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Comparative Effectiveness of Two Catheter Locking Solutions to Reduce Catheter-Related Bloodstream Infection in Hemodialysis Patients

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Abstract

Background and objectives Infection is the second leading cause of death in hemodialysis patients. Catheter-related bloodstream infection and infection-related mortality have not improved in this population over the past two decades. This study evaluated the impact of a prophylactic antibiotic lock solution on the incidence of catheter-related bloodstream infection and mortality.

Design, setting, participants, & measurements This prospective, multicenter, observational cohort study compared the effectiveness of two catheter locking solutions (gentamicin/citrate versus heparin) in 555 hemodialysis patients dialyzing with a tunneled cuffed catheter between 2008 and 2011. The groups were not mutually exclusive. Rates of catheter-related bloodstream infection and mortality hazards were compared between groups.

Results The study population (n=555 and 1350 catheters) had a median age of 62 years (interquartile range=41–83 years), with 50% men and 71% black. There were 427 patients evaluable in the heparin period (84,326 days) and 322 patients evaluable in the antibiotic lock period (71,192 days). Catheter-related bloodstream infection in the antibiotic lock period (0.45/1000 catheter days) was 73% lower than the heparin period (1.68/1000 catheter days; P=0.001). Antibiotic lock use was associated with a decreased risk of catheter-related bloodstream infection compared with heparin (risk ratio, 0.23; 95% confidence interval, 0.13 to 0.38 after multivariate adjustment). Cox proportional hazards modeling found that antibiotic lock was associated with a reduction in mortality (hazard ratio, 0.36; 95% confidence interval, 0.22 to 0.58 in unadjusted analyses; hazard ratio, 0.32; 95% confidence interval, 0.14 to 0.75 after multivariate adjustment). The rate of gentamicin-resistant organisms decreased (0.40/1000 person-years to 0.22/1000 person-years) in the antibiotic lock period (P=0.01).

Conclusions The results of this study show that the use of a prophylactic, gentamicin/citrate lock was associated with a substantial reduction in catheter-related bloodstream infection and is the first to report a survival advantage of antibiotic lock in a population at high risk of infection-related morbidity and mortality.

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Introduction

Over 370,000 patients undergo maintenance hemodialysis in the United States, with up to 80% initiating with a central venous catheter (1). Recent data from the Centers for Medicare and Medicaid Services (CMS) show that the overall prevalence of catheter use is 29%; however, the prevalence is as high as 69% in the first 6 months of dialysis and as high as 41% at the end of the first 1 year (2). There is general consensus that use of catheters as opposed to permanent arteriovenous fistulae or grafts contributes to excessive mortality not only during this period but throughout a patient's course on hemodialysis. The rate of catheter-related bloodstream infection (CRBSI) reported in the literature varies, with rates from 2.5 to 6.6 per 1000 catheter days reported (3–7). The Centers for Disease Control and Prevention (CDC) reports that CRBSI rates have remained steady in hemodialysis patients over the last decade, with an estimated 37,000 CRBSIs occurring in 2008 (8). Overall, there has been a reduction in all-cause mortality over the past three decades in hemodialysis patients; however, the rate of infection-related mortality has remained steady (9,10).

Many randomized, controlled studies have confirmed that a prophylactic antimicrobial lock strategy reduces the incidence of CRBSI, and it has been suggested that, for every four patients treated with antimicrobial lock, one CRBSI is prevented (11–15). Furthermore, two small randomized, controlled trials showed a reduction in mortality on crude analysis by use of a prophylactic antimicrobial lock solution (16,17). However, this approach has not been widely adopted. In fact, the CDC and the Infectious Diseases

Society of America do not recommend the routine use of these solutions and suggest reserving this treatment for those patients with a history of multiple CRBSIs, citing concerns for the potential emergence of antimicrobial resistance associated with the agent used (18). We conducted the present study to evaluate the clinical outcomes associated with antimicrobial lock therapy, including CRBSI and mortality, and to better characterize the safety implications, particularly antimicrobial resistance, in a hemodialysis population with a high incidence of CRBSI.

