Prevention of Tunneled Hemodialysis Catheter-Related Infections Using Catheter-Restricted Filling with Gentamicin and Citrate: A Randomized Controlled Study

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Abstract. Tunneled catheters are widely used for the provision of hemodialysis. Long-term catheter survival is limited by tunneled catheter-related infections (CRI). This study assesses the efficacy of catheter-restricted filling with gentamicin and citrate in preventing CRI in hemodialysis patients. A double-blind randomized study was conducted to compare heparin (5000 U/ml) with gentamicin/citrate (40 mg/ml and 3.13% citrate; ratio 2:1) as catheter-lock solutions. A total of 112 tunneled catheters in 83 patients were enrolled at the time of catheter insertion for commencement or maintenance of hemodialysis. The primary end point was CRI. Catheter malfunction, defined as blood flow rate of <200 ml/min for three consecutive dialyses and/or the use of urokinase, was also assessed as a secondary end point. Infection rates per 100 catheter-days were 0.03 in the gentamicin group and 0.42 in the heparin group (P = 0.003). Kaplan-Meier survival analyses showed mean infection-free catheter survival of 282 d (95% CI, 272 to 293 d) in the gentamicin group versus 181 d (95% CI, 124 to 237 d) in the heparin group (log rank, 9.58; P = 0.002). Cox regression analyses showed a relative risk for infection-free catheter survival of 0.10 (95% CI, 0.01 to 0.92) in the gentamicin group when adjusted for gender, race, diabetes mellitus, catheter malfunction, and hemoglobin (P = 0.042). The incidence of catheter malfunction was not significantly different between groups. Predialysis gentamicin levels were significantly higher in patients randomized to gentamicin (gentamicin/citrate: median 2.8 mg/L [range, 0.6 to 3.5 mg/L], n = 5; heparin: median <0.2 mg/L [range <0.2 to 0.2 mg/L], n = 5; P = 0.008). Tunneled hemodialysis catheter-restricted filling with gentamicin and citrate is a highly effective strategy for prevention of CRI. Although citrate as a catheter-lock solution provides adequate anticoagulation for the interdialytic period, gentamicin levels suggest significant risk for chronic aminoglycoside exposure and associated ototoxicity. Before this technique is adopted, these preliminary observations warrant replication in future studies that will examine the efficacy and safety of lower doses of gentamicin or alternative agents with a reduced potential for toxicity.

In the absence of a functioning arteriovenous fistula or synthetic graft, tunneled hemodialysis catheters are essential for the provision of hemodialysis. Approximately 19% of new hemodialysis patients in the United States rely on tunneled catheters for the initiation of hemodialysis, and nearly 70% of these patients are still using tunneled catheters after 60 d (1). The most important factors limiting long-term survival of tunneled catheters are poor blood flow and catheter-related infections, each of which can predispose to the other (2). The infection rate for tunneled catheters averages 0.08 to 0.7 per 100 catheter-days (1,3,4). Catheter-related infections (CRI) are associated with a substantial morbidity, mortality, and additional cost per infective episode. Data from nontunneled catheters used in intensive care units indicate an average 3% per annum mortality rate and a cost-per-infective-episode of between US$3700 and US$29,000 (5).

CRI are a consequence of colonization of the catheter hub or surrounding skin followed by intraluminal or extraluminal spread (4). Prevention strategies are directed at decreasing growth and/or adherence of pathogens to the catheter hub and surface (1,5). Catheter-restricted filling with antibiotics as a prophylaxis against infection has recently emerged as a promising option, but evidence in the form of randomized controlled trials is lacking. Animal studies comparing catheters filled with gentamicin and chymotrypsin with heparin-filled catheters showed an absence of infection in the antibiotic treated group (6). As gentamicin is incompatible with heparin in solution (7), human studies have used catheter-restricted filling with gentamicin in combination with citrate, but they have only been published in abstract form (8–10). Two of these studies were
uncontrolled observations showing an absence of CRI using 40 mg/ml gentamicin in one study (8) and a marked 65% reduction in CRI using only 2.3 mg/ml gentamicin in another study (9). A small controlled study using 40 mg/ml gentamicin reported 0 infections per 100 catheter-days in the gentamicin group compared with 0.3 infections per 100 catheter-days in the heparin-treated group without signs or symptoms of ototoxicity (10).

