Locking of tunneled hemodialysis catheters with gentamicin and heparin

CHRISTOPHER W. MCINTYRE, LISA J. HULME, MAARTEN TAAL, and RICHARD J. FLUCK

Department of Renal Medicine, Derby City General Hospital, Derby, United Kingdom

Introduction. Catheter-related infection (CRI) is a major cause of morbidity and mortality in patients receiving hemodialysis. Antibiotic locking of these catheters has been shown to increase both the success of systemic antibiotic treatment in line sepsis, and to reduce the incidence of sepsis. We have studied the use of gentamicin locking of catheters (in combination with standard heparin rather than previously reported citrate) to reduce CRI rates. Furthermore, we have investigated the effects of this strategy on epoetin requirements and vascular access function.

Methods. Fifty patients were studied. Patients were randomized to catheter-restricted filling with either standard heparin (5000 IU/mL) alone, or gentamicin and heparin (5 mg/mL). Epoetin requirements and hemoglobin response were monitored over the study period.

Results. The gentamicin-locked group suffered only one infective episode (0.3/1000 catheter days) compared to 10 episodes in six patients in the heparin alone group (4/1000 catheter days, \(P = 0.02\)). The isolated organisms were equally split between Staphylococcal species and coliforms. There were no statistically significant differences in delivered dialysis dose (Kt/V) or \(Q_A\) between the two groups. Use of antibiotic locking was associated with both a higher mean hemoglobin (10.1 ± 0.14 g/dL vs. 9.2 ± 0.17 g/dL in the heparin group, \(P = 0.003\)) and a lower mean epoetin dose (9000 ± 734 IU/week vs. 10790 ± 615 IU/week in the heparin group, \(P = 0.04\)).

Conclusion. The practice of locking newly inserted tunneled central venous catheters with gentamicin and heparin is an effective strategy to reduce line sepsis rates, and is associated with beneficial effects on epoetin requirements.

Because of the failure to have formed definitive access before commencing hemodialysis, or subsequent failure of established vascular access tunneled and cuffed, central venous catheters are being increasingly relied upon for the provision of vascular access. This is either until adequate permanent provision can be made [1], or permanently in selected groups of patients [2].

The prevention and management of bacteremia remains a significant clinical challenge in the management of this form of vascular access. The rates of catheter-related infection (CRI) associated with this sort of catheter have been reported to be between 0.2 [3] and 3.9 episodes [4] per 1000 catheter days. The organisms responsible have been reported, in one representative study, to be predominantly gram-positive (52.5%), gram-negative rods (26.7%), and polymicrobial in a further 20.9% [5]. When bacteremia does result, adequate treatment with systemic antibiotics alone is seen in only 25% to 32% of patients [4]. The use of central venous catheters is also associated with a reduction in responsiveness to epoetin, presumably as a consequence of an inflammatory response brought about by both overt CRI and occult colonization [6].

There have been a number of strategies utilized to reduce the incidence of bacteremia when dealing with long-term central venous catheters. These include the use of universal precautions, antibiotic impregnated catheters [7], silver impregnation of the cuff [8], and avoiding the use of the femoral vein [9].

Interest has also focused on the use of antimicrobial locking of the catheters in between each hemodialysis session. The possible utility of such an approach is reinforced by the observation that bacteremia is often associated with luminal infection rather than migration of organisms around the catheter [4]. Concerns have been raised about stability of the commonly used antibiotics with heparin, possibly resulting in a concentration insufficient to be active as an antimicrobial, and potentially reducing long-term catheter function and patency rates (due to precipitation). Gentamicin has been studied combined with sodium citrate (with its own intrinsic antibacterial action) as an alternative catheter restricted anticoagulant in an attempt to negate this theoretic problem [10]. Its use has been shown to reduce line sepsis rates in a prospective controlled study of new line insertions [11] and increasing clearance rates when combined with systemic antibiotics in the treatment of CRI.

