A prospective observational study of catheter-related bacteraemia and thrombosis in a haemodialysis cohort: univariate and multivariate analyses of risk association

Peter Thomson¹, Catherine Stirling¹, Jamie Traynor², Scott Morris¹ and Robert Mactier¹

¹Glasgow Royal Infirmary, Renal Unit and ²Monklands Hospital, Renal Unit

Correspondence and offprint requests to: Peter Thomson; E-mail: peter.thomson@nhs.net, pcthomson@yahoo.com

Abstract

Background. Central venous catheterization is a fundamental component in delivering haemodialysis yet is associated with significantly higher complication rates than other methods of vascular access. In this study, we report results of univariate and multivariate analyses designed to identify and quantify independent risk association for catheterization type, clinical variables and laboratory variables with regard to the development of catheter-related bacteraemia (CRB) and catheter failure due to poor haemodialysis flow.

Methods. A 2-year prospective study of all incident haemodialysis vascular access catheter insertions was conducted. Laboratory and clinical variables were recorded at catheter insertion, and the clinical course was followed up to the point of catheter removal. CRB and catheter failure due to poor flow were recorded as outcome events. Univariate and multivariate analyses were used to test for association between clinical and laboratory variables and outcome.

Results. Forty-four thousand five hundred seventy-six catheter days were accumulated over the study period. Multivariate analysis demonstrated an independent association between non-tunnelled catheterization procedures and adverse outcomes compared with tunnelled central venous catheter insertions. Elevated modified Charlson comorbidity score was independently associated with the development of CRBc. Elevated C-reactive protein and comorbidity score was independently associated with the venous catheter insertions. Elevated modified Charlson and adverse outcomes compared with tunnelled central venous catheterization where possible and in those dependent on central venous catheters, limiting their complication rates [1,8].

Conclusions. The data demonstrate that tunnelled central venous catheter insertions have an association with lower complication rates than non-tunnelled central venous catheter insertions that is independent of whether patients have acute or chronic renal failure, or high levels of comorbidity. The degree to which this adverse complication profile reflects the simple consequences of creating a fixed conduit for organisms between the external environment and the bloodstream is uncertain. Alternatively, whether these complications are a result of a higher burden of comorbidity seen in selected groups of complex patients is yet to be conclusively demonstrated. Regardless of this, there is now a strong emphasis on limiting the use of central venous catheterization where possible and in those dependent on central venous catheters, limiting their complication rates [1,8].

In this report, we describe rates of bacteraemia and thrombosis experienced with all types of vascular access catheter used in an incident renal replacement therapy (RRT) cohort over a 2-year period of prospective observation. We report results of univariate and multivariate analyses designed to identify and quantify independent risk association with clinical variables, laboratory variables and measures of comorbidity, with regard to each of these outcomes. Finally, we discuss how our observed pattern of catheter complications relates to those described in current haemodialysis vascular access guidelines.

Subjects and methods

We performed a prospective analysis of all incident vascular access haemodialysis catheter insertions within the Glasgow Royal Infirmary Renal Unit over the period starting 05 August 2005 and ending 05 August 2007. Haemodialysis catheter insertion procedures undertaken in the hospital’s intensive care unit were not included. The date of each catheter insertion was recorded along with the type of catheter inserted, the anas...
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tomical location of catheter insertion and whether the catheter insertion was conducted as a catheter exchange procedure over a guidewire. Clinical case notes and our unitary electronic patient record were used to obtain details of a number of clinical and laboratory variables that were routinely collected as part of our standard care, on the date of catheter insertion. Tunnelled GamCath® (Gambro, Sweden) 11Fr double lumen polyurethane haemodialysis catheters were used with 150- or 200-mm catheters used for right- or left-sided internal jugular cannulation, respectively. Standard unitary practice required all femoral non-tunnelled catheterizations to be conducted with 200-mm catheters. Tunnelled Ash Splirit® (Medcomp, USA) 14Fr double lumen polyurethane haemodialysis catheters were used with 280- or 320-mm catheters used for right- or left-sided cannulation, respectively.

Clinical variables including age, sex and concurrent antibiotic, anticoagulant, statin and immunosuppressive therapy were recorded. A steroid dose of ≥10 mg prednisolone and/or an active prescription of a recognized cytotoxic were regarded as having a clinically significant level of immunosuppression. Modified Charlson comorbidity scores [9–11], a diagnosis of diabetes, cause and duration of renal failure, body mass index, systolic blood pressure, diastolic blood pressure and haemodialysis blood flow on dialysis immediately following catheter insertion were also obtained. Laboratory variables including haemoglobin, platelet count, neutrophil count, lymphocyte count, C-reactive protein (CRP), albumin, adjusted calcium, phosphate and urea reduction ratio prior to catheter insertion were recorded.

Outcomes

Patients were prospectively followed up to the point of catheter removal or the cessation of the study. During this period, we assessed two main outcomes, catheter-related bacteremia (CRB) and catheter failure with removal due to poor haemodialysis blood flow. All patients who died or were discharged to another renal unit with a central venous catheter in situ were assigned a census date corresponding to the date of discharge from the renal unit. Patients who remained on haemodialysis at the end of the observation period with a central venous catheter in situ had a census date of 5 August 2007 recorded.

