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Original Investigation

A Randomized Trial Comparing Gentamicin/Citrate and Heparin Locks for Central Venous Catheters in Maintenance Hemodialysis Patients

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Background: Central venous catheters (CVCs) are used for vascular access in hemodialysis patients who have no alternative access or are awaiting placement or maturation of a permanent access. The major complications of CVCs are catheter-related bloodstream infection and clotting in the catheter lumen.

Study Design: Parallel-group, randomized, multicenter clinical trial, with patients blinded to study intervention.

Setting & Participants: 16 free-standing dialysis facilities in Northern California belonging to a single provider. 303 adult maintenance hemodialysis patients who were using a tunneled cuffed CVC for vascular access.

Intervention: The treatment group received an antibiotic lock containing gentamicin 320 μg/mL in 4% sodium citrate, whereas the control group received the standard catheter lock containing heparin 1,000 U/mL. Both groups received triple-antibiotic ointment on the catheter exit site during dressing changes at each dialysis treatment.

Outcomes: Catheter-related bloodstream infection and catheter clotting.

Measurements: Catheter-related bloodstream infection was defined as the occurrence of symptoms consistent with bacteremia together with positive blood culture results in the absence of another obvious source of infection. Catheter clotting was measured as the rate of thrombolytic agent use required to maintain adequate blood flow. A single patient could contribute more than one infection or clotting episode.

Results: The rate of catheter-related bloodstream infection was 0.91 episodes/1,000 catheter-days in the control group and 0.28 episodes/1,000 catheter-days in the treatment group ($P = 0.003$). The time to the first episode of bacteremia was significantly delayed ($P = 0.005$). The rates of tissue plasminogen activator use were similar in the treatment and control groups: 2.36 versus 3.42 events/1,000 catheter-days, respectively ($P = 0.2$).

Limitations: The requirement for dialysis facility staff to prepare the treatment intervention prevented a completely blinded study.

Conclusion: Gentamicin 320 μg/mL in 4% sodium citrate used as a routine catheter lock in CVCs in patients on maintenance hemodialysis therapy markedly decreases the incidence of catheter-related bloodstream infection and is as effective as heparin 1,000 U/mL in preventing catheter clotting.
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INDEX WORDS: Hemodialysis; catheter-related bloodstream infection; central venous catheters; antimicrobial catheter lock; triple-antibiotic ointment.

Central venous catheters (CVCs) remain an essential but flawed tool to provide vascular access in patients on maintenance hemodialysis therapy. Even if every effort is made to minimize their use, they are required in patients who do not have an established permanent vascular access or those who have no other possible access.[1] The most serious complication of CVC use is catheter-related bloodstream infection, which leads to major patient morbidity and has a high mortality rate.[2] The frequency of catheter-related bloodstream infection is reported to be 2-5 episodes/1,000 patient-days,[3] and it often results in hospitalization, metastatic infections, such as osteomyelitis, endocarditis, septic arthritis, and epidural abscesses, or death. Catheter replacement usually is required to resolve the infection.[4]

Four recent meta-analyses have concluded that prophylactic antibiotic locks are safe and effective in preventing such infections.[5-8] The ideal locking solution would prevent catheter-related bloodstream infection, at least by the transluminal route, be effective against all organisms (including yeasts), not lead to antimicrobial resistance, and effectively prevent clotting within the catheter.

Heparin has a number of disadvantages as an interdialytic lock for CVCs. Especially with higher concentrations (5,000 or 10,000 U/mL), there is a risk of systemic anticoagulation due to inadvertent or deliberate overfill of the lumen. Furthermore, heparin has

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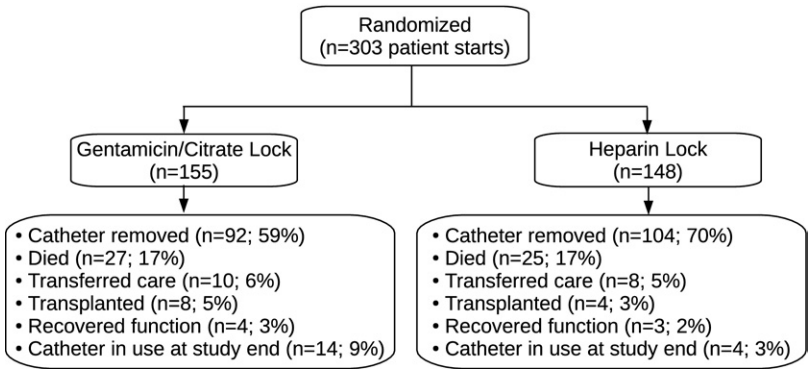