Key words: hemodialysis, gentamicin locking, catheter-related infection.
Gentamicin (at a dose of 5 mg/mL), however, does appear sufficiently stable when combined with heparin to maintain a concentration sufficient to decrease the incidence of infection in central venous catheters, with an in vitro reduction in intralumenal concentration of only 8% [12]. Heparin is both more familiar and readily available than citrate in most dialysis units.

The aims of this study were to determine whether a strategy based on locking with gentamicin and heparin could reduce the rate of CRI without undesirable effects on vascular access function. Furthermore, we aimed to study the impact of such a strategy on anemia and epoetin requirements.

METHODS

Study design and patients

The investigatory protocol was approved by the Local Regional Ethics Committee, and all patients gave explicit written consent. The study was undertaken within a single hemodialysis (HD) facility based at Derby City General Hospital. Fifty patients were recruited at the time of insertion of newly tunneled central venous HD catheters over a one-year period between March 2002 and April 2003. Patients were randomly allocated to either the standard catheter restricted solution of heparin (5000 IU/mL in saline), and antibiotic locking with gentamicin in conjunction with heparin (gentamicin 5mg/mL, heparin 5000 IU/mL) before insertion of catheter (replicating concentration associated with heparin stability). The study was block randomized with sealed envelopes for patient allocation, with 25 patients being allocated to each group. Because of the requirement to make up the gentamicin-locking solution before instillation (as there was lack of suitable stability data), it was not possible to blind the study. Patients were excluded if the catheter was an exchange reinsertion, or insertion at a separate site (with previous catheter still in situ). Patients with recent infection were excluded, as well as those on immunosuppressant medications. All patients were required to have had no evidence of CRI, having been antibiotic free for at least 28 days before catheter insertion. A single catheter type was used (Kimal KSC split Ash, Kimal, Ltd., Ubridge, England), and was inserted under fluoroscopic control into either jugular or subclavian veins by an experienced nephrologist. Femoral devices were excluded from the study. Patient characteristics in both groups at initiation of study are summarized in Table 1.

CRI was treated with an empirical regimen based on vancomycin and gentamicin. This was modified at day three in light of blood culture data. Catheters were only exchanged (or removed) if sepsis persisted despite the initiation of antibiotic therapy. This was defined as failure to render the patient apyrexial within 48 hours of initiating therapy. Patients were allowed to remain in the study after an episode of CRI. However, further CRI episodes were only classified as new infections if they occurred at least two weeks after cessation of initial successful antibiotic therapy.

All patients remained with their originally assigned locking solution throughout the study unless the patient was removed from the study due to catheter removal (failure or removal due to an adequate arteriovenous fistula being available for use). Exit sites were dressed with oxygen permeable dressings (Op-site, Smith and Nephew, Hull, England). Additional antimicrobials such as topical muciprocin were not used. Each exit site was kept under surveillance by nursing staff at each HD treatment session. There were no changes in any practices relating to dressings or handling of bloodlines over the study period. Variable infusion rate of heparin was used for anticoagulation, individualized to patient requirements. Catheter malfunction was defined as a consistent failure to provide a blood flow >200 mL/min.

Catheter function was followed-up using central automatic downloading HD-related data from dialysis monitors to a central server into patient specific files. Treatments were monitored for blood flow rate and delivered Kt/V using on-line measurement of Kt/V ( Diascan, Hospal Dasco, Emilia Romagna, Italy). This was further supplemented by monthly measurement of Kt/V based on blood urea reduction. Access function was followed by line failure, urokinase use, and the measurement of Qs utilizing a nonoperator-dependent technique based on dual measurement of ionic dialysance and flow reversal (using specific crossed line extensions and clamps to avoid the need to disconnect blood lines) (Hospal Dasco) [13]. Random predialysis gentamicin levels were taken to ensure that there was no evidence of systemic exposure to long-term aminoglycoside. All patients had gentamicin levels checked at least twice over the study period. Blood was sampled from the catheter immediately before connection to dialysis line. Formal hearing tests were not performed, but the patients were subjected to direct clinical inquiry by staff administering the study of any evidence of aminoglycoside ototoxicity. Patients’ hemoglobin and epoetin requirements were monitored over the study period (Eprex, Ortho Biotec administered iv on HD).

