PERFORMANCE PROPERTIES OF MODERN LOCKSOLUTIONS:

COMPARISON OF CITRATE SOLUTIONS WITH TAUROLOCK™/TAUROLOCK™-HEP500 AS LOCK SOLUTIONS IN CATHETERS AND PORTS

Status April 2015
TAUROLOCK™ vs. HIGHLY CONCENTRATED CITRATE (≥ 30%) LOCK SOLUTIONS

PERFORMANCE PROPERTIES OF MODERN LOCK SOLUTIONS
(HIGHLY CONCENTRATED CITRATE VS TAUROLOCK™)

A) Effective Prevention of Infections

B) Maintenance of the Access Device’s Patency

C) Safe Application (Even in Case of incorrect Application)

Ad A) Effective Prevention of Infections

The German Dialysis Standard 2014 recommends the use of highly concentrated citrate (30% or 45%) or taurolidine-citrate solutions since they are antimicrobial, and the rate of catheter-related bacteraemias can be reduced. Although the bactericidal (respectively bacteriostatic) activity of highly concentrated citrate solutions is in vitro much weaker and more specific to single organisms than TauroLock™ (see attachment, brochure TauroLock™, killing curves, and Schilcher 2015) it seems to be efficient enough to reduce catheter related infections in clinical practice.

Ad B) Maintenance of the Access Device’s Patency

In a study comprising 232 patients, Power et al. (see attachment) showed that the application of a citrate block (46.7%) required an increased use of urokinase which was twice as high compared to the heparin block. This might be due to the reduction of the locking volume on account of patients’ complaints which then resulted in a reduced filling of the catheter tip. The high concentration of citrate may also lead to protein precipitation with concomitant blockage of the catheter (Schilcher et al, 2012). Alternatively it should be discussed whether the lack of heparin results in an increased adhesion of fibrin or fibrous material to the inner lumen. This hypothesis is supported by the findings of Solomon et al., 2010 (see attachment) which confirm the results of Power regarding the increased use of urokinase with heparin-free taurolidine-citrate (TauroLock™) in dialysis patients. The addition of 500 IU/mL of heparin (TauroLock™-Hep500) reduced the need of thrombolytic intervention to a level comparable to heparin 5000 IU/mL. Apparently – at least in dialysis – the use of small concentrations of heparin in lock solutions provides patency of the device.

Ad C) Safe Application (even in case of inaccurate application)

c1) Cardiac Risks:

Highly concentrated citrate solutions used as catheter lock solutions are banned in the USA (see attachment, FDA warning letter). In a clinical unit in the Netherlands, the use of highly concentrated citrate (30%) as a lock solution was responsible for two cardiac arrests in the same patient within 24 hours. The over-instillation though had just been ≤ 1 ml per lumen (Punt et al., see attachment). Therefore, highly concentrated citrate used as a catheter block is only recommended by the manufacturer if the exact catheter volume is known. These risks resulted in a limited use of highly concentrated citrate only by trained personnel only according to the German Dialysis Standard 2014.

c2) Embolic Risks:

Willicombe et al., 2009 (attachment) reported embolic complications while using highly concentrated citrate (46.7%) as a lock solution. There were eight cases of pulmonal or cerebral embolic events, three of which are well documented. Schilcher et al., 2012 (see attachment) reported the interaction between whole blood and citrate and detected protein precipitations during their interaction in vitro at levels of >12% citrate. In vivo, protein precipitates were found in all ten catheters applied with 20% and 46.7% citrate lock solution, but not when filled with 4% and 10% citrate. The authors also showed that these protein precipitates blocked a 20 µm mesh filter resembling small vessels. Therefore, hypertonic citrate locks are potentially dangerous and may be the decisive cause for reported embolic events and the increased use of Urokinase to deblock the catheter.
TAUROLOCK™ vs. HIGHLY CONCENTRATED CITRATE (≥ 30%)
LOCK SOLUTIONS
Excerpt

**B14.2 Prevention of Infection in Central Venous Catheters**

… Between dialysis treatments the central venous access device may be blocked using a diluted heparin solution. Heparin, however, does not have any antibacterial properties. Antibacterial lock solutions should therefore be preferred, which reduce the rate of catheter-related bacteraemias considerably. The use of antibiotics can not be recommended due to the potential development of resistance. Alternatively, highly concentrated citrate (30% or 45%) or taurolidine-citrate solutions can be used. Due to the risk of severe cardiac arrhythmias highly concentrated citrate must be strictly administered by trained staff according to the instructions of the manufacturer.

**B16.3 Hygiene measures regarding exceptional pathogens**

Note to Chapter B16.3 of the German Dialysis Standard: The commission for hospital hygiene and infection prevention at the Robert-Koch-Institut (KRINKO) recommends the application of the Hygieneguideline 2008 (Bundesgesundheitsblatt 2014, 57:696, 719, 721). Thereby the relevant paragraph that is now identically included in the German Dialysis Standard 2014 becomes binding according to the national law of infection protection (Infektionsschutzgesetz §23 (3)).
ANTIMICROBIAL CATHETER LOCK SYSTEM TO PROVIDE PATENCY AND INFECTION CONTROL
Prophylaxis against catheter related bloodstream infections:
Central venous catheters (CVC) are used as short or long term vascular access devices in hemodialysis, oncology, ICU and total parenteral nutrition. High risks for CVC malfunction are catheter related infections (CRI). These infections may be triggered by microbial colonization of the catheter and the microorganisms can spread from here to the bloodstream. CRI may develop septic symptoms which require the immediate removal of the catheter.

TauroLock™ catheter lock solutions do not contain antibiotics and were developed for prophylactic use. They reduce catheter related infections significantly (~90%).

The combination of citrate (4%) with (cyclo)-taurodilidone and heparin/urokinese has excellent anticoagulative and anti-microbial properties also against resistant microorganisms like MRSA und VRE.

Therefore TauroLock™ is recommended in different guidelines such as the Hygiene Guidelines completing the German Dialysis Standard, the guidelines from the German Society of applied Hygiene in Dialysis and the evidence-based recommendations of the German Society for Paediatric Oncology and Hematology (GPOH).

Prophylaxis against biological occlusion in the catheter:
The TauroLock™ Catheter Lock System contains a threefold prophylaxis against occlusion in the catheter: All locking solutions contain 4% citrate as anticoagulant. This concentration removes calcium safely and effectively from the clotting cascade.

The optional use of low concentrated heparin supports an additional anticoagulative effect via binding to antithrombin. The prophylactic use of TauroLock™-HEP500 (which contains 25,000 IU of urokinase) achieves the best prophylaxis against occlusion by prevention of biological clotting.

The decision which locking solution is most adequate depends on the individual patient situation. The alternative use of different locking solutions in the same catheter (e.g. TauroLock™-HEP500, TauroLock™-U25.000) is possible.
TauroLock™ is bactericidal and fungicidal within 2 hours:

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<thead>
<tr>
<th>TauroLock</th>
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Legend:
- S. aureus (MRSA)
- P. aeruginosa
- A. niger
- E. coli
- C. albicans
- S. epidermidis

*detection limit (10 cfu/ml)*

Clearly superior in comparison to the activity of Citrate and Heparin:

<table>
<thead>
<tr>
<th>46,7% Citrate</th>
<th>30% Citrate</th>
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If used prophylactically, TauroLock™ prevents the development of a biofilm on the surface of the catheter lumen:

- **Heparin Lock — 7 months implanted** — S. epidermidis biofilm covers surface completely
- **TauroLock™** — 5 months implanted — No colonization
Instillation of TauroLock™

Follow the manufacturer’s instructions that accompany the particular vascular access product utilized. Specific catheter lock volumes are associated with each device.

1. Flush the device with 10 mL of saline.
2. Withdraw TauroLock™ from the container using an appropriate syringe.
3. Instill TauroLock™ slowly (not more than 1 mL per second, infants and children less than two years of age not more than 1 mL per 5 second) into the access device in a quantity sufficient to fill the lumen completely. Consult the manufacturer’s instructions for the specific fill volume or specify fill volume during implantation. The volume has to be strictly respected. TauroLock™ will remain inside the access device until the next treatment.
4. If aspiration of TauroLock™ is needed and possible, it should be withdrawn from the port/catheter and discarded prior to initiation of next treatment.
5. Flush the device with 10 mL of saline.

Product selection for application

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TauroLock™ catheter lock solutions are available in different containers:

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<td>Vial (5 x 5 mL)</td>
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<td>✓</td>
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Manufacturer:

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Fax: +49 931 304299-29

ISO13485

85100/08/14
1. GUIDELINES AND RECOMMENDATIONS


1.3. Clinical Practice Guidelines for Renal Association (United Kingdom), R. Frock, M. Kumwenda (2011)

1.4. Guidelines for the Prevention of Infection in Dialysis (2011) CDC, Center of Disease Control, USA, 2011

2. PUBLICATIONS: PROPHYLAXIS OF INFECTION IN DIALYSIS


2.2. Prophylaxis of catheter-related bloodstream infection with a citrate–taurodine-containing lock solution M. G. H. Betjes and M. van Agteren, Nephrol Dial Transplant. 2004, 19:1544–1551. Department of Internal Medicine, Division of Nephrology, Erasmus Medical Center, Dijkerhoef Rotterdam.


2.9. Preventing infections of central venous catheters with a taurolidine/citrate solution O. Xramenko, Western Galilee Hospital, Nahariya, Israel, Presentation at EDTNA/ERCAC Congress 2006, Madrid.


3. PUBLICATIONS: PROPHYLAXIS OF INFECTION IN ONCOLOGY


3.5. Taurodine is effective in the treatment of central venous catheter-related bloodstream infections in cancer patients M. Koldehoff, J. L. Zazrekowski, Int. J. Antimicrobial Agents (2009), 491-496.


4. PUBLICATIONS: PROPHYLAXIS OF INFECTION IN PARENTERAL NUTRITION


5. PROVIDE PATIENTS TO ACCESS DEVICES BY USING UROKINASE


6. PUBLICATIONS ON ANTIBACTERIAL ACTIVITY OF TAUROLOCK – PREVENTION OF BIOFILM


WWW.TAUROLOCK.COM
Loss of antimicrobial effect of trisodium citrate due to ‘lock’ spillage from haemodialysis catheters

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ABSTRACT

Background. Due to its reported antimicrobial effects, hypertonic citrate (46.7%) is a widely used catheter lock solution, but following instillation, citrate inevitably spills into the systemic circulation. This process is mainly driven by hydraulic effects during instillation and density differences between blood and lock solution. Hence, in haemodialysis catheters, intra-luminal citrate concentration ranges from 0% (at the tip in catheters with side holes), 3% (between the side holes and the highest point of the catheter) to 46.7% (at the Luer end) with possible differences in antimicrobial effects. We investigated in vitro the antimicrobial effect of pure citrate 46.7%, citrate 46.7% diluted with saline and blood to a net concentration of 3% (=citrate 3%), and of citrate-free blood, simulating in vivo conditions in different catheter sections.

Methods. Time–kill studies measuring the antimicrobial effect of citrate 46.7%, citrate 3% and citrate-free blood were performed with overnight cultures of Escherichia coli (E. coli) and Staphylococcus aureus (S. aureus).

Results. Citrate 46.7% reduced the number of E. coli by 2 log units but after 24 h, 10⁶ CFU/mL were still present. Citrate 3% and citrate-free blood had no antimicrobial effect on E. coli. Citrate 46.7%, citrate 3% and citrate-free blood had scarce antimicrobial effect on S. aureus within 24 h.

Conclusions. Spillage of catheter lock solution leading to reduced intra-luminal citrate concentrations considerably reduces the antimicrobial effect of citrate 46.7% on E. coli. As none of the solutions tested had relevant antimicrobial effect on S. aureus, the antimicrobial effect of 46.7% citrate lock solution in vivo has to be seriously questioned.

Keywords: catheter-related bloodstream infection, central venous catheter, lock solution, lock spillage, trisodium citrate

INTRODUCTION

Central venous catheters (CVCs) provide reliable venous access for haemodialysis and are still in common use despite the emphatic recommendations in national guidelines favouring arteriovenous fistulae [1]. Anticoagulative, fibrinolytic or antimicrobial catheter lock solutions are used as prophylaxis or therapy to maintain the intra-luminal patency of CVCs in an attempt to avoid thrombosis and infection [2, 3]. Trisodium citrate (30–46.7%) is widely used and considered effective in reducing catheter-related bloodstream infections (CRBSI) in haemodialysis patients [4, 5]. However, the use of hypertonic citrate remains controversial due to reported adverse events such as a decrease of ionized calcium due to chelation, which can cause cardiac arrhythmia, or pulmonary embolisms when plasma proteins precipitate in the lumens of the CVC [6–11].

Instillation of the listed filling volume of lock solutions, such as citrate 46.7%, is generally believed to ‘lock’ the CVC, suggesting that the entire injected volume remains inside the CVC. Recent studies report, however, that ~20% of the catheter locking volume leaks into systemic circulation at the time of instillation [12]. This spillage during instillation is a physical consequence of a parabolic flow profile within cylindrical tubes, such as CVCs. Furthermore, gravity-induced loss of lock solution into the systemic circulation should be considered when lock solutions with different densities compared with blood (e.g. trisodium citrate 46.7%) are used [13–15].
Finally, in catheters with side holes, the lock solution is completely washed out of the tip region immediately after instillation, representing additional loss of locking anticoagulant [16]. The aforementioned flow and exchange phenomena cause inhomogeneous intra-luminal dilution of lock solution which, depending on the individual design, divides the catheter into sections with different citrate concentrations. The antimicrobial effect of citrate 46.7% can therefore be expected to vary among these catheter sections. Previous in vitro studies using pure citrate lock solution showed an antimicrobial effect for concentrated citrate [17]. In vivo studies, however, reported conflicting results regarding the efficacy of concentrated citrate in reducing CRBSI in haemodialysis patients [4, 18].

The objective of this in vitro study was to investigate the antimicrobial effect of pure citrate 46.7%, citrate 46.7% diluted with blood and saline to a net concentration of 3% (=citrate 3%), and of citrate-free blood, simulating in vivo conditions in different sections of haemodialysis catheters ‘locked’ with citrate 46.7%.

### Materials and Methods

The methodological approach is based on recent reports regarding mechanisms and quantification of the lock spillage phenomenon [12, 13, 16, 19]. In brief, physical effects following instillation of trisodium citrate 46.7% into the lumens of a catheter dilute the lock solution and divide the catheter into different sections corresponding to the particular citrate concentrations (Figure 1). As the citrate concentration within the ‘connector section’ remains nearly unaffected by dilution, pure trisodium citrate 46.7% was used to characterize the antimicrobial effect in this catheter section. The residual trisodium citrate concentration of ∼3% within the ‘core section’ arises from two successive physical effects. Firstly, the saline used to flush and clear the catheter of blood is not completely replaced when a Newtonian lock solution (aqueous solution) is used. This is due to the parabolic flow profile and incomplete saline removal from the catheter wall during injection. The magnitude of this saline dilution is in the range of 20% regardless of injection time and patient position (injection spillage). Secondly, the density difference between trisodium citrate 46.7% and blood promotes gravity-induced seepage of citrate out of the catheter, which is accompanied by blood inflow into the catheter. The end point of this process is reached after 20 min, resulting in a final citrate concentration of ∼3% (gravitational spillage). The exchange of trisodium citrate 46.7% against blood continues up to the highest point of the catheter, i.e. the vertex, which is usually the venous insertion point in patients with jugular or subclavian catheters. The section boundaries in our model were set accordingly. To prepare the citrate 3% test solution, pure trisodium citrate 46.7% was consecutively diluted with saline and with blood. A mixture of four parts citrate 46.7% with one part saline 0.9%, corresponding to the initial dilution effect of 20% (injection spillage), was the source of further dilution with blood (gravitational spillage) to a net concentration of 3% trisodium citrate. In haemodialysis catheters with side holes, the region between the tip and the most distal side hole, the ‘tip section’, contains citrate-free blood following complete wash-out of lock solution within seconds after instillation. The antimicrobial effect of pure citrate 46.7%, citrate 3% and citrate-free blood thus was investigated by time-kill studies adopted from previous literature [17]. Briefly, *Staphylococcus aureus ATCC 29213* and *Escherichia coli ATCC 35218* were cultured overnight in brain heart infusion broth and diluted with each of the test solutions to a final concentration of $10^8$ CFU/mL. At the start of the microbiological tests and at 1, 3 and 24 h, 100 µL of the suspensions were plated on chocolate agar (*S. aureus*) or MacConkey blood agar plates (*E. coli*) (Biomerieux, Marcy l’Etoile, France) and incubated for 24 h at 37°C in ambient air. Colonies were then counted and recalculated to CFU/mL. All tests were performed in duplicate. Saline 0.9% (Fresenius Kabi AG, Bad Homburg, Germany) and blood from a healthy adult male donor,
provided via sterile venipuncture technique into blood collection tubes (Vacuette®, Greiner Bio-One, Austria), was used for dilution of trisodium citrate 46.7% (Department of Hospital Pharmacy, Medical University of Graz, Austria). Written informed consent was obtained from the blood donor. Haematocrit, albumin and total protein of the blood sample were measured. The study was approved by the Ethics Committee of the Medical University of Graz, Austria.

RESULTS

Compared with baseline, the pure citrate 46.7% lock solution reduced the number of E. coli by 2 log units but, after 24-h incubation, 10⁶ CFU/mL were still present (Figure 2). Citrate 3% and citrate-free blood had no antimicrobial effect on E. coli (Figure 2). Citrate 46.7%, citrate 3% and citrate-free blood barely reduced the number of S. aureus within 24 h of incubation (Figure 3). Sample characteristics of blood used for citrate dilution were haematocrit 0.42, albumin 4.5 g/dL and total protein 6.5 g/dL.

DISCUSSION

The current standard for in vitro evaluation of the antimicrobial effect of lock solutions focuses solely on the pure lock solution [20, 21]. This might be inadequate when Newtonian fluids (aqueous solutions) and fluids that differ from blood in terms of fluid density such as hypertonic citrate are investigated. Physical phenomena, i.e. sequential dilutions with saline (injection spillage) and blood (gravitational spillage), as well as the wash-out effect in catheters with side holes, considerably reduce the intra-luminal citrate concentration. For Newtonian fluids, standard tests may only be valid for the region between the Luer connector and the highest point of the catheter (vertex), where the lock solution is conserved in nearly its original concentration. Numerous factors such as lock spillage should be considered to better translate in vitro tests into general practice recommendations.

Recently, Polaschegg [19] published a method for the quantitative measurement of catheter lock spillage. When citrate 46.7% was used as locking anticoagulant, within 20 min a citrate concentration approaching 3% was found in the catheter section containing a blood/trisodium citrate 46.7% mixture. These results are reasonable due to the high-density difference between trisodium citrate 46.7% (1.24 g/cm³) and blood (∼1.05 g/cm³) [10, 22]. Even a very low-density difference of 0.0094 (0.9%) causes leakage of lock solution in exchange against blood within 60 min under the influence of gravity (gravitational spillage) [13]. Subsequently, we developed a distributed model of intra-luminal citrate concentrations in standard haemodialysis catheters filled with citrate 46.7% (Figure 1). Similarly, in femoral catheters, gravity forces citrate 46.7% to leak out in any patient position, supine or head down tilt, with the tip of the catheter lowered relative to its insertion point into the vein. Hence, the same gravitational spillage process, lock dilution with blood, as occurs in jugular or subclavian catheters, can be assumed. The only exception might be patients in permanent upright position with a femoral catheter.

In previous in vitro studies, pure citrate 30% reduced the number of E. coli by 3 log units whereas no antimicrobial effect was detected in S. aureus time–kill studies [17]. In our study, we obtained comparable results with a 2-log unit reduction of E. coli but nearly unchanged colony counts of S. aureus after 24 h of incubation in pure citrate 46.7% (Figures 2 and 3). These results are, however, only representative for the connector section. Neither citrate 3%, representing intra-luminal conditions within the core section, nor citrate-free blood, representing the tip section in catheters with side holes.

FIGURE 2. Time–kill curves of E. coli suspended in citrate 46.7% (solid line with circles), citrate 3% (dashed line with squares) and blood without citrate (dotted line with triangles) after 0, 1, 3 and 24 h of incubation.
holes, reduced _E. coli_ or _S. aureus_ colony counts (Figures 2 and 3). From a clinical point of view, the antimicrobial effect of trisodium citrate catheter lock solution may therefore be considered insufficient. _Staphylococcus aureus_ is one of the leading causes of CRBSIs in haemodialysis patients; however, based on this study, its intra-luminal catheter colonization is affected neither by citrate 3% (core section) nor by citrate 46.7% (connector section). Although citrate 46.7% had some effect on _E. coli_ in the connector section only, intra-luminal catheter eradication cannot be expected from our experiments and previous data [17]. In addition, bacterial load in CRBSI reaches 10^6 CFU/mL or more and so is, in fact, much higher than in previous _in vitro_ tests [17, 23]. The catheter lock spillage phenomenon resulting in lower intra-luminal citrate concentrations will abolish any antimicrobial effect of citrate 46.7% on non-adherent (planktonic) organisms freely floating in liquid medium in proximal catheter sections, as shown by our experiments. Conflicting clinical data about the efficacy of concentrated citrate in reducing CRBSI in haemodialysis patients have been reported. A randomized, controlled trial by Weijmer et al. [4] comparing citrate 30% with heparin 5% showed a significant reduction of the CRBSI rate attributed to citrate use. That trial, however, included a heterogeneous group of patients with both acute and chronic renal failure using uncuffed and cuffed CVCs. In an observational retrospective analysis, there was a decrease in CRBSIs due to _S. aureus_ after the standard locking anticoagulant was changed from heparin 5000 IU/mL to citrate 46.7% [5]. However, an antimicrobial effect against planktonic _S. aureus_ is absent throughout all intra-luminal catheter sections, as shown by our data and previous studies [17]. It is noteworthy that CRBSI is caused only by spread of planktonic bacteria from the biofilms on CVCs into the bloodstream [24]. Power et al. [18] reported a randomized, controlled trial comparing citrate 46.7% against heparin 5% in a homogeneous cohort of chronic haemodialysis patients with a single type of cuffed jugular catheters. There was no significant difference in rates of exit-site infection or CRBSI between the two groups. The authors concluded that the use of citrate 46.7% to prevent CRBSI was not justified. Interestingly, a wide range of baseline CRBSI rates from <1 up to 17/episodes per 1000 catheter-days have been reported in clinical trials before initiation of antimicrobial or antibiotic lock solutions [4, 18, 25]. Regarding CRBSI prevention, some studies using heparin or citrate 4%, i.e. solutions that have no proven antimicrobial effect on planktonic bacteria, showed data comparable with those using antimicrobial lock solutions [26–28]. Confounding factors such as differences in adherence to catheter exit site care or line connection techniques may have considerable bearing on study results and conflicting data. A wider adoption of care standards by health personnel is desirable and might limit the use of antimicrobial lock solutions to high-risk patients [29, 30]. _In vitro_ studies have demonstrated that citrate inhibits _S. aureus_ biofilm formation [31]. Biofilm formation, thought to be a key factor in development of CRBSI, is probably similarly influenced by the lock spillage phenomenon, just as is the effect on planktonic bacteria. Citrate 46.7% is not able to kill planktonic bacteria sufficiently; however, a substantial effect due to chelation of Ca^{2+} and Mg^{2+} to reduce biofilm formation and CRBSI is conceivable [32]. Even low citrate concentrations ranging from 0.5 up to 4% efficiently inhibit _S. aureus_ biofilm formation; blood components present in different catheter sections might also have an influence, but this has not yet been studied _in vitro_ [31, 33]. Additionally, the outer surface of the extravascular catheter segment was the most common site of bacterial growth in a study of chronic haemodialysis patients with positive blood cultures [34]. As the outer surface of catheters is not affected by lock solutions, these findings should be considered in designing further strategies to prevent CRBSI. The lock spillage effect is also important for antibiotic lock

![Time–kill curves of Staphylococcus aureus suspended in citrate 46.7% (solid line with circles), citrate 3% (dashed line with squares) and blood without citrate (dotted line with triangles) after 0, 1, 3 and 24 h of incubation.](http://ndt.oxfordjournals.org/)

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techniques. In catheters filled with vancomycin, there was a decreasing gradient along the catheter lumens [35]. Sequential intra-luminal dilution of antibiotic lock solutions with saline (injection spillage) and blood (gravitational spillage) may promote failure of antibiotic lock therapy and even induce bacterial resistance in prophylactic use. The blood influx into the catheter reduces the antibacterial effect of certain antibiotics due to plasma protein binding [36]. Biocompatible thixotropic gels rather than purely Newtonian fluids can be expected to completely lock the vascular access without spillage and might be a future direction for antimicrobial lock solutions but they have not yet been tested.