Figure 1. Patient randomization and follow-up.

been shown by in vitro studies to promote *Staphylococcus aureus* biofilm formation in a dose-dependent manner, whereas sodium citrate in concentrations >0.2% prevents it.[9,10] A randomized clinical trial in patients with CVCs showed that 4% sodium citrate was as effective as heparin in preventing thrombosis in hemodialysis catheters.[11] This result also was shown in 2 nonrandomized sequential studies.[12,13] In these studies, sodium citrate alone did not decrease the rate of catheter-related bloodstream infection.[11-13]

A trial with gentamicin in sodium citrate showed efficacy in preventing catheter-related bloodstream infection. However, the gentamicin concentration used (27 mg/mL) resulted in detectable serum levels of gentamicin and some evidence of vestibular toxicity.[14] Gentamicin 5 mg/mL in heparin 5,000 U/mL also was able to markedly decrease the incidence of catheter-related bloodstream infection,[15] as was gentamicin 4 mg/mL in 3.13% sodium citrate.[16]

We hypothesized that a lower concentration of gentamicin would be effective in decreasing the incidence of catheter-related bloodstream infection while avoiding systemic gentamicin accumulation. We therefore evaluated the use of gentamicin 320 μg/mL in 4% sodium citrate as a routine catheter lock to prevent catheter clotting and bacteremia.

METHODS

The study was a randomized prospective multicenter trial. Patients were blinded to the study intervention.

The trial was performed in 16 freestanding dialysis facilities in Northern California belonging to a single provider (Satellite Healthcare, San Jose, CA). All adult patients with either newly placed or existing tunneled cuffed catheters were eligible for enrollment. Patients were excluded if they had an active exit-site or tunnel infection or other systemic or localized infection that was unresponsive to antibiotic therapy and/or was life-threatening. Patients who had any infection associated with one or more positive blood culture results were not eligible until 14 days after blood culture results had become negative and clinical resolution of the episode had occurred. Patients with known allergy to heparin or gentamicin or known intravenous drug use also were excluded. All cultures were performed in a central laboratory (Satellite Laboratory Services, Redwood City, CA), except for occasional after-hours cultures sent to local hospital laboratories.

Eligible patients were randomly assigned 1:1 to treatment or control groups using a central randomization system with participants randomly assigned within centers in blocks of 2 and 4 to ensure an approximate balance in the number of participants in each group within each center.[17]

The study was carried out under good clinical practice and according to the principles of the Declaration of Helsinki. Informed consent was obtained from all patients, and the study design was approved by the RCRC Institutional Review Board. Patients were randomly assigned to receive either the usual catheter lock of 1,000 U/mL of heparin or a solution of 320 μg/mL of gentamicin in 4% sodium citrate. At the end of the dialysis treatment, blood was returned per standard unit protocol and each lumen of the catheter was flushed with 10 mL of 0.9% saline solution. A sufficient volume of the treatment or control solution then was instilled to fill each catheter lumen according to the manufacturer's instructions. Triple-antibiotic ointment (neomycin, bacitracin, and polymyxin) was applied to the exit site at each dressing change in both the control and treatment groups, as described by Lok et al[18]; this was the routine practice at Satellite Healthcare during the time of the study. The catheter exit site was covered with a gauze dressing that was changed at each dialysis session. Apart from study procedures, 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.

Catheter-related bloodstream infection was defined as the presence of a positive blood culture result for a micro-organism, including bacteria or fungi, associated with clinical manifestations

Table 1. Baseline Characteristics

	Control	Treatment	*P*
No. of patients	148	155	
Age (y)	62.8 ± 16.8	63.4 ± 15.6	0.8
Men (%)	54.7	49.0	0.3
Diabetes (%)	58.1	54.8	0.6
Dialysis vintage (mo)	44.3 (1.1-131.8)	42.4 (0-198.5)	0.9
Incident catheters	15	5	
Catheter site			
Internal jugular	104	113	
External jugular	12	12	
Femoral	1	2	
Subclavian	6	7	
Unknown	25	21	

Note: Continuous variables expressed as mean ± standard deviation or median (range).