When CRI was clinically suspected cultures were taken from both peripheral blood and catheter. If the catheter needed to be removed, both the tip and cuff were sent to microbiology for culture. CRI was diagnosed using the

| Table 1. Patient characteristics in the two study groups at inclusion |
|-------------------------|-------------------------|-----------------------|
|                         | Gentamicin/heparin locked | Heparin locked |
| Age years              | 63.6 ± 2.8               | 57.8 ± 3.2        |
| (26–80)                | (20–79)                 |
| Sex M:F                | 18:7                    | 14:11               |
| Diabetic patients %    | 29%                     | 23%                 |
| Serum ferritin µg/L    | 245 ± 52.2              | 298 ± 36.4         |
| Hemoglobin g/dL        | 9.64 ± 0.31             | 9.56 ± 0.28        |
| Epoetin dose IU/wk     | 9756 ± 521              | 9540 ± 471         |
|                       | p value 0.22             | 0.45                |
criteria as defined by the Centers for Disease Control (CDC). This required at least one of the following: (1) clinical exit site infection with evidence of inflammation within 2 cm of the exit site; (2) definite bloodstream infection, with isolation of a plausibly significant organism from catheter and peripheral blood, with no other apparent source of infection; (3) probable bloodstream infection with defervescence after catheter removal in patients where both blood and catheter tip infection is not confirmed in a symptomatic patient with no other apparent sources of infection; and (4) possible bloodstream infection in a symptomatic patient with defervescence after catheter removal, but who remains culture negative.

**Statistical analysis**

All analyses were performed on an intention-to-treat basis. Unpaired data were analyzed using the Mann-Whitney U test. Cumulative infection-free catheter survival was assessed by the use of Kaplan-Meier method and calculated hazard ratio. All data were analyzed using GraphPad Prism version 3.00 for Windows (GraphPad Software, San Diego, CA, USA; www.graphpad.com). Where not otherwise stated, data are expressed as mean ± SEM (range).

## RESULTS

There was no statistically significant difference in mean number of catheter days per patient in either group [130.1 ± 16.4 (13–258) and 103 ± 14.6 (14–251) days for the gentamicin-locked group and heparin-locked groups, respectively]. Fifty patients were studied; 48% of the catheters were inserted to start HD in new patients, and 52% were inserted because of existing vascular access failure pending further surgical intervention. Patients who had a history of line sepsis with previous catheters in the previous six months before entry into the study were equally distributed to both of the study groups (five patients in the gentamicin-locked arm and four patients in the heparin alone group).

All episodes of CRI were confirmed on paired culture of blood from peripheral and line sources from pyrexial patients. No episodes were associated with exit site infection alone. There were 10 episodes of CRI in six patients in the heparin alone treated group. This compared with a single episode in the gentamicin-locked group. Mean number of episodes per patient was therefore 0.4 ± 0.16 (0–3) and 0.04 ± 0.04 (0–1) for heparin-locked group and gentamicin-locked group, respectively ($P = 0.03$). If only patients who suffered one episode of CRI are analyzed, the mean number of CRI episodes is 0.29 ± 0.1 for the heparin-treated group ($P = 0.06$). Total number of catheter days accrued in the gentamicin-locked group was 3252, and 2470 in the heparin alone group. This equated to a CRI rate of 0.3/1000 catheter days and 4/1000 catheter days for gentamicin-locked group and heparin alone group, respectively. The mean time to first episode of CRI was also significantly longer in the gentamicin-treated group [130 ± 16.4 (13–258) days] as compared with the heparin alone group [85.3 ± 14.2 (14–251) days, $P = 0.03$]. This difference remained significantly different if patients who suffered multiple episodes were excluded [gentamicin-locked group 130 ± 16.4 (13–258) days] as compared with the heparin alone group [74 ± 13.1 (14–244) days, $P = 0.02$]. In patients who experienced multiple episodes of CRI during the study, the minimum interval of being sepsis free off antibiotic therapy between infections was 27 days (CRI data are summarized in Table 2). On retrospective review, 11 of the 25 patients in the gentamicin-locked group had had a catheter in place in the previous six months prior to recruitment into the study. This was in comparison to only 6 patients in the heparin only group. There were 10 episodes of CRI in five of the patients during a total of 1257 catheter days (rate 7.9/1000 catheter days). There were no documented exit site infections. During the study the 10 episodes of CRI had resulted from three *Staphylococcus aureus*, two *Staphylococcus epidermis*, one MRSA, three *Escherichia coli*, and one *Klebsiella* isolate. In the four patients who experienced two episodes of CRI over the study period, all of the second episodes of CRI were a different isolated organism from the first. This indicates that colonization was not a significant factor in these patients. Infection-free survival (to first CRI episode only) was significantly different in the two groups ($P = 0.05$, hazard ratio 0.16) (Fig. 1). The single CRI in the gentamicin-locked group was due to MRSA.