Our study has some limitations. Firstly, the spillage during injection also causes saline dilution within the connector section; however, the very small amount of dilution was not taken into account and can be neglected for in vitro testing. Secondly, to quantify the antimicrobial effect within the core section, time-kill studies were conducted with a single citrate concentration. Actually, due to the parabolic flow profile during lock instillation (instillation spillage) as well as during blood inflow into the catheter (gravitational spillage), the experimental data might differ from the in vivo quantification and shorten the connector section resulting in further reduction of antimicrobial effect [10, 19]. Finally, in vitro quantification of antimicrobial activities inevitably requires some dilution of the studied lock solution. Thus, in vitro results cannot be completely extrapolated to in vivo settings.

In conclusion, spillage of catheter lock solution leading to reduced intra-luminal citrate concentrations considerably reduces the antimicrobial effect of citrate 46.7% on E. coli. As there was no relevant antimicrobial effect on S. aureus, even with citrate 46.7%, its antimicrobial potential to prevent infections in dialysis patients has to be seriously questioned. Furthermore, as inevitable lock spillage alters the antimicrobial effect of a given lock solution in general, additional in vitro tests accounting for dilution effects might better characterize the ‘real’ antimicrobial properties of lock solutions.

CONFLICT OF INTEREST STATEMENT

None declared.

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Sodium Citrate Versus Heparin Catheter Locks for Cuffed Central Venous Catheters: A Single-Center Randomized Controlled Trial

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Background: Sodium citrate has antibacterial and anticoagulant properties that are confined to the catheter when used as a catheter lock. Studies of its use as a catheter lock have suggested its efficacy in preventing infection and bleeding complications compared with sodium heparin.

Study Design: Open-label randomized controlled trial of 2 catheter locks to examine the hypothesis that sodium citrate catheter locks will reduce catheter-related bacteremia and exit-site infection.

Settings & Participants: 232 consenting long-term hemodialysis patients in 4 satellite dialysis units to a large dialysis program with protocolized treatment and targets. All patients were using twin-catheter single-lumen Tesio-Caths (MedComp, Harleysville, PA).

Intervention: 6 months’ use of 46.7% sodium citrate (citrate) or 5% heparin (heparin) locked postdialysis in the dead space of the central venous catheter.

Outcomes & Measurements: Primary end point of catheter-related bacteremia and exit-site infection. Secondary end points of catheter thrombosis defined by the use of urokinase lock and infusion, new catheter insertion, catheter-related admission, blood transfusions, parenteral iron, and erythropoietin requirements.

Results: Catheter-related bacteremia did not differ in the 2 groups, with an incidence of 0.7 events/1,000 catheter-days. There was no significant difference in rates of exit-site infection (0.7 versus 0.5 events/1,000 catheter-days; \( P = 0.5 \)). The secondary end point of catheter thrombosis defined by the use of a urokinase lock was significantly more common in the citrate group, with an incidence of 8 versus 4.3/1,000 catheter-days (\( P < 0.001 \)). Other secondary end points did not differ. Citrate treatment was curtailed compared with heparin because of a greater incidence of adverse events, with a mean treatment duration before withdrawal of 4.8 ± 2.0 versus 5.7 ± 1.2 months, respectively (\( P < 0.001 \)).

Limitations: Low baseline catheter-related bacteremia and exit-site infection event rates may have underpowered this study. High adverse-event rates may have been related to high-concentration citrate that led to increased overspill and reduction in lock volume. This may also explain the increased rates of thrombosis in this group.

Conclusion: Widespread and long-term use of 46.7% citrate catheter locks with Tesio-Cath access is not justified by this study.


INDEX WORDS: Hemodialysis; heparin; sodium citrate; catheter lock.
initially as an alternative for patients with heparin sensitivity. However, in vitro, citrate has a demonstrated antibacterial effect, whereas heparin has none.

Overspill of 15% to 30% of the catheter lock after injection of a volume of solution equal to the dead space of the CVC specified by the manufacturer is recognized from in vitro studies. Inadvertent spillage of catheter lock and systemic anticoagulation is not desirable for hemodialysis patients who are at heightened risk of bleeding from medical interventions and gastrointestinal causes. This bleeding tendency may be compounded by uremic platelet dysfunction and use of antiplatelet agents. Citrate has an anticoagulant action confined to the catheter because its action is overwhelmed by the concentration of ionized calcium in the systemic circulation. In contrast, small amounts of heparin have a systemic anticoagulant effect because of its greater potency.

To date, there have been mainly small and short-term studies suggesting the benefits of citrate over heparin catheter locks on these grounds. One randomized controlled trial comparing 30% citrate with 5% heparin showed a significant decrease in infective and bleeding complications, but the trial was in a mixed group of patients with both acute renal failure and end-stage renal failure (ESRF) with use of both uncuffed and cuffed CVCs.

Our study is the first randomized controlled trial to compare the use of 46.7% citrate and 5% heparin catheter locks exclusively in patients with ESRF and a single type of cuffed single-lumen CVC, the TC, intended as long-term vascular access. We compare the effects of these catheter locks on the primary end point of catheter-related infection and the secondary end points of measures of catheter patency, dialysis efficacy, and bleeding.

METHODS

A total of 232 hemodialysis patients with internal jugular venous TCs (Bio-Flex TC) gave consent and were randomly assigned to open-label treatment for 6 months (Fig 1). All patients who had been on dialysis therapy for longer than 90 days were eligible. Patients with a bleeding diathesis, an intervention, or pathological state within 3 months of entry that would heighten the risk of bleeding and those with hypocalcemia were excluded from the study. Patients were assigned to treatment arms by using single random-number allocation. However, randomization was unintentionally weighted by a systematic error: odd random numbers from 0 to 9, and including 0, were allocated to citrate (ie, 0, 1, 3, 5, 7, and 9), and even random numbers from 0 to 9 excluding 0 were allocated to heparin (ie, 2, 4, 6, and 8). This resulted in increased treatment allocation to citrate: 132 patients were randomly assigned to citrate, and 100, to heparin.

Administration of Catheter Locks and TC Care

TCs were manipulated by using strict aseptic technique, and catheter locks were instilled slowly in a volume equal to the dead space of the TC to minimize overspill at the end of each dialysis session. Each administration was registered. Catheter locks were evacuated at the beginning of the next dialysis session. An additional 20 mL of blood was evacuated before venesection for blood tests to avoid contaminating test samples. This blood was then instilled back to the patient after tests had been performed to prevent wastage. The exit site was cleaned at each dialysis session with sterile normal saline followed by chlorhexidine solution, 4%, and air dried before application of a bio-occlusive dressing. No antimicrobial ointment was applied to the exit site. Adverse effects were systematically assessed and recorded at each dialysis session. Patients were asked to report any symptom and were not led by questioning to report any symptom in particular during the course of the study. However, as a result of the consent process, patients were aware that citrate might induce digital and facial paresthesia. Digital and facial paresthesias with the use of citrate were considered an indication of overspill, and the catheter lock volume was reduced by 0.1 mL at the next dialysis treatment.

TC Infection

Dialysis patients with pyrexia, defined as a tympanic temperature of 38°C or greater with or without a systemic inflammatory response were investigated for a TC-related source of infection by means of exit-site swabs and multiple blood cultures before starting antibiotic therapy. Antibiotic therapy starts preempted microbiological confirmation of infection and followed an initial protocol of intravenous vancomycin, 500 mg, after dialysis as Gram-positive cover tailored to maintain trough levels greater than 10 mg/L and oral ciprofloxacin, 250 mg, twice daily as gram-negative cover. Antibiotics were continued according to culture results and antibiotic sensitivity for a minimum of 2 weeks.

Exit-site swabs were used if there were exudates or crust, redness, or induration at the exit site. Exit-site infections were treated initially with oral clarithromycin, 250 mg, twice daily and oral ciprofloxacin, 250 mg, twice daily, and adjustment was made according to response and culture results for a minimum of 2 weeks. Tunnel infections were defined as pain, redness, or induration along the subcutaneous course of the catheter with or without exudates at the exit site. Tunnel infections were treated from the outset with vancomycin and ciprofloxacin, and these were adjusted when culture results were available with the addition of a second appropriate oral antibiotic for a minimum of 4 weeks.

Patients with pyrexia showing a systemic inflammatory response, relative hypotension determined from the indi-
individual patient’s usual range for blood pressure, or persistent tunnel infection were admitted to the hospital. Bacteremia alone did not qualify the patient for admission. If TC-related infection resulted in hypotension requiring inotrope support, persistent bacteremia despite antibiotics, or a tunnel infection for longer than 3 days, the TC was removed and a new catheter was sited.

TC Dysfunction

Target blood flow for the TC was 350 mL/min or greater. Suboptimal blood flow less than 250 mL/min and/or decreasing dialysis adequacy was used as a marker for TC dysfunction. Single-pool Kt/V (spKt/V) was measured monthly, and 3 sequential monthly decreases in spKt/V, irrespective of magnitude, defined decreasing dialysis adequacy. Catheter displacement or kinking was excluded by means of a chest x-ray. Each affected patient then had 5,000 units of urokinase locked into each catheter of the TC for 2 hours, and dialysis was reattempted on an outpatient basis. If this strategy failed, patients were admitted to the ward for a 12-hour intraluminal infusion of 12,500 units of urokinase into each catheter of the TC, as previously described in the literature.16 If this final strategy was unsuccessful, the TC was removed and replaced using the over-the-wire technique. Oral antiplatelet or anticoagulant agents were not used with the intent to improve blood flow rate.

Dialysis Adequacy and Hematologic and Biochemical Variables

All patients had thrice-weekly dialysis using low-flux synthetic AM-BIO-1000Wet hemodialyzers (Asahi Kasei Medical Europe GmbH, Frankfurt, Germany). Dialysis adequacy was measured by using spKt/V on a monthly basis by means of the Daugirdas method.17 Postdialytic urea was sampled after 1 minute by using the slow-flow method. Measurements of spKt/V were subject to monthly consultant audit, and the dialysis prescription was adjusted to achieve a target spKt/V of 1.6 or greater. Routine hematology and biochemistry tests were performed monthly.

Power, Statistics, and Ethical Permission

The bacteremia rate at our center was established to be 0.68 events/1,000 catheter-days through our participation in a Centers for Disease Control and Prevention study.18 With recruitment of 100 patients to each arm for this 6-month
One hundred thirty-two patients were administered 46.7% citrate catheter locks (DuraLock C; MedComp) and 100 patients were administered 5% heparin catheter locks (Monoparin sodium heparin, 5,000 IU/mL; CP Pharmaceuticals, Wrexham, UK). There were no significant differences between treatment groups at the time of randomization (Table 1).

Cumulative patient survival at 6 months was 95% for both groups (log-rank test, $P = 0.9$) censored for drop-out defined by change in dialysis modality, transplantation, or use of an AVF. There were 5 deaths in the citrate group (2 from bronchopneumonia, 2 from sudden cardiac death, and 1 from nonhemorrhagic cerebrovascular accident) and 5 deaths in the heparin group (4 from sepsis unrelated to the CVC, and 1 from sudden cardiac death; Table 2).

There were no significant differences in the primary end point of CVC-related bacteremia or exit-site infection rates (Table 2). Rates of cumulative survival free of CVC-related bacteremia at 6 months were 91% in the citrate group and 89% in the heparin group (log-rank test, $P = 0.7$; Fig 2).

In regard to secondary end points, CVC-related admission rates and new CVC insertion rates were not significantly different (Table 2). Rates of cumulative catheter survival at 6 months with optimal flow were 95% in the citrate group and 100% in the heparin group (log-rank test,

### Table 1. Baseline Characteristics of Study Participants

<table>
<thead>
<tr>
<th></th>
<th>Citrate</th>
<th>Heparin</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>132</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Men/women</td>
<td>73:59</td>
<td>59:41</td>
<td>0.6</td>
</tr>
<tr>
<td>Age (y)</td>
<td>63 ± 14</td>
<td>62 ± 13</td>
<td>0.5</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>62 (47)</td>
<td>44 (44)</td>
<td>0.7</td>
</tr>
<tr>
<td>South Asian</td>
<td>38 (29)</td>
<td>32 (32)</td>
<td>0.7</td>
</tr>
<tr>
<td>Afro-Caribbean</td>
<td>29 (22)</td>
<td>20 (20)</td>
<td>0.7</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (2)</td>
<td>4 (4)</td>
<td>0.5</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25 ± 6</td>
<td>26 ± 6</td>
<td>0.3</td>
</tr>
<tr>
<td>Diabetes</td>
<td>56 (42)</td>
<td>44 (44)</td>
<td>0.8</td>
</tr>
<tr>
<td>Dialysis vintage (mo)</td>
<td>37 ± 40</td>
<td>34 ± 28</td>
<td>0.5</td>
</tr>
<tr>
<td>Tesio-Cath vintage (mo)</td>
<td>19 ± 14</td>
<td>20 ± 17</td>
<td>0.4</td>
</tr>
<tr>
<td>Mean single-pool Kt/V</td>
<td>1.7 ± 0.3</td>
<td>1.7 ± 0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Blood flow rate (mL/min)</td>
<td>350 ± 40</td>
<td>353 ± 33</td>
<td>0.6</td>
</tr>
<tr>
<td>Venous pressure (mm Hg)</td>
<td>247 ± 45</td>
<td>243 ± 43</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Note: Values expressed as mean ± SD or number (percent) unless noted otherwise.

### Table 2. Study Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Citrate</th>
<th>Heparin</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths (/1,000 patient-y)</td>
<td>94 (31-222)</td>
<td>102 (34-246)</td>
<td>0.9</td>
</tr>
<tr>
<td>Mean single-pool Kt/V over 6 mo</td>
<td>1.7 ± 0.2</td>
<td>1.7 ± 0.2</td>
<td>0.9</td>
</tr>
<tr>
<td>Catheter-related admissions (/1,000 catheter-d)</td>
<td>0.9 (0.56-1.5)</td>
<td>0.7 (0.36-1.2)</td>
<td>0.4</td>
</tr>
<tr>
<td>New catheters (/1,000 catheter-d)</td>
<td>0.5 (0.22-0.89)</td>
<td>0.7 (0.36-1.2)</td>
<td>0.4</td>
</tr>
<tr>
<td>Catheter-related bacteremia (/1,000 catheter-d)</td>
<td>0.7 (0.40-1.2)</td>
<td>0.7 (0.36-1.2)</td>
<td>0.9</td>
</tr>
<tr>
<td>Exit-site infections (/1,000 catheter-d)</td>
<td>0.7 (0.36-1.2)</td>
<td>0.5 (0.24-1.0)</td>
<td>0.5</td>
</tr>
<tr>
<td>Urokinase locks (/1,000 catheter-d)</td>
<td>8 (6.6-9.2)</td>
<td>4.3 (3.4-5.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>12-h urokinase infusions (/1,000 catheter-d)</td>
<td>0.2 (0.03-0.46)</td>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>Bleeding complications</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mean hemoglobin over 6 mo (g/dL)</td>
<td>12.0 ± 0.3</td>
<td>12.1 ± 0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Mean ferritin over 6 mo (mg/mL)</td>
<td>510 ± 9</td>
<td>543 ± 9</td>
<td>0.2</td>
</tr>
<tr>
<td>Blood transfusions (/1,000 catheter-d)</td>
<td>0.8 (0.44-1.3)</td>
<td>0.52 (0.2-1.0)</td>
<td>0.3</td>
</tr>
<tr>
<td>Mean intravenous erythropoietin dosage (U/wk)</td>
<td>8,534 ± 55</td>
<td>8,070 ± 57</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Note: Values expressed as mean ± SD and event rate (95% confidence interval). Conversion factor: hemoglobin in g/dL to g/L, ×10. No conversion is necessary for ferritin in ng/mL and μg/L.
There was significantly greater use of urokinase locks in the citrate group, but not 12-hour urokinase infusions (Table 2). Dialysis adequacy was equivalent for both groups (Table 2). No significant clinical bleeding episodes were seen. Mean hemoglobin and ferritin levels were not statistically different. Blood transfusion and erythropoietin requirements were equivalent for the 2 groups (Table 2).

Adverse Effects

There were no withdrawals from heparin treatment because of adverse effects. Citrate was associated with more reported side effects. Seventy-one of 132 patients who received citrate (3.72 events/1,000 catheter-days) had side effects ($P < 0.001$). These resolved in 24 of 132 patients (34%) with dose reduction. Twenty of 132 patients (15%) receiving citrate withdrew early from the study because of adverse effects of metallic taste and facial and/or digital paresthesia. As a result, citrate treatment was curtailed compared with heparin (mean follow-up, 4.8 ± 2.0 versus 5.7 ± 1.2 months, respectively; $P < 0.001$). Cumulative study survival rates after withdrawal for adverse effects were 85% for citrate versus 100% for heparin after 6 months ($P = 0.02$; Fig 4).

**DISCUSSION**

Citrate was not associated with a reduction in infection. There was increased use of thrombolytic therapy to restore functional patency in the citrate arm, but no differences in CVC survival, dialysis adequacy, hospital admissions, or consequences of bleeding. This study is the first randomized controlled trial to compare citrate with heparin as catheter locks for a single twin-catheter system in a large number of prevalent hemodialysis patients.

The only randomized controlled trial published to date, by Wejimer et al.15 analyzed a similar number of patients (n = 291), although only 98 had tunneled cuffed catheters (5 were

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**Figure 3.** Cumulative study survival censored for suboptimal flow. Sodium citrate, blue line; heparin, red line.

**Figure 4.** Cumulative study survival censored for withdrawal through adverse effects. Sodium citrate, blue line; heparin, red line.
TCs and the remainder were dual-lumen catheters. Patient demographics was considerably different in their study: 30% were on twice-weekly hemodialysis therapy, 25% were on treatment for acute renal failure rather than established on long-term hemodialysis therapy, and 30% were on oral anticoagulation therapy (coumarins). In the study by Weijmer et al, all enrolled patients had a newly inserted catheter versus 2 patients in our study with a newly inserted TC. Mean catheter vintage in our study was 24 months. Patients were of a younger dialysis vintage in the study by Weijmer et al (mean, 1.2 years on dialysis therapy) compared with our study (mean, 3 years on dialysis therapy). Other studies to date are heterogeneous in terms of design: type of study, concentration of locking solutions, and type of catheter studied (Table 3).

In vitro studies had shown that citrate has a dose-dependent antibacterial effect that surpasses heparin related to the chelation of calcium ions and not the osmolality of the solution. Ash et al showed that the bactericidal effect of citrate in vitro was manifest only with concentrations greater than 23%. Shanks et al showed that citrate at a concentration of 2% or greater prevented the in vitro formation of bacterial biofilm by staphylococci on a number of synthetic surfaces. This may help explain in part the antimicrobial effect of citrate catheter locks. In vivo, Ash et al noted a significant decrease in the incidence of catheter-related bacteremia with differing concentrations of citrate in a prospective cohort study of patients with ESRF: the incidence of symptomatic bacteremia was 4.13% with heparin, 1.79% with 23% citrate ($P < 0.05$), and 0% with 47% citrate ($P < 0.05$). Subsequently, the randomized controlled trial by Weijmer et al compared 30% citrate versus 5% heparin and showed a significant decrease in CVC-related bacteremia with citrate (1.1 versus 4.1 events/1,000 catheter-days; $P < 0.001$). Analysis of the 98 patients with tunneled cuffed catheters in this study shows a decrease in CVC-related bacteremia from 4.2 to 0.8 events/1,000 catheter-days with the use of 30% citrate. These results were used to power our study. However, at our center, we had a much lower bacteremia rate in the control group (0.7 events/1,000 catheter-days) than in the study by Weijmer et al. This could be the result of catheter type and our catheter care protocols and is likely to have reduced the impact of citrate in our study compared with others. A recent Canadian prospective cohort study reported less catheter-related bacteremia in the 4% citrate group, but a change in exit-site care may have confounded the data. No beneficial effect of citrate on the incidence of exit-site infections has been shown.