CRB events were sought through analysis of all positive blood culture results from the renal patient population as reported by the bacteriology laboratory in conjunction with analysis of the patient's clinical notes and electronic patient record. CRB was defined as the presence of positive blood cultures associated with a raised systemic inflammatory response (e.g. pyrexia, raised CRP, raised white-cell count) and the absence of clinical or radiological signs of a non-catheter-related source of infection. Sub-clinical bacteremia was not evaluated. This approach is in keeping with the definition of CRB commonly reported in the literature and consistent with that used in routine clinical practice. Where patients were found to have developed CRB, the date of the first positive blood culture result was entered as the event date and the time to event subsequently calculated. This was purely a time to first CRB analysis i.e. further episodes of CRB in a patient were not considered event-related. In our analysis, independent variables for entry into the models were selected according to their P-values on univariate testing. On multivariate analysis, all reported P-values ≤0.05 were regarded as significant.

Results

Over the 2-year period, a total of 365 patients underwent 823 central venous catheter insertions. Patients were of median age 66.4 years (range 19.8–87.1 years) with 203/365 (55.6%) male. One hundred and thirty of 365 (35.6%) patients were found to have acute renal failure (ARF) defined as a recovery of renal function with cessation of dialysis within 90 days. Sixty of 365 (16.4%) patients underwent catheter insertion in the context of acute-on-chronic renal failure (A/CRF) whilst 175/365 (47.9%) patients underwent catheter insertion in the context of established chronic renal failure (CRF). All patients received intermittent haemodialysis therapy. No patients had more than one central venous catheter in situ at any one time.

In total, 301/823 (36.6%) of procedures were insertions of TCVCs whilst 522/823 (63.4%) were insertions of NTCVC. Of the NTCVC insertions, 373/522 (71.5%) were inserted as a recovery of renal function with cessation of dialysis after 90 days. Sixty of 365 (16.4%) patients underwent catheter insertion in the context of acute-on-chronic renal failure (A/CRF) whilst 175/365 (47.9%) patients underwent catheter insertion in the context of established chronic renal failure (CRF). All patients received intermittent haemodialysis therapy. No patients had more than one central venous catheter in situ at any one time.

In total, 301/823 (36.6%) of procedures were insertions of TCVCs whilst 522/823 (63.4%) were insertions of NTCVC. Of the NTCVC insertions, 373/522 (71.5%) were inserted into the internal jugular veins with 149/522 (28.5%) inserted into the femoral veins. Seventy-three of 522 (14.0%) of NTCVC insertions were conducted as catheter exchange procedures over a guidewire. Clinical and laboratory variables recorded at the point of catheter insertion are detailed in Table 1.

A total of 44 576 catheter days were accumulated over the study period during which time there were 115 cases of CRB (2.57 per 1000 catheter days) and 131 cases of catheter removal due to poor haemodialysis blood flow (2.94 per 1000 catheter days).
Catheter days 13 (6, 59) 92 (1, 692) 9 (0, 200) 5 (0, 34) 7 (0, 97) 6 (0, 32)
Modified Charlson score 2 (0, 3) 2 (0, 13) 2 (0, 8) 2 (0, 9) 1 (0, 4) 1 (0, 5)
Antibiotic (%) 523/823 (63.5%) 294/301 (97.7%) 128/313 (40.9%) 62/136 (45.6%) 32/60 (53.3%) 7/13 (53.8%)
Immunosuppression (%) 86/823 (10.4%) 32/301 (10.6%) 35/313 (11.2%) 11/136 (8.1%) 7/60 (11.7%) 1/13 (7.7%)
Statin (%) 423/823 (51.4%) 183/301 (60.8%) 150/313 (47.9%) 61/136 (44.6%) 22/60 (36.7%) 7/13 (53.8%)
Diabetes (%) 320/823 (38.9%) 129/301 (42.9%) 116/313 (37.1%) 48/136 (28.9%) 22/60 (36.7%) 5/13 (38.5%)
CRF (%) 491/823 (59.7%) 260/301 (86.4%) 141 (45.0%) 66 (48.5%) 15 (25.0%) 9 (69.2%)
A/CRF (%) 118/823 (14.3%) 21 (7.0%) 63 (20.1%) 23 (16.9%) 10 (16.7%) 1 (7.7%)
ARF (%) 214/823 (26.0%) 20 (6.6%) 109 (34.8%) 47 (34.6%) 35 (58.3%) 3 (23.1%)
BMI (kg/m²) 27.4 27.2 (7.1) 27.6 (6.6) 26.6 (5.5) 30.0 (6.5) 28.2 (7.8)
CRB events
n Poor Flow events
n
Variable Cohort TCVC NTCVC IJug NTCVC Fem NTCVC IJug (G) NTCVC Fem (G)
Patients n = 823 n = 301 n = 136 n = 60 n = 13
CRB events n = 115 n = 25 n = 8 n = 8 n = 2
Poor Flow events n = 131 n = 40 n = 27 n = 12 n = 3
ARF (%) 214/823 (26.0%) 20 (6.6%) 109 (34.8%) 47 (34.6%) 35 (58.3%) 3 (23.1%)
A/CRF (%) 118/823 (14.3%) 21 (7.0%) 63 (20.1%) 23 (16.9%) 10 (16.7%) 1 (7.7%)
ARF (%) 214/823 (26.0%) 20 (6.6%) 109 (34.8%) 47 (34.6%) 35 (58.3%) 3 (23.1%)
BMI (kg/m²) 27.4 27.2 (7.1) 27.6 (6.6) 26.6 (5.5) 30.0 (6.5) 28.2 (7.8)
DBP (mmHg) 73.3 74 (16) 73 (16) 71 (17) 73 (18) 84 (12)
SBP (mmHg) 137 130 (28) 137 (27) 130 (28) 135 (28) 145 (20)
Phosphate (mmol/L) 1.76 1.64 (0.56) 1.83 (0.75) 1.95 (0.73) 1.67 (0.59) 1.93 (0.61)
Calcium (adjusted) (mmol/L) 2.35 2.42 (0.18) 2.31 (0.21) 2.32 (0.24) 2.26 (0.24) 2.38 (0.16)
Albumin (g/L) 28 (22, 32) 29 (13, 43) 26.5 (10, 45) 27 (12, 43) 25.5 (11, 38) 29 (11, 39)
C-reactive protein (mg/L) 42.5 (18, 100) 27 (1, 297) 53 (1, 487) 64 (2, 375) 91 (3, 282) 23 (11, 402)
Neutrophil count (×10⁹/L) 6.3 (4.4, 9.1) 5.1 (1.0, 26.6) 7.1 (0.8, 30.6) 7.1 (1.5, 31.7) 8.6 (3.9, 18.5) 5.9 (3.8, 11.1)