### Table 2. Summary of data pertaining to CRI during the study period

<table>
<thead>
<tr>
<th></th>
<th>Gentamicin/heparin locked</th>
<th>Heparin locked</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRI total</td>
<td>1</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Mean number of episodes/patient</td>
<td>0.04 ± 0.04</td>
<td>0.4 ± 0.16</td>
<td>0.03</td>
</tr>
<tr>
<td>CRI rate/1000 catheter days</td>
<td>0.3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Time to first CRI days</td>
<td>129.8 ± 16.4</td>
<td>85.3 ± 14.2</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Fig. 1. Kaplan-Meier cumulative infection-free catheter survival comparing gentamicin and heparin (solid line) to heparin alone (dashed line), $P = 0.05$. 
There were no significant differences in catheter function in either group. Delivered mean $K_t/V$ was 0.98 ± 0.05 (0.4–1.5) and 1.05 ± 0.05 (0.5–1.5), $P = 0.24$, for gentamicin-locked and heparin alone groups, respectively. Mean $Q_A$ over the study period was also not different in the two groups, 1484 ± 95.6 (954–2141) mL/min and 1373 ± 94.5 (1054–2091) mL/min, $P = 0.62$, for gentamicin-locked group and heparin, respectively. There was no difference in the amount of urokinase infusions or locks required to maintain patency in either group. Only two catheters in the heparin group, and one in the gentamicin-locked group, were removed due to access failure. No catheters were removed due to failure of initial antibiotic therapy to treat CRI.

Mean hemoglobin (mean derived from measurements taken over the entire study period) was lower in the heparin-treated group at 9.24 ± 0.17 (5.6–12.6) g/dL compared with a mean hemoglobin of 10.05 ± 0.14 (6.2–13.6) g/dL in the gentamicin-locked group ($P = 0.003$) (Fig. 2). This was despite the mean epoetin dose (mean derived from measurements taken over the entire study period) being higher at 10,790 ± 615 (3000–20,000) IU/week in the heparin group compared to 9000 ± 735 (2000–20,000) IU/week in the gentamicin-locked group ($P = 0.04$) (Fig. 3). These were still significantly different when adjusted for body weight, 163.2 ± 11.4 IU/kg/week in the heparin group compared to 126.7 ± 10.2 IU/kg/week in the gentamicin-locked group ($P = 0.03$). Any patients who received a transfusion were excluded from this section of the analysis (only two patients in each group received blood transfusion). When patients who had experienced CRI were excluded the trend toward higher hemoglobin concentration (mean Hb 9.8 ± 0.3 vs. 9.23 ± 0.04 in the heparin alone–treated group) and lower epoetin requirements (8780 ± 458 U/week vs. 9560 ± 632 U/week in the heparin-treated group) in the gentamicin group persisted but did not reach statistical significance ($P = 0.06$). There was no difference in the mean ferritin (298 ± 35.1 and 312 ± 32.7 µg/L for gentamicin-locked and heparin patients, respectively, $P = 0.34$), parathyroid hormone (PTH) (214 ± 22.8 and 256 ± 31.5 nmol/L for gentamicin-locked and heparin patients, respectively, $P = 0.25$), or $K_t/V$ between the two groups over the study period. There was a similar use of statins in the two groups (32% and 25% in the heparin alone and gentamicin-locked groups, respectively).

