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Tunneled catheters' outcome optimization among diabetics on dialysis through antibiotic-lock placement

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Efficacy and safety of antibiotic 'locks', in prevention of thrombotic and infectious complication-related morbidity and mortality, among diabetics dialyzed through tunneled-cuffed catheters (TCCs) has not been effectively investigated. This trial was designed to investigate the outcome of TCCs ($n = 109$), inserted among 96 diabetic end-stage renal disease patients (March 2002–February 2003), by comparing the catheter thrombosis, catheter-related bloodstream infections (CRBSI), catheter survival, and mortality rates, between the cohorts of 49 patients who had TCCs ($n = 51$) 'locked' with cefotaxime/heparin (group I) and 47 patients with TCCs ($n = 58$) filled with standard heparin (group II). Thrombosis was defined as the inability to use catheter at a blood flow of 200 ml/min despite intraluminal thrombolysis. Primary end points were catheter thrombosis and CRBSI; elective catheter removal and CRBSI-related death led to sensor of TCCs follow-up. Patients with intraluminal cefotaxime/heparin lock, on cumulative survival analysis, showed a superior thrombosis-free (86.3 vs 63.8%, $P = 0.023$, log rank), infection-free (72.9 vs 27.1%, $P = 0.004$, log rank), and thrombosis- and infection-free TCC survival (78.4 vs 37.9%, $P = 0.001$, log rank) at 365 days, besides having significantly lower incidence of CRBSI (1.56 vs 3.68 episodes/1000 catheter days, $P < 0.0001$) and CRBSI-related mortality (9.8 vs 23.4%, $P = 0.015$), compared with the heparin-alone group. Deployment of cefotaxime–heparin 'lock' enhances catheter survival; reduces thrombotic and infectious complications and ensuing mortality, among diabetics on dialysis. However, further studies are needed to define the long-term implications of antibiotic locks in terms of the risk of emergence of antimicrobial resistance.

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Diabetes mellitus has emerged as the most common cause of end-stage renal disease (ESRD) accounting for nearly 25–40% of patients on renal replacement therapy, worldwide.[1,2] The selection bias of surgical services and the worsening vascular configuration among diabetic ESRD patients, who frequently have other comorbidities, such as advanced age, obesity, coronary artery disease, congestive heart failure, cerebrovascular accidents, and/or peripheral vascular disease leading to limb ischemia, limit their prospect of having safer permanent vascular accesses—arteriovenous fistula and polytetrafluoro ethylene grafts – leaving tunneled-cuffed catheters (TCCs) with the inherent risk of thrombotic and infectious complications, the lone long-term dialysis – access option, for them.[2,3]

A close relationship exists between catheter colonization and thrombogenesis.[4,5] Catheter surface provides a nidus for the fibrin sheath formation that facilitates bacterial adherence, colonization, and development of biofilm. Biofilms facilitate rapid multiplication of microorganisms on the external, as well as luminal, surfaces of the catheter, enhance platelet aggregation, coagulation activation and also promote thrombogenesis. This suggests that the prevention of catheter colonization and biofilm formation through deployment of an antimicrobial – anticoagulant lock early in the course of catheter placement could be a plausible approach towards achieving reductions in the incidence of catheter thrombosis, catheter-related bloodstream infections (CRBSI) and ensuing mortality, besides enhancing the endurance of hemodialysis (HD) catheters.[6]

Antimicrobials including antibiotic – anticoagulant intraluminal 'lock' solutions using gentamicin/cephalosporins in combination of heparin/citrate, have been reported to improve the outcome of TCCs.[7–9] However, the role of antibiotic 'locks' among diabetic ESRD patients who appear to be particularly vulnerable to thrombotic and infectious

complications of TCCs and resultant morbidity and mortality during long-term HD, has not been exclusively studied.[10,11]

RESULTS

The mean age (±s.d.) of 59.7±17 (range, 31–87 years) in the cefotaxime group (group I) was comparable to that of 57.5±15 (range, 32–82 years) in the heparin-alone group (group II). The gender ratio, proportions of the elderly and comorbid conditions, type of TCCs (subclavian (SC)/internal jugular catheter (IJC)), hematocrit, serum iron/ferritin, serum albumin, glycosylated hemoglobin levels, and adequacy of HD (K_t/V) were also comparable between the two groups (Table 1).

