Trisodium citrate 46.7% selectively and safely reduces staphylococcal catheter-related bacteraemia

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Abstract

Background. Trisodium citrate (TSC) 30% has been shown in a randomized control trial to be an effective antimicrobial catheter locking solution, able to significantly reduce catheter-related bacteraemia (CRB) in haemodialysis patients. Since that report, the formulation in Europe has been changed to 46.7% TSC without confirmatory data on efficacy. We report a 55 915 patient-day at risk experience in tunnelled lines of 46.7% TSC, emphasizing efficacy and changes in microbiology seen.

Methods. On 1 July 2006, inter-dialytic catheter locking solution was changed from 5000 IU/ml heparin to Citra-lock™ (46.7% TSC) in all haemodialysis patients at Barts and the London Renal Unit dialysing through an incident or prevalent tunnelled catheter. Prospectively collected blood culture data for the 6 months prior to the switch and 3 months at the end of the first year of TSC use were analysed. TSC tolerability was excellent with only a single withdrawal for intolerance of the agent. No major adverse events were reported.

Results. A major fall in CRB rates was noticed with a change from heparin (2.13/1000 catheter-days) in 2006 to TSC (0.81/1000 catheter-days) in 2007. This was due to significant reductions in staphylococcal CRB, true for sensitive, methicillin-resistant and coagulase-negative staphylococci. No increase in catheter malfunction was observed.

Conclusions. We found that 46.7% TSC is a safe, convenient and highly effective catheter locking solution, leading to significant reduction in CRB largely by preventing staphylococcal bloodstream infections. Given that *Staphylococcus aureus* in particular is associated with serious and often disseminated infection, TSC seems to be a powerful tool for dialysis units.

Keywords: antibiotic locking solutions; catheter-related bacteraemia; *Staphylococcus aureus*

Introduction

Patients undergoing haemodialysis are at increased risk of infection [1]. In particular, dialysis via a central venous catheter is associated with a 10-fold excess relative risk of bloodstream infection when compared to arteriovenous fistulae [2–4]. However, despite recommendations favouring native arteriovenous fistulae over tunnelled dialysis catheters, the rapid growth of patients reaching end-stage renal disease (ESRD) requiring haemodialysis has led to an increasing reliance on catheters [5].

Catheter-related bacteraemia (CRB) is a major cause of morbidity and mortality with an incidence ranging from 3.4 to 6.5 episodes per 1000 catheter-days [6–10]. Gram-positive organisms are responsible for most CRB, with staphylococci the most likely causative organisms [7,10,11]. *Staphylococcus aureus* infection is associated with more costly and lengthy hospitalizations [12] and a 20% higher risk of death when compared to other organisms [13]. If the causative *S. aureus* is methicillin-resistant (MRSA), these outcomes are even [14]. CRB may also result in catastrophic metastatic complications such as osteomyelitis, endocarditis and septic arthritis [8], again most markedly with *S. aureus* infections [15].

Different mechanisms are thought to contribute to CRB: migration of bacteria from exit-site infections, contamination of the catheter hub and internal colonization of the catheter by organisms forming a biofilm [6,16]. Strategies to minimize CRB have included using universal precautions, eradication of nasal *S. aureus* carriage [17], topical exit-site antimicrobial application [18], antibiotic-impregnated catheters [19] and using catheters with a silver-impregnated cuff [20].

At present, due to its anticoagulant properties, heparin is widely used as the standard intra-dialytic locking solution. This is despite a lack of evidence-based literature to support the efficacy and safety of heparin as a locking agent. In fact, heparin has been associated with unintentional systemic anticoagulation, interference with lab assessments of clotting, heparin-induced thrombocytopenia and potentially increases the bleeding risk of uraemic patients already at risk of a coagulopathy [21,22]. In vitro studies have also demonstrated that heparin in clinically relevant
concentrations actually enhances staphylococcal biofilm formation [23]. Sodium citrate has been successfully used as an anticoagulant in blood products and dialysis for years. Its anticoagulant properties are the result of chelation of ionized calcium in the blood therefore preventing activation of calcium-dependent pro-coagulants [22]. In contrast to heparin, in vitro studies have demonstrated that sodium citrate inhibits S. aureus and S. epidermidis biofilm formation on materials commonly used for indwelling dialysis catheters [24]. Trisodium citrate (TSC) 30% has been shown in a randomized control trial to be an effective antimicrobial [24]. Sodium citrate has been successfully used as an anticoagulant in blood products and dialysis for years. Its anticoagulant properties are the result of chelation of ionized calcium in the blood therefore preventing activation of calcium-dependent pro-coagulants [22]. In contrast to heparin, in vitro studies have demonstrated that sodium citrate inhibits S. aureus and S. epidermidis biofilm formation on materials commonly used for indwelling dialysis catheters [24]. Trisodium citrate (TSC) 30% has been shown in a randomized control trial to be an effective antimicrobial 