We report the first randomized, controlled trial that tests the hypothesis that catheter-restricted filling with gentamicin and citrate reduces hemodialysis CRI.

**Materials and Methods**

**Study Design and Patients**

We undertook a double blind, randomized controlled trial comparing the efficacy of hemodialysis catheter-restricted filling with gentamicin and citrate versus the standard practice of catheter-restricted filling with heparin in the prevention of CRI. All patients were recruited between May 1999 and June 2001 from two tertiary hemodialysis referral centers and their associated Satellite Dialysis Units in Perth, Western Australia. Patients were eligible for the study if they required insertion of a tunneled catheter for the maintenance or commencement of hemodialysis. Patients having reininsertion of a tunneled catheter through a new entry site were also included. Patients were excluded if they had active sepsis, were on parenteral or prolonged (>5 d) oral antibiotic therapy, and if they had an allergy to gentamicin and/or citrate. Failure to randomize a patient within three dialysis sessions of new catheter insertion and rewiring of a tunneled catheter through the same exit site were also exclusion criteria. Block randomization using random number tables was performed by Clinical Trials Pharmacists, thereby ensuring allocation concealment. All investigators, patients, and renal and microbiology staff were blinded to treatment allocation. The Ethics Committee of both centers approved the study, and all subjects gave written informed consent.

Tunneled catheters were inserted by experienced radiologists under direct image guidance and were dual-lumen, cuffed catheters to be used only for hemodialysis (Mahurkar Permcath, Quinton Instrument Company, Bothell WA; Bard Vascath, Bard Access Systems, Inc, Salt Lake City, UT; Ash Split Cath, Medcomp, Harleysville, PA). All patients had a chlorhexidine body wash and application of nasal mupirocin before catheter insertion. Cephalothin (1 g) was administered intravenously before insertion, and strict asepsis was used for catheter insertion. Catheter care after insertion involved daily administration of nasal mupirocin for 1 wk and weekly nasal mupirocin thereafter. The routine use of nasal mupirocin in our dialysis centers is based on evidence for an associated reduction in *Staphylococcus aureus* CRI (11,12). The catheter exit site was inspected at each dialysis, cleaned with chlorhexidine or iodine, and covered with a transparent, oxygen-permeable dressing (Ospite; Smith and Nephew Ltd., Largo, CA). Intradialytic anticoagulation was standardized to 1mg/kg enoxaparin for both the gentamicin/citrate and heparin catheter-lock group. Catheter malfunction was defined as a blood flow rate of <200 ml/min for three consecutive dialyses and/or the use of urokinase.

Patients were randomly allocated to receive either gentamicin and citrate (2 ml of 40 mg/ml gentamicin and 1 ml of 3.13% tri-sodium citrate in a 3-ml syringe) or heparin (5000 U/ml heparin in a 3-ml syringe) as a catheter-lock solution. Each patient was provided with two 3-ml syringes per dialysis, and nurses were advised to withdraw the lock solution before dialysis and to lock the catheters after dialysis with a volume equivalent to the lumen volume plus 0.2 ml.

Patient demographic data collected included age, gender, race, presence of diabetes mellitus, etiology of renal disease, time on dialysis, hemoglobin, serum ferritin, and serum albumin at entry into study, use of warfarin, and history of malignancy or use of immunosuppressive medications. Predialysis gentamicin levels were measured from a peripheral venous blood sample in the last ten patients randomized in the study.