Overall, 109 TCCs placed among 96 diabetic ESRD patients recorded 28 episodes of catheter thrombosis (25.7%), 107 episodes of CRBSI in 39 785 catheter days (2.68/1000 catheter days) and this amounts to a mean percent catheter survival at 365 days of 56.9% (62/109) and a CRBSI-related mortality of 16.7% (16/96) during the study period.

Patients with cefotaxime/heparin lock (group I) had higher thrombosis-free (86.3 vs 63.8%, log rank, $P=0.023$), infection-free (72.9 vs 27.1%, log rank, $P=0.004$), and thrombosis- and infection-free TCC survival (78.4 vs 37.9%, log rank, $P=0.001$) at 365 days, besides having significantly lower CRBSI rate (1.56 vs 3.68 episodes/1000 catheter days, $P<0.0001$) and CRBSI-related mortality (9.8 vs 23.4%, $P=0.015$), compared with heparin-alone (group II). No statistically significant survival advantage for either IJC or SC, in any of the two groups, was observed during the study period (Tables 2 and 3, Figures 1–3).

DISCUSSION

As catheter surface represents the real battlefield between the bacteria and host defense mechanisms, the common objective with the use of an antimicrobial – anticoagulant 'lock' had been to create an intraluminal microenvironment intimidating to invading microorganisms and to prevent biofilm formation that facilitates bacterial multiplication, platelet adhesion, coagulation activation, and, consequently, thrombogenesis.[4,12]

The results from recent randomized controlled studies on the use of antimicrobials (e.g. citrate taurolidine and 30% trisodium citrate) and catheter-restricted filling with antibiotic lock solutions (aminoglycosides – gentamicin/amikacin and cephalosporins – cefazolin/cefotaxime), in combination of anticoagulants (heparin/citrate), are clearly supportive of a significant role that antibiotic – anticoagulant locks could play in reducing the incidence of catheter thrombosis and CRBSI and these locks, thus, can enhance the infection- and/or thrombosis-free survival rates of TCCs.[13]

Jurewitsch[14] reported the efficacy of 2% taurolidine as a catheter lock in the prevention of sepsis primarily in parenteral nutrition patients with the reduction in infection rate from 8.5 to 0.5 episodes/1000 catheter days. Later, Sodermann[15] evaluated 1.35% taurolidine and 4% sodium citrate combination (Neutrolin™, Biolink, Norwell, MA,

Table 1 | Clinical characteristics and demographic profile of diabetic ESRD patients in heparin-alone and cefotaxime/heparin 'locked' groups

Patient characteristics	Group I 'Locked' with cefotaxime/heparin (TCCs, *n*=51)	Group II Heparin alone (TCCs, *n*=58)	*P*-value
Patients number (*n*=96)	49	47	
Age (years±s.d., range)	59.7±17 (31–87)	57.5±15 (32–82)	0.887
Male (*n* (%))	29 (59.2)	26 (55.3)	0.668
Female (*n* (%))	20 (40.8)	21 (44.7)	0.667
Elderly (>65 years)	31 (63.3)	29 (61.2)	0.885
Comorbid conditions			
IHD	9 (18.4)	8 (17.0)	0.854
CHF	9 (18.4)	10 (16.9)	0.709
PVD	10 (20.4)	9 (19.1)	0.946
CVA	3 (6.4)	4 (8.2)	0.782
Hematocrit (%, mean±s.d.)	32.6±1.9	34.5±2.4	0.769
Serum iron (μg/dl, mean±s.d.)	76.4±8.2	79.4±7.6	0.735
Serum ferritin (ng/ml, mean±s.d.)	82.9±179	263.4±169	0.874
Serum albumin (g/dl±s.d.)	3.29±0.16	3.33±0.11	1.000
HbA1C (%±s.d.)	7.2±0.73	6.9±0.91	1.000
Kt/V (mean±s.d.)	1.25±0.23	1.31±0.19	1.000
Type of TCCs (n (%))			
SC	15 (29.4)	14 (24.1)	0.623
IJC	36 (70.6)	45 (77.6)	0.636

CHF, congestive heart failure; CVA, cerebrovascular accidents; ESRD, end-stage renal disease; HbA1C, glycosylated hemoglobin; IHD, ischemic heart disease; IJC, internal jugular catheter; PVD, peripheral vascular disease; SC, subclavian catheter; s.d., standard deviation; TCCs, tunneled-cuffed catheters.
Figures in parentheses indicate percentage.