Materials and methods

Patient selection

On 1 July 2006, the inter-dialytic catheter-locking solution was changed from 5000 IU/ml heparin to 46.7% TSC (Citra-lockTM) in all haemodialysis patients at Barts and the London in-centre and satellite renal units dialysing through an incident or prevalent tunnelled catheter. Prospectively collected blood culture data for the 6 months prior to switch and 3 months at the end of the first year of TSC use were analysed. All patients receiving dialysis through a tunnelled haemodialysis catheter were identified using our electronic patient database. Patients dialysing via temporary or uncuffed haemodialysis catheters were excluded from this study. Two satellite dialysis centres (total prevalent patients, 90) had to be excluded as their microbiology samples are analysed at other hospitals.

Catheter care guidelines

A catheter care bundle was introduced between July 2005 and July 2006 (1 year preceding the switch from heparin to 46.7% TSC). Mandatory specific competencies and assessments were introduced for all haemodialysis nursing staff in relation to the theory and practice of tunnelled haemodialysis line care. A single tunnelled catheter (Medcomp Ashsplit III™, Medical Access, UK) was used in all patients, and inserted under sterile technique under screening by trained operators. Single-dose antibiotic prophylaxis was administered at insertion in all cases as vancomycin 500 mg and gentamicin 80 mg 1 h prior to the procedure. Vancomycin allergic patients were administered teicoplanin as an alternative. Dialysis catheters were only handled by trained, competent staff wearing sterile gloves. Chlorhexidine spray 0.5% was used to sterilize the exit hub prior to handling. In addition, catheter exit-site dressings were changed after each treatment.

The procedure for locking catheters with 46.7% TSC was identical to that previously used with heparin 5000 IU/ml (identical to that used for 30% TSC instillation under trial conditions [6]). After each dialysis, both catheter lumens were flushed with 10 ml 0.9% NaCl and then locked with 46.7% TSC using a volume exactly equivalent to the internal volume of the lumen noted on each catheter. For preventing accidental infusion of 46.7% TSC, the maximum syringe size used was 2.5 ml and filled with only enough 46.7% TSC to lock a single lumen.

Bloodstream infections

Catheter-related bacteraemia was defined as a temperature >37.5°C and one positive blood culture result with no other obvious source of infection. In all cases and throughout the study period, blood cultures were taken through both limbs of the tunnelled catheter as 10 ml blood in each BacT/ALERT™ FA (aerobic) and SN (anaerobic) bottle (bioMerieux, Basingstoke, UK). Catheter hubs were decontaminated with chlorhexidine for 2 min, and then 20 ml blood was withdrawn using a no-touch technique through a single limb for the culture bottle pair. Blood cultures were transferred at room temperature to a single central laboratory (Royal London Hospital) and incubated within 6 h in accordance with manufacturer’s guidelines. On colorimetric detection within the BacT/ALERT™ incubator/reader, a sample of medium was aspirated for Gram stain, and appropriate culture and sensitivity plating.

All febrile patients on dialysis were reviewed by a physician to ascertain a diagnosis, prescribe antibiotics (in accordance with unit protocol) and consider admission. Examination findings and investigation results are recorded on the electronic database. Tunnelled dialysis catheters were removed if fever persisted beyond 48 h despite antibiotics, if patients were haemodynamically compromised or once S. aureus was cultured in blood. These practices were consistent for both periods studied.

Microbiology

All positive blood cultures were collected prospectively by the microbiology department. A second positive culture was considered to represent a new infection after a previous positive culture if a new organism was grown or if the culture was positive at least 30 days after the previous culture and completion of an intravenous antibiotic course.