Materials and Methods

Study Population

This prospective, multicenter, observational cohort study compared two locking solutions (heparin versus gentamicin/trisodium citrate) on the incidence of CRBSI and mortality in chronic hemodialysis patients dialyzing with permanent tunneled cuffed catheters (TCCs). This study evaluated a cross-over from heparin (control) to gentamicin/trisodium citrate (lock) in patients dialyzing with a TCC during the period from September 1, 2008, to June 1, 2011 in three outpatient hemodialysis centers in the Detroit metropolitan area. The cross-over occurred on October 1, 2009, in center A, October 13, 2010, in center B, and November 10, 2010, in center C. To be included, patients had to have their catheter placement and follow-up by the vascular surgery department within the Henry Ford Health System. Each patient was followed for the duration that a TCC was their primary vascular access until a TCC was no longer medically necessary, the patient died or transferred out of the unit, or censorship at the end of the study period. If a patient spanned both treatment periods, the time period for follow-up was recorded and allocated to its appropriate locking solution group. Each catheter was followed from the time of placement until a CRBSI, removal for other reasons (clotting, malfunction, or no longer medically necessary), the patient died or transferred out of unit, or censorship at the end of the study period. If a catheter spanned both treatment periods, the time period for each solution was recorded and allocated to its appropriate locking solution group. Patients were excluded if they were less than 18 years of age, were pregnant or lactating, had known allergy or contraindication to heparin or gentamicin, or were currently being treated for a CRBSI at time of enrollment (a lapse interval of 14 days was required between last administration of antibiotic and enrollment). Catheters that were locked chronically with tissue plasminogen activator (t-PA) at any time during the control or lock period were excluded from the analysis. This study was approved by the Institutional Review Board at Henry Ford Hospital with a waiver of informed consent and conducted in adherence to the Declaration of Helsinki.

Catheter Maintenance Protocols

Catheter care in the three units followed established policies and procedures related to hemodialysis initiation, discontinuation, dressing changes, and exit site care over the duration of the study. Standard precautions using aseptic technique were followed, including masking of the patient and staff in addition to the staff wearing face shields, gowns, and clean gloves. Disinfection of the catheter ports was performed at the start of hemodialysis by using two gauze pads soaked in chlorine (Alcavis). One gauze pad was used to rub the catheter port caps and connection sites, and one gauze pad was used to soak the catheter hubs for 2 minutes. Catheter dressing changes were performed at each hemodialysis session and included visual inspection and cleansing of the exit site with chlorhexidine (3.15%). After it was dry, triple antibiotic ointment (containing bacitracin, neomycin, and polymyxin B) was applied to the exit site, and a sterile dry gauze dressing was applied (19). All care was directed by the patient's treating nephrologist, including management of infections and catheter malfunction and the need for catheter removal or exchange. The procedures followed for catheter insertion and exchange by the vascular surgery department within the Henry Ford Health System did not change over the study period (20).

Catheter Locking Solutions

The two locking solutions evaluated were heparin (1000 units/ml) and a gentamicin/citrate antibiotic solution (0.32 mg/ml gentamicin in 4% trisodium citrate) (21). The antibiotic lock solution was prepared by either the inpatient pharmacy or an affiliated home infusion pharmacy under sterile conditions (22,23). The locking solution was instilled in a volume sufficient to fill each catheter lumen at the end of dialysis and aspirated at the next dialysis session before connection.

Data and Definitions

Study data were collected on patients from September 1, 2008, to June 1, 2011. Study data were extracted from the medical record using a standardized case report form. Comorbid conditions were collected from both the medical record and the CMS Form 2728. Data collected on each catheter included insertion and removal indication and date, procedure for placement (guide wire exchange or new tunnel), location of placement, bloodstream infection in the previous 90 days, and outcome at end of catheter follow-up. A catheter was classified by the locking solution used. If the same catheter was exposed to both solutions over the duration of the study, the time period for each solution was recorded and subsequently allocated to its appropriate locking solution group. For catheters in place at study initiation (September 1, 2008), the age of the catheter was also recorded. Laboratory data were collected at study enrollment, and monthly averages were calculated for the time period that the patient was using a TCC. We determined all-cause mortality and hospitalizations based on death dates and hospitalization dates, which were recorded prospectively by each dialysis center.