Small controlled studies have reported equivalent short-term patency rates with citrate versus heparin. Buturovic et al showed in 30 patients with ESRF that 4% citrate catheter locks in temporary single-lumen CVCs maintained an equivalent duration of access patency as heparin or polygeline. Stas et al compared 30% citrate catheter locks with 5% heparin catheter locks in 11 patients with ESRF and cuffed double- and single-lumen CVCs using a crossover study design. There were no CVC occlusions, no need for thrombolytics, and no significant differences in thrombus formation for either type of lock. Hendrickx et al prospectively evaluated 5% citrate versus 5% heparin in 19 patients with ESRF with cuffed single-lumen CVCs and found a significantly larger number of dialysis sessions with thrombus formation in those treated with citrate, but no differences in dialysis adequacy, blood flow, number of occlusions, or urokinase use. Weijmer et al found no difference in the num-

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of Patients</th>
<th>Citrate (%)</th>
<th>Heparin (%)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buturovic et al, 1998</td>
<td>30</td>
<td>4</td>
<td>5</td>
<td>No difference</td>
</tr>
<tr>
<td>Stas et al, 2001</td>
<td>11</td>
<td>30</td>
<td>5</td>
<td>No difference</td>
</tr>
<tr>
<td>Hendrickx et al, 2001</td>
<td>19</td>
<td>5</td>
<td>5</td>
<td>No difference in use of thrombolytic or infection</td>
</tr>
<tr>
<td>Weijmer et al, 2005</td>
<td>291</td>
<td>30</td>
<td>5</td>
<td>No difference in use of thrombolytic, reduced central venous catheter–associated bacteremia with citrate</td>
</tr>
<tr>
<td>Grudzinski et al, 2007</td>
<td>189</td>
<td>4</td>
<td>10</td>
<td>No difference in use of thrombolytic</td>
</tr>
<tr>
<td>Lok et al, 2007</td>
<td>129</td>
<td>4</td>
<td>5</td>
<td>Reduced use of thrombolytic with citrate</td>
</tr>
</tbody>
</table>
number of catheters removed because of poor flow or amount of urokinase used in their trial of 30% citrate versus 5% heparin catheter locks. We show significantly greater use of urokinase catheter locks in patients treated with 46.7% citrate. Three of 132 patients in the citrate group accounted for 32% of the urokinase locks used, and this conferred statistical significance to the difference between groups. The reduction in lock volume because of side effects may have increased the rate of thrombosis in the citrate arm. More recently, Grudzinski et al found no difference in the rate of flow-related catheter change, use of thrombolytic therapy (alteplase), and bacteremias between 4% citrate catheter locks versus 10% heparin catheter locks in a retrospective analysis of their Canadian hemodialysis cohort. In an accompanying Canadian prospective longitudinal cohort study comparing 4% citrate versus 5% heparin catheter locks, there were fewer CVC exchanges and a longer time to thrombolytic use and catheter change in the citrate-treated group. It is worth noting that although these 2 studies looked at patients on the hemodialysis program, ie, not treated for reversible acute renal failure and with tunneled CVCs, there was heterogeneity in the type of CVC used, and this may have influenced results. More than 50% of patients in the study by Grudzinski et al were on warfarin therapy, with greater than 80% of these to maintain access patency. It is not clear whether patients were on anticoagulant or antiplatelet treatment in the study by Lok et al.

There were no changes in markers of bleeding in our study; patient hemoglobin levels, ferritin levels, and blood transfusion and erythropoietin requirements were similar. No bleeding events were recorded in either group. This is in contrast to Weijmer et al, who found less bleeding in the 30% citrate group. Despite evidence of more overspill in our study with greater concentrations of citrate, the anticoagulant effect of citrate would have been overwhelmed in the circulation. The study by Weijmer et al included patients with acute renal failure and uncuffed catheters who might have been at greater risk of bleeding, compounded by the combination of oral anticoagulation in 30%. Only 1 patient in our study was concurrently on warfarin therapy (heparin-treated group).

Citrate was associated with a significant number of early withdrawals (15%) because of adverse effects, greater than the 10% quoted in a prior study using 47% citrate. Patients in that study received 47% citrate for only 3 months in a unit with a 10% prevalence of TCs. In a study using a dual-lumen cuffed catheter (AshSplit Cath; MedComp, Harleysville, PA), remarkably, only 1 of 207 patients reported side-effects. Studies show systemic leakage of 15% to 30% of the lock solution in a variety of catheters. An in vitro study showed that the majority leaked from side holes on the catheter tip. The number of symptoms associated with citrate in our study suggests a significant degree of systemic leakage from venous catheters. This may relate to the side holes in TCs. Also, this may relate to our use of the highest concentration of citrate clinically available, which is more dense and thereby more prone to overspill. Overspill may be caused by variable intraluminal volume because TCs can be cut to a desired length after insertion and repair. Fill volumes are clearly marked on the catheter. As in the study by Weijmer et al, patients were asked to report symptoms after catheter locking in a systematic way in our study, although reporting bias may have influenced results as a consequence of the informed consent process for the trial. Concern about 47% citrate had been raised after a report of a hemodialysis patient who received a total of 10 mL of 47% citrate through a CVC and subsequently experienced cardiac arrest. There were no adverse cardiovascular events in the citrate group in our study. High-dose citrate is not approved by the Food and Drug Administration for use as a catheter-locking solution in the United States.

The financial cost of citrate catheter locks at £8.34/lock was 16 times greater than that for heparin, at £0.5/lock, in the course of this trial. Since the conclusion of the trial, the cost of the citrate lock has decreased to £2.65/lock, with no significant change in the cost of heparin.

Based on the lack of a significant effect on catheter-related infection and the greater rate of adverse effects, widespread use of 46.7% citrate is not justified by this study.

ACKNOWLEDGEMENTS

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REFERENCES

Trisodium citrate induced protein precipitation in haemodialysis catheters might cause pulmonary embolism

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Abstract

Background. The locking anticoagulant plays a decisive role in the patency of central venous catheters (CVCs) used for haemodialysis. During injection, the hydraulic effects inevitably cause lock solution to spill into the systemic circulation. Density differences between whole blood (WB) and the lock solution cause further gravity-induced seepage of lock solution. This is followed by an influx of WB into the catheter, also described for trisodium citrate, which is a common agent for serum protein precipitation. Embolic complications from haemodialysis catheters locked with hypertonic trisodium citrate have been reported. We aimed to investigate protein precipitation in trisodium citrate locked catheters as a possible cause of pulmonary embolisms.

Methods. In vitro, WB and trisodium citrate (concentrations ranging from 4.7 to 46.7%) mixtures in a ratio of 1:4 were used to assess protein precipitation. Additionally, WB/trisodium citrate mixture was pumped through a 20-μm mesh filter, simulating pulmonary vessels, and filtrate pressure was measured. In vivo, listed filling volumes of haemodialysis catheters locked with trisodium citrate 4% (n = 10), 10% (n = 10), 20% (n = 10) or 46.7% (n = 10) were aspirated and then analysed for protein precipitation.

Results. In vitro, protein precipitation capable of causing filter occlusion was observed in test solutions containing trisodium citrate above a concentration of 12%. In vivo, protein precipitation was detected in all samples from the CVCs filled with trisodium citrate 46.7% (n = 10) and 20% (n = 10). In contrast, there were no signs of precipitation in samples from the catheters filled with trisodium citrate 4% (n = 10) or 10% (n = 10).

Conclusions. Our in vitro results demonstrate that protein precipitates inside haemodialysis catheters when trisodium citrate is used above the concentrations of 12%. Precipitated protein may have contributed to the pathophysiology of reported embolisms from haemodialysis catheters filled with hypertonic trisodium citrate. Based on our findings, we suggest that trisodium citrate lock solution up to the concentration of 10% can be used safely.

Keywords: central venous catheter; haemodialysis access; lock spillage; protein precipitation; trisodium citrate lock solution

Introduction

Central venous catheter (CVC) use, representing a major vascular access modality for haemodialysis, is steadily increasing despite recommendations favouring arteriovenous fistulae [1, 2]. Maintaining the intraluminal patency of a CVC requires instillation of a prophylactic locking anticoagulant, such as heparin [3]. Trisodium citrate (citrate) is currently used worldwide and considered a safe alternative to heparin [4, 5]. However, the use of hypertonic citrate remains controversial [6–8].

Although leakage of catheter lock solutions into the systemic circulation of ~20–25% has been repeatedly demonstrated [9, 10], in the European Union lock solutions are regarded as a ‘medical device’ rather than a systemic drug [11]. The spillage during instillation of the listed filling volume into the CVC is a consequence of laminar flow distribution within the catheter and thus cannot be avoided. Further loss of lock solution due to gravity should be considered if lock solutions (e.g. citrate 30 or 46.7%) with a density higher than blood are used [12–14]. In this case, the mentioned seepage is followed by a reverse whole blood (WB) flow into the CVC and has been observed in vivo [13].

Hence, this WB remains inside the CVC while the catheter is not in use. This is of utmost importance if the instilled lock solution has potential protein precipitating effects. Since the 19th century, ‘salting out’ of plasma proteins using high concentrations of salts (e.g. citrate) has been a common technique to precipitate a target protein [15, 16]. Reported embolisms from CVCs used with hypertonic citrate locking solution might be due to serum protein precipitation in the CVC [17].

The objective of this study was therefore to investigate whether there might be protein precipitation in citrate-locked CVCs. In vitro test solutions consisting of WB and
citrate in a ratio of 1:4 (20% WB to 80% citrate) were used to assess precipitation. Citrate catheter locks were analysed in vivo after aspiration of the filling volume noted on each port of the CVC. Additionally, in vitro filtration experiments using a 20-μm mesh filter, representing the diameter of pulmonary arterioles [18], were performed.

Materials and methods

In vitro

WB containing 0.6% citrate from blood donors was obtained from the Department of Blood Group Serology and Transfusion Medicine (Medical University of Graz, Austria). A stock solution of 46.7% citrate (Department of Hospital Pharmacy, Medical University of Graz, Austria) was diluted with distilled water to the concentrations indicated in Table 1 (dilution series). One millilitre of WB was mixed with 4 mL of citrate (concentrations ranged from 4.7 to 46.7%). A wide range of citrate concentrations mixed with WB was studied. The tests were repeated in triplicate at room temperature (20°C). Standardized investigation for precipitation was performed as described below.

In vivo

The study was approved by the Ethics Committee of the Medical University of Graz, Austria (registration number: 21-359 ex 09/10). Written informed consent was obtained from 40 prevalent patients using a tunneled jugular CVC for haemodialysis treatment (Medcomp Split Cath® III 14FR:32 cm with side holes). The study period, representing the time between lock installation and removal, was standardized as 48 h. Citrate 14FR/32 cm with side holes). The study period, representing the time between lock installation and removal, was standardized as 48 h. Citrate in a ratio of 1:4 (20% WB to 80% citrate) was diluted with distilled water to the concentrations indicated in Table 1 (dilution series). One millilitre of WB was mixed with 4 mL of citrate (concentrations ranged from 4.7 to 46.7%). A wide range of citrate concentrations mixed with WB was studied. The tests were repeated in triplicate at room temperature (20°C). Standardized investigation for precipitation was performed as described below.

Standardized investigation for precipitation

The sample was centrifuged at 20°C and 4000 r.p.m. for 10 min (Eppendorf centrifuge 5810R, Germany). If there were visible signs of precipitation, serum and precipitate were transferred into polypropylene tubes and centrifuged at 20°C and 10 800 r.p.m. for 10 min (Abbott Laboratories centrifuge 3530, Germany). The supernatant was removed and the precipitate washed twice with citrate. The precipitate was dissolved in 0.9% sodium chloride. Albumin and total protein were determined with an automated analyser (Modular; Roche Diagnostics, Germany) using standard reagents from Roche Diagnostics. To investigate whether the precipitate might reversibly become soluble again, we added 2 mL of WB to the precipitate of the in vitro tests and gently shook the mixture for 5 min.

In vitro filtration experiments

WB from a healthy male volunteer with a haematocrit of 0.43 was mixed with hypertonic citrate 46.7% in a ratio of 1:4 (20% WB to 80% citrate) resulting in a net concentration of citrate of 37.4% and a dilution of plasma proteins to 20%. This solution, as well as undiluted WB, was pumped through a 20-μm mesh filter in a filter holder with 25 mm diameter using a syringe pump. The 20-μm mesh filter simulates pulmonary arterioles [18]. A calibrated pressure transducer (Merit Medical Systems, Inc., South Jordan, UT) positioned between syringe and filter holder allowed continuous recording of the filtration pressure using software operating under LabView 6.0 (National Instruments, Austin, TX).

Results

In vitro

Using different concentrations of citrate lock solutions (4.7–46.7%), protein precipitation was detected visually in test solutions containing citrate above a concentration of 12% in all test series performed (Table 1, Figure 1). The analysis of the precipitate showed that albumin was the predominant protein. Furthermore, we were able to detect IgG, beta- and pre-beta lipoproteins. There was no evidence for the presence of thrombin, fibrinogen or other clotting proteins. The precipitate could be dissolved again by the addition of WB.

In vivo

Protein precipitation was visually detected in all CVCs filled with hypertonic citrate 46.7% solution (n = 10) as

![Fig. 1. The arrow indicates the precipitated protein within the test tube (B3) after centrifugation of the test solution consisting of 1 mL WB and 4 mL citrate 32.7%. The tubes with test solutions containing citrate of <12% in the dilution series (B6 with 11.7%; B7 with 9.3% and B8 with 4.7%) revealed no signs of protein precipitation.](http://ndt.oxfordjournals.org/)

Table 1. Results of in vitro protein precipitation test series

<table>
<thead>
<tr>
<th>Test solution</th>
<th>Citrate concentration of lock solution (%)</th>
<th>Visible precipitation</th>
<th>Predominant protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citrate/WB&lt;sup&gt;a&lt;/sup&gt;</td>
<td>46.7</td>
<td>++ +</td>
<td>Albumin</td>
</tr>
<tr>
<td>Citrate/WB&lt;sup&gt;b&lt;/sup&gt;</td>
<td>42.0</td>
<td>++ +</td>
<td>Albumin</td>
</tr>
<tr>
<td>Citrate/WB&lt;sup&gt;c&lt;/sup&gt;</td>
<td>37.4</td>
<td>++</td>
<td>Albumin</td>
</tr>
<tr>
<td>Citrate/WB&lt;sup&gt;d&lt;/sup&gt;</td>
<td>32.7</td>
<td>+</td>
<td>Albumin</td>
</tr>
<tr>
<td>Citrate/WB&lt;sup&gt;e&lt;/sup&gt;</td>
<td>28.0</td>
<td>+</td>
<td>Albumin</td>
</tr>
<tr>
<td>Citrate/WB&lt;sup&gt;f&lt;/sup&gt;</td>
<td>23.4</td>
<td>+</td>
<td>Albumin</td>
</tr>
<tr>
<td>Citrate/WB&lt;sup&gt;g&lt;/sup&gt;</td>
<td>18.7</td>
<td>+</td>
<td>Albumin</td>
</tr>
<tr>
<td>Citrate/WB&lt;sup&gt;h&lt;/sup&gt;</td>
<td>16.3</td>
<td>+</td>
<td>Albumin</td>
</tr>
<tr>
<td>Citrate/WB&lt;sup&gt;i&lt;/sup&gt;</td>
<td>14.0</td>
<td>+</td>
<td>Albumin</td>
</tr>
<tr>
<td>Citrate/WB&lt;sup&gt;j&lt;/sup&gt;</td>
<td>11.7</td>
<td>+</td>
<td>Albumin</td>
</tr>
<tr>
<td>Citrate/WB&lt;sup&gt;k&lt;/sup&gt;</td>
<td>9.3</td>
<td>+</td>
<td>Albumin</td>
</tr>
<tr>
<td>Citrate/WB&lt;sup&gt;l&lt;/sup&gt;</td>
<td>4.7</td>
<td>+</td>
<td>Albumin</td>
</tr>
</tbody>
</table>

<sup>a</sup>The test series was performed repeatedly, revealing the same results.

<sup>b</sup>Test solutions consisted of 1 mL WB and 4 mL citrate lock solution (concentrations ranged from 4.7 to 46.7%) representing the conditions inside the catheter during the interdialytic interval.

<sup>c</sup>Precipitation was assessed with a visual score, ranging from +++ (much) to ¬ (none).

<sup>d</sup>WB sample characteristics for in vitro testing: albumin 4.6 g/dL and total protein 6.6 g/dL.
The results for the WB experiment are illustrated in Figure 2. In vitro filtration experiments

The pump was started at Time 0 with a flow of 199.5 mL/min. After 0.5 min, the pressures began to rise. With WB only, the pressure settled at 3 mmHg. For the WB plus citrate mixture, the pressure began to increase after 2.5 min up to a peak pressure of 1700 mmHg, indicating filter occlusion.

Discussion

Guidelines for clinical use of antimicrobial lock solutions for CVCs demand tests to exclude visual precipitation that occurs when some antibiotics are mixed with heparin or citrate [19]. Precipitation observed in a given antibiotic–anticoagulant mixture is considered to indicate pharmacological incompatibility and consequently to alter the mixture’s antimicrobial activity [20–22]. In practical application, lock solution is always split into the systemic circulation when instilled [9] or has to be completely injected if the lock solution cannot be aspirated from the catheter. Therefore, the presence of any visible precipitation or turbidity of the tested lock solution can be defined as physical incompatibility of an antibiotic lock solution [23–25].

The current standard for exclusion of precipitation of anticoagulant or antimicrobial agents used as lock solutions for CVCs focuses solely on the pure lock solution [26, 27]. This, however, is an inadequate approach if the lock solution analysed differs from WB in terms of fluid density. If such lock solutions are evaluated, these findings require in vitro test solutions containing a certain amount of WB to rule out protein precipitation. We therefore performed in vitro and in vivo analyses to demonstrate that there could be precipitation in CVCs filled with citrate. Our results confirm that protein, predominantly albumin, is ‘salted out’ if citrate is used at concentrations >12% (Table 1, Figure 1).

In general, spillage of lock solution has two underlying mechanisms: unavoidable spillage due to laminar flow distribution inside the CVC during instillation [9] and, additionally, gravity-induced seepage out of the CVC if there are differences in fluid density between WB and lock solution [12–14]. The fluid density of WB is ~1.05 g/cm³ compared to 1.24 g/cm³ of citrate 46.7% solution. Consequently, gravity forces citrate to leak out of the CVC, to be replaced by WB (Figure 3) [13]. The catheter design may slightly affect the time course of the exchange process of citrate for WB but in any case, the region between the side holes is flushed out within seconds. Although catheters may be deformed slightly when inserted, an impact on the fluid exchange that is governed by laws of hydraulics is not expected [28]. The catheter position (jugular versus femoral) influences the lock spillage effect. While the spillage due to injection (20–25%) is unaffected by the catheter position, the density (gravity force)-induced spillage is, on the contrary, greatly affected by the relative catheter position. Assuming a vertical position of the patient, WB enters a catheter in the jugular position but not in the femoral position. However, if the point of insertion into the femoral vein is relatively higher compared to the tip of the catheter, as is to be expected in the supine position, the same process as in jugular catheters can be predicted. Therefore, hypertonic citrate lock cannot be regarded a safe option either in jugular or in femoral catheters.

The reasoning for using a ratio of 1 part WB to 4 parts citrate solution is based on the physics of the lock solution exchange process, which results in a time-dependent range of concentration products. When the high-density lock solution is injected, 20–25% will spill out immediately, resulting in a mean concentration of the lock solution of only 50% at the proximal end of the tube [9]. The less-dense WB then rises in the centre of the tube, forming a parabolic cone as is known from laminar flow. Simultaneously, the dense lock solution flows down alongside the wall of the tube. The volumes of entering WB and spilt lock solution are identical. The flow is laminar and the hydraulic cross sections behave proportionally to the viscosities. Citrate diffuses into the rising WB column. In the immediate contact zone, the concentration of citrate is close to the lock concentration. The concentration will be decreased towards the centre of the rising WB column. This means that during this exchange process, different parts of blood will be exposed to different concentrations of citrate. Further mixing will occur when the rising WB reaches the highest point and is

![Fig. 2. Filtration experiment: pressure versus time curves for WB (dashed line) and WB mixed with trisodium citrate (solid line). Pump was stopped at maximum pressure.](image)

![Fig. 3. Shortly after instillation of citrate 46.7% lock solution, the venous part of the catheter (see arrow) was completely filled with WB up to the clamp. The patient was supine. Gravity forced citrate lock solution to leak out of the catheter followed by WB influx. Depending on the position of the catheter connections relative to the catheter tip, blood may rise until it becomes visible in the venous and/or arterial line.](image)
diverted to the wall of the lumen before succumbing to gravity because it has picked up citrate during ascension and is now denser than WB. With the catheter in a non-vertical position, the flow pattern will become asymmetric. The altered effective height increases the exchange time, resulting in increased precipitation inside the catheter.

During the exchange of lock solution for WB, the catheter plasma proteins are exposed to a range of citrate concentrations up to a maximum that is the concentration of the pure lock solution. In order to simulate the exposure to high citrate concentration, a ratio of 1 part WB to 4 parts citrate was used, this is a compromise that results in a reduced protein concentration. In reality, mixing in the catheter is by radial diffusion of citrate into WB resulting in a higher (more favourable for precipitation) citrate–protein concentration product. We questioned whether the precipitate caused by citrate is able to occlude lung vessels and performed further in vitro ‘filtration experiments’ to address this problem. These experiments revealed that the precipitate induced by the addition of 46.7% citrate to WB contains large numbers of particles with diameters $>20 \mu m$ that are able to occlude lung vessels. From these experiments, it cannot be excluded that the precipitate also contains particles $<20 \mu m$. Such particles may pass the lung capillaries but may occlude vessels in other tissues [29]. Additional in vitro analyses revealed that the precipitate could be re-dissolved by the addition of WB, suggesting that protein precipitation might also be reversible in vivo. However, because of the short transfer time of the precipitate from the catheter to the pulmonary circulation, dissolution is unlikely.

Chronologically and pathophysio logically, one might hypothesize that following the WB influx into the catheter, citrate induces intraluminal protein precipitation. Subsequently, some of the precipitate will leak out of the catheter. Thus, protein embolism might occur not only when the lock solution and the precipitate are injected as a bolus; subclinical protein embolisms might occur additionally following every single instillation of citrate. Possible side effects include pulmonary hypertension, which has also been claimed to be a consequence of air microbubble embolism during haemodialysis [30]. Tumour micro-embolism, when clusters of tumour cells occlude small pulmonary arterioles [31], or lipoprotein micro-embolism from microaggregates following application of unfiltered fresh frozen plasma [32], might represent entities similar to our findings. If the precipitate occludes the side holes and the tip, which might be the case for catheters with a tapered tip, this process is interrupted. Aspiration of the lock solution becomes difficult or impossible. Bolus injection might then cause pulmonary protein embolism. Our hypothesis that protein embolism is of clinical relevance is well supported by different observational studies in humans, experimental studies in animals and theoretical models. Clark et al. [33] published a model predicting that occlusion of small vessels (extra-acinar pulmonary arteries) can have a significant effect on pulmonary arterial pressures. Experimental observations have shown that small emboli (diameter $<170 \mu m$) can have a disproportionate effect on pulmonary vascular resistance compared with larger emboli for the same tissue occlusion [34]. Our findings thus might explain why the use of hypertonic citrate locking solution resulted in symptomatic emboli in a reported series of eight patients [17]. We hypothesize that the precipitated protein might have played a crucial role in the pathophysiology of these embolisms. Although the authors pointed out that hypertonic solutions are more likely to seep out of the CVC, thus increasing risk of clotting and causing thrombo-embolism if injected, we hold the view that precipitated protein may have contributed to the pathophysiology of the reported embolisms. Clinical signs indicating protein precipitation could be catheter malfunction and difficulties in aspirating the citrate catheter lock, as occurs with thrombus formation. In these situations, especially flushing the catheter could cause life-threatening embolic complications [17].