### Table 2. Univariate analysis of central venous catheter type with regard subsequent event rates for CRB and catheter removal due to poor haemodialysis flow (all statistical comparisons are made with reference to the event rate for the TCVC group)

<table>
<thead>
<tr>
<th>Variable</th>
<th>CRB (event/1000 days)</th>
<th>P-value</th>
<th>Poor flow (event/1000 days)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCVC</td>
<td>1.7694</td>
<td></td>
<td>0.9830</td>
<td></td>
</tr>
<tr>
<td>NTCVC IJug</td>
<td>6.300</td>
<td>&lt;0.001</td>
<td>12.3412</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NTCVC IJug (G)</td>
<td>9.7357</td>
<td>&lt;0.001</td>
<td>20.2020</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NTCVC Fem</td>
<td>13.468</td>
<td>&lt;0.001</td>
<td>37.5522</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NTCVC Fem (G)</td>
<td>21.5054</td>
<td>&lt;0.001</td>
<td>32.2581</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Univariate analysis of clinical and laboratory variables with regard to subsequent CRB and catheter removal due to poor haemodialysis flow. ‘TCVC’ = tunnelled central venous catheter. ‘NTCVC = non-tunnelled central venous catheter. ‘IJug’ = internal jugular vein insertion site. ‘Fem’ = femoral vein insertion site. ‘(G)’ = catheter exchange procedure conducted over a guidewire. ‘CRB = catheter-related bacteraemia. ‘ARF’ = acute renal failure. ‘A/C’ = acute-on-chronic renal failure. ‘CRF’ = chronic renal failure. ‘RRT’ = renal replacement therapy. ‘SBP’ = systolic blood pressure. ‘DBP’ = diastolic blood pressure. ‘BMI’ = body mass index.

### Bacteraemia

One hundred and fifteen cases of CRB occurred with 122 bacterial isolates identified on blood culture. Staphylococcal sub-species accounted for the majority of cases with 47/122 (38.5%) isolates of *Staphylococcus epidermidis*, 29/122 (23.8%) isolates of *Staphylococcus aureus* and 9/122 (7.4%) isolates of methicillin-resistant *S. aureus*. Gram-negative bacilli accounted for 19/122 (15.6%) isolates, other gram-positive cocci in 14/122 (11.5%) bacterial isolates and gram positive bacilli in 4/122 (3.3%) isolates.

Rates of CRB were 1.77 per 1000 catheter days in the TCVC group, 6.3 per 1000 catheter days in the internal jugular vein NTCVC group and 13.5 per 1000 catheter days in the femoral vein NTCVC group. Internal jugular and femoral NTCVCs exchanged over a guidewire demonstrated CRB rates of 9.7 and 21.5 per 1000 catheter days, respectively. Events occurred at median (range) of 54 (28–127) days in the TCVC group, 50 (5–18) days in the internal jugular NTCVC group, 4 (4–5) days in the internal jugular guidewire exchange group, 6 (1–8) days in the femoral NTCVC group and 8 days in the femoral guidewire exchange group.