Each bloodstream infection was evaluated by the same Infection Prevention Specialist as part of routine surveillance activities. Criteria established by the CDC were used to classify an infection as a CRBSI (24). In summary, the patient must have had an indwelling TCC, a recognized pathogen (*e.g.*, *Staphylococcus aureus*, *Enterococcus* spp., or *Escherichia coli*) cultured from one or more blood cultures (collected peripherally or through the dialysis circuit), and no other source of infection. Alternatively, a patient with an indwelling TCC must have one or more of fever

(>38°), chills, or hypotension when growing a common skin commensal (*e.g.*, coagulase negative staphylococci) from two or more blood cultures drawn on separate occasions (collected within 2 days of each other).

Safety
In vitro gentamicin susceptibility testing was conducted on each isolate using automated microdilution with Vitek 2 (bioMerieux, Durham, NC) by the microbiology laboratory at Henry Ford Hospital. Isolates with intermediate resistance to gentamicin were classified as resistant. Catheter lifespan, vascular access procedures, and use of t-PA for the purpose of establishing catheter patency were recorded.

Statistical Analyses
The two groups, heparin and antibiotic lock, were not mutually exclusive. For this reason, a generalized estimating equations approach was used to test the various demographic characteristics (25). The laboratory mean values were calculated and compared using ratio estimators (26). A negative binomial model was used to compare the rate of CRBSI between the two time periods (27). The negative binomial model was needed, because individual patients could have multiple occurrences of CRBSI over the study period. A log time of catheter use was used as an offset in the model. To examine death, a Cox proportional hazards model with a time-dependent covariate for group membership was used. In both the negative binomial and Cox model, a univariate model with just the antibiotic lock variable and a multivariate model adding covariates were examined. Safety characteristics were modeled with a ratio estimator approach for all of the variables except catheter lifespan, which was analyzed with a Kaplan–Meier approach. Data were analyzed using SAS software, version 9.1 (SAS Institute).

Results
Study Population
Overall, 594 patients received dialysis through a TCC during the study period. Thirty-nine patients were excluded, because they did not have their catheters placed by vascular surgery at the Henry Ford Health System. The overall study population (n=555, 93% of all TCC-requiring patients and 1350 catheters) had a median age of 62 years (interquartile range=41–83); 50% were men, 71% were black, 21% were Caucasian, and 7% were of other ethnicity. There were 427 evaluable patients in the heparin period (84,326 days of exposure) and 322 evaluable patients in the antibiotic lock period (71,192 days). There were 233 individual patients in the heparin period, 128 patients in the antibiotic lock period, and 194 patients who spanned both periods. Baseline demographics and laboratory values are presented in Table 1. The populations were similar, with the exception of more black patients in the antibiotic lock period (70% versus 75%, P=0.04).

Clinical Outcomes
There were a total of 174 CRBSIs over the study period: 142 CRBSIs in the heparin period and 32 CRBSIs in the antibiotic lock period (Tables 2 and 3). The rate of CRBSI in the antibiotic lock period (0.45/1000 catheter days) was

Table 1. Baseline characteristics according to catheter locking agent

Variable	Heparin (n=427)	Antibiotic Lock (n=322)	P Value
Age, yr	62±15	62±15	0.67
Women	213 (50%)	164 (51%)	0.73
Race (black)	299 (70%)	241 (75%)	0.04
Dialysis vintage, mo	27±48	33±48	0.13
Heart failure	262 (61%)	189 (59%)	0.49
Coronary artery disease	151 (35%)	115 (36%)	0.76
Other heart disease	209 (49%)	148 (46%)	0.28
Cerebral vascular disease	90 (21%)	62 (19%)	0.42
Peripheral vascular disease	70 (16%)	51 (16%)	0.89
Hypertension	413 (97%)	311 (97%)	0.94
Diabetes	278 (65%)	203 (63%)	0.42
COPD	101 (24%)	74 (23%)	0.89
Smoker	75 (18%)	65 (20%)	0.08
Cancer	76 (18%)	57 (18%)	0.74
Alcohol dependence	7 (2%)	5 (2%)	0.77
Drug dependence	7 (2%)	8 (3%)	0.24
Albumin, g/dl	3.6±0.6	3.7±0.4	0.09
Calcium (corrected), mg/dl	9.2±0.7	9.2±0.6	0.39
Phosphorus, mg/dl	4.9±1.5	5.0±1.0	0.63
Creatinine, mg/dl	7.0±4.6	7.5±2.9	0.08
Hemoglobin, g/dl	11.2±1.1	11.1±0.8	0.18
Iron saturation, %	29±10	29±6	0.74
Ferritin, ng/ml	566±418	575±273	0.75
White blood cells, K/μl	7.0±2.8	6.9±2.0	0.35

Values are n (%); mean±SD.
COPD, chronic obstructive pulmonary disease.