Thrombosis, safety and tolerability

Catheter malfunction was not examined prospectively. However, to ensure that change in practice was not associated with an increase in catheter malfunction (thrombosis), alteplase use was analysed as a surrogate. All patients with catheter malfunction (defined as failure to successfully achieve dialysis through any tunnelled catheter, or blood flow rates of < 220 ml/min despite positional changes and/or additional flushes on dialysis) received alteplase as a thrombolytic. In each case, 2 mg reconstituted in an appropriate volume were locked into each lumen for 1 h, after which dialysis was re-attempted. A complete record of each dose given is recorded centrally by the unit pharmacist.
Alteplase is not used for any other indication in our renal unit.

Any unintended effects of 47.6% TSC were recorded on our adverse events reporting system (DATIX forms). Patients were asked to report any symptoms after switching from heparin to 46.7% TSC on every dialysis (particularly altered taste or paraesthesiae), and a 0.1 ml/lumen reduction in volume was used for subsequent inter-dialysis locks. All patients were given the option to return to inter-dialytic locking with heparin 5000 IU/ml if symptoms were intolerable.

### Statistical analysis

Graphpad InStat for Windows™ (GraphPad Software Inc., San Diego, CA, USA) was used for analysis. Chi-squared testing with Yates correction was used to compare patient demographics and alteplase usage. Mann–Whitney-U testing was used to compare infection rates between the two audit periods. A P-value of <0.05 was considered significant.

### Results

#### Baseline characteristics

Out of 540 patients on haemodialysis, a total of 206 patients were suitable for analysis (identified as dialysing through a tunnelled haemodialysis catheter in a relevant centre) in 2006 during the 6-month audit period of heparin use. A total of 207 patients out of 557 days (Table 1). Correspondingly, during the 3-month audit of 182 days were analysed giving a total of 37 492 catheter-days compared to 15 catheter-related Microbiology and bacteraemias

In the heparin period, 80 catheter-related BSI were identified in 37 492 catheter-days compared to 15 catheter-related BSI in 18 423 catheter-days in the 46.7% TSC period. CRB was reduced from 2.13/1000 catheter-days in the heparin period to 0.81/1000 catheter-days in the 46.7% TSC period (P < 0.0001). This represents a 62% reduction (Table 2).

In the year preceding the switch to intra-dialytic locking with 46.7% TSC, other measures were initiated as part of a care bundle to lower CRB rates including catheter-care guidelines. It was feasible that the CRB rate was already falling significantly before the introduction of 46.7% TSC. We therefore analysed the CRB rates on a month-by-month basis (Figure 1). CRB were also calculated by causative organism for each assessment period. We analysed CRB rates for methicillin-resistant *S. aureus* (MRSA), methicillin-sensitive *S. aureus* (MSSA), *S. epidermidis* (coagulase-negative Staphylococcus), other Gram-positive organisms and Gram-negative organisms (Figure 2). In the 46.7% TSC-locked cohort compared to the heparin-locked cohort, there was a statistically significant reduction in staphylococcal CRB true for methicillin-resistant (relative risk 2.0, 95% CI 1.99–2.01; P < 0.0001), methicillin-sensitive (RR 2.0, 95% CI 1.99–2.01; P < 0.0001) *S. aureus* and *S. epidermidis* (RR 1.65, 95% CI 1.54–1.79; P < 0.0001). There was no difference in CRB caused by other Gram-positive bacteria (RR 0.83, 95% CI 0.59–1.17) or all Gram-negative bacteria (RR 0.78 95% CI 0.56–1.09) (Table 3).

We also examined particular subgroups of patients thought to be at particular risk of infection (Figure 3). Those who have had an episode of CRB often have a further episode (either due to patient factors such as chronic immunosuppression or catheter factors such as biofilm formation). We analysed our outcomes for patients with one or more infections per 1000 days (using only first episode of infection). A significantly reduced CRB rate with TSC use was again observed (P < 0.001).

We compared those with diabetes mellitus against those without, and specifically examined infection rates in prevalent patients to see whether or not those presumed to have formed biofilm would benefit equally when compared to those with new catheters. Those without diabetes mellitus saw significant improvement in CRB rates (P < 0.001), but no significant benefit was observed in diabetic patients (P = 0.08) and prevalent patients (P = 0.11).
Catheter malfunction as measured by thrombolytic usage, safety and tolerability

During both audit periods, alteplase was used as the sole thrombolytic for all malfunctioning catheters. Every vial used for catheter malfunction was recorded centrally for pharmacy reporting. A single 4 mg vial was used to prepare two luminal 2 mg thrombolytic locks. In the heparin group, 71 vials/1000 catheter-days (284 mg/1000 catheter-days) were used compared to 62/1000 catheter-days (248 mg/1000 catheter-days) in the 46.7% TSC group (Figure 4). This equates to a 13% reduction (relative risk 0.87; 95% CI 0.83–0.92; \( P < 0.0001 \)) with significant cost-saving.