Although no serious adverse events ‘that could be contributed to the locking solution’ were reported in a randomized controlled trial comparing heparin to 30% citrate, we believe that hypertonic citrate is not without risk for the patient [5]. We conclude that the protein precipitation observed inside the catheter, due to the density-induced WB influx, should be regarded as a physical incompatibility. We suggest that lock solutions in general should be investigated according to the criteria for solutions given intravenously. This would include testing to rule out (protein) precipitation [24, 25].

Our study has several limitations. Firstly, precipitation was examined visually and smaller amounts might have been missed. Secondly, precipitation analyses were conducted at room temperature. In fact, precipitation depends on temperature, and the quantitative difference caused by the body room temperature differential was not taken into account. Nevertheless, the salting out reaction in vitro (at room temperature) is slightly less than in vivo (body temperature). To demonstrate that plasma proteins precipitate in the vicinity of a concentrated citrate lock solution, the test setup (dilution, room temperature) has a high safety margin in the sense that it underestimates the effect quantitatively. The risk of reporting a false positive effect is remote. Although in vitro analysis revealed a limit of 12% with regard to this temperature effect, we advise a concentration limit of 10%. Thirdly, also in terms of physical influence, in vivo conditions are not completely comparable to in vitro conditions. Furthermore, WB for in vitro experiments contained 0.6% citrate, but the impact on the citrate concentration for the mixture of WB and citrate in a ratio of 1:4 is far less than 1% and therefore negligible.

In conclusion, our results demonstrate that citrate induces protein precipitation in CVCs.

To avoid severe embolic complications, we suggest 10% as the maximum admissible concentration of citrate lock solutions.

Furthermore, each lock solution containing plasma precipitating agents with density characteristics different from WB, whether less or more dense, should be evaluated for protein precipitation prior to clinical use.

Conflict of interest statement. None declared.

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Observational Study of Need for Thrombolytic Therapy and Incidence of Bacteremia using Taurolidine-Citrate-Heparin,Taurolidine-Citrate and Heparin Catheter Locks in Patients Treated with Hemodialysis

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ABSTRACT

Catheter-related blood stream infections may be reduced by interdialytic locking with Taurolidine, a nontoxic antimicrobial agent. A formulation of 1.35% Taurolidine in 4% citrate (TC) is associated with a greater need for thrombolysis to maintain catheter patency than 5000 U/ml heparin. Our aim was to determine whether addition of 500 Units/ml of heparin to TC reduces the need for thrombolysis. TCH (1.35% taurolidine, 4% citrate and 500 U/ml heparin) was compared to TC and Heparin 5000 U/ml using retrospective data. Hundred and six adult hemodialysis patients with internal jugular tunelled intravascular catheters using TCH were compared with 34 patients using TC and 34 patients using heparin 5000 U/ml respectively. Outcomes were time to first use of thrombolysis and bacteremia rates. TCH reduced the need for thrombolysis compared to TC (hazard ratio, 0.2; 95%CI: 0.06, 0.5; p < 0.001) and was not significantly different from heparin 5000 U/ml (hazard ratio, 1.4; 95%CI: 0.5, 3.9; p = 0.5). The bacteremia rates from all causes were 1.33, 1.22 and 3.25 per 1000 catheter-days (p < 0.001) in the TCH, TC and heparin groups respectively. Addition of 500 U/ml heparin to TC reduces the need for thrombolysis without increasing bacteremia and may achieve patency comparable to heparin 5000 U/ml.

Catheter-related blood stream infections (CRBSI) is the second most common cause of morbidity and mortality in patients with hemodialysis (1). Several randomised clinical trials and meta-analyses have demonstrated the efficacy of antimicrobial catheter locks including gentamicin, minocycline and cefotaxime for the prevention of CRBSI (2–7), but systemic complications and the emergence of bacterial resistance are potential concerns with antibiotic locks. There are reports of gentamicin-resistant enterobacter species developing when gentamicin is employed as a lock (8–10).

Taurolidine is a broad-spectrum antimicrobial agent that has been reported to reduce bacteremia rates in patients with hemodialysis, nutrition and pediatric catheters (11–13). It acts by a direct effect on bacterial cell walls and has never been associated with resistance (12,14–16). In a recent multi-center double-blind randomized-controlled clinical trial, we compared catheter locks containing 1.35% taurolidine in 4% citrate (TC) with heparin 5000 U/ml and demonstrated a trend to reduction of all-cause bacteremia and a significant reduction in gram-negative infection (17). The potential benefit was offset by a greater need for thrombolytic therapy for occlusion or flow problems. This confirmed results from three other non-randomised trials (12,14,18). Since then, a preparation of taurolidine-citrate with 500 U/ml of heparin (TCH) has become available. We wished to determine whether the addition of 500 U/ml heparin achieved patency rates comparable with 5000 U/ml heparin without affecting antimicrobial activity. It was no longer considered possible to undertake a randomised comparison with heparin because the Renal Association and European Renal Best Practice now recommend that an antimicrobial agent should be included in catheter locks (19,20). We therefore compared prospectively all-cause bacteremia rates and need for thrombolytic therapy using TCH with retrospective data from our original trial (17).
Subjects and Methods

Patients

The study was undertaken at one of three centers (Center A), which had participated in a double-blind randomised trial comparing TC with 5000 U/ml unfractionated heparin (17). To exclude a center effect, only patients who had dialysis at Center A were included. For this reason, numerical values are different from those previously reported (17). Patients were dialyzed at one central and five satellite dialysis units. All patients requiring a new tunneled intravascular catheter between March 1 and December 31, 2009, which was the censor date, were included.

Study Procedures

The details of the original trial have been described elsewhere (17). After completion of the trial, Center A used TCH as the standard lock for new dialysis catheters from the time of insertion and after every dialysis. All adult patients aged >18 years receiving tunneled intravascular catheters in an internal jugular vein for hemodialysis were included in the study. Data on the use of thrombolytic therapy were collected prospectively by the nursing staff and recorded on an Excel database. Results of all blood cultures were collected prospectively, and the microbiology laboratory records of all patients were checked to ensure that no positive blood culture was overlooked. The catheter lock solutions were drawn into a syringe by nursing staff at the end of dialysis, and the exact locking volume was injected into the catheter lumens.

Thrombolytic therapy was given when dialysis was impossible because of poor or no flow. This was usually given when the blood flow rate was 150 ml/minute or less. A locking volume of either urokinase 5000 U/ml or tissue plasminogen activator 1 mg/ml was instilled into both catheter lumens for half an hour before retrying. If flows remained poor, a locking dose of thrombolytic agent was left in the catheter throughout the next interdialytic period. Interdialytic locking with tissue plasminogen activator is outside FDA guidelines but has been used by others (21). Three doses could be given after one episode before considering other options such as catheter removal.

The decision to take blood cultures was based on symptoms, which suggested infection such as fever (temperature >37.5°C) or rigors associated with dialysis. A single-positive blood culture bottle defined a bacteremic episode. Whenever possible, blood samples were obtained using aseptic technique from the side port on the arterial line of the dialysis circuit without interrupting blood flow. If the same organism was isolated in cultures taken <3 weeks apart, it was considered the same infection. When different organisms were identified, or if cultures were more than 3 weeks apart, these were considered separate episodes. Vancomycin and gentamicin were administered intravenously and in catheter locks (final concentration of vancomycin: 100 μg/ml; final concentration of gentamicin 20 μg/ml) made up in heparin (final concentration 5000 U/ml) to treat suspected catheter infections using exact locking volumes depending on the infecting organism.

Materials

Taurolidine-citrate was supplied as 1.35% taurolidine and 4% citrate (Taurolock; Tauropharm AG). Taurolidine-citrate-heparin was supplied as 1.35% Taurolidine, 4% citrate and 500 U/ml (final concentration) heparin (Taurolock-Hep. Tauropharm AG, Würzburg, Germany). Unfractionated heparin was supplied as heparin sodium, Ph Eur (porcine) at 5000 U/ml with 1% benzylic acid as preservative (Braun, Melun, Germany). Urokinase was supplied as powder in 25,000 Unit vials (Syner-KINASE; Syner-Med, Purley, UK) and tissue-type plasminogen activator as powder for reconstitution in 10-mg vials (Alteplase; Boehringer Ingelheim, Bracknell, UK).

Statistical Analysis

Analysis was undertaken on an intention-to-treat basis. A Cox proportional hazard model with saturated linear predictor was used to calculate hazard ratios, their accompanying confidence intervals, and p-values. The effects of lock type (heparin, TC, and TCH), catheter type, catheter site (left- or right-hand side), patient ethnicity group, age, and gender were all accounted for in the linear predictor of the model. Estimated survival curves were derived using Kaplan–Meier analysis. Likelihood ratios (chi-squared) tests were used to compare gender, catheter type, and side of insertion. Catheter survival was calculated after censoring for elective removals and deaths. Removals on account of bacteremia, exit-site infection, and poor flow or occlusion were considered adverse outcomes.

Results

One hundred and six patients receiving TCH were compared with 34 patients who had received TC and heparin, respectively. Demographic details are summarized in Table 1. Approximately 17%, 80%, and 2% of patients with hemodialysis at Center A had a catheter, fistula, or graft at any one time during the study period. Five patients in the TCH, two patients in the TC, and four patients in the heparin group had two catheters during the course of the study. The total numbers of catheter days were 12,036, 5718, and 6471 in the TCH, TC, and heparin groups, respectively. A greater proportion of patients on TCH had left-sided catheters. This reflected logistical difficulty in the original trial recruiting patients who had left-sided catheters.

Fifteen of 174 patients received warfarin for all or part of the study period (11 TCHep, 2 Hep, 2 TC). Reasons for warfarin were as follows: six cardiac conditions, three pulmonary embolisms, two deep vein thromboses, one fistula problem, and one catheter dysfunction.
Time to First Use of Thrombolysis

There was a significant difference between the effects of the three lock types upon the time to first use of thrombolytic therapy ($p < 0.001$) (Fig. 1). The hazard ratio of TCH to heparin was $1.4$ (95%CI: 0.5, 3.9; $p = 0.5$), of TCH to TC was 0.2 (95%CI: 0.06, 0.5; $p < 0.001$), and of TC to heparin was 5.9 (95%CI: 2.2, 16.2; $p < 0.001$).

The hazard ratio for left-sided versus right-sided catheters for TCH was 2.2 (95%CI: 0.8, 5.5; $p = 0.1$), suggesting that the time to first use of thrombolytic therapy may be shorter for left-sided lines. We therefore did an analysis for right-sided lines. The estimated hazard ratio of TCH to heparin was 1.4 (95%CI: 0.5, 4.1: $p = 0.6$), of TCH to TC was 0.24 (95%CI: 0.1, 0.5; $p < 0.001$), and of TC to heparin was 5.7 (95%CI: 2.0, 16.2: $p < 0.001$). The number of left-sided lines was too small to analyze separately.

Time to First Bacteremia

There was a borderline difference between the effects of the three lock types upon the time to first bacteremia ($p = 0.06$) (Fig. 2). The hazard ratio of TCH to heparin was $0.4$ (95%CI: 0.2, 1.0; $p = 0.06$), of TCH to TC was $0.8$ (95%CI: 0.3, 2.1; $p = 0.6$), and of TC to heparin was $0.5$ (95%CI: 0.2, 1.4; $p = 0.2$).

The hazard ratio for time to first bacteremia for left-sided versus right-sided catheters was 1.1 (95%CI: 0.4, 3.0; $p = 0.9$). The hazard ratio for right-sided lines of TCH to heparin was 0.4 (95%CI: 0.2, 1.1; $p = 0.06$), of TCH to TC was 0.8 (95%CI: 0.2, 2.5; $p = 0.7$), and of TC to heparin was 0.5 (95%CI: 0.2, 1.5; $p = 0.2$).

Bacteremias

There were 16, 7, and 21 bacteremias giving rates of 1.33, 1.22, and 3.25 per 1000 catheter days ($p < 0.001$) in the TCH, TC, and heparin groups, respectively. The infection rates for gram-negative bacteremias were 0.42, 0.17, and 1.24 ($p = 0.01$) and for gram-positive bacteremias were 0.91, 1.05, and 2.01 ($p = 0.04$). There were six, three, and nine *Staphylococcus aureus* infections in three, two, and seven patients giving rates of 0.50, 0.52, and 1.39 per 1000 catheter days in the TCH, TC, and heparin groups, respectively ($p = 0.002$).

Catheter Survival

Catheter survival was estimated after censoring for elective removals and deaths (Fig. 3). There was a borderline difference between the effects of the three lock types ($p = 0.1$). The hazard ratios for non-elective line removal were 0.6 (95%CI: 0.2, 2.2; $p = 0.5$) of TCH to heparin, 0.6 (95%CI: 0.2, 2.2; $p = 0.4$) of TCH to TC, and 1.0 (95%CI: 0.3, 3.5 $p = 0.9$) of TC to heparin. The hazard ratio for time to first catheter removal for
left-sided versus right-sided catheters was 2.6 (95% CI: 0.25, 26.5; p = 0.4). There were five non-elective removals in the TCH groups (three catheters fell out, one bacte-
meria, one poor flow rate), six in the TC group (two bacte-
merias, one exit-site infection, three poor flow rate), and six in the heparin group (one catheter fell out, four bacte-
merias, one exit-site infection).

Discussion

The data show that the addition of 500 U/ml heparin to TC substantially reduces the need for thrombolytic therapy compared with TC. This is consistent with two other reports (12,18) using taurolidine in 500 and 2500 U/ml heparin, respectively. There was no sign-
ificant difference compared to locks containing 5000 U/ml unfractionated heparin, although confidence intervals were too wide to exclude a clinically relevant difference. The results also suggest that the addition of heparin does not impair the antibacterial effect of TC.

For many years between 1000 and 10,000 U/ml unfractionated heparin has been the usual anticoagulant in catheter locks. If large amounts leak or are injected systemically, heparin increases the risk of hemorrhage, but lower doses are associated with greater need for thrombolytic therapy (22–24). A recent retrospective study reported a twofold higher need for thrombolysis in patients using locks containing 1000 compared with 2000 U/ml (25). Furthermore, heparin may promote biofilm and antagonise the effect of aminoglycosides (26–28). Thus, the optimum dose of heparin is uncertain. We studied taurolidine-citrate in 500 U/ml heparin because it was commercially available and the manu-
facturers advised that the combination with 4% citrate would give a similar anticoagulant effect to 5000 U/ml heparin.

Trisodium citrate is also an anticoagulant which may have antimicrobial or bacteriostatic properties (23). In a randomised trial, 30% trisodium citrate was associated with a significant reduction of CRBSIs compared with 5000 U/ml unfractionated heparin (29). However, 46.7% and 30% citrate may be unsafe and the FDA issued a warning following a fatality associated with the inadvertent intravenous administration of 46.7% citrate (30,31). This led to the use of lower concentrations of citrate. In one study, 4% citrate reduced the need for thrombolytic therapy and number of days in hospital and was associated with a lower rate of bacteremia when compared to retrospective data using heparin 10,000 U/ml (32). Another study reported that 4% citrate was associated with less need for thrombolysis; although this did not reach statistical significance, more clots were observed during dialysis, and there was no reduction in bacteremia (33). A third study using 4% citrate without an additive found a similar rate of throm-
bolysis and CRBSIs compared with heparin 5000 U/ml (34). On this evidence, The American Society of Diagnostic and Interventional Nephrology proposed 4% citrate as an acceptable choice for patients who cannot tolerate heparin and a recent statement from European Best Practice (ERBP) concludes that “the 4% solution seems to offer at present the best benefit/risk ratio” (19,24).

On the other hand, our reported finding of a greater need for thrombolytic therapy using 4% citrate com-
pared with heparin is consistent with three other reports using TC (12,14,18). Furthermore, 46.7% sodium citrate did not reduce bacteremia and was associated with an increased incidence of catheter thrombosis in another open-label trial (35).

The question arises why these reports reached different conclusions. In the study by Grudzinski et al. (33), which found a trend to reduced need for thrombol-
ysis, the majority of patients were treated with warfarin, which was used to maintain catheter patency in more than 80% of cases. In our current study, only 10% of patients took warfarin at any time and this was intro-
duced for catheter dysfunction on only one occasion. The study by MacRae et al. (34), which found similar rates of thrombolysis in the heparin and citrate groups, was undertaken in patients with established catheters, many of whom had already required thrombolytic therapy or experienced catheter-associated bacteremia and most episodes of catheter dysfunction occurred within 30 days of randomisation in both heparin and citrate groups. This was much sooner than we observed with heparin and TCH when the locking solution was used from catheter insertion. These features suggest a high-risk group of patients, in whom it may have been di-
hard to maintain catheter patency with any agent (34). In Lok’s study, which was a retrospective compar-
sion, 33% (174 of 527) of prevalent catheters were excluded from analysis and the data suggest that a much higher proportion of prevalent patients with hemodialy-
sis required intravascular catheters than at our center (32).

Recently, a clinical trial of another new antimicrobial catheter lock solution containing 7% sodium citrate, 0.05% methylene blue, 0.15% methylparaben, and 0.015% propylparaben (Zuragen) has been reported (36). As in our trial, this was associated with a significant reduction in gram-negative infections. In this study, there was no difference in the proportion of dialyses requiring thrombolysis between the new solution and heparin 5000 U/ml. It is not possible to compare directly with our study because we used time to first use
of thrombolytic therapy as the index of occlusion. However, we collected data (unpublished) on all use of thrombolysis in our original trial. This was required in 2.1% and 0.9% of dialyses in the tauroline-citrate and heparin groups, respectively, compared with 14.8% and 16.4% in the heparin and Zuragen groups in the Zuragen study (36). Individual Unit practices such as the target blood flow, use of warfarin, proportion of patients dialyzing through catheters, and the casemix of patients may explain different rates of thrombolysis in different studies.

Further examination of our data suggested that the time to first use of thrombolytic therapy was shorter for left- compared with right-sided lines. A study of heparin-coated catheters gave similar findings (37). This may reflect the longer and more tortuous anatomy of the left internal jugular and brachiocephalic veins compared with the right internal jugular vein, which opens directly into the superior vena cava. A catheter placed through the right internal jugular lies on the left side of the superior vena cava and enters the middle of the atrium. A catheter placed from the left side lies along the right side of the vena cava and right atrium, where sheathing may reduce blood flow very quickly. Secondly, these patients may have been at risk of catheter complications, because the left side is often chosen when right-sided catheters have failed or are difficult to insert. We therefore undertook a separate analysis for right-sided lines, which confirmed no significant difference for TCH compared with heparin. There were too few left-sided catheters for separate analysis. We recommend separate analysis for left- and right-sided catheters in future studies. Catheter gauge, material, size, the number of side holes, and whether there is an exact volume or slight overfill of the lumen are other factors, which may influence patency and warrant further evaluation.

The bacteraemia rates using TCH of 1.33, 0.91, and 0.50 per 1000 catheter days for all-cause, gram-positive and gram-negative bacteraemia, respectively, were comparable with those achieved with TC. When the three groups were compared, there were significant differences in the rate of both gram-positive and gram-negative bacteraemias with the lowest values for gram-positive infection in the TCH group. The low rate of gram-negative infection was consistent with the findings of the original double-blind trial, but the reduction in gram-positive infection, which included S. aureus, was a new finding which requires explanation. In the original trial, Center A showed a trend toward a reduction in gram-positive as well as gram-negative bacteraemias, which was not observed when combined with data from the other centers. A genuine effect may have been missed because of differences between Centers.

Our study may under-estimate the reduction of CRBSI because we included all bacteraemic episodes. Ideally, a diagnosis of CRBSI would have been based on simultaneous quantitative central and peripheral cultures or catheter segment culture and/or semi-quantitative culture of the internal and external catheter segments, but this would have been difficult to achieve across several dialysis units. While alternative definitions of catheter-related infection have been used (21), these do not conclusively exclude the catheter as a possible source in cases where the chosen criteria are not met. We therefore included all positive blood cultures in the analysis. The study is not therefore specific to CRBSI associated with intraluminal infection and some bacteraemias may have been associated with low-grade exit-site or tunnel infections or infection at unrelated sites. Contamination at the time of blood culture despite aseptic non-touch protocols may have been another confounding factor.

It is of note that there was a trend to improved survival time for first catheters on TCH compared with both TC and heparin. This reflected fewer removals on account of infection compared to heparin and flow problems when compared to TC.

There are limitations to this study. It does not determine the optimal concentration of heparin. Although there was no significant difference compared with heparin 5000 U/ml, time to first use of thrombolysis was intermediate and it is possible that a higher concentration would reduce the need for thrombolytic therapy further, but this might also increase the risk of bleeding and formation of heparin-induced antibodies (20). We investigated taurolidine with 500 U heparin/ml, because it was the only commercially available containing heparin, but a comparison with a higher concentration of heparin is needed. The small number of patients, wide confidence intervals, and comparison with retrospective data are further limitations. We used TCH in all patients requiring tunneled catheters during the study period whereas only 62% of eligible patients had participated in the trial.

In conclusion, this observational study suggests that the addition of 500 U/ml of heparin to taurolidine-citrate catheter locks reduces the need for thrombolytic therapy compared with taurolidine-citrate, without compromising antimicrobial activity.

Transparency Declaration

The original trial was supported in part by a grant from the Preston branch of the North West Kidney Research Association and a grant from the Liverpool Regional Dialysis Unit Fund. Trial Registration: www.isrctn.org study number: ISRCTN07668752

Financial Conflict of Interest

None to declare for any author.