Table 2. Clinical outcomes and safety end points according to catheter locking agent

Variable	Heparin (*n*=427)	Antibiotic Lock (*n*=322)	*P* Value
Observation period, d	84,326	71,192	
Clinical outcomes			
Episodes of CRBSI	142	32	
CRBSI/1000 catheter d	1.68±3.28	0.45±1.56	0.001
Death (all cause)	77 (18%)	31 (10%)	0.001
Hospitalizations per patient-yr	3.5±3.6	3.0±3.1	0.06
Indications for hospitalization per patient-yr			
Infection	1.3±1.7	0.9±3.1	0.001
Cardiovascular	0.6±1.3	0.9±1.7	0.09
Other	1.1±1.5	0.9±1.2	0.28
Safety end points			
t-PA use per patient-yr	8±14	6±15	0.34
Gentamicin-resistant organisms/1000 patient-yr	0.40	0.22	0.01
Average catheter lifespan, d	122±144	169±231	0.42
Vascular procedures per patient-yr	3.7±3.3	3.5±3.6	0.46
Infection	1.0±1.6	0.3±0.9	0.001
Malfunction/clotting	1.1±2.5	1.4±2.9	0.11

CRBSI, catheter-related bloodstream infection; t-PA, tissue plasminogen activator.

Table 3. Pathogens-causing catheter-related bloodstream infection according to locking agent

Bacterial Pathogens[a]	Heparin	Antibiotic Lock
Gram-positive	105 (74%)	24 (75%)
Methicillin-resistant *S. aureus*	7 (5%)	4 (13%)
Methicillin-susceptible *S. aureus*	18 (13%)	7 (22%)
S. epidermidis	47 (33%)	4 (13%)
Other coagulase-negative staphylococci	1 (1%)	0 (0%)
Enterococcus spp. (vancomycin-susceptible)	22 (16%)	6 (19%)
Enterococcus spp. (vancomycin-resistant)	4 (3%)	1 (3%)
Other Gram-positive	9 (6%)	2 (6%)
Gram-negative	56 (39%)	8 (25%)
E. coli	10 (7%)	1 (3%)
Serratia spp.	5 (4%)	1 (3%)
Proteus spp.	2 (1%)	1 (3%)
Enterobacter spp.	17 (12%)	1 (3%)
Pseudomonas spp.	5 (4%)	2 (6%)
Stenotrophomonas	5 (4%)	0 (0%)
Klebsiella spp.	15 (11%)	0 (0%)
Acinetobacter spp.	0 (0%)	1 (3%)
Other Gram-negative	8 (6%)	1 (3%)
Polymicrobial	29 (20%)	2 (6%)
Fungal	0 (0%)	2 (6%)
Candida albicans	0 (0%)	0 (0%)
Candida glabrata	0 (0%)	0 (0%)
Other *Candida* spp.	0 (0%)	2 (6%)

[a]In total, 176 pathogens were identified in 142 CRBSI episodes during the heparin period, and 34 pathogens were identified in 32 CRBSI episodes during the antibiotic lock period.

73% lower than in the heparin period (1.68/1000 catheter days; *P*=0.001). The reduction in CRBSI coincided temporally with implementation of antibiotic lock therapy (Figure 1). Use of the antibiotic lock was associated with a decreased risk of CRBSI compared with heparin lock (risk ratio [RR], 0.17; 95% confidence interval [95% CI], 0.10 to 0.29); this decreased risk remained significant after multivariate adjustment (adjusted RR, 0.23; 95% CI, 0.13 to 0.38) (Table 4). The attributable risk of heparin contributing to CRBSI was 51.7%. The risk of CRBSI was significantly increased in patients with coronary artery disease (adjusted RR, 1.82; 95% CI, 1.07 to 3.10) and femoral placement of the TCC (adjusted RR, 5.84; 95% CI, 1.84 to 18.55).