Also, 46.7% TSC chelates calcium with systemic injection and may lead to cardiac instability if >10 ml is injected. Smaller volumes may be associated with unpleasant perioral or finger paraesthesiae or altered taste. Only one patient withdrew from the 46.7% TSC group, and no critical or serious incidents were reported. Minor side effects were common, and serial 0.1 ml/lumen dose reductions abolished or made tolerable these symptoms.
Catheter-related bacteraemia/1000 patient days

<table>
<thead>
<tr>
<th>Year</th>
<th>Overall</th>
<th>Infected patients</th>
<th>Diabetes</th>
<th>No diabetes</th>
<th>Prevalent patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>2.13</td>
<td>1.76</td>
<td>1.86</td>
<td>2.29</td>
<td>1.45</td>
</tr>
<tr>
<td>2007</td>
<td>0.81</td>
<td>0.81</td>
<td>1.15</td>
<td>0.57</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Fig. 3. Significant benefit in using 46.7% TSC was observed overall, in non-diabetic patients, and also in the number of patients with more than one bloodstream infection during the analysis periods (*P < 0.001). No difference was observed in diabetic patients (P = 0.08) and in prevalent patients dialysing through the same line during the two analysis periods (P = 0.11).

Discussion

In 2005, Weijmer et al. [6] reported a randomized controlled trial of a 30% TSC solution as a catheter locking solution, and demonstrated significantly improved CRB rates (from 4.1 to 1.1 catheter-related bacteraemias/1000 patient-days) in a mixed population of patients dialyzing through untunnelled and tunnelled catheters. This trial remains the best-designed and most robust evidence for any antimicrobial inter-dialytic locking solution. It suggested that fewer patients would die of sepsis as a result of using 30% TSC, with no increase in catheter malfunction for abandoning heparin as a lumen lock. This trial led to widespread adoption of initially 30% TSC, and when the formulation was changed to more concentrated trisodium citrate, 46.7% TSC in the low countries and United Kingdom.

However, TSC has not been widely adopted elsewhere. In 2000, case reports of fatalities using high concentrations of 46.7% TSC due to systemic administration led to the withdrawal of the product (Tricitrosol™) by the US Food and Drug Administration [25]. TSC is a potent chelator of calcium, and the side effects of accidental systemic administration (principally paraesthesiae and altered taste, but potentially tachyarrhythmias precipitated by acute hypocalcaemia) are often cited in limiting TSC use. This is despite 46.7% TSC being a potentially ideal catheter lock: free of

Alteplase in mg/1000 catheter days

<table>
<thead>
<tr>
<th>Period</th>
<th>Alteplase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin period (2006)</td>
<td>284</td>
</tr>
<tr>
<td>46.7% TSC period (2007)</td>
<td>248</td>
</tr>
</tbody>
</table>

Fig. 4. Significant reductions in alteplase as a thrombolytic for catheter malfunction were found with 46.7% TSC usage (*P < 0.001).
antibiotic, it poses no risk in promoting the (theoretical) emergence of bacterial antibiotic resistance, and has significant thrombolytic properties that may prolong functioning catheter lifespan.

We now report our single-centre, 55 915 patient-day at risk experience of inter-dialytic 46.7% TSC (Citralock™) locks in tunneled haemodialysis catheters. We found 46.7% TSC to be associated with a major fall in CRB rates (from 2.13 with heparin to 0.81/1000 catheter-days with 46.7% TSC). The reduction in CRB using higher concentration TSC was similar to that observed by Weijmer et al. with 30% TSC. We also report that the reduction in CRB was due to a significant reduction in staphylococcal CRB, true for sensitive, methicillin-resistant and coagulase-negative staphylococci. There was no significant effect on CRB caused by Gram-negative or other Gram-positive organisms.