References

FDA Issues Warning on TRICITRASOL

The Food and Drug Administration is issuing an urgent warning to all hospital pharmacies and hemodialysis units that triCitrasol, an unapproved product that has been used to keep bloodlines open, may cause death when infused into patients. TriCitrasol is marketed in individual, sterile, 30 ml glass vials, distributed both individually and in hemodialysis kits.

FDA has learned that a patient died of cardiac arrest shortly after triCitrasol, a 46.7% concentration of sodium citrate anticoagulant, was injected full strength into a hemodialysis permanent blood access catheter that had just been implanted. Rapid or excessive infusion of citrate solutions can cause fatal heart rhythm disruption, seizures or bleeding due to loss of blood calcium.

Other incidents that may involve triCitrasol in the hemodialysis setting are under FDA review.

TriCitrasol is manufactured by Cytosol Laboratories, Braintree, Mass., and is distributed by Medcomp, Harleysville, Pa., and previously by Citra Anticoagulants, Inc. Both Cytosol Labs and Medcomp are voluntarily recalling triCitrasol for use with blood access catheters.

FDA is urging hospital pharmacies and hemodialysis units across the U.S. to stop using the product. Alternative 4% solutions of citrate are available for use in these and most other medical settings.

Because there is a need for this product in some procedures to prepare white cells for transfusion, FDA is working with the company to see that the product currently remains available for this use, which involves dilution.

In an April 9, 2000 letter to its customers, Medcomp announced a recall of its kits (or trays) containing triCitrasol and the Medcomp Ash Split Catheter II, for hemodialysis or apheresis, a blood separation and re-transfusion process. Approximately 3000 Medcomp catheter kits with triCitrasol were distributed nationwide. They were also distributed to Puerto Rico and Canada.

For more information or to report incident contact MedWatch at 1-800-FDA-1088
LETTER TO THE EDITOR

Cardiac arrest following injection of concentrated trisodium citrate

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Sir, – concentrated trisodium citrate (TSC) has been successfully used as a catheter-locking solution in hemodialysis, having several advantages as compared to heparin. The systemic anticoagulant effects of citrate are transient and TSC has bactericidal properties [Ash et al. 2000, Weijmer et al. 2005], thereby reducing the incidence of catheter-related bacteremia. Because of this antibacterial activity, we initiated the use TSC in our intensive care unit. We report a serious complication with concentrated trisodium citrate used as a locking agent for a dialysis catheter.

A 70-year-old female patient was admitted with a severe hypercalcemia: Ca 5.04 mmol.l⁻¹, Ca-ion 2.63 mmol.l⁻¹. An immobile tumor in the left breast suggested a malignancy with ossal metastases as the cause of the hypercalcemia. Hydration and diuretics were not effective to lower the serum calcium level, therefore the patient was admitted to the intensive care unit for continuous veno-venous hemofiltration (CVVH) via a 12 Fr 3-lumen dialysis catheter (Arrow, reading, PA) inserted in the left femoral vein. During hemofiltration filter coagulation was prevented using a continuous infusion of unfractionated heparin. On the second day hemofiltration was stopped temporarily because of filter obstruction. Laboratory results that moment, Na⁺ 144 mmol.l⁻¹, K⁺ 3.6 mmol.l⁻¹, Ca 2.90 mmol.l⁻¹, Ca-ion 1.45 mmol.l⁻¹, Mg²⁺ 0.63 mmol.l⁻¹, and PO₄³⁻ 0.81 mmol.l⁻¹. The patient was in atrial fibrillation, had a ventricular rate of 118 bpm and a blood pressure 107/51 mmHg. After disconnection, the two main ports of the catheter were flushed with normal saline and filled with 30 % TSC. The whole 5 ml ampoule was used, 2.5 ml for each port. Immediately after the injection, a period of cardiac arrest occurred, which lasted 10 seconds. Heart rhythm returned spontaneously after a short period of bradycardia with some escape beats. It was then realized that a similar incident had occurred the day before, though citrate was not thought to have been causative then.

Transient tingling of the fingers and a “metallic” or strange taste are reported to occur after the injection of citrate [Ash et al. 2000, Stas et al. 2001]. However, more serious side effects have also been reported. Two cases of ventricular fibrillation were described after discontinuation of hemodialysis using citrate as anticoagulant. These patients were not successfully resuscitated until they received intravenous calcium [Charney and Salmond 1990]. A second report describes a cardiac arrest shortly after two 5 ml injections in two lumens of a newly inserted catheter [FDA 2000].

The volumes of the main catheter ports of the catheter we used are 1.6 and 1.5 ml, and are indicated on this catheter. Consequently, in our patient overinjection of 1.9 ml of 30 % trisodium citrate had taken place, despite education in the use of TSC previous to its use. This surplus volume contains 2.3 mmol citrate, easily leading to a concentration of > 6 mmol.l⁻¹ passing through the heart. This concentration can lower the serum calcium level in such a manner [Polaschegg and Sodemann 2003], that influx of calcium into the myocardium is impossible.

In conclusion, despite the fact that our patient was hypercalcemic, a citrate overdose probably caused a hypocalcemic bolus of blood, leading to a period of cardiac arrest. Strict adherence to the appropriate volumes of the catheter is mandatory.

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Many hemodialysis patients continue to dialyze using central venous access catheters in clinical practice. Catheters are associated with a number of recognized complications, including infection, catheter-associated fibrin sheath and thrombus leading to malfunction, central venous stenosis, and right atrial thrombus. However, symptomatic catheter embolus rarely is reported. We report our experience of catheter-associated emboli in patients dialyzing with a twin catheter designed with multiple small side holes in combination with a hypertonic citrate locking solution. 8 patients developed symptomatic emboli from catheter-associated thrombus, typically resulting in sudden hypotension and chest pain shortly after starting hemodialysis, with documented pulmonary and cerebral emboli in 3 cases. Catheters with multiple side holes are susceptible to seepage of the catheter locking solution through the side holes and therefore may be at greater risk of catheter thrombus formation. This may be exacerbated by the use of a hypertonic citrate lock given to just fill the internal catheter lumen because hyperosmolar locks are more likely to leave the catheter tip, resulting in increased risk of catheter associated thrombus.


INDEX WORDS: Hemodialysis; catheter; embolus; pulmonary embolism; embolic stroke.

Although arteriovenous fistulas are recommended as the preferred choice of vascular access for hemodialysis patients, many patients dialyze using central venous catheters (CVCs). During the past 30 years, these catheters have changed from relatively simple single-lumen to large-bore dual-lumen catheters designed to achieve high blood flows. The increased size of catheters has led to a number of mechanical complications, including venous thrombosis and thrombus around the catheter tip, including right atrial thrombus. In addition, CVCs can lead to venous medial hypertrophy, with narrowing resulting in venous stenosis, and fibrosis at the site of insertion into the vein, leading to difficulties on removal.

To prevent catheter clotting, heparin typically is placed into the catheter at the end of dialysis as a catheter lock. The concentration of heparin used varies markedly from 1,000 to 10,000 IU/mL. The risk of clot formation is greater using 1,000 IU/mL; however, high-dose heparin locks potentially can lead to leaking of heparin systemically, with the consequent risk of hemorrhage, and also the risk of heparin-induced thrombocytopenia. As a result, other locking solutions have been introduced in an attempt to reduce catheter-associated thrombus and prevent catheter dysfunction.

We have recently observed a number of cases of symptomatic emboli from hemodialysis CVCs in patients in whom hypertonic citrate was used as the locking solution, causing pulmonary and cerebral emboli and symptomatic hypotension during hemodialysis.

CASE REPORTS

All patients described dialyzed using an Ash Split Cath (Medcomp, New Orleans, USA) for vascular access, which then was locked using 43% trisodium citrate (Dura Lock; Medcomp) after dialysis, with 1.6 and 1.7 mL instilled into the artery and venous lumens, respectively. Patients underwent systemic anticoagulation using a single bolus dose of low-molecular-weight heparin, tinzaparin, except for 2 patients, 1 prescribed daily subcutaneous prophylactic tinzaparin, and the other, warfarin (Table 1).

Before the acute presentation, all patients were noted to have developed catheter malfunction, with increased arterial and/or venous pressures during dialysis, or required reversal of blood flow because of poor flows.
Case 1

The patient had been receiving dialysis treatment for 5 years after a scleroderma renal crisis and was attended for routine outpatient dialysis. Flows through the CVC were noted to be decreased, with high arterial and venous access pressures and online recirculation > 10%. The following day, she developed sudden weakness of the right arm and leg and was admitted to the local hospital with a diagnosis of acute cerebrovascular event. This started to recover within 24 hours, and she made a full recovery. She was normoten-sive. A computed tomographic brain scan suggested an ischemic infarct. Additional investigation with a standard transthoracic echocardiogram excluded atrial thrombus or valvular heart disease, and Doppler studies showed normal carotid and femoral vessels. A nuclear medicine isotope brain scan suggested an embolic stroke (Fig 1), and a second echocardiogram using a bubble test showed a patent foramen ovale.

Case 2

The patient, who had been established on dialysis therapy for 4 months, suddenly lost consciousness shortly after starting an outpatient session, with a precipitous decrease in blood pressure. A recent transthoracic echocardiogram had shown a CVC-associated clot, and computed tomographic scanning after collapse showed that the CVC thrombus had disappeared, but he had experienced a left upper lobe pulmonary embolus (Fig 2).

Case 3

An elderly man had been stable on dialysis therapy for 18 months when the nurses had difficulty aspirating the catheter lock. After multiple attempts at aspiration and then forced flushing, he was started on dialysis, but suddenly felt unwell and became markedly hypotensive, reporting nausea and severe left-sided loin and thoracic back pain. He was resuscitated and his symptoms settled after 30–40 minutes. An acute cardiac event was excluded and he declined further immediate investigations. On the dialysis treatment before this event, catheter malfunction with poor blood flows had been recorded. A subsequent isotope ventilation perfusion scan was reported as compatible with a left lower lobe pulmonary embolus.

### Table 1. Characteristics of Patients With Catheter Emboli

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Catheter Position</th>
<th>Duration (mo)</th>
<th>Anticoagulant</th>
<th>Hypotension</th>
<th>Embolus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32</td>
<td>F</td>
<td>Right subclavian catheter</td>
<td>24</td>
<td>Tinzaparin 1,500 IU</td>
<td>No</td>
<td>Cerebrovascular accident</td>
</tr>
<tr>
<td>2</td>
<td>79</td>
<td>M</td>
<td>Left internal jugular central venous catheter</td>
<td>4</td>
<td>Daily tinzaparin</td>
<td>Yes</td>
<td>Pulmonary embolus</td>
</tr>
<tr>
<td>3</td>
<td>64</td>
<td>F</td>
<td>Right internal jugular central venous catheter</td>
<td>3</td>
<td>Tinzaparin 3,500 IU</td>
<td>Yes</td>
<td>Pulmonary embolus</td>
</tr>
<tr>
<td>4</td>
<td>86</td>
<td>M</td>
<td>Left internal jugular central venous catheter</td>
<td>6</td>
<td>Tinzaparin 2,500 IU</td>
<td>Yes</td>
<td>Pulmonary embolus</td>
</tr>
<tr>
<td>5</td>
<td>68</td>
<td>F</td>
<td>Right internal jugular central venous catheter</td>
<td>5</td>
<td>Tinzaparin 2,500 IU</td>
<td>Yes</td>
<td>Pulmonary embolus</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>M</td>
<td>Right internal jugular central venous catheter</td>
<td>3</td>
<td>Warfarin</td>
<td>Yes</td>
<td>Pulmonary embolus</td>
</tr>
<tr>
<td>7</td>
<td>23</td>
<td>F</td>
<td>Right internal jugular central venous catheter</td>
<td>1</td>
<td>Tinzaparin 1,500 IU</td>
<td>Yes</td>
<td>Pulmonary embolus</td>
</tr>
<tr>
<td>8</td>
<td>56</td>
<td>M</td>
<td>Right internal jugular central venous catheter</td>
<td>3</td>
<td>Tinzaparin 4,500 IU</td>
<td>No</td>
<td>Pulmonary embolus</td>
</tr>
</tbody>
</table>

Note: Duration refers to the time since the central venous catheter was inserted; hypotension refers to hypotension shortly after starting dialysis; and type of embolus is categorized as pertaining to brain (cerebrovascular accident) or lung (pulmonary embolus).

![Figure 1. Isotope brain scan (neuralite) shows results of a cerebral embolus in a patient with a patent foramen ovale. Area of cerebral infarction indicated with arrow.](image)
Case 4

This patient had started dialysis therapy 2 months earlier because of underlying myeloma for which he was administered thalidomide and therefore had been prescribed warfarin, although international normalized ratio (INR) was ≤ 1.4. He attended outpatient dialysis, and the nurses had difficulty aspirating the catheter lock and obtaining good blood flows. Shortly after starting dialysis, he reported sudden-onset right-sided pleuritic chest pain associated with marked hypotension and tachycardia. He was resuscitated, and after 30-40 minutes, his symptoms resolved. An acute cardiac event was excluded. A computed tomographic scan a few weeks later showed a new peripheral wedge-shaped area of atelectasis that developed post embolus, then subsequently resolved (Fig 3).

Cases 5-8

Four additional patients (Table 1) who were found to have thrombus attached to the tip of their dialysis CVC with poor blood flows were investigated for sudden hypotensive episodes, typically occurring during the first hour of hemodialysis, associated with acute onset of severe pleuritic chest pain and dyspnea, with either sinus tachycardia or palpitations. Although clinical presentations were highly suggestive of acute pulmonary emboli, specific imaging was not obtained.

DISCUSSION

All cases reported used the same type of CVC, which ends with 2 separate twin catheters, each with a “D”-shaped terminal hole, and multiple side holes in all directions.7 Catheters differ in their performance, and similarly, design also affects leakage of the catheter lock between dialysis sessions.1 The size of the catheter, in particular, catheter diameter, also determines the frequency of catheter-associated thrombus, particularly in pediatric practice.8 The Ash Split Cath has been designed to provide good blood flows and also to create a high shear jet effect around the tips to disrupt catheter-associated thrombus.7 However, it also creates areas of stagnation, thus allowing blood to clot and form a thrombus.9 One of our patients also had pacing wires, and the thrombus formed between the CVC and the pacing wires. Thus, other mechanical devices may increase the risk of thrombus formation and subsequent potential embolization.

Although multiple side holes provide good blood flow, they also may allow the catheter lock to seep out, thus increasing the risk of clotting.10 Seepage of the catheter locking solution increases the risk of clotting and thrombus formation between the last of the side holes and the catheter tip.11

Catheter-associated bacteremias have been the predominant complication of dialysis CVCs, and as such, many dialysis centers have turned from traditional heparinized catheter locks to antiseptics, including various concentrations of citrate and/or antibiotics in heparin solutions,12 because both types of lock have been shown to reduce the risk of catheter-associated bacteremia.13 In our center, the introduction of citrate reduced Staphylococcus aureus CVC-associated bacteremias from 39 to 17 per year. Although citrate locks have been noted to reduce infection rates compared with heparin, they have not been universally reported to reduce catheter malfunction caused by thrombus formation.12

Figure 2. Pulmonary embolus from a central venous catheter tip clot in upper lobe pulmonary artery (arrow).
of citrate used for catheter locks vary from iso-osmolar citrate solutions, typically in combination with an additional antiseptic, such as methylene blue and parabens, to hypertonic solutions ranging in strength from 23%-46.7%. We used a very hyperosmolar solution (4,160 compared with 154 mOsm/kg for unfractionated heparin, 5,000 IU/mL), and some authors have suggested that hypertonic solutions are more likely to be lost by seepage from CVCs. This may explain in part the superior results reported with 4% trisodium citrate.

Shortly after citrate initially was introduced as a catheter locking solution, concerns were expressed about overfilling the catheter and introducing hypertonic citrate directly into the heart. Because of these concerns, only the exact amount required to fill the catheter lumen was instilled, and this may have led to possible underfilling. In addition, our nursing staff only tried to aspirate the catheter lock, then when the locking solution had been removed, the catheter was flushed. This may have led to less mechanical flushing of the catheter compared with when heparin locks were used.

Most, if not all, catheters develop fibrin sheaths, and this may be associated with thrombus in 25%-42% of cases, although clinical sequelae from emboli are uncommon, with very few clinical reports. We report 8 cases, with an estimated prevalence of 4%, probably caused by a combination of events: using a small volume of very hypertonic catheter lock designed to just fill the internal lumen; a catheter with multiple side holes, both of which increased the risk of seepage, coupled with a probable decrease in manual catheter flushing; and anticoagulation with bolus low-molecular-weight heparin.

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REFERENCES

4% CITRATE

Status 31.03.2015
Recommendation: Antimicrobial lock solutions

Do the European Renal Best Practice (ERBP) guidelines recommend the use of 4% citrate solution as antimicrobial catheter lock solution and is this inconsistent with the German hygiene guideline?

Recently, several manufacturers have started supplying a 4% citrate solution as catheter lock solution justifying the efficacy of the solution on the recommendations of the ERBP guideline:

Vanholder et al, Diagnosis, prevention and treatment of haemodialysis catheter-related bloodstream infections (CRBSI), Chapter titled: “Preventive antimicrobial catheter locks and catheter surface treatment”: a position statement of European Renal Best Practice (“ERBP recommendation”).

If this expresses a recommendation of the 4% citrate solution, it would be inconsistent with the recommendations of the hygiene guideline of the German Societies for Nephrology supplementing the German Dialysis Standard 2006 (“Hygiene Guideline”). Aside from tauroidine-citrate solutions, this guideline exclusively recommends highly concentrated citrate solutions, but not 4% citrate solutions, as antimicrobial lock solutions for reducing the incidence of catheter-associated infections.

The present paper aims to discuss whether or not in fact there is a difference between the two recommendations with regard to the use of 4% citrate lock solutions. The pertinent text sections of the two recommendations are as follows:

ERBP recommendation

Chapter: Preventive antimicrobial catheter locks and catheter surface treatment
B.3.1 The preventive use of antimicrobial locks is advocated to reduce the rate of CRBSI
B.3.2 In view of the potential risks of spillover of the locking solution, associated risks (arrhythmias, toxicity, allergic reactions, development of resistance to antibiotics) should be balanced with the benefits in terms of prevention of infection. Citrate locks have, for the time being, most extensively been studied. The 4% solution seems to offer at present the best benefit / risk ratio.
B.3.3 Antimicrobial lock solutions should not replace hygienic standards with regard to catheter care and handling.

Hygiene guideline

Chapter 2.5.1 Central venous catheters

... Between the dialysis treatment sessions, the central venous catheter can be blocked with diluted heparin solution. However, this solution does not have an antibacterial effect. Blocking with lock solutions having an antibacterial effect is preferable since it allows the rate of catheter-associated bacteremia to be reduced significantly. However, the use of antibiotics must be viewed with a critical eye due to the possible development of resistance. Alternatively, concentrated citrate solutions (30% or 45%) and tauroidine-citrate solutions are conceivable in this regard. Due to the risk of serious cardiac arrhythmias, high dose citrate solutions must be applied by expert professionals complying with the prescriptions of the manufacturer.

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Both publications recommend the use of lock solutions that have an antimicrobial effect, but contain no antibiotics.
Firstly, it is important to note that both recommendations include a central recommendation for lock solutions that have an antimicrobial effect. Lock solutions containing antibiotics are not recommended, though, due to the risk of resistance developing.

Whereas recommendation B.3.2 of the ERBP seems to suggest that the 4% citrate solution is considered to be the solution with the best benefit/risk ratio (“The 4% [citrate] solution seems to offer at present the best benefit / risk ratio”), the hygiene guideline specifies a positive list of solutions that have an antimicrobial effect and are recommended (highly-concentrated citrate solution, taurolidine-citrate) and thus excludes the 4% citrate solution explicitly.

An ERBP recommending 4% citrate solution as antimicrobial lock solution would contradict the German Hygiene Guideline.
The benefit-risk assessment of the different citrate concentrations in the ERBP recommendation might be based on the erroneous assumption that both highly concentrated and low concentration citrate solution (4%) show the same efficacy with respect to the prevention of catheter-associated infections (“Over time progressively lower concentrations of citrate have been applied (from 46.7 to 4%) with even in the latter case still significantly better [infectious] results than with heparin”).

This assumption is based on five studies which are reviewed in the following:


The clinical studies of Weijmer\textsuperscript{24} and Winnett\textsuperscript{22} document the antimicrobial efficacy of highly concentrated citrate solutions (30% or 46.7%) and are therefore consistent with the German hygiene guideline.

Of the three remaining studies, the publications of Allon\textsuperscript{23} and Betjes\textsuperscript{26} cannot be used to review the antimicrobial efficacy of a 4% citrate solution, since a 4% citrate solution was not used therein. Both studies compared a taurolidine-citrate solution to heparin. Although the citrate concentration is in fact 4% in the taurolidine-citrate combination, the reduction of catheter-associated infections is undoubtedly related to the benefit of the additional antimicrobial agent, taurolidine, as was clearly described by the authors.

Finally, it just needs to be clarified whether or not the present ERBP recommendation can apply to a 4% citrate solution in the absence of additional antimicrobial agents. However, this can be the case only if the sole reference cited, which actually uses 4% citrate solution (Lok\textsuperscript{25}) finds catheter-associated infections to be reduced as compared to heparin. It is of note, though, that even the author herself puts her infection rate results into perspective (“The difference in bacteraemia rate in this study should be interpreted with caution since a hospital policy instituting a nursing medical directive to apply a polyantibiotic ointment to the catheter exit site for catheter infection prophylaxis was instituted during the study”).

Moreover, the result obtained by Lok is contrary to the clinical studies of Grudzinski\textsuperscript{27} and McRae\textsuperscript{28}, which are assessed negatively in the ERBP recommendation in that they demonstrate no antimicrobial efficacy as they failed to demonstrate superiority of 4% citrate versus heparin in the prevention of catheter-associated infections (“In two studies, no benefit regarding infectious complications was observed for citrate at 4%”).


28 MacRae JM, Dojcinovic I, Djurdjev O et al, Citrate 4% versus heparin and the reduction

Accordingly, the recommendation given in the ERBP guideline can only be limited to 4% citrate-containing lock solutions containing additional substances with an antimicrobial effect (such as, e.g., taurolidine). In the absence of additional antimicrobial substances, 4% citrate solutions have no antimicrobial effect and fail to reduce the incidence of catheter-associated infections in clinical studies. The ERBP recommendation therefore does not contradict the hygiene guideline since it does not extend to 4% citrate solution. Likewise, the ASDIN paper discussed in the scope of the ERBP recommendation describes 4% citrate solution only as an option for maintaining the patency of the lumen. Antimicrobial variants are discussed therein clearly separate from the 4% citrate solution.