**Outcomes and Definitions**

The primary end point studied was symptomatic CRI defined according to the Centers for Disease Control (CDC) as one of the following (4,13,14): (a) clinical exit site infection defined as erythema, tenderness, and/or induration within 2 cm of the exit site with or without a purulent exudate or microbiologic exit site infection where the exudate yields a microorganism on culture; (b) definite blood stream infection defined as location of the same organism from a semiquantitative culture of the catheter tip (>15 colony-forming units per catheter segment) and from a peripheral and catheter blood sample in a symptomatic patient with no other apparent source of infection; (c) probable blood stream infection defined as defervescence after removal of catheter in the setting where blood cultures confirm infection but catheter tip does not or if catheter tip confirms infection but blood cultures do not in a symptomatic patient with no other apparent source of infection; (d) possible blood stream infection defined as defervescence after removal of catheter in the absence of laboratory confirmation of blood stream infection in a symptomatic patient with no other apparent source of infection.

If CRI was suspected (fever, pain, induration, erythema, exudate), study protocol required peripheral and catheter blood cultures to be collected. An exit site swab was also collected if indicated. After diagnosis, management of CRI was the responsibility of individual physicians and was not specified in the study protocol or as an outcome measure. If the catheter was removed as part of CRI management, the catheter tip was sent for culture to further assist in categorizing CRI according to CDC guidelines. For the purposes of this study, infection-free catheter survival was defined as the number of days from catheter insertion to diagnosis of CRI as previously defined. Exit from the study for any non-CRI-related cause was treated as a censored observation for the purposes of survival analysis. Catheter use was defined as the number of days from catheter insertion to diagnosis of CRI or censored observation.

**Statistical Analyses**

A 1997 audit of all hemodialysis patients with tunneled catheters in one of the tertiary Perth dialysis centers revealed a baseline risk of infection of 0.8 per 100 catheter-days. On the basis of this data, prospective construction of sample size revealed that 60 catheters per group were required to demonstrate an effect size of 30% with α of 0.05 and 80% power. All analyses were based on intention-to-treat and were performed using SPSS (version 10.0; SPSS Inc., Chicago, IL). Data are presented as mean ± SEM. Independent t-tests were used to compare continuous variables between groups. Skewed variables are described using median (range) and were compared using the Mann-Whitney U test. Correlations among continuous variables were tested using Pearson’s correlation coefficient (Pearson’s r). A χ² test was used to compare categorical variables among groups. Cumulative infection-free catheter survival was analyzed by using the Kaplan-Meier method and log-rank test. Infection-free catheter survival adjusted for baseline covariates was analyzed using Cox proportional hazards test. Catheter survival results are presented as mean...
(95% confidence interval [CI]) or relative risk (95% CI). \( P < 0.05 \) were considered significant.

**Results**

Of 125 catheter insertions identified between May 1999 and June 2001, 112 catheters in 83 patients were consented and randomized to trial medications. Two patients were discontinued in each group as shown in Figure 1, leaving 53 catheters in 42 patients completing study participation in the gentamicin/citrate group and 55 catheters in 37 patients completing the study in the heparin group. Table 1 shows the baseline demographic and laboratory characteristics of the patients. The groups were matched for age, gender, Australian aboriginal racial origin, and presence of diabetes mellitus. In both groups, approximately 70% of patients had been on hemodialysis for less than 6 mo. Although serum ferritin and serum albumin at entry were not different among groups, hemoglobin at entry was significantly lower in the gentamicin/citrate group compared with the heparin group (\( P = 0.012 \)). Three patients in the heparin group were on warfarin for cardiac indications versus none in the gentamicin/citrate group (\( \chi^2 P = 0.243 \)). Four patients in both groups were either on steroids or had a past history of a malignancy. During the study follow-up period (from randomization to CRI or censored event) patient survival was 100%.

Table 2 indicates the etiology of renal disease and indication for tunneled catheter insertion. Over 75% of patients had tunneled catheters inserted to start dialysis in the absence of an arteriovenous fistula. In the gentamicin/citrate group, 90.5% of patients received a jugular tunneled catheter versus 91% in the heparin group (\( \chi^2 P = 0.573 \)), and the remaining patients received tunneled subclavian catheters. Thirty percent of patients experienced catheter malfunction in the gentamicin/citrate group compared with 42% in the heparin group (\( \chi^2 P = 0.208 \)). Median catheter use was 40 d (range, 2 to 288 d) in the gentamicin/citrate group and 35 d (range, 1 to 269 d) in the heparin group (Mann-Whitney \( U \) test; \( P = 0.296 \)). Overall, 3280 catheter-days were accrued in the gentamicin/citrate group and 2643 catheter-days in the heparin group.