Using the TCVC group as a reference for comparison, all types of NTCVC insertion procedure were significantly associated with CRB on univariate analysis (P < 0.001).
(Table 2). Other variables significantly associated with the subsequent development of CRB included higher haemodialysis blood flow (265 ml/min vs 250 ml/min, *P* = 0.002) and shorter durations of catheter lifespan (50 days vs 83 days, *P* < 0.001). This, however, reflects our unitary practice of removing catheters once a diagnosis of CRB has been made unless there is a strong clinical reason to try and salvage the catheter.

Trends towards a significant association with CRB on univariate testing included higher serum adjusted calcium levels (0.004), an elevated modified Charlson comorbidity score (*P* = 0.005), being on antibiotic at the time of catheter insertion (*P* = 0.008), a diagnosis of diabetes (*P* = 0.011) and a longer duration on RRT (*P* = 0.013). All other variables were not significantly associated with outcome on univariate analysis including duration on RRT prior to catheter insertion and whether patients were classified as suffering from acute or chronic renal failure. Despite this, separate sub-analyses were conducted looking specifically at those patient groups in an effort to avoid potential confounding.

When considering only those patients with ARF, univariate testing demonstrated catheter insertion site as being the only variable significantly associated with CRB (*P* < 0.001).

When considering only those patients with chronic renal failure, catheter insertion site (*P* < 0.001) was also the only variable significantly associated with outcome. Antibiotic use (*P* = 0.006), elevated modified Charlson score (*P* = 0.008), elevated serum calcium (*P* = 0.022) and elevated serum phosphate (*P* = 0.025) demonstrated trends towards association with CRB.

When considering the full cohort, multivariate analysis demonstrated hazard ratios (HR) for the development of CRB in patients dialysing with internal jugular NTVCVs of 2.9 [95% confidence interval (CI) 1.5–4.8, *P* < 0.001], femoral NTVCVs of 5.9 [95% CI 2.1–12.9, *P* < 0.001], 6.4 [95% CI 2.5–13.2, *P* < 0.001] for internal jugular NTVCVs exchanged over a guidewire and 9.8 [95% CI 2.0–37.6, *P* = 0.002] for femoral NTVCVs exchanged over a guidewire (Figure 1). There was also a significant independent association between an elevated modified Charlson comorbidity score with a HR of 1.1 [95% CI 1.0–1.2, *P* = 0.034]. All other variables failed to reach statistical significance on multivariate testing (Table 3).

When considering only those patients with ARF, internal jugular NTVC insertion [HR 8.1 (95% CI 2.2–29.3), *P* < 0.001], internal jugular NTVC catheter exchange [HR 25.5 (95% CI 5.5–117.4), *P* < 0.001] and femoral NTVC insertion [HR 30.0 (95% CI 6.5–138.5), *P* < 0.001] were independently associated with adverse outcome (Table 3).

When considering only those patients with chronic renal failure, internal jugular NTVC insertion [HR 3.8 (95% CI 1.2–12.0), *P* < 0.001], femoral NTVC insertion [HR 10.0 (95% CI 1.3–75.6), *P* < 0.001], femoral NTVC catheter exchange [HR 9.4 (95% CI 1.5–58.9), *P* < 0.001] and lack of concurrent antibiotic use (HR of 4.03 [95% CI 1.06–15.4, *P* = 0.041) were independently associated with adverse outcome (Table 3).

**Poor flow**

Rates of catheter removal due to poor flow were 0.98 per 1000 catheter days in the TCVC group, 12.3 per 1000 catheter days in the internal jugular vein NTVCV group and 37.6 per 1000 catheter days in the femoral vein NTVCV group. Internal jugular and femoral NTVCVs exchanged over a guidewire demonstrated failure rates of 20.2 and 32.3 per 1000 catheter days, respectively. Events occurred at median (range) of 57.5 (6–337) days in the TCVC group, 6 (0–22) days in the internal jugular NTVCV group, 5 (1–10) days in the internal jugular guidewire exchange group, 3 (1–10) days in the femoral NTVCV group and 1 (0–2) days in the femoral guidewire exchange group.

When considering the full cohort, using the TCVC group as a reference for comparison, all types of NTVCV insertion procedure were significantly associated with catheter removal due to poor flow on univariate analysis (*P* < 0.001). Other variables significantly associated with catheter removal due to poor haemodialysis blood flow were low haemodialysis blood flow during the first dialysis following catheter insertion (237 ml/min vs 255 ml/min, *P* < 0.001) and elevated levels of CRP at the time of catheter insertion (61 mg/dL vs 40 mg/dL, *P* < 0.001). Patients who required catheter replacement due to poor flow were more likely to have their catheter removed earlier (36 days vs 58 days, *P* < 0.001). Trends towards a significant association with poor flow were seen with high platelet counts (*P* = 0.067) and lower levels of serum albumin (*P* = 0.087). All other variables were not associated with outcome on univariate analysis including duration on RRT.
prior to catheter insertion and whether patients were classified as suffering from acute or chronic renal failure. Despite this, separate sub-analyses were conducted looking specifically at those patient groups in an effort to avoid potential confounding.