The ERBP recommends 4% citrate-based solutions only if they have an antimicrobial effect that is related to the presence of additional agents (such as, e.g., taurolidine). It is therefore not inconsistent with the hygiene guideline of the German professional societies.

It needs to be noted that the risks of highly concentrated citrate solutions are discussed in more detail in the ERBP recommendation. Whereas the hygiene guideline discusses just the cardiac risks, the ERBP recommendation also includes the embolic risks in the benefit/risk assessment. These risks ultimately lead to the 4% citrate-containing lock solutions having a better benefit/risk ratio. However, it needs to be noted that the monitoring of embolic events during the use of highly concentrated citrate solutions in dialysis patients was published only in 2010 by Davenport et al. (Davenport et al, Am J Kid Dis; 2010, 55: 348-351), which means 2 years after publication of the hygiene guideline. The causal relationship between the embolic events and the highly concentrated citrate solution was then elucidated in 2012 by the publication of Schilcher (Schilcher et al, Nephrol Dial Transplant 2012; 27: 2953-2957).

The ERBP recommendation issues a more urgent warning of the risks of highly concentrated citrate solutions, since the embolic risks become known only after publication of the hygiene guideline.

Summary

Both recommendations place the main emphasis on the use of an antimicrobially efficacious lock solution. Solutions with an antimicrobial effect include highly concentrated citrate solution and 4% citrate solutions containing additional antimicrobial agents (e.g. taurolidine-citrate). 4% citrate solutions containing no antimicrobial agents are not recommended by either of these guidelines, since they possess no antimicrobial efficacy. Due to being published later, the ERBP can discuss the risks of highly concentrated citrate solutions in more detail. Both recommendations warn against the prophylactic use of antibiotics-containing lock solutions.
Special Feature

Diagnosis, prevention and treatment of haemodialysis catheter-related bloodstream infections (CRBSI): a position statement of European Renal Best Practice (ERBP)

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In the July 2009 issue of the journal Clinical Infectious Diseases, the Infectious Diseases Society of America (IDSA) published an update of their ‘Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infection’ [1]. The largest part of the IDSA text relates to non-dialysis catheters, and it is not always clear how far these general recommendations can be extrapolated to the haemodialysis condition. A specific section of the IDSA guidelines is, however, devoted to haemodialysis catheters.

In the present position statement by European Renal Best Practice (ERBP), we intend to focus on the items in these guidelines which are relevant for nephrologists and to amend them to haemodialysis conditions and/or for the European situation with regards to tunnelled catheters. ERBP is the new guidance body of the European Renal Association-European Dialysis and Transplantation Association (ERA-EDTA), replacing European Best Practice Guidelines (EBPG) since 2008.

We will discuss only those IDSA guidelines worth reflection or amendment. The corresponding IDSA guidelines will be mentioned between parentheses (). Guidelines which we did not consider for discussion, although they still might be relevant, are summarized in Table 1.

The present text has been issued in accordance with the new philosophy of ERBP to offer guidance by means of position statements commenting on documents issued by other guideline bodies or on recent relevant studies, next to ad hoc recommendations when not enough evidence is available [2,3]. Real guidelines are to be issued only in case of sufficient evidence. ERBP recently published two position statements along these principles [4,5].

Of note, earlier EBPG recommendations have been issued on vascular access and infectious disease in haemodialysis patients [6,7]. The current document further elaborates and updates these documents.

The IDSA guidelines are well written with a clear distinction between several subheadings, covering a general and a specific part. The same guidelines are frequently repeated, and the same items are also often covered both in the general and specific guidelines, albeit that the recommendations are not always exactly the same. The grading system is not the same as the one currently propagated by Grading of Recommendations, Assessment, Development and Evaluation (GRADE) and applied by ERBP and Kidney Disease: Improving Global Outcomes (KDIGO) [3,8,9]: it is a nine-tiered system with three levels of evidence and three levels of strength vs two levels of evidence and four levels of strength for the three bodies mentioned above. Although the majority of IDSA guidelines are based on only one or two non-randomized trials often generated by one single research group, most of them are graded as level A.II, with only seven of 123 recommendations (5.7%) having the highest level (A.I). Although A.II gives the impression of being based on robust evidence, ‘dramatic results even from uncontrolled experiments’ suffice to attribute this level. The result is that, without clear notification to the readership, poorly-evidenced statements or ‘parachute type’ guidelines (i.e. guidelines which seem obvious but have not been or cannot be evidenced, like the recommendation of using a parachute when jumping out of a flying plane) are classified as well evidenced. However, the real evidence level of these IDSA guidelines is not high, which unfortunately is also true for most nephrological recommendations [2].

For the sake of clarity, the present position statement contains recommendations which are not based on a systematic literature review and are not supported by an evidence review team. The reader should consider them rather
catheters currently dialysed population who have run out of native
are a life-saving option in a substantial proportion of the
of patients treated with them is still growing [10], and they
ysis is also generally discouraged as well [7], the proportion
the systemic circulation.
act as a barrier against inoculation from the exit site into
infectious disease, central vein thrombosis, malnutrition, in-
mortality, by inducing septic complications, metastatic in-
the risk of infection, which is a source of morbidity and
non-tunnelled catheters as an access for haemodialysis is
considered as an ultimate resource for vascular access in
mud walls vs non-tunnelled catheters

Permanent tunnelled central vein catheters are generally
as an ultimate resource for vascular access in
maintenance haemodialysis patients. One of the major
arguments for discouraging the use of tunnelled as well as
non-tunnelled catheters as an access for haemodialysis is
the risk of infection, which is a source of morbidity and
mortality, by inducing septic complications, metastatic in-
fecious disease, central vein thrombosis, malnutrition, in-
flammation and cardio-vascular damage.

Apart from their almost inevitable use in acute kidney
injury requiring renal replacement therapy, non-tunnelled
temporary catheters should be avoided as much as possible,
since the risk of infection as compared to tunnelled
catheters is even higher, reflecting the lack of a cuff to
act as a barrier against inoculation from the exit site into
the systemic circulation.

Although the use of permanent catheters in chronic dial-
ysis is also generally discouraged as well [7], the proportion
of patients treated with them is still growing [10], and they
are a life-saving option in a substantial proportion of the
currently dialysed population who have run out of native
vascular access possibilities. Presumed reasons for their
high prevalence, especially in the Western World, are the
increased frequency of dialysis patients of older age, with
cardio-vascular disease and/or with diabetes mellitus, in
whom creation or repair of an autogenous fistula or graft
appears technically challenging, risky or impossible.

ERBP recommendations:

- A.1.1: The use of non-tunnelled catheters, except in
  acute kidney injury (AKI), is undesirable. In chronic
  maintenance haemodialysis patients, it is recommended
to remove temporary catheters as soon as possible, even
  without or with only minor complications, and to have
  them replaced preferentially by an arterio-venous fistula
  (AVF) or, if that is impossible, an arterio-venous graft
  (AVG) or, if that is impossible, a tunnelled central vein
catheter (CVC).
- A.2.2: If haemodialysis catheters are required either due
to need or because patients refuse an AVF, the occur-
rence of a catheter-related complication should be a
trigger to re-evaluate options for alternative access, such
as an AVF.

Prevention of infection

The IDSA guidelines do not consider recommendations on
preventive measures. ERBP recommends the following.

Catheter insertion and position

Catheter insertion should be performed under strict aseptic
circumstances and according to the conditions formulated
by European Best Practice Guidelines [7].
Next to thrombosis, catheters inserted in the femoral position are also prone to a higher risk of infection and bacteremia [11,12] than those in the internal jugular one and should therefore be avoided as much as possible. If the femoral site is nevertheless considered, the benefit of preserving other central veins should be balanced with this increased risk of infection. Of the remaining positions, the subclavian is discouraged for other reasons than infectious risk (stenotic complications). Among the internal jugular positions, the right one is the most convenient [7].

ERBP recommendations:

- **B.1.1** Catheters should be inserted under strict aseptic conditions.

- **B.1.2** The right internal jugular vein position is the preferred location for insertion, followed by the left internal jugular vein position. The use of the femoral vein position is discouraged.

- **B.1.3** The use of the subclavian vein position is discouraged for reasons not related to infection (frequent stenosis).

**Nursing care**

Universal precautions using sterile material should be applied by caregivers whenever a central vein catheter is manipulated, connected or disconnected. The use of disposable sterile material such as masks and gowns has been suggested to protect against transmission of Staphylococci or other organisms [13,14], but, to the best of our knowledge, their protective effect has not convincingly been proven. In a collaborative intensive care unit (ICU) study, a set of five different preventive interventions including full barrier precautions was successfully implemented, but the study did not evaluate the relative importance of each of the individual interventions separately [15]. In another study, the use of surgical face masks reduced bacterial contamination of the area in front of the operator’s face [16], who, however, was asked to talk during the 20-min observation period and to turn his/her head 90° every 30 s [16]. The use of precautions such as masks and gowns should not be considered as an excuse to relax on general hygienic and sterile conditions.

Branching of central vein catheters to the dialysis machines as well as their disconnection is resource intensive, and therefore sometimes two trained staff members (one nurse focusing on the catheter and one helper for the management of the dialysis machine and to assist the nurse) are deployed to enable connection and disconnection. The basic and meticulous approach to handling catheters in a reliable and sterile fashion at the time of both connection and disconnection or at any other time the catheter connection site is manipulated forms the core of the prevention of infection.

**ERBP recommendation:**

- **B.2.1** Universal precautions, a sterile environment and aseptic technique should be applied at any occasion when a venous catheter is manipulated, connected or disconnected.

**Preventive antimicrobial catheter locks and catheter surface treatment**

There is increasing evidence that antimicrobial locks applied within the catheter lumen are effective at preventing catheter-related bloodstream infections (CRBSI).

Some locks may have extra antimicrobial or biofilm-removing properties [e.g. citrate, alcohol, ethylene diamine triacetic acid (EDTA)]. On the contrary, heparin tends to antagonize the bactericidal properties of certain antibiotics, e.g. the aminoglycosides [17,18]. It also promotes biofilm formation unless at very low concentrations [19].

The clinical advantages offered by citrate have been confirmed in at least two meta-analyses [20,21]. Over time, progressively lower concentrations of citrate have been applied (from 46.7 to 4%) with even in the latter case still significantly better results than with heparin [22–26]. In two studies, no benefit regarding infectious complications was observed for citrate at 4% [27,28].

Addition of antibiotics, either to heparin or to citrate solutions, has an additional beneficial effect vs vehicle alone [20].

One potential drawback of catheter locks is that some of the contents spill over to the circulation at injection and in between dialysis sessions [29,30]. A Food and Drug warning against citrate locks was issued in 2000 following a fatal accident with the 46.7% solution [31]. The reported fatal case was very likely related to abrupt hypocalcaemia followed by cardiac arrest, due to intracardiac injection of an excessive amount of 46.7% citrate, which is a potent chelator of calcium. The 46.7 and 30% concentration ranges have been considered unsafe [29]. For that reason, the low 4% concentration might be preferred, as also proposed by the American Society of Diagnostic and Interventional Nephrology (ASDIN) [32].

Of note, the capacity of citrate locks to prevent thrombus formation may be incomplete, especially at the highest concentrations. Recently, several cases of symptomatic pulmonary and cerebral embolisms were observed with hypertonic citrate locks [33]. This is probably attributable to seepage out of the lumen through the catheter side holes, a process that might be exacerbated if the solution is hyperosmolar.

For antibiotic locks, spillover may be a source of resistance [34]. This issue has not been sufficiently studied and remains a point of concern. With potentially toxic antibiotic locks such as those containing aminoglycosides, trough levels should regularly be checked.

According to ERBP, there is not enough evidence of clinical benefit of ethanol locks [35,36], although *in vitro* data, both for ethanol alone at 60% and for an ethanol 30%/citrate 4% mixture, are promising [37,38]. Also, ethylene EDTA has been proposed as an option [19,39].

For each type of lock, the corrosive or damaging potential on catheter polymers should be taken into consideration, and the manufacturer of the catheter should provide information regarding this issue.

Although findings might be influenced by differences in the definition of CRBSI, it nevertheless is of interest to note that several studies with application of locks achieve results in the treatment arm which are comparable to those obtained...
in centres of excellence with dedicated care to catheters without applying locks [21]. Hence, the use of antimicrobial locks should not be used as an excuse to relax on the application of universal precautions and hygienic measures.

Several options of catheter surface modifications have been proposed to combat biofilm, fibrin sheath, thrombus or infection [40]. They essentially consist of silver sulfadiazine, heparin, Trillium® [40] and/or coating with protective polymer layers preventing BaSO4 release from the catheter surface [41]. Results regarding clinical impact on colonization are contradictory [42,43]. By lack of convincing clinical data, it is at present difficult to justify their additional cost.

**ERBP recommendations:**

- **B.3.1** The preventive use of antimicrobial locks is advocated to reduce the rate of CRBSI.

- **B.3.2** In view of the potential risks of spillover of the locking solution, associated risks (arrhythmias, toxicity, allergic reactions, development of resistance to antibiotics) should be balanced with the benefits in terms of prevention of infection. Citrate locks have, for the time being, most extensively been studied. The 4% solution seems to offer at present the best benefit/risk ratio.

- **B.3.3** Antimicrobial lock solutions should not replace hygienic standards with regard to catheter care and handling.

**Exit-site dressings**

Next to skin antisepsis before placement, sterile precautions during placement and catheter site care at each dialysis session, the site should be covered with a dressing as long as the catheter is in place [44]. One meta-analysis comparing the complication profile of transparent and gauze dressings suggested a higher risk for catheter sepsis and bacteremia with transparent dressings [45]; another more recent meta-analysis showed no differences but registered a high level of uncertainty regarding the reliability of the studies included [46]. With long-term catheters, gauze is the preferred choice. Gauze should be replaced if it is no longer dry or clean. The patient should be instructed to respect strict hygienic measures, preserving the integrity and dryness of the dressing, and should know what to do in case of disintegration or wetness.

**ERBP recommendations:**

- **B.4.1** The catheter exit site should be covered by a dressing as long as the catheter remains in place. The exit site should be inspected at every haemodialysis session, and the exit-site dressing should be replaced on a routine basis if it is no longer clean or intact.

- **B.4.2** The patient should be instructed to maintain the hygiene and integrity of the dressing.

**Exit site and nasal antibiotic ointments**

The use of antibiotic ointment at the insertion site has a beneficial effect on CRBSIs and exit-site infections [47–49]. Their application is especially recommended after catheter placement until the insertion site has healed [44]. Application of mupirocin might be complicated by development of resistance [50–52]. Prolonging antibiotic ointment application after site healing probably offers no advantage and has the potential to increase the risk for development of resistance [48] and for *Candida* colonization [53].

In peritoneal dialysis (PD), ointments containing gentamicin applied to the exit site have been shown to be effective [54,55]. Gentamicin ointment was superior to mupirocin in at least one study [55]. To the best of our knowledge, similar treatment protocols have not been studied with haemodialysis catheters. One study showed that honey (Medihoney) was equivalent to mupirocin in haemodialysis catheters [56]. One potential advantage of Medihoney is that the theoretical risk of resistance is lower than with mupirocin [56].

Another option is Polysporin triple ointment, containing Bacitracin, gramicidin and polymyxin B, which was shown to be superior to placebo in haemodialysis catheters when applied to the exit site [57]. Comparative data with mupirocin or other antibiotic ointment formulations are, however, lacking.

Topical application of antibiotic ointments at the exit site is also the first option in case of exit-site infection without fever (see below, ‘Catheter removal and preservation of existing and future access options’ section).

Although there is ample literature on nasal mupirocin ointment in peritoneal dialysis, information in haemodialysis is scanty. In PD, nasal mupirocin decreases exit-site and tunnel infection but not peritonitis [58,59]. Application is, however, also related to an increase in MIC90 and frequent recolonization [60]. According to ERBP, there is not enough evidence to propagate nasal antibiotic ointment in a haemodialysis setting.

**ERBP recommendations:**

- **B.5.1** Application of antibiotic ointment at the exit site should be considered after catheter placement until the insertion site has healed but should be discontinued after healing.

- **B.5.2** With long-term exit-site and nasal antibiotic ointment applications, especially of mupirocin, development of resistance should be taken into account as an effect counterbalancing the potential benefit on infectious complications.

**Overall aspects**

*Diagnosis: cultures of intravenous catheter*

Several IDSA guidelines refer to the approach by the bacteriological laboratory; it might be important for the nephrologist to check the approach used in the laboratory to which he/she usually sends samples. Qualitative broth cultures of catheter tips are discouraged [61] (2), whereas the roll plate technique of 5 cm of the catheter tip is recommended especially for short-term catheters (in place since less than 14 days) (7) and the quantitative broth culture (luminal flushing or sonication) for catheters which have remained...
in place for a longer time. Other studies, however, showed no differences between both approaches [62]. In general, only detection of >15 colony forming units (CFU) is relevant for roll plate and >10² for quantitative broth culture (5)(90).

Although the IDSA guidelines explicitly recommend culturing of catheter tips upon removal (1), questions can be raised about the relevance of this approach. In a recent study [63] on 312 patients with a positive catheter culture and a negative blood culture, only eight patients (2.6%) subsequently developed CRBSI with the same germ as the one cultured from the tip, suggesting a low yield for this costly and time-consuming strategy.

ERBP recommendations:

- C.1.1 Preferred laboratory approaches for cultures of catheters are the semi-quantitative roll plate technique of 5 cm of the catheter tip (positive if >15 CFU are detected) or the quantitative broth culture (luminal flushing or sonication, positive if >10² CFU are detected).
- C.1.2 In general, the therapeutic relevance of culturing catheter tips in symptomatic patients with presumed CRBSI should be considered low when blood cultures are collected appropriately (see below, ‘Diagnostic blood cultures’) and if appropriate antibiotic treatment is instituted (see below, ‘Antibiotic and antymycotic treatment’).
- C.1.3 Nephrologists should be aware whether the bacteriological laboratory analysing their samples applies the appropriate techniques for culturing.

**Diagnosis: blood cultures**

A diagnostic test proposed in the IDSA monography not necessitating catheter withdrawal is simultaneous sampling from peripheral vein and from the catheter or from two different catheter lumens with appropriately marked bottles [64] (15), with colony count from inside the catheter or one of the two lumens being at least three times higher than for the other sample. Alternatively, cultures from the peripheral blood sample should become positive at least 2 h later than the ones from the catheter (differential time to positivity—DTP). Usefulness of DTP criteria in samples from two catheter lumens has not been clarified [65–67](17)(18)(19).

The ERBP considers that, although such recommendations may be valid for non-dialysis catheters, it may be more difficult to implement these in haemodialysis. Firstly, in many cases, it may be impossible to puncture a peripheral vein because of unavailability or because it is deemed desirable to preserve veins for future access creation. Secondly, since many of the fever episodes necessitating blood culture sampling occur during dialysis, during which high blood flows are created through the catheter, it is likely that blood cultures collected at that moment through the haemodialysis circuit, which is then directly linked to the catheter, will offer similar results as peripheral blood, so that peripheral sampling becomes redundant [68].

Fibrin sheath or biofilm collection via endoluminal brushing has been proposed as another option [69,70] but has been criticized because of risk of arrhythmia, embolization and bacteraemia [71]. Hence, data at present are not convincing enough to propagate its use.

When the approach of intradialytic collection through the catheter is followed, a risk exists that some of the positive blood cultures relate to other infectious sources than the catheter. To minimize this bias, alternative sources should be excluded as much as possible by history taking, clinical examination, imaging and targeted laboratory testing (e.g. urine culture if possible).

**ERBP recommendations:**

- C.2.1 If a haemodialysis catheter is not removed, blood cultures obtained during dialysis through the dialysis circuit linked to the catheter are a more realistic and practical method to isolate an organism related to catheter-associated infection than the dual-site approach including also a peripheral vein sample, which is propagated in the general population.
- C.2.2 When the catheter remains in place, alternative sources of infection should be considered with an appropriate clinical history, examination, imaging and targeted laboratory testing (e.g. urine culture if possible).

**Diagnosis: registration**

To guide empiric antibiotic therapy, it is of utmost importance that each haemodialysis centre maintains a database of all suspected and proven CRBSI and episodes of bacteraemia in general, the causative organisms, their sensitivity pattern to antibiotics, the potential source (catheter related, pneumonia, urinary tract, etc.) and the outcomes after therapeutic intervention. As a consequence, each unit should be aware of the epidemiology of its catheter-related infections.

**ERBP recommendation:**

- C.3.1 Haemodialysis units should record all details regarding CRBSI epidemiology as well as about all episodes of bacteraemia (events, causative organisms with their susceptibility and evolution in response to therapy).

**Unique aspects**

**Management of catheter infection in patients receiving haemodialysis**

Management of catheter infection is covered in two sections of the IDSA guidelines, one on general management and one on management of haemodialysis catheters. As the aim of this ERBP position statement is to discuss only haemodialysis catheter infections, we will merge the discussion on these two topics under the present heading.

It should be noted that only catheter-related infection and/or bacteraemia are discussed in this ERBP position statement. Bacteraemia related to AVF or AVG or bacteraemia in the presence of a dialysis catheter but attributable to other causes will not be covered.

**Catheter removal and preservation of existing and future access options.** In the following clinical situations, the re-
moval of the catheter should be considered as an additional intervention to systemic antibiotic treatment (see below, ‘Antibiotic and antimycotic treatment’) (Figure 1): severe complications (e.g. severe sepsis, suppurative thrombophlebitis, metastatic infection); persistent bloodstream infection or persistent clinical signs of infection in spite of 48–72 h of appropriate antimicrobial therapy; infection with Staphylococcus aureus, Pseudomonas aeruginosa, multiresistant organisms or fungi; and tunnel infection with fever. For exit-site infection without fever, topical antibiotic ap-
plication might be attempted first (see above, ‘Exit site and nasal antibiotic ointments’), but if infection does not resolve, systemic antibiotic treatment should be installed (47). If systemic antibiotics also fail, the catheter should be removed (49).

ERBP recommends the insertion of a new tunneled catheter preferably only when the patient remains afibrile for 48–72 h and shows a normalization of C-reactive protein (CRP) and negative blood cultures. If the interval needs to be prolonged for more than 48–72 h, a haemodialysis catheter could be inserted in the intermediate at another site. A strategy of placement per single dialysis session and removal immediately afterwards might be considered as an alternative to minimize the risk of colonization.

