidermidis* (*MRSE*), *P. aeruginosa,* and *E. coli* whereas these bacteria produced a biofilm in normal saline solution. The authors who conducted this study emphasized that this mixture would be effective and safe in HD patients as catheter lock solution if their findings are supported by other studies (31).

In our study, we observed that the mixture lock solution of E-TSC showed antibacterial activity against *E. coli, P. aeruginosa*, and *S. aureus* in high concentrations of inoculum (5 x 10^6 CFU/mL) and the effect continued in the simulation environment prepared with blood.

Bell et al. investigated *in vitro* the effect of 3 catheter locking solutions (heparin, 4% TSC, and 30% ethanol/4% TSC) on the mechanical properties of HD catheters including force at break, elongation at break, and elastic modulus. They found that the force at break and elongation at break were significantly lower in the ethanol/TSC group compared to the heparin and TSC groups and the elastic modulus was not significantly different among groups. They suggested that the ethanol/TSC lock solution shows promise as a new catheter locking solution to prevent CRIs (32). Another *in vitro* study has found that 70% ethanol had no unfavorable effect on the mechanical properties of polyurethane catheters after incubating for 9 weeks and suggested that ethanol catheter lock solution may be an effective method to prevent CRIs (33). Similarly, none of patients in E-TSC group in the present study experienced a mechanical problem.

A randomized controlled trial has assessed the efficacy of a 48-hour 70% ethanol lock solution versus heparin lock solution on catheter survival and catheter-related blood stream infection (CR-BSI) and found that catheter survival and CR-BSI were not significantly different. However, comparing the rates of all infective events (included definite or probable CR-BSIs, suspected CI-BSIs and exit site and tunnel infections), the rates in the ethanol and heparin groups were found to be 0.28 and 0.85 per 1000 catheter days, respectively (34).

A prospective study in which 64 immunosuppressed hematology patients with tunneled cuffed intravascular catheters inserted into the veins were randomized to prophylactic treatment using 70% ethanol or heparinized saline to prevent CR-BSI found that the development of CRI and bacteremia was significantly lower in the ethanol arm (35). Various concentrations of TSC have been used as catheter lock solutions. Lok et al. investigated the clinical effectiveness, safety and cost of 4% citrate vs. heparin and found that 4% citrate lock solution had equivalent or better outcomes in terms of catheter exchange, thrombolytic use and access-related hospitalizations compared with the heparin lock solution (36). In our study, although not statistically significant, the development of thrombosis was lower in E-TSC group than heparin group (23.5% vs. 33.3%, respectively).

In a multicenter, double blind, randomized, controlled trial, 30% TSC was compared with unfractionated heparin 5000 U/ml to prevent CRI, thrombosis, and bleeding complications. The study was stopped prematurely because of increased catheter-related bacteremia (CRB) in the heparin group. In addition, it was observed that catheter removal rates were 46% and 28% in the heparin group and the TSC group, respectively. The difference was statistically significant (37).

The most important side effects of solutions containing citrate are hypocalcemia, which results from spread of citrate in circulation, ventricular arrhythmias and sudden cardiac death. A patient died of cardiac arrest shortly after triCitrasol, which is a 46.7% concentration of sodium citrate anticoagulant, was injected full strength into a HD permanent catheter. Rapid or excessive infusion of citrate solutions could cause fatal heart rhythm disruption, seizures or bleeding due to loss of blood calcium. Therefore, the Food and Drug Administration (FDA) has urged hospital pharmacies and HD units across the U.S. to stop using triCitrasol in April 2000 and has indicated that alternative 4% solutions of citrate are available for use in these and most other medical settings (38). In the present study, TSC has been used in low concentrations (4%) and no side effect of the solution was observed.

In conclusion, mixture catheter lock solution of 45% ethanol and 4% trisodium citrate solution had favourable effects on the prevention of CRI development compared to a standard heparin solution. It was also as effective as heparin on the prevention of catheter thrombosis development. Further studies are necessary to determine its efficacy and safety in patients undergoing HD.

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