There were 77 deaths during the heparin period and 31 deaths during the antibiotic lock period (18% versus 10%; *P*=0.001) (Figure 2). Cox proportional hazards modeling found

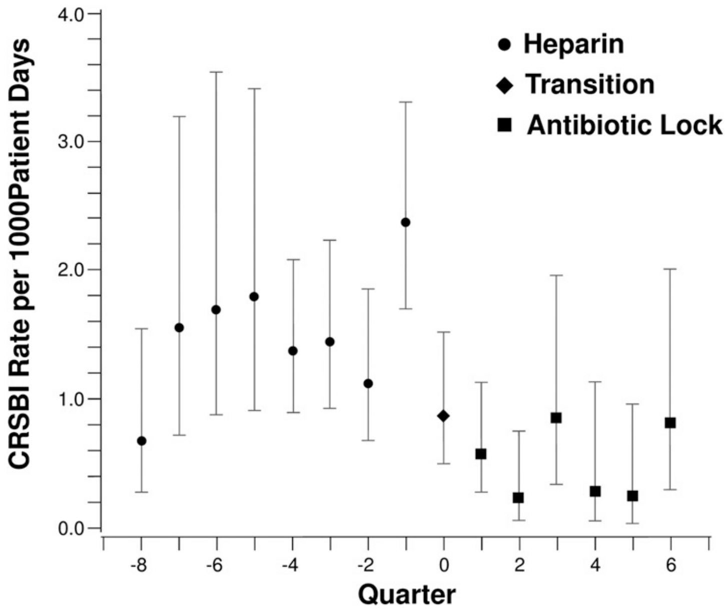

Figure 1. | **Quarterly CRBSI rates pre- and postimplementation of antibiotic lock therapy.** Error bars show the 95% confidence interval of the estimate. CRBSI, catheter-related bloodstream infection.

Table 4. Multivariate modeling for catheter-related bloodstream infection

Variable	Adjusted Risk Ratio (95% CI)	*P* Value
Antibiotic lock	0.23 (0.13 to 0.38)	0.001
Age, yr	1.15 (0.99 to 1.35)	0.07
Women	1.17 (0.73 to 1.89)	0.51
Race (black)	0.93 (0.54 to 1.62)	0.80
Dialysis vintage, mo	1.00 (0.95 to 1.05)	0.95
Heart failure	0.75 (0.42 to 1.35)	0.34
Coronary artery disease	1.82 (1.07 to 3.10)	0.03
Other heart disease	0.84 (0.51 to 1.38)	0.50
Cerebral vascular disease	1.09 (0.61 to 1.94)	0.78
Peripheral vascular disease	0.77 (0.39 to 1.51)	0.44
Hypertension	0.84 (0.08 to 8.30)	0.88
Diabetes	1.04 (0.60 to 1.80)	0.90
COPD	1.03 (0.56 to 1.92)	0.92
Smoker	0.84 (0.42 to 1.66)	0.61
Cancer	1.72 (0.82 to 3.60)	0.15
Alcohol dependence	9.07 (0.29 to 280.08)	0.21
Drug dependence	0.83 (0.35 to 1.95)	0.66
Catheter placement (new tunnel)[a]	0.76 (0.47 to 1.22)	0.26
Catheter location (femoral)[b]	5.84 (1.84 to 18.55)	0.003
Catheter length, cm	0.71 (0.40 to 1.27)	0.25

Risk ratios are for change of 1 for all except age and catheter length, where change was 10. A negative binomial model was used to examine the catheter infection rates in the two groups. 95% CI, 95% confidence interval; COPD, chronic obstructive pulmonary disease.
[a]New tunnel versus exchange over a guide wire.
[b]Catheter placement into femoral vein versus internal jugular vein.

that use of antibiotic lock was associated with a significant reduction in mortality (hazard ratio [HR], 0.36; 95% CI, 0.22 to 0.58 in unadjusted analyses; HR, 0.32; 95% CI, 0.14 to 0.75 after multivariate adjustment) (Table 5). The attributable risk of heparin contributing to death was 35.3%. The risk for mortality was significantly increased for an increased white blood cell count (HR, 1.19; 95% CI, 1.10 to 1.29 after multivariate adjustment) and significantly decreased for higher albumin (HR, 0.47; 95% CI, 0.25 to 0.86 after multivariate adjustment).