However, in patients on haemodialysis, options for access may be limited. Firstly, removal of a catheter will require another catheter to be inserted, increasing the potential risk to generate further damage to the central vein. This could have adverse consequences on the creation of an AVF in the future. Secondly, access options may already be extremely limited and further attempts at central vein cannulation impossible or risky. Of note, even in the non-dialysed population, catheter-sparing strategies have recently been employed to avoid unnecessary and wasteful removal of catheters [71]. Therefore, removal of the catheter might be considered, if clinically indicated, but the strategy for future access should be part of this consideration. For example, one should be sure that an alternative site for insertion of a new catheter is available before the original catheter is removed.

If any problems are anticipated, an alternative strategy is to exchange the catheter over a guidewire. The optimal time for guidewire-assisted replacement is after 48–72 h of appropriate and effective antibiotic treatment (59). However, guidewire-assisted replacement increases the risk of venous wall sclerosis and stenosis and is associated with a high treatment failure rate. An alternative option is to leave the catheter in place and to attempt catheter salvage instilling an antibiotic lock (see below, ‘Antibiotic locks’) in addition to systemic antibiotic therapy [72,73] (30)(60). In a recent study, catheter salvage after incident bacteremia achieved a cure, defined as no recurrence or complication, in 66.1% of cases [74]. Recurrent bacteremia was less common after catheter removal and reinsertion than after salvage (8.1 vs 33.0%) but at the expense of dramatically more complications (14.3 vs 0.9%). In this study, salvage consisted of systemic antibiotic treatment but not of antimicrobial or antibiotic locks. Both in the case of guidewire-assisted replacement and of catheter salvage, close follow-up by assessment of clinical status and repetitive blood cultures is imperative, and if persistent clinical signs of infection and bacteremia are found after 48–72 h, the catheter should still be removed and replaced (33).

Surveillance blood cultures should be obtained 1 week after completion of antibiotic treatment for CRBSI if the catheter has not been removed. If these cultures are positive, the catheter should still be removed (67).

In order to preserve future access options, the practice of peripheral blood culture sampling from vessels that potentially could be used in the future for creation of vascular access should be limited or avoided [7] (53).

**Antibiotic and antifungal treatment (Figure 2).** In all circumstances, systemic antibiotic therapy should be administered.

For the approach in the general population, instructions in the IDSA Guidelines are given separately for gram-positive and gram-negative bacteria. According to ERBP, empiric coverage should be inspired by the recorded infections in the unit (see above, ‘Diagnosis: registration’). If the registry indicates that current catheter infections are regularly caused by both gram positives and gram negatives, coverage for both classes of organisms should be provided when empiric antibiotic therapy is started for CRBSI, with eventual refinement of the antibiotic regime once the responsible organism has been isolated and sensitivities are known.

Although the choice of antibiotic treatment may depend on individual preference, local or regional patterns, and/or recommendations from hospitals and organizations, according to ERBP, preference should be given to antibiotics with a pharmacokinetic profile allowing administration after each dialysis session only; this is the case for vancomycin, teicoplanin, cefazolin, ceftazidime and daptomycin. Although the same is correct for aminoglycosides, it might be impossible to reach appropriate trough levels as pursued in the general population with simple post-dialysis administration, hence increasing the risk for ototoxicity, loss of residual renal function, treatment failure and development of resistance. Nevertheless, in view of their rapid bactericidal effect, a single shot of aminoglycosides might be considered useful. If no alternative is available, a longer therapeutic course might be considered; in that case, administration 1 h before dialysis followed by a highly efficient dialysis procedure is probably the most efficient approach to mimic pharmacokinetics and pharmacodynamics observed in the general population.

In settings where methicillin-resistant *S. aureus* (MRSA) is highly prevalent, vancomycin or teicoplanin is the first choice for empirical treatment of gram-positive germs (23).

In patients on empirical vancomycin or teicoplanin in whom infection with methicillin-sensitive *S. aureus* appears, antibiotic treatment should be switched to cefazolin (62). Potential advantages of cefazolin are its broader spectrum; its favourable pharmacokinetics necessitating only IV administration in direct relation to dialysis compared to a need for additional interdialytic IV or PO administrations for the methicillin group; and compared to vancomycin, a bactericidal instead of a bacteriostatic activity. Continued treatment with vancomycin in case of methicillin sensitivity substantially increases the risk of treatment failure [75].

When minimum inhibitory concentration (MIC) for vancomycin exceeds 2 µg/mL, alternative antibiotics should be used such as daptomycin [76] (23). Daptomycin has also the advantage of being cleared by the kidneys, which allows long intervals between administrations. In haemodialysis patients, post-dialysis administration of one dose (4 to 6 mg/kg depending on the seriousness of the infection) is considered sufficient. Daptomycin is, however, not yet available in all European countries (e.g. not in Belgium). Linezolid should not be used for empirical treatment (24).
Fig. 2. Flow chart summarizing approaches for systemic antibiotic treatment.
with fluconazole only for selected cases (e.g. if risk of *Candida krusei* or *Candida glabrata* is low) [77] (29). Candida infection is, however, rare in haemodialysis catheters, probably reflecting a different immune predisposition as compared to other populations at risk (e.g. HIV, long-term antibiotic treatment). Candida catheter infection is associated with a high rate of treatment failure or early recurrence, so that catheter removal is a first-line therapeutic option.

Usual length of treatment for uncomplicated cases is 3 weeks. For tunnel infection without bacteraemia or fungaemia and if the catheter has been removed, 7 to 10 days is sufficient. Prolonged (6 weeks) antibiotic treatment should be administered if fungaemia or bacteraemia persists 48–72 h after catheter removal, since very likely serious metastatic complications such as endocarditis are present; 6-week treatment should be installed as well in case of a definite diagnosis of metastatic infection (31). For osteomyelitis, antibiotic treatment should be prolonged to 8 weeks.

For uncomplicated infections with other organisms than those mentioned above, antibiotic treatment without catheter removal should be attempted first (both systemic and local), because catheter reinsertion is not free of risk (35). With a single positive blood culture of coagulase-negative *Staphylococci*, a careful clinical evaluation and additional positive cultures should have been obtained before therapy and/or catheter removal [78] (38).

For antibiotics with substantial removal via the kidneys, such as vancomycin, residual renal function should be taken into account when determining the dose and frequency of administration. Highly efficient dialysis strategies (high-flux haemodialysis, haemodiafiltration, daily dialysis, prolonged dialysis sessions such as in nocturnal dialysis) can equally remove substantial amounts of antibiotic [79], and also in these cases the dose should be adapted accordingly. To guide treatment, pre-dialysis trough levels are the optimal approach.

ERBP recommendations:

- **D.1.1** Systemic antibiotic treatment should be always administered as part of the therapy of catheter infection.

- **D.1.2** Catheter removal is the first therapeutic option in case of severe complications and metastatic infections; infection with *S. aureus*, *P. aeruginosa*, multiresistant organisms or fungi; and tunnel infection with fever.

- **D.1.3** The therapeutic advantages of catheter removal should be balanced against the risk of reinserion, and removal might not be appropriate, if an alternative insertion site is not available or if reinserion of a catheter is associated with excess risk. In this scenario, the catheter could be replaced over a guidewire, preferably 3 days after appropriate and effective antibiotic treatment.

- **D.1.4** If guidewire-assisted exchange is also impossible or too risky, a valid option is to keep the catheter in situ and to combine this with a treatment consisting of systemic antibiotics and antibiotic locks (catheter salvage).

- **D.1.5** With either guidewire-assisted exchange or if the original catheter is left in place for salvage and if the clinical picture is not improving or if blood cultures remain positive after 48–72 h, the option to remove the catheter should be re-evaluated as indicated under D.1.2.

- **D.1.6** If a catheter is not removed, blood cultures should be checked 1 week after completion of antibiotic treatment, and if those cultures remain positive, the catheter should be removed.

- **D.1.7** For exit-site infection without fever, topical antibiotic application can be considered as an alternative. If infection does not resolve, systemic antibiotics should be administered. For tunnel infection without fever, systemic antibiotics are the preferred option, although peroral treatment may be sufficient. If these treatments fail, the catheter should be removed.

- **D.1.8** When haemodialysis catheter infection is suspected, primary antibiotic approach should be inspired by the previously recorded responsible organisms in the unit. If both gram-positive and gram-negative organisms are registered on a regular basis, both types should be covered with eventual refining of the antibiotic regime once the organisms and their sensitivities are known.

- **D.1.9** In general, antibiotics necessitating administration post-dialysis only (vancomycin, teicoplanin, ceftazolin, cefazidime, daptomycin) should be preferred.

- **D.1.10** Vancomycin or teicoplanin is the first choice for empirical therapy of gram positives in settings where MRSA is highly prevalent.

- **D.1.11** For methicillin-sensitive *S. aureus*, haemodialysis patients should receive cefazolin.

- **D.1.12** Doses of antibiotics of which the active concentration is affected by residual renal function and/or dialysis adequacy should be adapted accordingly. If possible, predialysis trough levels should be obtained to guide therapy.

**Antibiotic locks**

Recommendations for removal (either with catheter-free interval or over a guidewire) should be applied as detailed above (‘Catheter removal and preservation of existing and future access options’). If removal is deemed unnecessary, undesirable or impossible, antibiotic lock is an important therapeutic option (71). Antibiotic lock should not be used alone but always in conjunction with systemic antibiotics for the recommended periods (see above, ‘Antibiotic and antymycotic treatment’) (69). Although dwell times generally should not exceed 48 h and even 24 h for ambulatory patients with femoral catheters, for haemodialysis lock renewal after every dialysis session is considered sufficient (70). For vancomycin, the concentration in the lock should at least be 1000 times higher than the MIC of the micro-organism involved [80] (73). For all other antibiotics, at least 100-fold greater than therapeutic plasma concentrations should be pursued [68]. Antibiotic concentrations as they are reported in the literature are summarized in Table 2.

The success rate of salvage in case of *S. aureus* is low (approximately 40%) [81] and therefore should be considered only in problematic cases. Success rate for *Enterococcus* is approximately 60% [82]. For all other organisms, success rates are substantially higher [68].
Antibiotic locks can be dissolved in different vehicles. Some of these might have extra antimicrobial or biofilm removing properties (see above, ‘Preventive antimicrobial catheter locks and catheter surface treatment’). Urokinase and other thrombolytic locks are not recommended as adjunctive therapy for patients with CRBSI (37).

ERBP recommendations:

- D.2.1 When catheter salvage is attempted, the combination of an antibiotic lock and systemic antibiotic therapy should be applied.
- D.2.2 Salvage of the catheter in case of S. aureus infection should only be considered when catheter removal and replacement are expected to be problematic.
- D.2.3 Urokinase and other thrombolytic locks are not recommended. The use of heparin locks alone in case of CRBSI is discouraged.

Diagnosis and management of an outbreak of CRBSI

Criteria defining the exposed patients should be established (117). A root cause analysis or case control study should be undertaken to elucidate the potential aetiology of contamination (118). Micro-organism patterns should be evaluated by studying antibiotic sensibility and molecular fingerprinting to understand recurrence and relapsing episodes (119).

ERBP recommendation:

- D.3.1 Outbreaks of CRBSI should be scrupulously checked by case definition, case control studies and root cause analysis.

Standard care

Centres should establish standard care protocols around prevention and treatment and a quality improvement program. In case of an outbreak of CRBSI, the root cause analysis should assess compliance with these protocols. If compliance is below expectation, retraining and eventually reorganization of care should be considered. If compliance with the protocol is deemed appropriate, modification of the protocol could be considered and the process of care re-audited.

ERBP recommendation:

- D.4.1 Standard protocols detailing all aspects of preventive care (catheter manipulation and exit-site care), diagnosis, treatment and follow-up should be established in each centre. These protocols should include hygienic measures for catheter manipulation (see above, ‘Nursing care’ and ‘Exit-site dressings’) and should be assessed by quality control and quality improvement strategies, in conjunction with clinical audit. In case of an outbreak, adherence to those protocols should be improved if it is considered inappropriate. If adherence is appropriate, modification of the protocols should be considered in function of the findings.

Research recommendations

Studies of outcome (or surrogate endpoints like CRP) with central vein catheters for haemodialysis compared to other access methods, if optimum prevention against CRBSI is applied

International multicentric registry of frequency of access infection, type of organism, resistance profile, recurrence profile

Evaluation whether wearing a mask (doctor, nurse, patient) during catheter insertion/ manipulation protects against catheter infection

In vivo studies comparing citrate with alternative lock vehicle solutions such as EDTA, ethanol, urokinase

Head-to-head comparisons of lock solutions with different citrate concentrations

Studies on the effect of spillover of antibiotics from preventive antibiotic locks on antibiotic resistance and on the impact of citrate spillover on symptoms and side effects

Studies on the impact of lock solutions on catheter polymers

Comparison of topical applications of gentamicin, Methylone or Polysporin Triple ointments in the prevention of infection, as compared to mupirocin ointment

Studies on application of hypertonic saline solutions at exit site as preventive measure

To evaluate the laboratory strategies for culturing dialysis catheters in Europe

To check the concordance between blood cultures taken from the dialyser blood lines and peripheral blood samples

Studies of protocols optimizing aminoglycoside pharmacokinetics in haemodialysed patients

Studies comparing the impact on catheter infection of broad catheter salvage (including systemic antibiotics as well as antibiotic and antimicrobial locks) vs removal and reinsertion

Studies on the usefulness of antibiotic locks in infections with other organisms than S. aureus, P. aeruginosa when catheters are left in place

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Disclaimer. The present text is based upon the information available to the work group at the moment of the preparation of this publication. It has been designed to provide information and assist decision making but is not intended to define a standard of care or to impose an exclusive course of diagnosis, prevention or treatment. Individual decision making is essential in the approach to any disease and thus also CRBSI. Variations in practice are inevitable when physicians take into account individual patient needs, available resources and limitations specific for a geographic area, country, institution or type of practice. In addition, evidence may change over time as new information becomes available, so that practice may be modified subsequently. Every practitioner using this text is responsible for its application to any particular clinical situation. The work group members involved in the development of the present text have disclosed all actual and potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional or business interest.

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Diagnosis, prevention and treatment of haemodialysis CRBSI


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Trisodium citrate 4%—an alternative to heparin capping of haemodialysis catheters

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Abstract

Background. Central venous catheters (CVCs) continue to be used at a high rate for dialysis access and are frequently complicated by thrombus-related malfunction. Prophylactic locking with an anticoagulant, such as heparin, has become standard practice despite its associated risks. Trisodium citrate (citrate) 4% is an alternative catheter locking anticoagulant.

Methods. The objective was to prospectively study the clinical effectiveness, safety and cost of citrate 4% vs heparin locking by comparing rates of CVC exchanges, thrombolytic use (TPA) and access-associated hospitalizations during two study periods: heparin period (HP) (1 June 2003–15 February 2004) and Citrate Period (CP) 15 March–15 November 2004. Incident catheters evaluated did not overlap the two periods.

Results. There were 176 CVC in 121 patients (HP) and 177 CVC in 129 patients (CP). The event rates in incident CVC were: CVC exchange 2.98/1000 days (HP) vs 1.65/1000 days (CP) (P=0.01); TPA use 5.49/1000 (HP) vs 3.3/1000 days (CP) (P=0.002); hospitalizations 0.59/1000 days (HP) vs 0.28/1000 days (CP) (P=0.49). There was a longer time from catheter insertion to requiring CVC exchange (P=0.04) and TPA (P=0.006) in the citrate compared with the heparin lock group. Citrate locking costs less than heparin locking but a formal economic analysis including indirect costs was not done.

Conclusion. Citrate 4% has equivalent or better outcomes with regards to catheter exchange, TPA use and access-related hospitalizations compared with heparin locking. It is a safe and less expensive alternative. Randomized trials comparing these anticoagulants with a control group would definitively determine the optimal haemodialysis catheter locking solution.

Keywords: citrate; haemodialysis catheters; heparin; TPA

Background

Since the early 1980s, when the first double lumen central venous catheters (CVCs) were introduced for haemodialysis (HD) vascular access [1], they continue to be used at a high rate despite national guidelines recommending the contrary [2,3]. Up to 70% of North American patients initiate HD with a CVC and a further 40% continue to use it 90 days after dialysis initiation [4,5]. A common challenge associated with CVC use is maintaining the intraluminal patency required to provide sufficient blood flow to achieve adequate dialysis. Aside from mechanical disturbances, such as catheter kinks and malposition, the most common cause of intraluminal disturbance resulting in poor blood flow is intraluminal thrombus formation [6]. Once fully formed, the thrombus may be difficult to treat and often requires repeated intervention with thrombolytic agents or catheter exchange. The standard prophylaxis for intra-luminal thrombus formation is catheter locking with an anticoagulant, such as heparin.

Heparin is composed of sulphated polysaccharides that undergo a conformational change when it binds with antithrombin III. Its anticoagulant effect occurs through the subsequent inhibition of factor Xa and thrombin II. While heparin has been used as the standard locking solution, usually with an amount based on the capped luminal volume, there are few studies addressing the efficacy or safety of different concentrations of heparin. There is a considerable range in the requirement for thrombolytic agents (3.0–9.5/1000 CVC days) [7–9], a surrogate marker for failure of anticoagulation, which may reflect variation in heparin lock concentrations. Heparin is also associated with potential systemic anticoagulation, heparin induced thrombocytopenia and bleeding risks, especially in uraemic patients already at risk of bleeding [7,10–12].
Trisodium citrate (citrate) 4% has been used as an anticoagulant in blood products, for dialysis and apheresis since 1914 [13,14]. Trisodium citrate acts locally as an anticoagulant by chelating ionized calcium in blood, resulting in the blockage of calcium-dependent clotting pathways. Inter-dialytic citrate locking has been reported in the literature [7,15,16] using full strength or diluting the concentrated formulation (46.7% diluted to 23.3%; 30%) but there are potential risks when used in high concentration [17–19]. Case reports of fatal cardiac arrest following the use of high concentrations of trisodium citrate (i.e. 46.7%) led to the withdrawal of a commercially marketed product, Tricitrosoft® by the US Food and Drug Administration (FDA) 5 years ago [20]. In contrast, studies that used a dilute citrate formulation (4%) demonstrated efficacy as an anticoagulant with minimal to no risk of bleeding, but these were small studies with limited generalizability to stable out-patient haemodialysis patients [21–24]. To date, there have been few reported comparisons of its efficacy, safety or cost with heparin locking [25]. In our institution, citrate 4% is less expensive than heparin on a per catheter basis. However, this reduced cost would be misleading should the use of citrate capping be associated with more costly events such as greater TPA use and CVC exchanges due to CVC malfunction. Therefore, we set out to study the clinical effectiveness, safety and cost of citrate 4% vs heparin locking in a prospective, longitudinal cohort of HD patients using permanent tunnelled cuffed CVC in our institution. We hypothesized that there would be no difference in thrombolytic use, CVC exchanges and access-associated hospitalizations, thus demonstrating the cost effectiveness of citrate vs heparin for CVC locking.

Methods

Study design

This study was planned and implemented as a prospective cohort study from 1 June 2003 to 15 November 2004 within the University Health Network (UHN) haemodialysis programme. This programme manages between 300 and 350 haemodialysis patients and has incorporated a multidisciplinary approach to access management since January 1996 [26]. It consists of a full-time vascular access coordinator, a part-time nurse whose responsibilities include access monitoring, nephrologists, interventional radiologists and vascular surgeons. There is a weekly vascular access clinic and bimonthly interdisciplinary meeting to review and discuss complicated cases.

All chronic haemodialysis patients with a permanent, cuffed internal jugular tunnelled CVC were studied. Our programme primarily used the Uldall-Cook Catheter (Cook Canada Inc.) dual lumen catheter (95%). However, the following dual lumen CVCs may have been used as our programme was randomly sampling other types: HIGHLFLOW Dialysis Catheter (CardioMed Supplies Inc., Gormley, ON, Canada), Opti-flow/HemoGlide dual-lumen permanent dialysis catheter (Bard Access Systems, Utah, USA) and Vaxcel® Plus Chronic Dialysis Catheter (Boston Scientific, MA USA). When this was the case, the choice of CVC type and side of insertion was left to the discretion of the radiologist performing the procedure. Catheter exchanges were performed by the interventional radiology department as an out-patient procedure unless the patient was already hospitalized. All filling volumes were documented and acknowledged by the haemodialysis nurse who was responsible for capping the catheters post dialysis. Baseline demographic and access information was collected. The access coordinator prospectively tracked the number of CVC insertions and removals, use of TPA and vascular access-related hospitalizations. All information was entered into a clinically based, centralized vascular access database that is updated daily.

The study defined two study periods: The ‘Heparin Period (HP)’ (1 June 2003–15 February 2004) that was intended to determine the baseline rate of catheter exchanges, TPA use and access-related hospitalizations using our standard of practice of locking CVC with heparin using 5000 U/lumen total (0.5 ml of a 10 000 unit/ml heparin concentration with normal saline 9% to fill the lumen volume) after each dialysis session. Specifically, after a 10 cc normal saline flush, haemodialysis nurses prepared the heparin solution in a 3 or 5 cc syringe by mixing 0.5 ml of 10 000 U/ml heparin with the required amount of normal saline to fill the catheter lumen and then instilled the solution into each catheter port. All patients were then switched to locking CVC with citrate 4% after each dialysis session, starting on 15 February 2004 ['Citrate Period' (CP)]. Data were collected from 15 March 2004 to 15 November 2004 to evaluate outcomes during the CP. The citrate was provided in 5 ml preloaded syringes, prepared by the on-site pharmacy. While this study involved only permanent catheters, the rare temporary catheters used in the dialysis unit were capped with the same solution used during the study period.

Outcome measures

The primary endpoint of this study was the number of catheter exchanges required/1000 catheter days. The secondary endpoints were the rate of TPA use/1000 catheter days and the rate of access-related hospitalization. The time to catheter exchange and time to TPA requirement, using these locking solutions were also compared. Lastly, the costs of administering heparin vs citrate 4% capping irrespective of these endpoints were compared.

Catheters were exchanged when blood flow through the CVC was so limited that the CVC could not provide dialysis and was considered a salvage procedure. All conservative measures to improve catheter patency and function were first attempted. For example, patients were repositioned, had their lines saline flushed and reversed and received TPA. The dialysis nurses were able to administer TPA under a medical directive allowing them to provide TPA to a patient’s CVC without doctor’s orders, used only in strict accordance with the institutional protocol for TPA administration. Briefly, nurses were trained to perform the conservative manoeuvres noted above to exclude non-thrombus or mechanical problems prior to instituting TPA when peak blood flow rate fell below 250 ml/min or if dialysis adequacy was threatened due to reduced flows that were clinically deemed
related to catheter thrombosis. If the nurses required confirmation prior to using TPA, the attending nephrologist was consulted. It is not logistically or practically feasible in our dialysis unit to routinely send patients to radiology to determine if the cause of catheter malfunction was related to an intraluminal thrombus due to resource and time constraints.