Table 2 | Catheter events in diabetic ESRD patients in group-I (cefotaxime/heparin 'locked) and group-II (heparin-alone)

Catheter events	Group I 'Locked' with cefotaxime/heparin (TCCS, *n*=51)	Group II Heparin alone (TCCs, *n*=58)	RRR (%)	OR	95% CI	*P*-value
Duration of catheterization (in catheter days)	18 615	21 170				
Catheter thrombosis (*n* (%))	7 (13.7)	21 (36.2)	62.2	3.455	1.639–7.368	<0.001
CRBSI episodes (*n*)	29	78	—			
CRBSI/1000 catheter days	1.56	3.68	57.6	8.680	4.373–17.388	<0.0001
Exit site infections (*n*/total (%))	9/51 (17.6)	9/58 (15.5)	—	1.190	0.389–3.644	0.937
TCC survival at 365 days (*n*/total (%))	40/51 (78.4)	22/58 (37.9)	—	4.580	2.444–8.626	<0.0001
CRBSI-associated mortality (*n*/total (%))	5/49 (9.8)	11/47 (23.4)	58.2	2.842	1.206–6.824	0.015

95% CI, 95% confidence interval; CRBSI, catheter-related bloodstream infection; ESRD, end-stage renal disease; OR, odds ratio; RRR, relative risk reduction; TCCs, tunneled-cuffed catheters.
Figures in parentheses indicate percentage.

Table 3 | Bacterial flora isolated from the diabetic ESRD patients with CRBSI

Bacterial flora isolated	Episodes of CRBSI: Group I 'Locked' with cefotaxime/heparin (TCCs, *n*=51)	Episodes of CRBSI: Group II Heparin alone (TCCs, *n*=58)
Gram-positive bacteria (*n*, total, %)	19/107 (17.8)	32/107 (29.9)
Staphylococcus epidermidis	7	13
Staphylococcus aureus	12	19
Gram-negative bacteria (*n*, total, %)	10/107 (9.3)	46/107 (42.9)
Escherichia coli	3	9
Klebsiella pneumoniae	3	9
Pseudomonas aeruginosa	2	11
Acenetobactor species	1	7
Enterococcus faecalis	1	7
Serratia marcesens	0	3
Total	29/107 (27.1)	78/107 (72.8)

CRBSI, catheter-related bloodstream infection; ESRD, end-stage renal disease; TCCs, tunneled-cuffed catheters.
Figures in parentheses indicate percentage.

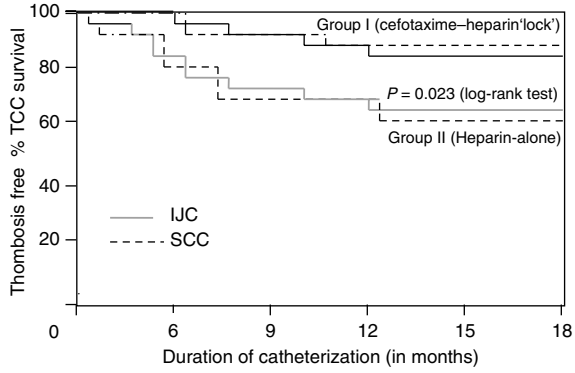

Figure 1 | Kaplan–Meier cumulative survival curves demonstrating the probability of thrombosis-free survival of TCCs (IJC and SC) group I (diabetic ESRD patients with cefotaxime–heparin 'lock') and group II (with heparin alone) on long-term HD.