When considering only those patients with ARF, only elevated CRP was significantly associated with outcome ($P < 0.001$) although type of catheter insertion procedure ($P = 0.007$), decreased haemodialysis blood flow ($P = 0.013$) and elevated neutrophil count ($P = 0.042$) demonstrated trends towards association with catheter removal due to poor flow.

When considering only those patients with chronic renal failure, only catheter insertion procedure was significantly associated with catheter removal due to poor flow ($P < 0.001$). Elevated platelet counts ($P = 0.019$) and lack of concurrent anticoagulation ($P = 0.046$) demonstrated trends towards association with catheter removal due to poor flow.

When considering the full cohort, multivariate analysis demonstrated significant independent association with the removal of catheters due to poor haemodialysis blood flow in patients dialysing with internal jugular NTCVCs of [HR 4.7 (95% CI 2.4–92), $P < 0.001$], femoral NTCVCs [HR 9.2 (95% CI 4.3–20), $P < 0.001$], internal jugular NTCVCs exchanged over a guidewire [HR 5.3 (95% CI 2.3–13.4), $P < 0.001$] and femoral NTCVCs exchanged over a guidewire [HR 11.7 (95% CI 3.2–43.1), $P < 0.001$] (Figure 2). Significant independence of association was demonstrated with elevated CRP [HR 1.004 (95% CI 1.002–1.006), $P < 0.001$] and low haemodialysis blood flow immediately following catheterization [HR 0.992 (95% CI 0.988–0.996), $P < 0.001$] (Table 4).

When considering only those patients with ARF, multivariate analysis demonstrated femoral NTCVC insertion [HR 17.2 (95% CI 2.1–138.9), $P = 0.008$], elevated CRP

![Fig. 2. Graphical output of the catheter survival function generated following Cox proportional hazards adjustment for all univariates included in the multivariate analysis with regard to episodes of catheter removal due to insufficient haemodialysis blood flow. Survival plotted for each central venous catheter sub-type. ‘TCVC’ = tunnelled central venous catheter. ‘NTCVC’ = non-tunnelled central venous catheter. ‘IJug’ = internal jugular vein insertion site. ‘Fem’ = femoral vein insertion site. ‘(G)’ = catheter exchange procedure conducted over a guidewire.](image-url)
Catheter-related bacteraemia and thrombosis

Table 4. Variables entered into multivariate analysis and the associated risk of subsequent catheter removal due to poor haemodialysis blood flow

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P-value</td>
<td>Hazard ratio (95% CI)</td>
</tr>
<tr>
<td>Full cohort (131 events/44 576 catheter days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCVC</td>
<td>–</td>
<td>1.0</td>
</tr>
<tr>
<td>NTCVC femoral (guidewire)</td>
<td>P &lt; 0.001</td>
<td>11.7 (3.2–41.1)</td>
</tr>
<tr>
<td>NTCVC femoral</td>
<td>P &lt; 0.001</td>
<td>9.2 (4.3–20.0)</td>
</tr>
<tr>
<td>NTCVC internal jugular (guidewire)</td>
<td>P &lt; 0.001</td>
<td>5.3 (2.3–13.4)</td>
</tr>
<tr>
<td>NTCVC internal jugular</td>
<td>P &lt; 0.001</td>
<td>4.7 (2.4–9.2)</td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)</td>
<td>P = 0.002</td>
<td>1.004 (1.002–1.006)</td>
</tr>
<tr>
<td>Haemodialysis blood flow (ml/min)</td>
<td>P = 0.002</td>
<td>0.992 (0.988–0.996)</td>
</tr>
<tr>
<td>Acute renal failure (56 events/7034 catheter days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCVC</td>
<td>–</td>
<td>1.0</td>
</tr>
<tr>
<td>NTCVC femoral</td>
<td>P = 0.007</td>
<td>17.2 (2.1–138.9)</td>
</tr>
<tr>
<td>NTCVC internal jugular (guidewire)</td>
<td>P = 0.007</td>
<td>–</td>
</tr>
<tr>
<td>NTCVC internal jugular</td>
<td>P = 0.007</td>
<td>–</td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)</td>
<td>P &lt; 0.001</td>
<td>1.003 (1.000–1.006)</td>
</tr>
<tr>
<td>Haemodialysis blood flow (ml/min)</td>
<td>P = 0.013</td>
<td>0.989 (0.981–0.997)</td>
</tr>
<tr>
<td>Neutrophil count (&lt;10^9/L)</td>
<td>P = 0.042</td>
<td>–</td>
</tr>
<tr>
<td>Chronic renal failure (75 events/37 542 catheter days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCVC</td>
<td>–</td>
<td>1.0</td>
</tr>
<tr>
<td>NTCVC femoral (guidewire)</td>
<td>P &lt; 0.001</td>
<td>27.8 (7.6–101.3)</td>
</tr>
<tr>
<td>NTCVC femoral</td>
<td>P &lt; 0.001</td>
<td>14.3 (5.9–34.5)</td>
</tr>
<tr>
<td>NTCVC internal jugular (guidewire)</td>
<td>P &lt; 0.001</td>
<td>7.2 (2.1–25.3)</td>
</tr>
<tr>
<td>NTCVC internal jugular</td>
<td>P &lt; 0.001</td>
<td>5.6 (2.7–11.6)</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>P = 0.046</td>
<td>0.4 (0.2–0.9)</td>
</tr>
<tr>
<td>Platelets</td>
<td>P = 0.019</td>
<td>1.003 (1.001–1.005)</td>
</tr>
</tbody>
</table>