There were 883 hospitalizations during the heparin period and 598 hospitalizations during the antibiotic lock period. When comparing the rate of all-cause hospitalization, the rate was 3.5±3.6 per person-year in the heparin period compared with 3.0±3.1 per person-year in the antibiotic lock period

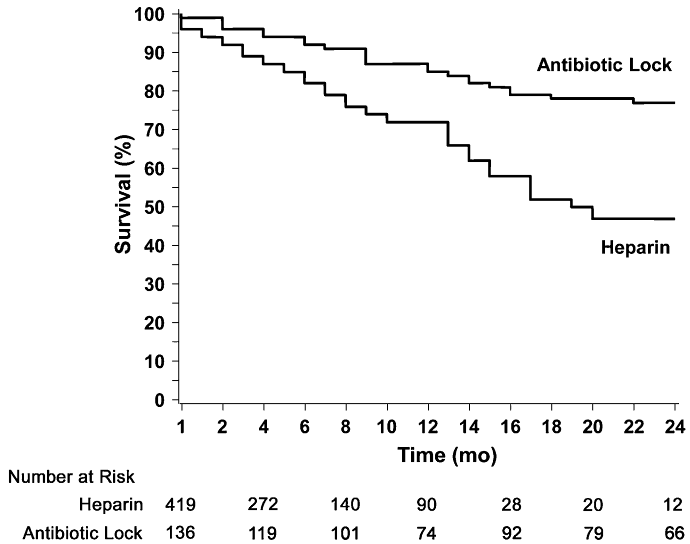

Figure 2. | Kaplan–Meier estimates of all-cause mortality. Hazard ratio to time of death, 0.36; 95% confidence interval, 0.22 to 0.58.

Table 5. Cox proportional hazards regression analysis for all-cause mortality

Variable	Unadjusted Hazard Ratio (95% CI)	*P* Value	Adjusted Hazard Ratio (95% CI)	*P* Value
Antibiotic lock	0.36 (0.22 to 0.58)	0.001	0.32 (0.14 to 0.75)	0.008
Age, yr	1.28 (1.10 to 1.47)	0.001	1.05 (0.79 to 1.38)	0.73
Women	1.03 (0.70 to 1.51)	0.89	0.74 (0.38 to 1.44)	0.37
Race (black)	0.72 (0.48 to 1.07)	0.10	0.94 (0.47 to 1.88)	0.85
Dialysis vintage, mo	0.90 (0.54 to 1.49)	0.69	1.93 (0.98 to 3.81)	0.06
Heart failure	1.38 (0.91 to 2.11)	0.13	1.08 (0.48 to 2.45)	0.85
Coronary artery disease	1.24 (0.85 to 1.82)	0.27	0.88 (0.93 to 1.81)	0.73
Other heart disease	1.72 (1.16 to 2.56)	0.007	2.12 (0.99 to 4.54)	0.05
Cerebral vascular disease	1.70 (1.13 to 2.55)	0.01	1.00 (0.49 to 2.03)	>0.99
Peripheral vascular disease	1.04 (0.64 to 1.67)	0.88	0.91 (0.40 to 2.08)	0.82
Hypertension	0.29 (0.15 to 0.55)	0.001	0.47 (0.15 to 1.50)	0.20
Diabetes	0.91 (0.61 to 1.36)	0.65	0.94 (0.47 to 1.89)	0.86
COPD	1.31 (0.87 to 1.97)	0.21	1.53 (0.77 to 3.04)	0.23
Smoker	0.80 (0.47 to 1.36)	0.41	0.65 (0.26 to 1.63)	0.36
Cancer	1.20 (0.75 to 1.92)	0.45	0.97 (0.46 to 2.06)	0.94
Albumin, g/dl	0.18 (0.13 to 0.24)	0.001	0.47 (0.25 to 0.86)	0.01
Calcium (corrected), mg/dl	1.67 (1.18 to 2.34)	0.003	1.28 (0.88 to 1.87)	0.20
Phosphorus, mg/dl	0.87 (0.74 to 1.02)	0.09	1.20 (0.92 to 1.57)	0.17
Creatinine, mg/dl	0.72 (0.65 to 0.80)	0.001	0.83 (0.68 to 1.00)	0.05
Hemoglobin, g/dl	0.67 (0.58 to 0.78)	0.001	0.87 (0.69 to 1.10)	0.24
Iron saturation, %	1.14 (0.93 to 1.38)	0.20	1.12 (0.90 to 1.40)	0.34
Ferritin, ng/ml	2.11 (1.43 to 3.12)	0.001	1.04 (0.69 to 1.58)	0.85
White blood cells, K/μl	1.18 (1.14 to 1.21)	0.001	1.19 (1.10 to 1.29)	0.001