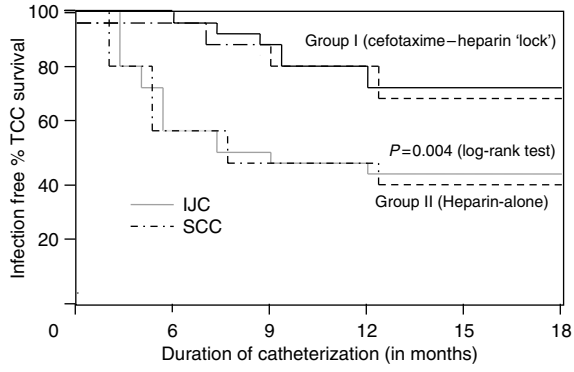

Figure 2 | Kaplan–Meier cumulative survival curves demonstrating the probability of infection-free survival of TCCs (IJC and SC) group I (diabetic ESRD patients with cefotaxime–heparin 'lock') and group II (with heparin alone) on long-term HD.

USA) on 71 long-term HD patients with TCCs, treated for an average period of 16 months. Of these patients 64% had no catheter-related infections, only 11% had CRBSI at the rate of 0.3 episodes/1000 catheter days, which was significantly lower than in historical controls. Recently, Betjes and Van Agteren,[16] in a single-center open-label clinical trial on 76 TCCs placed among 58 patients, reported four episodes of CRBSI in heparin group as opposed to none in patients with catheters locked with Neutrolin ($P<0.05$).

Following encouraging preliminary reports by Ash *et al.*[17] on the use of high concentration of trisodium citrate (23% TSC), a non-antibiotic antimicrobial with local anticoagulation properties) as catheter– locking solution to prevent CRBSI, Weijmer *et al.*,[18] in their multicenter, randomized trial also observed enhanced overall patency ($P=0.005$) and reduced CRBSI rates (87%, $P<0.001$) for TCCs locked 30% TSC compared with those filled with standard heparin. However, flow problems were not reduced, and no significant difference in the catheter-thrombosis rates between the two groups was observed.[16]

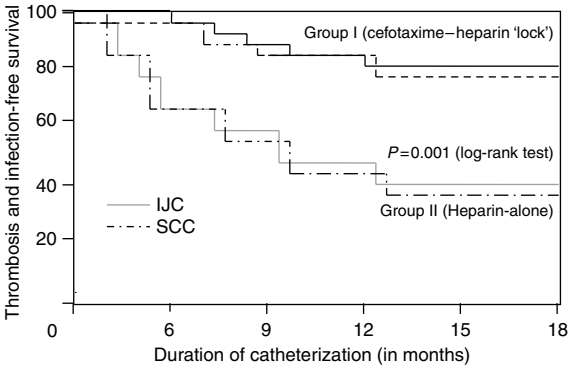

Figure 3 | Kaplan–Meier cumulative survival curves demonstrating the probability of thrombosis and infection-free survival of TCCs (IJC and SC) group I (diabetic ESRD patients with cefotaxime–heparin 'lock') and group II (with heparin-alone) on long-term HD.

Earlier Pervez *et al.*, in a randomized controlled trial ($n=33$), had observed a significant decline in CRBSI (0.62 vs 2.11/1000 patient days) and catheter-thrombosis episodes (2.5 vs 3.2/1000 patient days) besides longer mean catheter-survival percentage at 60 days (74.0 ± 12 vs 59.0 ± 11, $P=0.03$) in gentamicin-citrate 'locked' (40 mg/ml) plus 4.6% TSC) group compared with control group having TCCs filled with standard heparin.[17] However, the study was prematurely terminated as TSC in higher concentrations (>10%) was thought to be unsafe as TSC provides local anticoagulation by binding to Ca^{2+}; even small amounts of citrate entering the right atrium of heart could cause life-threatening depression of ionic Ca^{2+} levels in the cardiac muscle leading to serious pacemaker dysfunction and fatal cardiac arrhythmias. *In vivo* experiments suggest that the degradation of cardiac function could occur even at lower concentrations if TSC spills out of the catheter.[15] For this reason, Food and Drug Administration issued a warning against the use of TSC in concentrations above 4%.[18,19]