Variables that underwent both univariate and multivariate analysis and their association with subsequent catheter removal due to poor haemodialysis blood flow. ‘Guidewire’ refers to catheter exchange procedures over a guidewire.

[HR 1.003 (95% CI 1.000–1.006), P = 0.029] and low haemodialysis blood flow [HR 0.989 (95% CI 0.981–0.997), P < 0.001] to be independently associated with adverse outcome (Table 4).

When considering only those patients with chronic renal failure, multivariate analysis demonstrated internal jugular NTCVC insertion [HR 5.6 (95% CI 2.7–11.6), P < 0.001], internal jugular NTCVC catheter exchange [HR 7.2 (95% CI 2.1–25.3), P < 0.001], femoral NTCVC insertion [HR 14.3 (95% CI 5.9–34.5), P < 0.001], femoral NTCVC catheter exchange [HR 27.8 (95% CI 7.6–101.3), P < 0.001], elevated platelet count [HR 1.003 (95% CI 1.001–1.005), P = 0.006] and lack of concurrent anticoagulation [HR 0.4 (95% CI 0.2–0.9), P = 0.02] to be independently associated with adverse outcome (Table 4).

Discussion

Central venous catheterization for haemodialysis is regarded as a significantly less favourable option to arteriovenous fistula and synthetic graft use due to the higher rate of complications [1]. Within the different types of catheter insertion procedures, TCVCs are associated with lower rates of bacteraemia and catheter failure than NTCVCs [12–14]. What has been uncertain is the degree to which adverse events that occur following catheterization are a function of the type of catheter procedure or the type of patient undergoing the catheter procedure. This study brings clarity to this debate.

From this data, it can be concluded that the characteristics of the catheterization procedure in terms of tunneling and site of insertion had the greatest independent effect on risk of developing both CRB and catheter failure due to poor haemodialysis blood flow of all the variables studied. The trends towards a clear hierarchy of complication rates across different types of catheter insertion procedure were demonstrated as being independent of established measures of comorbidity in haemodialysis patients, including haemoglobin, bone biochemistry, dialysis dose, markers of inflammatory burden, in the setting of ARF, diabetes and modified Charlson comorbidity index score [9–11].

The only other factor independently associated with CRB was an elevated modified Charlson comorbidity index score at the time of catheter insertion. The only other factor independently associated with catheter failure due to poor haemodialysis blood flow was elevated CRP at the time of catheter insertion.

No association between time on RRT and outcome was found on any of the analyses. Whether a patient was categorized as having ARF, acute-on-chronic renal failure or chronic renal failure, no effect was seen on risk of developing either outcome. Similarly, when time since starting RRT was recorded as a continuous variable, no effect was seen on either outcome. We nonetheless reported results within the ARF and chronic renal failure groups. This demonstrated similar findings to those described when the full cohort was analysed, but with wider confidence intervals for the hazard ratio estimates. This finding is important. The expectation would be that patients with ARF would demonstrate worse outcomes due to concurrent acute comorbidity, heightening the risk of bacteraemia and catheter failure. The demonstrated lack of association
between ARF and adverse outcome suggests that either this is not the case, or that the spectrum of comorbidity in CRF, whilst often different in phenotype, is sufficient in magnitude to offset this difference. We demonstrated NTCVC use to be associated with adverse outcome and thus the especially high prevalence of NTCVC use in patients with ARF suggests this is a significant contributor to the higher rates of bacteraemia and catheter failure traditionally expressed by this group.

All our findings were made using clinically relevant outcome measures which have been used in other previous studies. Our definition of CRB required a positive blood culture, pyrexia, raised CRP and no clinical, radiological or concurrent microbiological evidence of infection from a separate source. Only if each of these criteria were fulfilled was an event recorded. The use of this definition is open to criticism due to its potential to include positive blood cultures from sources other than the vascular access catheter which were not clinically apparent. We felt, however, that this is the definition most used in clinical practice and thus of most interest to the clinician. Use of a more strict definition such as that requiring concurrent positive catheter and peripheral blood cultures with either (i) a 5-fold greater colony count from the catheter culture or (ii) first appearance of growth 2 hours from the catheter culture before peripheral culture are limited by the difficulties of ensuring such peripheral cultures are achieved and correctly handled in a busy outpatient haemodialysis unit. Such a definition would be most applicable when performing a randomized controlled trial, however, in observational studies such as this, may lead to an under-reporting of the burden of bacteraemia. These results thus reflect clinically significant CRB in our cohort and demonstrate a spectrum of bacterial isolates that is typical of those reported in other studies and was similar in both TCVC and NTCVC groups.

