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Original Investigation

Cathasept Line Lock and Microbial Colonization of Tunneled Hemodialysis Catheters: A Multicenter Randomized Controlled Trial

Muhammad Kanaa, MD,[1] Mark J. Wright, MD,[2] Habib Akbani, FRCP,[3] Paul Laboi, MD,[4] Sunil Bhandari, PhD,[5] and Jonathan A.T. Sandoe, PhD[2,6]

Background: Catheter-related bloodstream infections (CRBSIs) cause morbidity and mortality in hemodialysis (HD) patients. Cathasept (tetra-sodium EDTA) solution has antimicrobial and anticoagulant activities.

Study Design: Multicenter prospective randomized controlled study.

Setting & Participants: 117 maintenance HD patients with confirmed uncolonized tunneled HD catheters from 4 HD centers.

Intervention: Patients were randomly assigned to receive Cathasept 4% locks (Cathasept group) or stayed with heparin 5,000 U/mL locks (heparin group), filled thrice weekly according to catheter lumen volume until the catheter was removed or for a maximum of 8 months.

Outcomes: Primary outcome was clinically significant microbial colonization of the catheter, defined as a through-catheter quantitative blood culture yielding ≥ 1,000 colony-forming units/mL of bacteria or yeast. Secondary outcomes included CRBSI rate, catheter patency, and biomarkers of inflammation and anemia.

Measurements: Weekly through-catheter quantitative blood culture, high-sensitivity C-reactive protein fortnightly, and full blood count and ferritin monthly.

Results: Incidence rates of catheter colonization were 0.14/1,000 catheter-days in the Cathasept group and 1.08/1,000 catheter-days in the heparin group (incidence rate ratio [IRR], 0.13; 95% CI, 0.003-0.94; $P = 0.02$). CRBSI rates were 0.28/1,000 catheter-days in the Cathasept group and 0.68/1,000 catheter days in the heparin group (IRR, 0.40; 95% CI, 0.08-2.09; $P = 0.3$). The proportion of dialysis sessions with achieved prescribed blood flow rate was significantly lower in the Cathasept group (66.8% vs 75.3%; $P < 0.001$), with more patients requiring thrombolytic locks or infusions to maintain catheter patency (22 vs 9; $P = 0.01$). Mean high-sensitivity C-reactive protein level was 11.6 ± 5.3 (SE) mg/L lower for patients in the heparin group ($P = 0.03$). Anemia marker levels were similar in both groups.

Limitations: Study was underpowered to assess effect on CRBSI, terminated early due to slow recruitment, and not double blinded.

Conclusions: Cathasept significantly reduced tunneled hemodialysis catheter colonization, but the reduction in CRBSIs was not statistically significant, and it was associated with more thrombotic complications. Its safety profile was comparable to heparin lock solution.

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INDEX WORDS: Hemodialysis; central venous catheters; catheter-related bloodstream infection (CRBSI); colonization; bacteria; bacteremia; yeast; antimicrobial; catheter lock; EDTA; Cathasept; heparin; patency; inflammation; end-stage renal disease (ESRD).

Infection is the second most common cause of death in the dialysis population in the United Kingdom and the Western world, accounting for 18% of deaths in the prevalent dialysis population in the United Kingdom alone.[1] Patients receiving hemodialysis (HD) have a higher incidence of bloodstream infections (BSIs) compared with patients on peritoneal dialysis therapy,[2-4] with central venous catheters being a major and independent risk factor for developing BSIs.[3,5-8] Although discouraged as a permanent form of vascular access, the use of tunneled HD catheters has remained steady and even increased in most countries participating in the Dialysis Outcomes and Practice Patterns Study (DOPPS).[9-11] BSIs are associated with significant cardiovascular morbidity,[4] and intraluminal colonization of catheters, which usually precedes BSI,[12] is reported to cause subclinical inflammation in the HD

From the [1]Doncaster & Bassetlaw Hospitals NHS Foundation Trust, Doncaster Royal Infirmary, Doncaster, South Yorkshire; [2]Leeds Teaching Hospitals NHS Trust, Leeds; [3]Bradford Teaching Hospitals NHS Foundation Trust, Bradford; [4]York Teaching Hospital NHS Foundation Trust, York; [5]Hull and East Yorkshire Hospitals NHS Trust and Hull York Medical School, Hull; and [6]University of Leeds, Leeds, United Kingdom.

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Address correspondence to Muhammad Kanaa, MD, Doncaster & Bassetlaw Hospitals NHS Foundation Trust, Doncaster Royal Infirmary, Armthorpe Road, Doncaster, South Yorkshire, DN2 5LT, United Kingdom. E-mail: muhammad.kanaa@dbh.nhs.uk

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population,[3,13-17] contributing to anemia,[18-20] malnutrition, and atherosclerosis.[3,21-23]