Dogra *et al.*[7] demonstrated a clear decline in the incidence of CRBSI (0.03 vs 0.42/100 catheter days, $P=0.003$) and substantial increase in mean infection-free catheter survival rate (282 vs 181 days, $P=0.002$) in the gentamicin/TSC (40 mg/ml and 3.13% TSC; ratio 2:1) group compared to that of heparin group. However, predialysis gentamicin levels were found to be significantly higher in patients randomized to gentamicin group (2.8 mg/l vs <0.2 mg/l, $P=0.008$). Authors cautioned to establish the safety of 'locked' dose of gentamicin for ototoxicity before the adoption of the technique.[7] McIntyre *et al.*[8] recently reported symptoms compatible with aminoglycoside ototoxicity in about 10% of patients when TCCs had been locked with high dosages of gentamicin (40 mg/ml) for long periods. Earlier, Saxena *et al.*[20] in a case report noted manifestation of sudden irreversible ototoxicity in a diabetic ESRD patient having TCC 'locked' with amikacin, to prevent recurrent episodes of CRBSI.[21]

Thus, the efficacy and safety of currently available antimicrobial/antibiotic/lock protocols using sodium citrate and/or aminoglycosides for the TCCs placed among diabetic ESRD patients, who often have underlying cardiac and/or hearing disability, clearly become questionable. The preference of cefotaxime plus heparin over other antimicrobials/anticoagulant combinations, in the present study on the diabetic ESRD patients, was primarily based on the lack of cardio/ototoxic potentials of the basic components of this TCCs 'locking' solution.[9] Even though cefotaxime was not used earlier in catheter locks, its excellent clinical efficacy and microbiological safety profile has been demonstrated in the management of infections in critically ill patients.[22]

In the present study, the overall catheter thrombosis, CRBSI incidence, CRBSI-related mortality, were much lower than the published reports, whereas the percent catheter-survival rates were comparable to those reported elsewhere.[2,7–11,15–18,23–25] Additionally, the diabetic ESRD patients in cefotaxime/heparin group recorded significantly higher thrombosis-free (log rank, $P=0.023$), infection-free (log rank, $P=0.004$), and thrombosis- and infection-free TCC survival (log rank, $P=0.001$) at 365 days, besides having significantly lower CRBSI rate (1.56 vs 3.68 episodes/1000 catheter days, $P<0.0001$) and CRBSI-related mortality (9.8 vs 23.4%, $P=0.015$), compared with heparin-alone group. There is no experience of any adverse reaction to the components of lock solution.

The CRBSI episodes were mainly caused by Gram-positive cocci – *Staphylococcus aureus*, *S. epidermidis* and Gram-negative bacilli in both groups. Cefotaxime appeared significantly more effective against Gram-negative bacilli than the Gram-positive organisms. Of over all CRBSI reduction rate of 59.5%; 78.4% reduction was observed in the infections owing to Gram-negative bacilli against that of 40.5% in Gram-positive organisms (odds ratio = 5.12, 95% confidence interval, 2.635–9.948; $P<0.0001$), in cefotaxime group compared with heparin group.

No resistance to cefotaxime was observed among the bacterial strains isolated from CRBSI episodes that occurred during 1 year of study period. This was perhaps attributable to the reasonably higher intraluminal concentrations of cefotaxime and heparin in the 'lock' that was applied since the time of catheter placement, permits little chance for bacteria to enter, colonize, and form biofilm in the catheter lumen while the 'lock' solution is kept locally restricted by making even volumes of locking solution pass to the catheter lumen to prevent the systemic spill-out of the antibiotic. Nonetheless, there remains a concern of long-term development of antimicrobial resistance with the use of antibiotic in catheter locks.

Conclusion

Thus, catheter-restricted interdialytic filling of cefotaxime/heparin seems to be a safe and effective approach towards prevention of thrombotic and infectious complications and related mortality with enhancement of TCC lifespan, among diabetics on dialysis who are also vulnerable to comorbidities related to heart and hearing. However, long-term studies

would be necessary to address the issue of potential emergence of resistant bacterial infections before antibiotic locks could clearly become the part of standard care for diabetics on dialysis.