Hazard ratios are for change of 1 for all except age and iron saturation, where change was 10. COPD, chronic obstructive pulmonary disease.

(*P*=0.06). When comparing the rate of infection-related hospitalization, the rate was 1.3±1.7 per person-year in the heparin period compared with 0.9±3.1 per person-year in the antibiotic lock period (*P*=0.001).

Safety End Points

When comparing the gentamicin resistance rates, the rate decreased from 0.40/1000 person-years in the heparin period to 0.22/1000 person-years in the antibiotic lock period (*P*=0.01). There were 28 resistant organisms in the control period: 21 (75%) organisms were Gram-positive, and 7 (25%) organisms were Gram-negative. There were 15 resistant organisms in the antibiotic lock period: 10 (67%) organisms were Gram-positive, and 5 (33%) organisms were Gram-negative. Particularly, the gentamicin-resistant organisms occurring in the heparin period include methicillin-resistant *S. aureus* (2), *Staphylococcus epidermidis* (11), *Enterococcus* spp. (28), *E. coli* (10), *Klebsiella* spp. (2), and other Gram-negative (1) organisms. The gentamicin-resistant organisms occurring in the antibiotic lock period include methicillin-resistant *S. aureus* (1), *S. epidermidis* (9), *Enterococcus* spp. (3), *E. coli* (1), *Proteus* spp. (1), *Enterobacter* spp. (1), *Pseudomonas* spp. (1), and other Gram-negative (1) organizations. The average catheter lifespan was 122±144 days during the heparin period compared with 169±231 days during the antibiotic lock period (P=0.42). When comparing the rate of catheter-related vascular access procedures, the rate was 3.7±3.3 per person-year in the heparin period compared with 3.5±3.6 per person-year in the antibiotic lock period (P=0.46). The rates of vascular access procedures for infection decreased in the antibiotic lock period (1.0±1.6 versus 0.3±0.9; P=0.001) and were similar for malfunction/clotting (1.1±2.5 versus 1.4±2.9; P=0.11) between the two periods. The rate of t-PA administration was 8±14 per person-year for the heparin period and 6±15 per person-year for the antibiotic lock period (P=0.34). We also compared the usage of common antibiotics (vancomycin, cefazolin, and cefepime) between the heparin and the antibiotic lock period. The geometric mean of the overall usage of the three antibiotics was 6.5 mg/d in the heparin period compared with 4.5 mg/d in the antibiotic lock period (difference of log-transformed data, 0.44; 95% CI, 0.10 to 0.75; P=0.01).

Discussion

This study evaluated the comparative effectiveness of heparin and a prophylactic antibiotic lock solution on clinical outcomes in a hemodialysis population with a high incidence of CRBSI. Our findings confirm the results of prior work, which showed a significant reduction in CRBSI from the use of the same prophylactic antibiotic lock (21). Our study is the first to show a survival advantage associated with use of a prophylactic, low-dose gentamicin/citrate locking solution, conferring a 68% relative reduction in mortality after multivariate adjustment.

Infection is the second leading cause of death in hemodialysis patients, second only to cardiovascular disease. Unfortunately, there has not been any major advancement in the past two decades that has been successful in reducing either infection-related morbidity or mortality in this patient population. Although we did not find a significant reduction in overall hospitalization rates by use of antibiotic lock, we did find a significant reduction (31%) in infection-related hospitalizations in the antibiotic lock period. In an era when infection-related hospitalizations in dialysis patients are up 43% over the past two decades and much focus is on reducing preventable healthcare use, a safe and effective intervention that could reduce this burden is desirable (1).