Heparin, which is commonly used to maintain catheter patency, has been implicated in the growth of biofilms on abiotic surfaces[24,25] and is associated with increased risk of bleeding, episodes of hyperkalemia, hair loss, and heparin-induced thrombocytopenia.[26,27] Alternative catheter lock solutions have been used to prevent intravascular catheter-related BSI (CRBSI) and avoid complications associated with heparin. Several meta-analyses of randomized controlled studies have demonstrated significant reductions in CRBSI rates when various antimicrobial lock solutions were used to prevent CRBSI in HD patients, but there was significant heterogeneity between the studies.[28-34] Concerns remain over the risk of bacterial resistance developing when antibiotic solutions are used and the potential side effects of some antibiotics.[35] One randomized controlled study in 110 HD patients showed that taurolidine (1.35%)/citrate lock (4%) solution did not reduce bacteremia rates from any cause with tunneled HD catheters.[36] A randomized trial of a novel catheter lock containing sodium citrate, 7%; methylene blue, 0.15%; methylparaben, 0.15%; and propylparaben, 0.015% showed a significant reduction in CRBSI compared with heparin locks.[37]

Cathasept is composed of 4% tetra-sodium EDTA and has both anticoagulant[38,39] and antimicrobial effects.[40] Therefore, it is a potentially useful line lock solution.

METHODS

Study Design

This was a multicenter, prospective, randomized (1:1), controlled, part-blinded (laboratory personnel were blinded), comparative study. The study was approved by the Leeds (West) Medical Research Ethics Committee, United Kingdom (reference: 05/Q1205/241) and was registered and regulated by the Medicines and Healthcare Products Regulatory Agency (reference: CI/2006/0003).

The study was conducted at 4 HD centers in the Yorkshire region in the United Kingdom August 2006 to October 2008.

Study Participants

Eligible participants were adult HD patients aged 18 to 85 years who met all inclusion criteria and had no exclusion criteria.

Inclusion Criteria

Participants had to be able to provide informed consent, have a history of established kidney failure, and be starting or undergoing HD using a tunneled HD catheter in an internal jugular or subclavian vein.

Exclusion Criteria

Patients were excluded if they met any of the following criteria: any medical, social, or psychological condition that would compromise participation and follow-up in the study; pregnancy or lactation; tunneled catheter with an expected duration of placement or use of less than 60 days; enrollment in another clinical study or having participated in a study; life expectancy less than 3 months; existing tunneled central venous catheter along with positive blood cultures or receipt of antimicrobial therapy, including antibiotic lock solution and/or antimicrobial catheters, for documented or suspected CRBSI within 14 days prior to enrollment; evidence of systemic infection or catheter exit-site infection at the time of enrollment; colonized catheters (screening quantitative through-catheter blood cultures yielding >20 colony-forming units [CFU]/mL of bacteria or yeast); catheters that demonstrated signs of dysfunction in 2 or more dialysis sessions during the last 2 weeks prior to enrollment (these signs were defined as blood flow rate < 200 mL/min, prescribed blood flow rate was not achieved, elevated venous pressure [>250 mm Hg], negative arterial pressure of greater magnitude than −250 mm Hg, line reversal [using the arterial port to aspirate and the venous port to return blood]); or known sensitivity to heparin, disodium EDTA, or natural rubber latex.

Outcomes

Primary Outcome

Incidence rate of clinically significant microbial colonization of tunneled HD catheters per 1,000 catheter-days, defined as through-catheter quantitative blood culture yielding ≥1,000 CFU/mL of bacteria or yeast.

Secondary Outcomes

Incidence rate of CRBSI; number of dialysis sessions in which the prescribed blood flow was achieved; incidence rate of interventions to improve catheter patency, including intracatheter lock or infusion of thrombolytic agents; and difference between groups for hemoglobin, high-sensitivity C-reactive protein (hs-CRP), serum ferritin, and Kt/V values and iron and erythropoiesis-stimulating requirements. Kt/V is a measurement used to quantify dialysis treatment adequacy (K is dialyzer clearance of urea, t is time spent on dialysis that day and not the prescribed time on dialysis, and V is volume of distribution of urea, which is approximately equal to total-body water). Kt/V was calculated monthly using the following formula from the NKF-KDOQI (National Kidney Foundation−Kidney Disease Outcomes Quality Initiative) guidelines[41]:

$$Kt/V = -\mathrm{Ln}(R - 0.008t) + (4 - 3.5R)\times (\Delta \text{ body weight/end dialysis body weight})$$

where R is postdialysis to predialysis urea ratio and Δ denotes change in body weight before and after dialysis.

Interventions

Eligible patients underwent through-catheter quantitative blood cultures to determine the colonization status of their catheters. After discarding the existing lock solution, 1 mL of blood was obtained from each catheter lumen and cultured for bacteria and yeast as described next. Clinically significant colonization was defined as blood culture from one or both lumens yielding ≥1,000 CFU/mL of bacteria or yeast. Patients with a through-catheter quantitative blood culture yielding ≤20 CFU/mL were randomly assigned to either receive Cathasept, 4% (Cathasept/intervention group), or continue heparin lock solution, 5,000 U/mL (heparin/control group). The amount of lock solution was determined by catheter lumen volume. Participants were followed up until the catheter was removed or for 8 months if the catheter was not removed.

Measurements

Baseline Characteristics

The following demographic, clinical, and laboratory data were collected: age, sex, height, weight, Davies comorbidity score,[42] drug history (including erythropoiesis-stimulating agents and iron supplements), allergies, cause of established kidney failure,