MATERIALS AND METHODS

This randomized, double-blind-controlled trial was conducted at the outpatients dialysis facility of a large tertiary care center of Eastern Province of Saudi Arabia, to compare the efficacy of intraluminally placed cefotaxime/heparin 'lock' with the regular practice of catheter-restricted filling with standard heparin – in the prevention of catheter thrombosis, CRBSI and ensuing mortality among the diabetic ESRD patients. This study also endeavored to check whether the 'locked' antibiotic solution had any favorable effect on the lifespan of TCCs used so frequently in this vulnerable group of patients on HD. Cefotaxime was selected primarily owing to its broad spectrum, proven clinical and microbiological efficacy and safety record, besides the lack of ototoxic potential.[9,22]

Patient population, selection criteria, study design, and randomization

All the diabetic ESRD patients were eligible for the study if they required insertion of a TCC (SC or IJC) for the maintenance or initiation of HD between March 2002 and February 2003 at our Tertiary Care Center. Patients who had reinsertion of a TCC through a new access site were also included. However, subjects having active sepsis/receiving prolonged (more than 7 days) antibiotic therapy (oral/parenteral) or allergy to cephalosporins, were excluded from the study. The patients who could not be randomized within three dialysis sessions of new TCC insertion and those who had the exchange over guidewire of a TCC through the same exit site, were also excluded.

The randomization was performed using sequentially numbered, opaque, sealed envelopes. The sequence of interventions was obtained from a computer-generated random number list to ensure the concealment of the patient's assignment to a particular group. All the authors/investigators, including microbiologists and HD staff involved in the study, were blinded to the patient's allocation to the treatment groups. The outcomes were analyzed independent of investigators by statisticians.

Of total identified ($n = 126$) TCC insertions among 110 diabetic ESRD patients enrolled during study period, eventually 96 patients with TCCs ($n = 109$) consented and were randomized to two groups: 49 patients with TCCs ($n = 51$) to group I with cefotaxime–heparin lock (cefotaxime, 10 mg/ml and heparin, 5000 U/ml) and 47 patients with TCCs ($n = 58$) to group II with standard heparin lock (5000 U/ml) (Figure 4).

All the patients were dialyzed three times per week for 3–4 h through double-lumen-cuffed Perm-cath® (Quinton Instrument Co., Seattle, Washington, DC, USA) placed by vascular surgeons with chest radiographs taken to confirm their correct positioning. The demographic profile, clinical characteristics, and reasons for the TCCs insertion in the patients of each group are shown in Tables 1 and 4.

Antibiotic 'lock' preparation and placement

Cefotaxime sodium (Claforan, Roussel) was dissolved directly in heparin sodium (PoM, Unihep® (Leo)) under aseptic conditions, to obtain a final concentration of 10 mg/ml for cefotaxime and 5000 U/ml for heparin in the 'lock' solution, prepared by the pharmacists, on daily basis. Each lock volume of approximately 2.5 ml contained 25 mg of cefotaxime and 12 500 U of heparin, to fill 1.3 ml of venous and 1.2 ml of arterial lumina of TCC, at the end of each HD session in group I patients.[26] The 'locks' were removed at the beginning of each HD using sterile syringe to avoid systemic spill-out of antibiotic during the procedure and placed again at the completion of HD to remain in-place till next HD.

Study end points

The development of symptomatic CRBSI and/or catheter thrombosis were the primary end points, whereas the events of elective removal of the catheter and CRBSI-related death were used to sensor the TCCs follow-up.

Thrombosis was defined as the inability to use the catheter at a blood flow of 200 ml/min that did not respond to initial attempt of intraluminal thrombolysis with *t*-plasminogen activator.