The wide range of clinical and laboratory variables included in the analysis allowed many potential confounders to be taken into account. Not all potential confounding variables were, however, included. The number and type of vascular access procedures each patient had undergone prior to catheterization and whether infection or thrombosis was attributed to their loss were potentially important variables that were not reliably recorded in the unitary electronic patient record used for data retrieval and as such was not recorded during data collection. It can be envisaged that patients with poor peripheral access or central venous stenosis may have a higher turnover catheter insertions and thus may gradually depend more heavily on NTCVCs, use of insertion sites such as the femoral veins and/or use of guidewire catheter exchange procedures. Such patients could account for the especially high HRs found with these procedures. Whilst the large number of procedures, long period of follow-up and inclusion of variables such as the patient’s duration on RRT may partly adjust for this issue in study design, this study does not sufficiently address this potentially important risk factor. Closer scrutiny of the complex vascular access patient could be achieved by future studies adjusting for variables such as the number of previous vascular access procedures, and reporting subsequent rates of conversion onto a functioning AVF or graft and subsequent sustainability of that fistula or graft. These areas represent the inherent limitations that observational studies incur and underline the role that randomized controlled studies could still have within this area.

Another important limitation concerns the data on guidewire catheter exchange procedures. The analysis was limited by not adjusting for the period of time spent with a catheter prior to it being exchanged via a guidewire. In this regard, we cannot exclude that the higher event rates seen in this group do not simply reflect the effect of increased time with a catheter *in situ*. Whilst increased catheter lifespan was associated with a lower rate of CRB, this simply reflected the local unitary practice of removing a catheter once CRB had been diagnosed and as such does not help clarify this issue. Additionally, the small number of patients who underwent femoral guidewire exchange suggests that this procedure was likely to be conducted in patients for whom physicians had no other vascular access choice open to them. This may account for the especially adverse outcomes in this patient group, albeit despite the adjustment for such confounding through our multivariate analysis. Previous observational work on guidewire exchange procedures has proven inconclusive, limited by the fact that catheter replacement was invariably conducted due to a preceding complication having developed in the previous access method [15]. Any randomized study on catheter exchange procedures would have to take this into account before definitive statements on the safety of guidewire exchange procedures can be made.

How does catheter insertion site contribute to bacteraemia risk? The favourable outcomes seen with internal jugular catheterization compared to femoral catheterization corroborate those seen in other studies within the renal population [15–17]. The pattern of these results suggest that catheters inserted into a site which has been previously used (i.e. a previous catheter tunnel used with a catheter exchange procedure over a guidewire) or in skin folds such as the femoral creases may herald locations where pathogens are more likely to reside. How does catheter tunneling relate to bacteraemia risk? The favourable outcomes seen with tunneled catheters in this study are in accordance with other published observational cohorts [14,18]. These data show that catheter entering the vein close to the skin surface without a period of subcutaneous tunnelling are more likely to become complicated by infection and/or thrombosis. The shorter physical distance between skin surface and vein, and thus a shorter length of exposure to innate immune defences may go some way to explain the better bacteraemia rates seen with subcutaneous tunnelling of the catheter. We also acknowledge the role of the cuff in generating a localized inflammatory and secondary fibrotic response that both secures the catheter and provides a physical barrier to transdermal colonization and infection of the external aspects of the catheter.

With regard to the differences between catheter types due to poor haemodialysis flow, the tunneled catheters used in this cohort were of greater diameter than their non-tunneled counterparts and thus may account for the better thrombosis rates seen in this group. Within the NTCVC groups, the main difference in flow rates was be-
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between catheters inserted into the internal jugular veins and the femoral veins. This may simply reflect the different calibre, tortuosity and extrinsic compression of the venous tree in these locations. Further study of these theories would be of benefit.

Several organizations have drawn up clinical guidelines to address the issue of optimal catheter practice. The UK Renal Association Guidelines, for instance, suggest that <20% of patients on long-term haemodialysis should use tunnelled or NTCVCs as their mode of vascular access [8]. National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) cite the lower complication rate associated with TCVCs compared with non-tunnelled catheters in their recommendation that tunnelled catheters are used where the period of catheter use is likely to be >3 weeks. In cases of suspected catheter thrombosis or low-grade CRB in the absence of subcutaneous tunnel infection, NKF-KDOQI suggests that the catheter may be exchanged over a guidewire [1]. Our data suggest that future guidelines should give greater emphasis on early tunnelled central venous catheterization where possible, minimizing NTCVC and limiting guidewire catheter exchange to cases where re-catheterization at a separate site is unachievable. It must be emphasized that, in patients with chronic renal failure, rapid conversion from a catheter onto a successfully functioning arteriovenous fistula or graft remains of paramount importance.