Table 3 shows the incidence of the primary end point of CRI in the study. There were no bloodstream infections (BSI) and only one exit-site infection (ESI) in the gentamicin/citrate group compared with seven BSI and four ESI in the heparin group. The infection rate of 0.03 per 100 catheter-days in the gentamicin group was significantly lower than the infection rate of 0.42 per 100 catheter-days in the heparin group (\( P = 0.003 \)). The number needed to treat based on infection rate per 100 catheter-days equates to 6.5 catheters to prevent 1 infection. The pathogens responsible for CRI are shown in Table 4. The only CRI in the gentamicin/citrate group was an ESI caused by *Pseudomonas aeruginosa* that was sensitive to gentamicin on *in vitro* testing.

Mean cumulative infection-free catheter survival in the gentamicin/citrate group was 282 d (95% CI, 272 to 293 d), which is significantly higher than mean infection-free catheter survival in the heparin group of 181 d (95% CI, 124 to 237 d; log-rank statistic, 9.58; \( P = 0.002 \); Figure 2). The unadjusted relative risk (RR) for infection with gentamicin/citrate treatment was 0.08 (95% CI, 0.01 to 0.62; \( P = 0.016 \)). Figure 3 and Table 5 show the Cox regression model for adjusted infection-free catheter survival and the RR for the study end point, respectively. Hemoglobin and serum albumin at entry were intercorrelated (Pearson’s \( r = 0.32; P = 0.001 \)). Stepwise Cox regression analysis indicated that hemoglobin at entry was the stronger predictor of infection-free catheter survival (regression coefficient B, 0.056; standard error, 0.02; \( P = 0.005 \)) and was therefore selected as the variable entered in the multivariate regression model. Cumulative infection-free catheter survival in the gentamicin/citrate group remained significantly higher than in the heparin group after adjustment for gender, Australian aboriginal racial origin, hemoglobin at entry, diabetes mellitus, and catheter malfunction (RR, 0.10; 95% CI, 0.01 to 0.92; \( P = 0.042 \); Table 5). Similarly, adjustment for age, serum ferritin, warfarin use, presence of other immunosuppressive conditions, and jugular or subclavian positioning of the tunneled catheter had no significant effect on the catheter survival benefit imparted by gentamicin/citrate use.

Four of the total 83 patients in the study complained of intermittent nonspecific dizziness without vertigo, deafness, or ataxia. All four had been randomized to receive gentamicin and citrate catheter-restricted filling. Symptoms resolved in two of these patients while they were still receiving the trial drug; in the third patient, symptoms resolved on ceasing study participation. The fourth patient continues to complain of intermittent dizziness and is known to have extensive bony myeloma deposits, including in the petrous temporal bone. There were no other adverse events reported. Of the ten patients who had gentamicin levels measured, the median level was 2.8 mg/L (range, 0.6 to 3.5 mg/L) in the five randomized to gentamicin and <0.2 mg/L (range, <0.2 to 0.2 mg/L) in the five randomized to heparin (\( P = 0.008 \); Mann-Whitney \( U \) test).

**Discussion**

This is the first randomized controlled trial to demonstrate the efficacy of gentamicin and citrate catheter-restricted filling
than therapy (8). Moreover, there were more gram-negative BSI at least 2000-fold that required for systemic antistaphylococcal treatment, and gentamicin obtained within the catheter lumen. Although gentamicin is not a recognized first-line antistaphylococcal agent, concentrations of citrate on both catheter malfunction and CRI. Nevertheless, there were seven BSI in the heparin group with no BSI in the gentamicin group. Excluding ESI, Kaplan-Meier survival analysis still shows significantly improved BSI-free catheter survival in the gentamicin group compared with the heparin group (log-rank, 7.88; \( P = 0.005 \)).