Table 2. Catheter Outcomes

	Control	Treatment	*P*
No. of patients	148	155	
Total follow-up (d)	32,933	39,827	
Days at risk per patient	222.9	256.9	0.2
Episodes of bacteremia	30	11	
Episodes of bacteremia/1,000 catheter-days	0.91	0.28	0.003
HR for bacteremia (95% CI)	3.22 (1.51-6.87)	1.00 (reference)	
tPA use/1,000 catheter-days	3.42	2.36	0.2
HR for tPA use (95% CI)	1.12 (0.70-1.78)	1.00 (reference)	

Abbreviations: CI, confidence interval; HR, hazard ratio; tPA, tissue plasminogen activator.

of systemic sepsis (eg, fever, chills, or hypotension). Blood cultures were obtained through the CVC; there was no requirement for simultaneous cultures from a peripheral vein. Cultures were obtained from the exit site only when signs of local infection (erythema and discharge) were noted. The rate of thrombolytic agent use required to maintain blood flow adequate for dialysis was used as an objective measure of clinically significant catheter clotting.

For both primary efficacy (number of infections) and safety (tissue plasminogen activator [tPA] use) outcomes, sample calculations were performed using the normal approximation.[17] It was determined that a minimal total sample size of 140 patients per treatment group was needed to show a 50% decrease in infection rate and 50% decrease in the hazard rate of thrombolytic infusion between the treatment and control groups, with the 1-sided probability of type I error at $\alpha = 0.05$ and power of 80%.

The χ^2 test was used to compare categorical baseline characteristics, and *t* test was used to compare continuous baseline characteristics of the 2 treatment groups. To account for nonindependence between multiple events from the same patient, comparisons of rates of infection and tPA use were performed by negative binomial regression.[19] Treatment group assignment was the only covariate included in regression analyses to draw inference about treatment effects. Goodness of fit for both regressions was assessed by deviance/*df* statistics and in both cases produced satisfactory results (~1.1). Log-rank test was used to compare groups with respect to time to first episode of bacteremia.

Kaplan-Meier estimates of survival curves were used to assess time to onset of the first episode of bacteremia.[20] This outcome was censored at 800 days for patients who did not experience an episode of bacteremia.

RESULTS

The first patient was randomly assigned in September 2003 and data collection ended in May 2008; study flow is shown in Fig 1.

Baseline characteristics of the control group (n = 148) and treatment group (n = 155) were similar with regard to age, sex, incidence of diabetes, and dialysis vintage. Total follow-up was 32,933 catheter-days (1,083 months) and 39,827 catheter-days (1,309 months) in the control and treatment groups, respectively (Table 1).

The catheter-related bloodstream infection rate of 0.28 episodes/1,000 catheter-days in the treatment group was significantly lower than the rate of 0.91 episodes/1,000 catheter-days in the control group ($P = 0.004$; Table 2), and time to onset of the first bacteremia episode was significantly delayed ($P = 0.005$; Fig 2). The risk of infection was higher in the control group by a

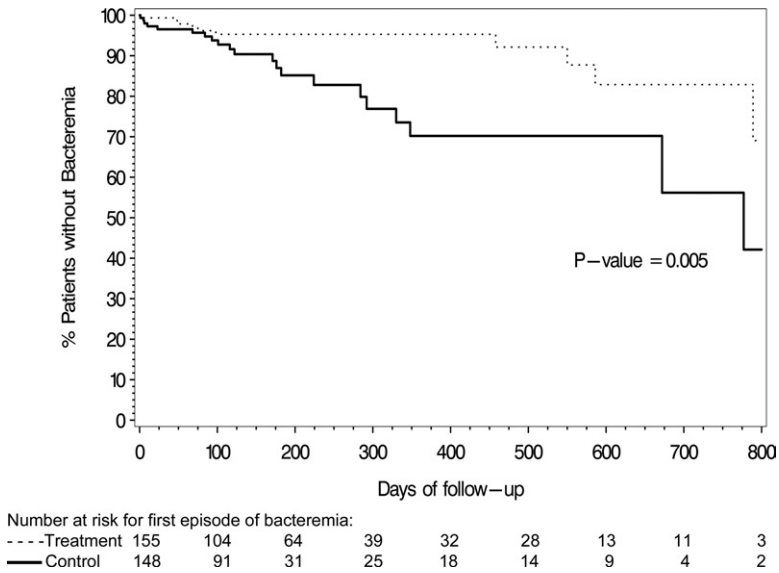

Figure 2. Kaplan-Meier bacteremia-free survival curves for the treatment and control groups. *P* for log-rank test of equality over strata = 0.005.