A major concern in using gentamicin as a catheter locking agent is the emergence of resistant organisms. This is a major concern for the CDC and the primary reason for the lack of a recommendation for the routine use of any prophylactic antibiotic lock, because studies showing efficacy in reducing CRBSI are numerous (11–15). Most studies evaluating efficacy of antibiotic lock have been of small size and/or short duration, not allowing for the ability to evaluate antibiotic resistance over longer periods of time or in a real world setting. A recent study reported a 95% reduction in CRBSI (17–0.83/1000 catheter days) in over 1400 patients by use of a prophylactic gentamicin/heparin lock (29). This study reported that the presence of gentamicin-resistant organisms over 4 years of use of the lock led to cessation of the lock protocol. However, the study lacked susceptibility data for the period before implementing the lock; therefore, it is not known if gentamicin resistance patterns actually changed after initiation of the lock or were similar to the patterns seen before using the lock. A randomized, controlled trial using the same prophylactic, low-dose lock as the current study found stable gentamicin susceptibility patterns over the 5-year course of the study in both treatment groups (21). Our study found that gentamicin resistance was present during the control period and that the incidence significantly decreased in the antibiotic lock period. This finding could be related to the lower dose of gentamicin used in the lock solution or the use of citrate as opposed to heparin, because heparin has been shown to increase biofilm production, which in turn, can increase antimicrobial resistance (30,31). Although the number of gentamicin-resistant organisms is relatively small, we did not find that specific organisms, particularly *S. aureus*, were more likely to be gentamicin-resistant after using the antibiotic lock. Other safety end points, such as t-PA use, vascular access procedures, and catheter lifespan, were similar between the two periods, showing that catheter patency was also maintained during the antibiotic lock period.

Our study has certain limitations. It was a prospective, observational study. As with any observational study, the presence of selection bias cannot be excluded. We attempted to control for it by collecting and adjusting for a large number of potential confounders that could have influenced outcome. Also, all prevalent patients dialyzing with tunneled catheters in the units were changed to prophylactic antibiotic lock. Use of antibiotic lock was not dependent on clinician behavior or particular patient characteristics beyond having a tunneled catheter. Importantly, there were no identifiable practice pattern changes between the control and lock periods, including the catheter maintenance protocol and procedures followed by vascular surgery. When evaluating the incidence of CRBSI over time, there was a direct and temporal relationship between the initiation of antibiotic lock and a significant reduction in CRBSI at each dialysis unit. Despite this finding, unidentified confounders may still be present that could have influenced outcome. Unfortunately, we were not able to accurately determine cause of death and, therefore, adequately assess infection-related mortality. Additionally, the period of follow-up for antibiotic lock was relatively short in two of three units (approximately 7–8 months). Important strengths of this study include its multicenter evaluation in a large number of hemodialysis patients and its real world evaluation in a captured patient population, which support its generalizability. Outcomes were captured in this population, because hemodialysis units are required to prospectively follow all vascular access-related infections, hospitalizations, and deaths. We were also able to critically evaluate antimicrobial resistance patterns between the two treatment periods over a longer period of time, which has been a limitation of prior work.

The results of this study show that the use of a prophylactic, low-dose gentamicin/citrate lock was associated with a lower rate of CRBSI, and this study is the first to report a significant survival advantage of antibiotic lock in a population at high risk of infection-related morbidity and mortality. This study supports the prophylactic use of a gentamicin/citrate lock in dialysis units exhibiting a higher rate of CRBSI (>1.68/1000 catheter days) but does not assess its use in units with lower rates of CRBSI, where its impact would be expected to be less. Despite our finding that a gentamicin/citrate lock was safe and effective, decisions to implement this protocol should be made judiciously and only when other standard attempts have failed to reduce rates.

Disclosures

C.L.M. was employed by Henry Ford Health System during the course of the study. She is currently employed by Amgen, Inc. The work on the present study was conducted before her employment at Amgen, Inc.

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