This study also showed a trend to an increased rate of catheter malfunction in the group randomized to heparin. Although catheter malfunction and consequent increased catheter manipulation may impart a greater risk for CRI (1,5), our Cox regression model showed that use of gentamicin/citrate was still associated with a significantly increased infection-free catheter survival independent of catheter malfunction (RR, 0.10; \( P = 0.042 \)). Furthermore, a study assessing the efficacy of mini-dose warfarin for the prevention of catheter malfunction showed no correlation between rate of urokinase dosing and CRI (20). Our study was not designed to compare the efficacy of heparin and citrate in preventing catheter malfunction, and we cannot rule out beneficial effects of higher concentrations of citrate on both catheter malfunction and CRI.

Hemoglobin at entry was significantly lower in the gentamicin/citrate group and while iron overload is a risk factor for in the prevention of tunneled CRI. In this study, CRI rate in the heparin group of 0.42 per 100 catheter-days is comparable to other published rates (3), and prophylaxis with gentamicin and citrate resulted in a 90% RR reduction in the CRI rate (0.03 per 100 catheter-days). The catheter malfunction incidence between the gentamicin/citrate group and the heparin group was not significantly different confirming, that citrate provides adequate anticoagulation for the interdialytic period (7,15,16).

Catheter-restricted filling with gentamicin and citrate is hypothesized to prevent CRI by inhibiting colonization of the catheter hub (2). The efficacy of heparin and citrate in preventing CRI, ESI and BSI are different entities and probably have different etiologies (2). The aim of our study was to examine the effect of gentamicin treatment on all CRI, as would be relevant to daily clinical use. However, the incidence of ESI and BSI has also been reported separately in Table 3; not unexpectedly, the only CRI in the gentamicin-treated group was an ESI, which on pathophysiologic bases, should not be prevented by an intraluminal antibiotic. Nevertheless, there appears to be some reduction in ESI (four ESI in heparin versus one ESI in gentamicin); this is probably consistent with the gentamicin levels obtained, which suggest systemic exposure to the antibiotic. The ESI event rate is too low to be analyzed as a separate primary endpoint. After exclusion of ESI cases, there were seven BSI in the heparin group with no BSI in the gentamicin group. Excluding ESI, Kaplan-Meier survival analysis still shows significantly improved BSI-free catheter survival in the gentamicin group compared with the heparin group (log-rank, 7.88; \( P = 0.005 \)).

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infection (1), serum ferritin was not different between the 2 study groups. Thus it is unlikely that the higher hemoglobin is a marker of increased iron load, thereby imparting a greater risk for infection, in the heparin group. Furthermore a hemoglobin difference of less than 10 g/L between groups has uncertain clinical significance (21) and after adjustment for hemoglobin at entry, gentamicin/citrate prophylaxis was still associated with significantly increased infection-free catheter survival (RR, 0.10; \( P = 0.042 \)).

The adjusted RR for CRI with gentamicin/citrate treatment was 0.10 (95% CI, 0.01 to 0.92; \( P = 0.042 \)). The lower statistical significance and wide CI suggest reduced precision of the estimated risk reduction. This is reflective of the overall low event rate observed in the study compared with the control event rate of 0.42 per 100 catheter-days, a sample size of 53 per group would have 80% power to detect a minimum effect size of 60%, and not 30%, with \( \alpha = 0.05 \). The statistically significant effect size seen in this study was in the order of 90%. Sample size calculations for subsequent studies in this area should include the lower estimate of 0.42 events per 100 catheter-days in the control arm to circumvent these methodologic concerns.

Figure 2. Kaplan-Meier cumulative infection-free catheter survival comparing gentamicin and citrate (solid line) versus heparin (dashed line).