As global trends demonstrate increasing numbers of older patients with greater comorbidity starting haemodialysis, there will inevitably be increased pressure on successful vascular access provision. Maintaining a high proportion of these patients on arteriovenous fistulae may become increasingly challenging [19]. Despite improvements in vascular access management, surveillance techniques and arteriovenous fistula or graft salvage [20–23], the number of patients using central venous catheters as a stop-gap measure between successful establishment of arteriovenous access or as a definitive last resort procedure is likely to increase. Pressure on catheterization procedures is thus likely to increase.

In conclusion, from the information these data have generated on independence of risk association with catheterization procedures, we suggest that tunnelled central venous catheterization be the primary method of access when patients have no functioning arteriovenous fistula or graft. In cases where access to tunnelled central venous catheterization is limited, non-tunnelled catheterization of the internal jugular veins should be sought. Whilst not reaching statistical significance, our data suggest trends towards a hierarchy in which insertion of a non-tunnelled femoral venous catheter should only be sought in emergency settings where internal jugular venous catheterization is unsuccessful or unattainable. The practice of catheter exchange over a guidewire should be restricted to cases where catheterization at a de novo site cannot be achieved.


Conflict of interest statement. None declared.

References

21. Wijnen E, Planken N, Keuter X et al. Impact of a quality improvement programme based on vascular access flow monitoring on costs,
Comparison of low-dose deferoxamine versus standard-dose deferoxamine for treatment of aluminium overload among haemodialysis patients

Wei-Chih Kan¹, Chih-Chiang Chien¹, Chia-Chun Wu¹, Shih-Bin Su²,³, Jyh-Chang Hwang¹ and Hsien-Yi Wang¹

¹Division of Nephrology, Department of Medicine, Chi-Mei Medical Center, Tainan, Taiwan, ²Department of Family Medicine, Chi-Mei Medical Center, Taiwan and ³Institute of Biomedical Engineering, Southern Taiwan University, Taiwan

Correspondence and offprint requests to: Hsien-Yi Wang; E-mail: why8@ms61.hinet.net

Abstract

Background. Patients on maintenance haemodialysis are at high risk of aluminium overload. While deferoxamine (DFO) has potential adverse effects, lower DFO dosages may afford good efficacy with fewer side effects. We evaluated the therapeutic response of low-dose (2.5 mg/kg/week) DFO among haemodialysis patients with aluminium overload.

Methods. We recruited the participants via basal predialysis serum aluminium (Al) levels of ≥20 μg/L with clinical suspicion of aluminium toxicity or hyperparathyroidism indicating parathyroidectomy and positive DFO tests. Patients were randomly divided into standard-dose (5 mg/kg/week) and low-dose (2.5 mg/kg/week) groups. We compared the differences of mineral biochemical and haematological parameters before and after DFO treatment. Successful treatment was defined as a serum aluminium increase of <50 μg/L by DFO test. Adverse events during DFO therapy between the groups were also compared.

Results. In total, 42 haemodialysis patients completed treatment (standard-dose group, n = 21; low-dose group, n = 21). The demographic characteristics of the groups did not differ. Serum corrected calcium and ferritin decreased in both groups, while serum total alkaline phosphatase increased in both groups. Serum phosphorus increased in low-dose group (P = 0.029), while plasma intact parathyroid hormone increased in standard-dose group (P = 0.004). The successful treatment response rates did not differ between the two groups (standard-dose: 12/21, 57% vs low-dose: 13/21, 62%; P = 0.75).

Conclusions. Low-dose DFO may offer similar therapeutic effects as standard-dose DFO therapy.

Keywords: aluminium overload; DFO; dialysis; haemodialysis; low-dose DFO

Introduction

Dialysis patients are at high risk for aluminium overload [1] due to long-term use of aluminium-containing phosphate binders [2,3], poor renal excretion of aluminium and contact with aluminium-containing dialysate. The Kidney Disease Outcomes Quality Initiative (K/DOQI) recommends deferoxamine (DFO) for treatment of dialysis patients with aluminium overload [4]. However, DFO has side effects of its own [5], such as itchy skin, nausea, myalgia and neurotoxicity [6]. Although most of these side effects are mild and reversible, severe or even life-threatening side effects are possible, especially anaphylactic shock and mucormycosis [7,8], even though these are rare. Because of the common side effects of DFO, dosing of 20 to 40 mg/kg of body weight [9–11] was abandoned. The toxicity of DFO is dose-dependent, and thus, many studies were designed to find the optimal dosage for aluminium overload treatment [12–14]. According to the recent K/DOQI clinical practice guidelines, the DFO standard dosage is 5 mg/kg of body weight [4]. Furthermore, several pharmacokinetic and small-scale, short-term studies found that even lower doses than 5 mg/kg could be as efficacious as the standard 5 mg/kg dose [15,16], but clinical trials verifying its efficacy at lower doses are lacking. Therefore, we compared the treatment response to standard-dose (5 mg/kg) versus lower-dose (2.5 mg/kg) DFO among dialysis patients with aluminium overload during 2 months of treatment.