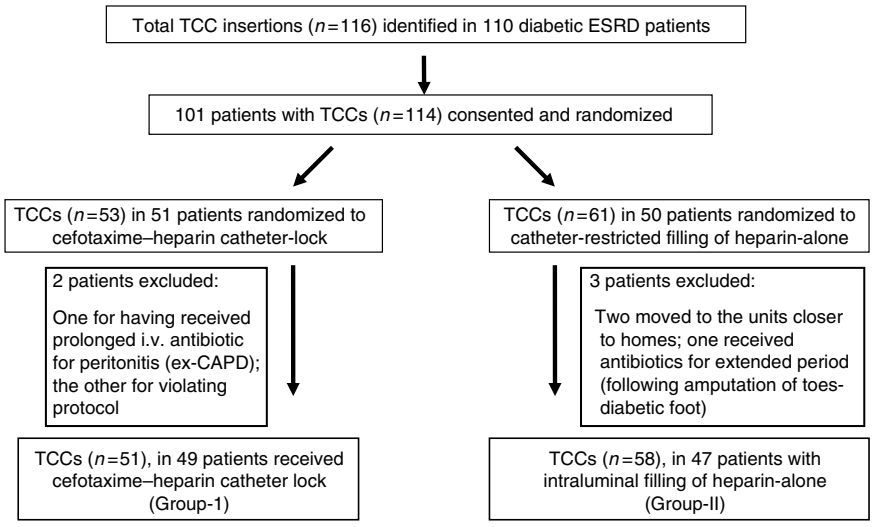

Figure 4 | Study design and plan of randomization.

Table 4 | Rationale of TCC placement

Rationale	Group I 'Locked' with cefotaxime/ heparin (TCCs, n=51)	Group II Heparin alone (TCCs, *n*=58)
Thrombosed vascular access	6	5
Commencement of HD	19	29
Pending maturation/repair of AVF	10	12
Multiple access failures	13	10
Failed CAPD	3	2

AVF, arteriovenous fistula; CAPD, continuous ambulatory peritoneal dialysis; HD, hemodialysis; TCCs, tunneled-cuffed catheters.

Definitions and diagnosis of CRBSI

Catheter infections were diagnosed using clinical and microbiological criteria as defined by the Centers for Disease Control.[27]

A catheter was considered colonized if growth of $\geqslant$15 colony-forming units was found by semiquantitative roll-plate technique from a proximal or distal catheter segment in the absence of clinical signs of infection at the catheter exit site.

A catheter exit-site infection was defined as a positive (semi-) quantitative culture of the drainage material with local signs of inflammation.

CRBSI was considered when the same organism (i.e. identical species, antibiogram) was isolated from a quantitative culture of the distal segment of catheter and from the blood of a patient with accompanying clinical signs of sepsis and no other apparent source of infection.

Suspected cases of CRBSI were treated for 2 weeks with an empirical regimen comprising of intravenous vancomycin and an aminoglycoside given post-dialysis; this regimen was modified following availability of blood culture results. Predialysis plasma levels of aminoglycosides were monitored regularly. Catheters were removed only if sepsis persisted (failure to render patient apyrexial within 48 h) despite initiation of antibiotic therapy. Further, CRBSI episodes were only categorized as new infections if they occurred no less than two weeks after the cessation of initial successful antibiotic therapy.[28]

CRBSI-related mortality was defined as death of a patient with clinical signs of sepsis with no other obvious source of infection and the isolation of the same organism from a quantitative blood culture from the catheter and the peripheral blood.

Exit sites were dressed with Opsite (Smith and nephew, Hull, UK) and kept under supervision at each HD treatment session. Time from catheter placement to infection and/or thromboses was estimated and expressed as period of catheterization.

Statistical analyses

The sample size of 110 TCCs (55 in each group) calculated to be of power to detect 30% difference in the two treatments at a one-sided 0.05 level of significance, was based on the previous experience of baseline risk of 2.5 CRBSI episodes/1000 catheter days, at this tertiary care center.

The SPSS, version 10.1 (Chicago, IL, USA) was used for data processing. The χ^2 test was used to assess the difference among the extent of HD catheter thromboses, CRB incidence and infection-free catheter survival between the two groups. The Student's *t*-test was used to compare between the means of two quantitative variables.

The cumulative survival curves were obtained by the Kaplan–Meier survival method. The prognostic significance of the catheter thromboses and CRBSI incidence on the percent survival of TCCs in relation to duration of catheterization was tested by cumulative survival analysis at the main time points (the time of HD catheter infection and/or thrombosis/removal, from the time of catheter placement). The differences in the cumulative survival curves were assessed by the Log-rank test.

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