Table 3. Incidence of tunneled catheter-related infections (CRI)

<table>
<thead>
<tr>
<th></th>
<th>Gentamicin/Citrate</th>
<th>Heparin</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CRI (n)</td>
<td>1</td>
<td>11</td>
<td>0.003</td>
</tr>
<tr>
<td>Infections per 100 catheter-days</td>
<td>0.03</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>Exit site infection (n)</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Definite blood stream infection (n)</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Probable blood stream infection (n)</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Possible blood stream infection (n)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Censored end points (n)</td>
<td>52</td>
<td>44</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Pathogens responsible for tunneled catheter-related infections

Blood stream infections (n = 7, all randomized to heparin)
- *Enterobacter aerogenes*
- *Proteus mirabilis* and *Staphylococcus epidermidis*
- *Klebsiella species* and *Staphylococcus epidermidis*
- *Enterococcus faecalis* and *Staphylococcus epidermidis*
- *Acinetobacter species* and *Staphylococcus epidermidis*
- *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus*
- *Enterococcus faecalis* and *Enterobacter aerogenes*

Exit-site infections (n = 1 randomized to gentamicin/citrate; n = 4 randomized to heparin)
- *Pseudomonas aeruginosa* (n = 1 on gentamicin/citrate; n = 1 on heparin)
- *Candida* species (n = 1 on heparin)
- *Staphylococcus aureus* (n = 2 on heparin)

catheters and recent sepsis, prevent confounding of the etiology of infective episodes and would contribute to a lower control event rate. With a control event rate of 0.42 per 100 catheter-days, a sample size of 53 per group would have 80% power to detect a minimum effect size of 60%, and not 30%, with \( \alpha = 0.05 \). The statistically significant effect size seen in this study was in the order of 90%. Sample size calculations for subsequent studies in this area should include the lower estimate of 0.42 events per 100 catheter-days in the control arm to circumvent these methodologic concerns.

The gentamicin concentrations obtained in the small number of patients sampled in our study, along with the reduction in CRI in the gentamicin/citrate group, suggest a low-grade systemic exposure to gentamicin. Our results differ significantly from a previous study that showed median gentamicin concentrations of 0.5 mg/L (range, <0.3 to 1.4 mg/L) (10). In our study, the maximum gentamicin dose per catheter, based on the largest catheter lumen volumes used, did not exceed 100 mg per dialysis; the solution should theoretically remain within the catheter lumen. Nevertheless, the detectable gentamicin concentrations imply diffusion of small amounts of gentamicin.
and/or that volumes of locking solution used may have occasionally exceeded the catheter lumen volume plus 0.2 ml. Although the median catheter use of 40 d in the gentamicin/citrate group is relatively short, gentamicin levels still rise concerns regarding chronic systemic aminoglycoside exposure. Longer periods of catheter use in conjunction with gentamicin/citrate locking may be associated with significant risks of loss of residual renal function, ototoxicity, and emergence of bacterial resistance.

Evidence for the efficacy of doses of gentamicin as low as 2.3 mg/ml has emerged since our study started (9) and we therefore plan to study lower doses of gentamicin in CRI prevention. Higher doses of citrate (3 to 15%) in combination with antimicrobials should be studied given the anticoagulant and antimicrobial properties of citrate. Although citrate concentrations of 3.13% and less have demonstrated safety (22), further studies employing higher citrate concentrations should monitor ionized calcium levels and clotting times for systemic effects of citrate. Alternative antibiotics such as vancomycin are not ideal because of the potential for emergence of vancomycin-resistant organisms (5), and much higher citrate concentrations of 46.7% can potentially result in life-threatening depletion of calcium (22). Taurolidine, a taurine-based antiseptic, together with citrate as a catheter locking solution, is reported to have an infection rate of 0.03 per 100 catheter-days in one uncontrolled study (22) and warrants testing in a controlled study. Undoubtedly, the safest and most efficacious method of avoiding CRI is to endeavor to provide our patients with a primary arteriovenous fistula in a timely manner that minimizes catheter use.

In conclusion, catheter-restricted filling with gentamicin and citrate appears to be a highly effective strategy for the reduction of morbidity, and potentially mortality and costs, associated with CRI. The implications of our study extend beyond renal units, as tunneled catheters are now widely used in other specialties. Concerns about chronic aminoglycoside exposure need to be addressed before this technique is adopted. In view of recently available information regarding the efficacy of lower doses of gentamicin (9,19) and alternative agents such as taurolidine (22), we propose that additional randomized controlled trials should explore these options with detailed documentation of safety parameters.

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References


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