Table 3. Pathogens Causing Bacteremia

	Gentamicin/Citrate		Heparin	
Type	Organism	No.	Organism	No.
Gram-positive	MSSA	2	MSSA	6
	MRSA	1	MRSA	1
	S simulans	1	*S epidermidis*	2
	S lugdunensis	1	*S haemolyticus*	1
	S bovis	1	*E faecalis*	2
	E faecalis	1	*Staphylococcus* species[a]	1
	Staphylococcus species[a]	1	*Streptococcus* species[a]	1
	Total	8	Gram-positive bacilli[a]	2
			Total	16
Gram-negative	*K pneumoniae*	1	*E coli*	1
	Total	1	*A lwoffii*	1
			E cloacae	3
			S maltophilia	1
			P mirabilis	1
			R paucula	1
			Pseudomonas species[a]	1
			G-bacilli[a]	1
			Total	10
Mixed	*K pneumoniae, P aeruginosa*	1	*A lwoffii, F oryzihabitans*	1
	Total	1	*S epidermidis, Pseudomonas* species[a]	1
			Total	2
Fungal	Yeast[a]	1	*C tropicalis*	1
	Total	1	Yeast[a]	1
			Total	2
All		11		30

Abbreviations: *A lwoffii, Acinetobacter lwoffii; C tropicalis, Candida tropicalis; E cloacae, Enterobacter cloacae; E coli, Escherichia coli; E faecalis, Enterococcus faecalis; F oryzihabitans, Flavimonas oryzihabitans; K pneumoniae, Klebsiella pneumoniae;* MRSA, methicillin-resistant *Staphylococcus aureus;* MSSA, methicillin-sensitive *Staphylococcus aureus; P aeruginosa, Pseudomonas aeruginosa; P mirabilis, Proteus mirabilis; R paucula, Ralstonia paucula; S bovis, Streptococcus bovis; S epidermidis, Staphylococcus epidermidis; S haemolyticus, Staphylococcus haemolyticus; S lugdunensis, Staphylococcus lugdunensis; S maltophilia, Stenotrophomonas maltophilia;S simulans, Staphylococcus simulans.*

[a]Organism not further characterized.

factor of 3 (hazard ratio, 3.22; 95% confidence interval, 1.51-6.87). One patient in each group died of sepsis, in each case caused by *S aureus.*

Rates of exit-site infection were not different between the treatment and control groups, 0.20 versus 0.27 infections/1,000 catheter-days, respectively (P = 0.6).

Rates of tPA use were not significantly different: 2.36 events/1,000 catheter-days in the treatment group versus 3.42 events/1,000 catheter-days in the control group (P = 0.2; Table 2). Thirty-five catheters were removed because of poor flow in the control group, and 42, in the treatment group, a rate of 1 exchange/941 catheter-days and 1 exchange/948 catheter-days, respectively.

The gentamicin/citrate lock was most effective in decreasing infections with Gram-negative organisms, but also decreased the incidence of Gram-positive organisms (Table 3). All blood cultures from the study centers were monitored over the course of the study (and after introduction of the lock as routine care in the facilities as of January 2008), and there has been no emergence of gentamicin resistance (Fig 3).

DISCUSSION

In this large-scale long-term randomized study, we showed the efficacy of gentamicin/citrate as a locking solution in preventing catheter-related bloodstream infection in hemodialysis patients using a tunneled CVC for vascular access. The overall catheter-related bloodstream infection rate was significantly lowered (0.28 vs 0.91 episodes/1,000 catheter-days; P = 0.004; HR, 3.22; 95% CI, 1.51-6.87) and the time to the first episode significantly delayed (P = 0.005; Fig 2) in the group treated with the gentamicin/citrate lock. The low frequency (0.91 episodes/1,000 catheter-days) of

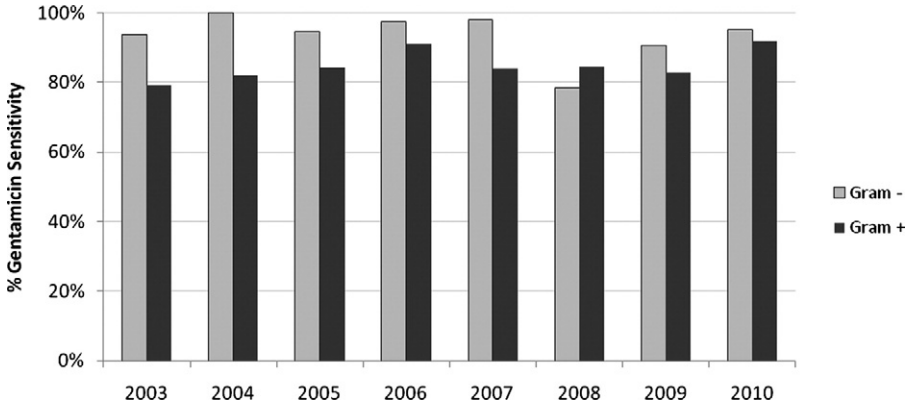

Figure 3. Gentamicin susceptibility in all blood cultures from patients in the 16 participating centers. From January 2008, the gentamicin/citrate lock was used in all patients on hemodialysis therapy using central venous catheters.