All random gentamicin levels were <0.2 mg/L, and no patients complained of any symptoms that might be attributable to aminoglycoside toxicity. No gentamicin/heparin solutions were discarded due to obvious turbidity after constitution. The total gentamicin costs per year/patient were around £100.

**DISCUSSION**

This is the first study to demonstrate that a low-cost strategy of combining gentamicin with heparin for the catheter-restricted filling of HD catheters is capable of reducing CRI incidence. Furthermore, such a strategy is also associated with improved hemoglobin concentrations and reduced epoetin requirements.

The incidence of CRI in the control group was in keeping both with unit specific historical data and published studies [11, 14]. The reduction in CRI rate was almost identical to that reported for the combination of gentamicin and bacteriociodal/anticoagulant citrate [11]. There was almost complete abolition of CRI in the gentamicin-treated group. This would support in vitro data [12] that gentamicin does remain biologically active, without significant precipitation when combined with heparin. Citrate is less desirable to use instead of heparin due to the increased treatment costs, increased difficulty in ensuring adequate and reliable anticoagulation of the extracorporeal circuit, and the possibility (at higher doses) of chelation of calcium. The issues of systemic exposure obviously are not an issue if the use of citrate is restricted to catheter volume alone. The use of high concentration...
gentamicin allows it to be bacteriocidal to a wide range of likely causative organisms (gram-positive and gram-negative). The causative organisms were also similar in distribution to the study by Dogra et al (despite mupirocin not being in use). The bacteriologic profile was also similar to those identified historically within our unit. The possibility of this approach encouraging the development of gentamicin-resistant organisms cannot be excluded from these data. However, the high concentration of gentamicin used and apparent lack of systemic exposure make this less likely. The risk needs also to be offset by the propensity of multiple exposures to antibiotics for the treatment of CRI, which this strategy markedly reduces.

Unlike the previous study of gentamicin locking, we found no adverse effects attributable to gentamicin toxicity. There was no measurable systemic exposure to gentamicin in any of the patients studied. This would imply no splannation or excessive locking of the catheters. However, the gentamicin levels were reported as <0.2 mg/L, and the authors cannot exclude the possibility of long-term exposure to such low levels of aminoglycoside. Although this did not appear to be associated with any clinical adverse effects, hearing was not formally tested, and it would be wise to review this practice in the light of long-term exposure make this less likely. The risk needs also to be offset by the propensity of multiple exposures to antibiotics for the treatment of CRI, which this strategy markedly reduces.

This study demonstrated an association between the locking of catheters with gentamicin and improved hemoglobin concentrations with reduced epoetin requirements. This may be as a result of the reduction in recognized CRI, or there might be an effect of reduction in covert bacterial colonization. This study only demonstrates an association of gentamicin locking of catheters with higher hemoglobin concentrations and lower epoetin doses. The use of iron therapy and PTH were not statistically significantly different between the two groups, but the study did not have sufficient patients within it to establish an effect of differences in the factors known to influence epoetin responsiveness in the patients who had experienced CRI. Likewise, there was difference in statin usage given the potential impact of this on epoetin responsiveness [15]. There were no differences in the level of small solute removal in the two groups. This makes differences in epoetin response between the two groups unlikely to be due to dialysis issues [16, 17].

CONCLUSION

The practice of catheter-restricted filling of tunneled HD catheters with gentamicin and heparin markedly reduces the incidence of CRI, with no obvious adverse consequences in terms of aminoglycoside exposure or vascular access function. This strategy appears to have further beneficial implications on treatment costs due to a reduction in epoetin requirements.

Reprint requests to Dr. C.W. McIntyre, Department of Renal Medicine, Derby City General Hospital, Uttoxeter Road, Derby, DE22 3NE, UK. E-mail: Chris.McIntyre@sdah-tr.trent.nhs.uk

REFERENCES