This novel observation provides clinical support to in vitro data suggesting that TSC prevents staphylococcal biofilm formation [24]. Sodium citrate at 2–4% concentration inhibits biofilm formation on a variety of abiotic surfaces used for the manufacture of indwelling dialysis catheters (conversely, 0.2% sodium citrate and heparin enhance biofilm formation). High concentration TSC (concentrations ≥ 30%) kills most organisms encountered as causative for CRB in anosmolality-independent manner. Chelation of calcium and magnesium appears to interfere with cellular integrity by degrading bacterial cell membranes, rendering bacteria increasingly permeable [26]. Given that ‘catheter leak’ of locking solutions occurs during the inter-dialytic interval [27,28], 46.7% TSC should theoretically maintain the luminal TSC concentration well above that at which biofilm formation will be inhibited. Given the major impact staphylococcal CRB has in cost and morbidity on haemodialysis, TSC may offer real advantages over other catheter locking solutions in this respect. It is not known whether higher concentrations of TSC may disrupt or abolish pre-existing biofilm (4% citrate does not). The subgroup of prevalent patients with a single catheter across both study periods did not experience a reduction in CRB, suggesting that the greater benefit will be seen in incident patients.

By comparison, combination gentamicin/citrate locks have also been assessed in vitro [24]. Although biofilm formation was inhibited by combination locks, adherent bacteria remained viable at even the highest concentrations of citrate (4%) and gentamicin used (40 mg/ml). Whether or not these viable bacteria may have relevance in the evolution of antibiotic resistance remains speculative—this combination (and also gentamicin/heparin in combination lock [29]) is associated with significant reduction in CRB [30].

Catheter malfunction may be an unintended side effect of abandoning heparin-based locking solutions. In vitro, TSC is a potent anticoagulant, and should offer advantages over solutions (such as taurolidine-containing locks [31]) that lack anti-coagulant potency. Weijmer et al. have confirmed that 30% TSC was not associated with any increase in the need for catheter replacement. However, the need to replace a catheter as a result of presumed luminal thrombosis is the final event in a longer process. At our centre, catheters achieving poor blood flow (<220 ml/min) or high venous pressures are locked with alteplase for 60 min in an attempt to restore flow. This is frequently successful, and prevents the need for catheter exchange. The use of 46.7% TSC led to significant reductions in alteplase usage, suggesting that in reducing biofilm formation and CRB, additive benefits in long-term catheter function may be seen. This remains to be proven prospectively. However, significant cost savings can accrue in switching to 46.7% TSC in a reduction in alteplase use.

TSC has long been safely used in Europe. No reports of patient death from accidental TSC administration have been reported since 2000, and the volume and rate of 46.7% TSC required in accidental systemic injection to induce dangerous hypocalcaemia remains unknown in humans. Indeed, accidental administration of 5000 IU/ml heparin has been associated with fatal haemorrhage in haemodialysis patients. A simple protocol can be adopted to limit the risk of accidental infusion [6], with maximal syringe sizes (2.5 ml) and locking protocols. In our hands, only one patient withdrew consent to use 46.7% TSC due to uncomfortable side effects, and no serious adverse events were reported. The substantial benefit in reduction in CRB seems to far outweigh any risk from accidental injection as a bolus in our 18 423-day experience.

There are obvious limitations to this data: the study is an observational and retrospective analysis of prospectively collected data and as such lacks the power of randomized trials. However, in a single centre with no other changes in dialysis or catheter practice, or in the method of data collection, we believe this to represent a ‘real life’ experience of TSC. For all the flaws inherent in cohort studies, these data add strong support for the use of 46.7% TSC as a catheter locking solution. We are able to report that 46.7% TSC is as efficacious, and as safe as the 30% formulation originally reported by Weijmer et al. in 2005. We also report that the reduction in CRB occurs principally as a result of a reduction in staphylococcal bloodstream infections, and note that 46.7% TSC use reduces the need for alteplase as a catheter thrombolytic.

We conclude that 46.7% TSC is a safe, convenient and highly effective catheter locking solution, leading to significant reduction in CRB largely by preventing staphylococcal bloodstream infections. Given that S. aureus in particular is associated with serious and often disseminated infection, 46.7% TSC seems to be a powerful tool for maintaining patient wellbeing on dialysis units.

Conflict of interest statement. Data has been presented in poster format at ASN November 2007, San Francisco. The authors declare no conflict of interest.


25. Food and Drug administration. FDA issues warning on tricitrosol dialysis catheter anticoagulant. 2000


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