bacteremia in the control group (which, like the gentamicin/citrate lock group, also received triple-antibiotic ointment to the exit site) was similar to that found in the treatment group (0.63 episodes/1,000 catheter-days) in the Toronto study.[17] This suggests that triple-antibiotic ointment on the exit site is itself a simple and effective intervention to prevent bacteremia. It is striking that a significant improvement in bacteremia rate was seen in the treatment group even though the rate in the control group was low.

The gentamicin concentration used in this study (320 μg/mL) is convenient because it is obtained by adding a standard 80-mg ampoule of gentamicin to a 250-mL bag of 4% sodium citrate. This high local concentration within the catheter lumen clearly is effective in decreasing the rate of bacteremia without significant systemic delivery of gentamicin. Assuming a volume of 2 mL for each catheter lumen, the total amount of gentamicin introduced into the catheter after each dialysis treatment is 1.3 mg. If the total volume of each lumen was inadvertently infused into the circulation before the next dialysis treatment, the resulting serum concentration would be <0.1 μg/mL, given a reported volume of distribution of 13.5 L.[21] Furthermore, dialytic clearance of gentamicin is $\sim$100 mL/min.[21] Thus, even in the worst-case scenario in which the entire amount of gentamicin was infused repetitively predialysis 3 times per week, significant gentamicin accumulation is not possible.

A major concern in using gentamicin as a routine catheter lock is the emergence of resistant organisms. However, no increase in gentamicin resistance was observed in either blood cultures from the study centers during the course of the trial or in the 3 years after the universal use of the gentamicin/citrate lock in all patients using tunneled catheters in our facilities in January 2008 (Fig 2). There are 2 reports of the emergence of gentamicin-resistant organisms after the routine use of gentamicin catheter locks.[22,23] The first has been published in only abstract form and it is difficult to follow the investigators' reasoning because there was an 83% incidence of gentamicin-resistant *Staphylococcus epidermidis* documented in the year the study was started; the timeline cannot be deduced from the abstract.[22] A recent publication documents the occurrence of septicemia with gentamicin-resistant organisms after the routine use of gentamicin catheter locks.[23] The gentamicin concentration used (4 mg/mL) was much higher than in our study, and one could speculate that it led to the leak of significant amounts of gentamicin systemically, with selection of gentamicin-resistance organisms. In contrast, there is no evidence of the emergence of gentamicin resistance in our general patient population, although the gentamicin/citrate lock has been the standard of care since January 2008. Conversely, and in conformity with our results, a group using a lock with gentamicin 3 mg/lumen, found no emergence of resistance during a 7-year experience.[24]

Two recent publications have shown a decrease in catheter-related bloodstream infection using other interventions.[25,26] Hemmelgarn et al[25] randomly assigned patients to routine catheter locking with heparin 5,000 U/mL, or to instillation of tPA (1 mg in each lumen) substituted for heparin once weekly. The infection rate in the treatment group was significantly lower than in the control group (0.40 vs 1.37 episodes/1,000 catheter-days; $P = 0.02$) while providing a marked decrease in catheter malfunction. This strategy avoids the risk of inducing antibiotic-resistant organisms, but is costly. Care must be taken to avoid contamination of laboratory samples with tPA.[27] It should be noted that heparin 5,000 U/mL is no longer the standard of care in the United States because all major dialysis providers routinely use heparin 1,000 U/mL.

Maki et al[26] used a novel proprietary locking solution containing 7.0% sodium citrate, 0.15% methylene blue, 0.15% methylparaben, and 0.015% propylparaben. In a randomized prospective trial comparing the solution with heparin 5,000 U/mL, there was a significant decrease in catheter-related bloodstream

infections in the treated group (0.24 vs 0.82 episodes/1,000 catheter-days; $P = 0.005$) and a significant decrease in catheter loss due to patency failure.

We conclude that the combination of triple-antibiotic ointment on the exit site and a catheter lock with gentamicin 320 μg/mL in 4% sodium citrate is a safe and effective means of decreasing the bacteremia rate in patients with tunneled hemodialysis catheters and we have not seen the emergence of gentamicin resistance in extensive use in more than 3 years.

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