Access-related hospitalizations were all-cause hospitalizations due to catheter complications, such as bleeding, sepsis and those related to catheter insertions or removals.

The costs of heparin vs citrate locking were independently determined by the hospital pharmacy and included the cost of the anticoagulant, equipment (e.g. syringes), manpower required to dispense and administer the locking solution. The financial direct and indirect (e.g. rental and equipment costs, professional fees, etc.) costs of catheters, catheter exchanges and hospitalizations did not differ between the two time periods. In this study, only direct cost differences between the two CVC locking solutions were evaluated.

Patients were prospectively followed for the above outcomes in both the HP and CP until the end of the study on 15 November 2004.

**Analysis**

The primary and secondary endpoints of this study were expressed as events/1000 catheter days. The primary analysis was performed on prospective patients who were in the dialysis unit who had incident catheters inserted during either the HP or the CP and did not overlap study periods. Incident catheters in the HP were censored on 15 February 2004 and those in the CP on 15 November 2004, respectively, if they were still in use at that time. A sensitivity analysis was performed that evaluated only the first incident catheter per patient per study period. Some patients and catheters were prevalent over both study periods ‘overlap group’; this group was not evaluated.

Rate specific outcomes (event/1000 CVC days) were compared using the exact binomial test for Poisson distributions (appropriate for rates using person-time denominators). Time to event analyses (catheter exchange and TPA requirement) were estimated using Kaplan–Meier survival curves and compared with the log-rank test. All tests of significance were two-sided, and differences were considered statistically significant with a P-value <0.05. The statistical software used was SAS (version 8.2) (SAS Institute Inc., Cary, NC, USA).

**Results**

In the total study period, there were 527 CVC used in 347 patients. There were 174 prevalent catheters in 97 patients that were excluded from analysis. The results of the primary analysis in 250 patients and their respective 353 catheters that were independent of each other in the HP or CP are presented. Of these patients, 176 catheters in 121 patients were used during the heparin locking period and 177 catheters in 129 patients during the citrate period. There were no differences in patient characteristics between these groups of patients (Table 1).

In the primary analysis, there were 16761 catheter days in the HP and 17593 catheter days in the CP. Subjectively, some nurses and patients noted clots in the dialysers of patients capped with citrate compared with heparin. For this and other reasons, seven patients refused citrate capping and were analysed in the heparin group. The CVC exchange rates were greater for catheters capped with heparin (2.98/1000 CVC days) compared with citrate (1.65/1000 CVC days; P = 0.01). The proportion of patients requiring at least one catheter exchange was 83% in the heparin group and 67% in the citrate group (P = 0.006) (Table 2). There was a longer time from catheter insertion to requiring catheter exchange for suspected thrombosis-related malfunction in the citrate locking group compared with the heparin lock group (Figure 1). The TPA rate during HP was 5.49/1000 CVC days and during CP, it was 3.3/1000 CVC days (P = 0.002). There was a longer time interval before requiring TPA in newly inserted catheters in the CP compared with the HP (Figure 2). The hospitalization rate was 0.59/1000 CVC days in the HP and 0.28/1000 CVC days in the CP (P = 0.49). The average hospitalization stay was longer in the HP (8.62 days) compared with that in the CP (3.34 days) (P = 0.02). The majority of hospitalizations during the HP were due to line-related bacteraemias or sepsis while this occurred minimally during the CP. The catheter-related bacteraemia rate was 1.7/1000 CVC days in HP compared with 0.2/1000 CVC days in the CP (P < 0.0001) in incident catheters.

**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Heparin</th>
<th>Citrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>121</td>
<td>129</td>
</tr>
<tr>
<td>Catheter days</td>
<td>16761</td>
<td>17593</td>
</tr>
<tr>
<td>Mean age (SD) (range)</td>
<td>60 (16.3) (20–92)</td>
<td>60 (16.0) (22–87)</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>67 (55.4%)</td>
<td>69 (53.5%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>72 (59.5%)</td>
<td>74 (57.4%)</td>
</tr>
<tr>
<td>Black</td>
<td>19 (15.7%)</td>
<td>13 (10.0%)</td>
</tr>
<tr>
<td>Other</td>
<td>30 (24.8%)</td>
<td>42 (32.6%)</td>
</tr>
<tr>
<td>Aetiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>22 (18.2%)</td>
<td>24 (18.6%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (14.9%)</td>
<td>17 (13.2%)</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>33 (27.3%)</td>
<td>36 (27.9%)</td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>3 (2.5%)</td>
<td>2 (1.6%)</td>
</tr>
<tr>
<td>Other</td>
<td>28 (23.1%)</td>
<td>33 (25.6%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>174 (14.0%)</td>
<td>17 (14.1%)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>46 (38.0%)</td>
<td>38 (29.5%)</td>
</tr>
<tr>
<td>HTN</td>
<td>85 (70.2%)</td>
<td>93 (72.1%)</td>
</tr>
<tr>
<td>CAD</td>
<td>30 (25.8%)</td>
<td>33 (25.6%)</td>
</tr>
<tr>
<td>CHF</td>
<td>25 (20.7%)</td>
<td>25 (19.4%)</td>
</tr>
<tr>
<td>CVA/TIA</td>
<td>10 (8.3%)</td>
<td>14 (10.9%)</td>
</tr>
<tr>
<td>PVD</td>
<td>17 (14.0%)</td>
<td>15 (11.7%)</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>28 (23.1%)</td>
<td>28 (29.7%)</td>
</tr>
</tbody>
</table>

DM, diabetes mellitus; HTN, hypertension; CAD, coronary artery disease; CVA/TIA, stroke or transient ischemic attack; PVD, peripheral vascular disease.
analysis and outcomes of first catheters per patient per study period demonstrated similar results to the primary analysis. For example, the proportion of patients requiring CVC exchanges was 66% (HP) vs 47% (CP), \( P = 0.01 \) and the TPA rates were 4.51/1000 CVC days (HP) vs 1.26/1000 CVC days (CP), \( P < 0.0001 \). Hospitalization rates were not determined for the first new catheter per patient per period as the numbers were too small (\( n = 5 \) in each group). No association was found between the varying types of catheters and outcomes (minimum \( P \)-value = 0.16; data not shown).

The total cost of preparing and administering heparin capping was $1.68 (Can) and for citrate capping $0.72 (Can).

### Discussion

Our study found that locking tunnelled, cuffed central venous dialysis catheters with trisodium citrate 4% had equivalent or better outcomes compared with interdialytic locking with heparin sulphate (5000 U/lumen) with regards to the frequency of catheter exchanges, intraluminal thrombolytic use and access-associated hospitalizations.

The results of our study are consistent with earlier trials of low-concentration citrate catheter locking compared with heparin locking. Two early small, prospective, randomized, non-blinded trials compared citrate to heparin as a lock to maintain single lumen

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Heparin</th>
<th>Citrate</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVC exchange</td>
<td>2.98/1000</td>
<td>1.65/1000</td>
<td>0.01</td>
</tr>
<tr>
<td>Proportion with at least one exchange</td>
<td>83%</td>
<td>67%</td>
<td>0.006</td>
</tr>
<tr>
<td>TPA rate</td>
<td>5.49/1000</td>
<td>3.3/1000</td>
<td>0.002</td>
</tr>
<tr>
<td>Hospitalization admit</td>
<td>0.59/1000</td>
<td>0.28/1000</td>
<td>0.49</td>
</tr>
<tr>
<td>Hospital days</td>
<td>4.12/1000</td>
<td>1.36/1000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean hospitalization days</td>
<td>8.62</td>
<td>3.34</td>
<td>0.016</td>
</tr>
</tbody>
</table>

### Table 2. Comparison of outcomes of incident catheters per study period

![Fig. 1. Time to catheter exchange of incident catheters.](image1)

![Fig. 2. Comparison of the time to TPA requirement in new catheters capped with heparin and citrate.](image2)
CVCs patency inserted in either the subclavian or internal jugular vein [23,24]. Hendrickx et al. [24] studied 10 patients who used citrate 5% lock while nine patients received heparin 5000 units/ml lock for 6 months. Based on a total of 1370 HD sessions, citrate 5% was comparable with heparin but the total number of clots (occlusive or non-occlusive) per dialysis session was significantly greater for the citrate (14.4%) vs the heparin (6.6%) lock group. Another study of citrate anticoagulation also noted clots in the dialyser (8.8%) but resulted in insignificant termination of dialysis (1.48%) [27]. Indeed, some nurses and patients in this study observed more obvious clotting, but this did not translate into functional abnormalities such as inadequate blood flow or greater need for thrombolytic therapy.

Buturovic et al. [23] evaluated 30 HD patients with temporary CVC who received locking with either citrate 4% (10 patients), heparin 5000 units/ml mixed with 2 ml normal saline (10 patients) or polygeline 3.5% (10 patients). There was no difference in the primary endpoints (volume of aspirated clot and removal of the catheter due to poor blood flow), but a low frequency of endpoint events (i.e. only one CVC per group removed due to clotting) was reported. Thus, a type II error (two groups considered equal but in fact are different) could not be excluded. Consistent with our findings, the citrate group also had a longer period of use (at least >20 days) compared with heparin or polygeline.

More recently, larger studies of citrate vs heparin locking have been performed in out-patient haemodialysis patients using tunnelled catheters. Plamondon et al. [25] performed a 4 week open label cross-over study of trisodium citrate 4% locking compared with heparin (5000 U/lumen) locking in 44 patients. Their primary endpoint was catheter thrombosis requiring intraluminal thrombolytic therapy. In contrast to our study (TPA use 3.3/1000 CVC days with citrate lock and 5.49/1000 with heparin lock), they found no difference using citrate (0.8%) or heparin (1.1%). This may be due to their shorter trial duration and fewer catheters such that the total catheter days were limited. Also, the cross-over design may have implications with regards to a lack of statistical and clinical independence of their data. Similarly, Weijmer et al. [7] did not find a difference in thrombolytic use between citrate 30% (4.11/1000 CVC days) and heparin (4.87/1000 CVC days) locks. However, the underlying finding of minimal outcome equivalency is consistent with our study.

Weijmer et al.’s [7] study was a randomized, multi-centre trial of heparin (5000 U/ml) vs trisodium citrate 30% to determine whether there was a difference in catheter patency and catheter-related infections. The rate of CVC removal due to flow problems in the 30% citrate group was 3.2/1000 CVC days, compared with our rate of 1.65/1000 CVC days. Their higher removal rate may be due to broader criteria for premature catheter removal that included removal for infection, thrombosis, catheter breakdown or leakage, unintentional and accidental removals and the use of both temporary and permanent catheters. They found superior cumulative survival in catheters locked with citrate vs heparin with a median of ~180 and 85 days, respectively. By the end of our study, 25% of patients had their incident catheters removed/exchanged at a point estimate of 170 days (citrate lock) compared with 84 days (heparin lock) ($P = 0.042$).

Due to our low baseline infection rates, we were surprised to find a difference in catheter-related bacteraemias. However, previous studies of citrate +/- gentamicin locking have found a graded response with fewer infective episodes with increasing concentrations of citrate [28,29]. The difference in bacteraemia rate in this study should be interpreted with caution since a hospital policy instituting a nursing medical directive to apply a polyantibiotic ointment to the catheter exit site for catheter infection prophylaxis [30] was instituted during the study. Thus, the relative contributions of polyantibiotic ointment application and citrate 4% locking in reducing bacteraemia rates are unclear. A prospective study using citrate 4% capping with catheter-related infections as a primary outcome would clarify this issue.

In our institution, since the direct costs of citrate locking was less than heparin locking, and given the minimum equivalency of outcomes, the total cost benefit is likely greater if indirect costs were considered. The savings related to less thrombolytic use and fewer average hospital stays were not evaluated. Other studies, such as the one by Plamondon et al. [25] also found direct cost saving using citrate lock ($1.35 CAD) compared with heparin lock ($2.50 CAD). At the end of the study, our institution switched over to commercially available sterile, trisodium citrate 4% solution in 5 ml pre-loaded syringes (MEDXL Inc., Canada) that costs $1.05 per syringe. The main reason for the switch was convenience for the pharmacy. After trisodium citrate 4% is drawn up into 5 ml polyvinyl chloride syringes, it is chemically stable (up to 10% loss in the original concentration) for at least 28 days stored at room temperature (21°C) and protected from sunlight [31]. At our centre, the cost saving with citrate capping is ~0.63–0.96/lock, depending on whether it is commercially available or pharmacy prepared pre-filled syringes, respectively. In a programme that uses 100 catheters, this translates into cost savings of $10—15000.00/year. This may not be applicable to other non-Canadian institutions as the availability and cost of citrate capping solutions may vary considerably.

This study has several clinical implications. Given the common problems with catheter malfunction, medical interventions for intra and inter-dialytic catheter anticoagulation are logical. Heparin is a standard choice for inter-dialytic catheter locking, but suboptimal doses are frequently used due to concerns of bleeding risks. Prior studies have noted greater haemorrhagic complications with low dose
heparin compared with even high concentrations of sodium citrate [19]. Even in critically ill patients with renal failure requiring continuous replacement therapy, the relative risk of haemorrhage has been reported to be less in patients receiving anticoagulation with citrate compared with heparin [32]. Increased bleeding risks were not found with citrate 4% use. The lower bleeding risk may be due to the shorter serum half-life compared with heparin. Overspill is known to occur when the volume of the catheter is 80% filled, with 15% spillage demonstrated with precise luminal volume instillation of an anticoagulant [33]. When heparin is used as the lock, ~2000 IU are injected into the patient when both sides of a two lumen catheter are filled with 5000 IU each [33]. While the amount of citrate leakage is unknown, when it enters into the systemic circulation, it is rapidly metabolized primarily by the liver to sodium bicarbonate [22,34]. In patients with normal liver function, the terminal serum elimination half-life is about 35 min, but is increased with liver disease [22,34]. Citrate clearance in HD patients is reported to be the same as non-dialysis patients [11]. Heparin has a longer serum elimination half-life of 60–90 min (but is unaltered by liver disease). Other safety concerns relate to citrate's ability to bind free ionized calcium, with the potential to cause hypocalcaemia and hypomagnesaemia, leading to cardiac dysrhythmias, seizures and bleeding [22,33]. High concentrations may also cause a ‘metallic’ taste in 10% of patients shortly after filling the catheter [35]. To date, our study inclusive, there have been no changes in serum calcium or magnesium or serious side effects with citrate 4% lock.

Our study had several limitations. It was not a prospective randomized blinded controlled trial. Sample size estimates for such a trial of adequate power to detect a difference in catheter patency would approximate 250–300 independent catheters per arm and was not feasible to perform in our institution. However, we determined a priori to prospectively compare predetermined outcomes and analysed independent groups of incident catheters that did not overlap study periods. We performed sensitivity analyses comparing only the first new catheter per patient per period and found similar results. These analyses were necessary from a quality assurance viewpoint; from daily clinical observations, the original perception of HD staff was that citrate was not different to heparin following conversion of locking solutions. Differences became apparent with analysis of incident catheters, highlighting the importance of objective appropriate analysis, and were necessary in order to implement change in inter-dialytic locking protocols. The economic evaluation was a basic one of direct costs only. A proper pharmacoeconomic evaluation was not performed. We estimate that the cost savings have been conservative and that the use of citrate would fall into the classic ‘new treatment dominant’ quadrant of standard incremental cost effectiveness ratio graphs [36].

Conclusions

Trisodium citrate 4% inter-dialytic locking has equivalent or better outcomes with regards to TPA use, need for catheter exchange, and access-related hospitalizations when compared with heparin locking. It is a safe and less expensive alternative to heparin locking of haemodialysis catheters. A large, randomized trial comparing heparin to trisodium citrate that includes a normal saline control group is needed to definitively resolve the issue of preferred locking solution for haemodialysis CVC.

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Conflicts of interest statement. None declared

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Critical Appraisal to the publication of Yon and Low (4% Citrate vs. Heparin)

1. Study design is not very convincing
2. Surprising results regarding reduction of infection.
3. High Catheter exchange rate during heparin period suggests that most of the problematic catheters were exchanged before starting the 4% citrate period
4. Surprising results are opposite to the findings of other authors

1. Study design is not convincing:
   a) historical comparison includes the possibility of additional improvements during both study periods which are not due to the study product
   b) Data were collected retrospectively in the heparin but prospectively in the citrate arm. This includes the possibility of a significant bias since the definition for catheter related infection was "fever or chills during or after a hemodialysis session...and at least one positive blood sample...with no other source of infection". Especially the search for "other source of infection" could result in significant quality problems during a retrospective search.
   c) to get a significant result the citrate period was prolonged from 12 to 15 month. It raises questions, why the authors did not prolong the heparin period from 12 to 15 month?
   d) The size of the study (Heparin 5.000 IU/mL, 12 month, 10.800 catheter days; 4% Citrate, 15 months, 13.530 Catheterdays) is acceptable

2. Surprising Results regarding reduction of infection
   a) It is very surprising that especially the Pseudomonas aeruginosa infection were reduced from 3 in the heparin group to 0 in the citrate group. The publication of Weijmer et al Nephrol. Dial transplanta (2002) 17: 2189-2195 says that citrate in concentration of up to 7.5% is not effective in reducing the growth of Pseudomonas aeruginosa.
   b) Also for Staph. aureus (reduction from 5 in the heparin period to 2 infection in the citrate period) no antimicrobial effect of 4% citrate could be reported by Weijmer et al.
   c) Further organisms which are characteristic for infections in HD-patients (e.g. CoNS) are not specified

3. High rate of Catheter exchanges in the heparin period:
   Table 2 gives a figure of 3.24 catheters exchange/1000 catheter days. This means 35 (not 34 as mentioned) catheters are exchanged during the 10.800 catheter days of heparin usage. 18 catheters are exchanged during the 4% citrate period. On the first view this is a very positive result regarding 4% Citrate on the second view it is not clear that saving of 9 infections could save 17 catheter changes (Note: thrombosis rate is similar in both arms).
   -> it seems that before introducing 4% citrate most of the problematic catheters were exchanged by new catheters to improve the result of the study.
4. Surprising results are contrary to the findings of other authors:

Discussion of the authors: The authors conclude that the result of the study is consistent with the result of other publications. This is clearly not the case:

a) Lok CE, Appleton D, Bhola C, Khoo B, Richardson RM. Trisodium citrate 4% - an alternative to heparin capping of haemodialysis catheters. Nephrol Dial Transplant 2007; 22: 477-483. Lok also compares 4% citrate with heparin historically and really gets lower infections. But the author herself says that “the difference in bacteraemia rate in this study should be interpreted with caution since a hospital policy...to apply a polyanthibiotic ointment was instituted during the study”.

Weijmer compares 30% Citrat vs. Heparin not 4% citrate. There is no doubt that 30% citrate reduces catheter related infection but this is a clearly different product to 4% citrate.

Grudzinski performed the same study (historical comparison of 4% citrate vs. Heparin) and did not observe any reduction of the infection rate. Moreover the infection rate was slightly higher in the citrate group (0.77 infections per 1000 catheter days in the heparin group and 0.94 infections per 1000 catheter days in the 4% citrate group, p=0.36). Yon and Low erroneously citing 0.36 (not 0.94) infections per 1000 catheter days in the Grudzinski paper. This means the results from Yon and Low are contradictory to the findings of Grudzinski.

McRae, which did the only randomized trial comparing heparin and 4% citrate, did not observe any significant reduction of the infection rate of 4% Citrate vs. Heparin (p=0.607). This is clearly not consistent with the result of Yon and Low.
Sodium citrate 4% versus heparin as a lock solution in hemodialysis patients with central venous catheters

CALANThA K. YON AND CHAI L. LOW

The National Kidney Foundation recommends the use of a fistula or graft for permanent hemodialysis vascular access. However, up to 70% of North American patients initiate hemodialysis with a central venous catheter (CVC), and 40% of these patients continue to use the CVC 90 days after the initiation of hemodialysis. The potential disadvantages of CVC use include thrombosis or stenosis of the catheter, infection, shorter expected life span of use, and decreased blood flow during hemodialysis. Catheter-related infections (CRIs) are of particular concern in patients using CVCs because of the increased rate of morbidity and mortality. The 2009 annual data report of the U.S. Renal Data System attributed the increase in hospitalizations due to vascular access infections to CVCs. CRIs can result from microbial biofilm formation, catheter hub contamination, or colonization of the catheter. Biofilm formation and colonization of the catheter also increase the risk of intraluminal thrombosis of the catheter.

To prevent these complications, anticoagulant prophylaxis with an interdialytic catheter lock solution is often used. CVCs have arterial and venous ports that remain outside the body. To maintain patency of the group and prospectively for the sodium citrate group.

Results. Data were collected from 360 patient-months among 60 patients during the heparin treatment period and from 451 patient-months among 58 patients during the sodium citrate period. Thirty-three patients were common to both study groups. There were significantly more CRIs and CRIs per 1000 catheter-days in the heparin than the sodium citrate treatment group. Secondary outcomes of hospitalizations and catheter thrombosis were comparable. CRIs and thrombosis led to significantly more catheter exchanges or removals in the heparin group than the sodium citrate group.

Conclusion. In patients with long-term hemodialysis catheters, a lock solution of sodium citrate 4% was associated with fewer CRIs and similar effectiveness when compared with heparin 5000 units/ml.

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CVC, a catheter lock solution is often injected to dwell in the catheter ports between hemodialysis sessions. The typical volume of a catheter port is 2–3 mL. The catheter lock solution is instilled after a hemodialysis session until the next hemodialysis session, with an average dwell time of 24–48 hours for patients receiving long-term hemodialysis.

Prophylaxis with an anticoagulant, such as heparin, is a common practice in many dialysis units. Heparin is a polysaccharide that exerts its anticoagulant effect by accelerating the activity of antithrombin III to inactivate thrombin. This conformational change in antithrombin III accelerates its ability to inactivate thrombin (factor IIa), factor IXa, and factor Xa. Heparin is the standard lock solution used in catheters; however, some studies have addressed the optimal dosage, efficacy, and safety of heparin as a lock solution.6,4

Common heparin concentrations for interdialytic catheter locks range from 5,000 to 10,000 units/mL. Since there is no standard optimal dosage of heparin, systemic anticoagulant effects may result from the use of catheter locks containing heparin. Studies have found an increase in activated partial thromboplastin time and bleeding risk with inadvertent systemic exposure to heparin from heparin lock solutions.4 This is particularly concerning, since patients with renal insufficiency have an increased risk of bleeding due to platelet dysfunction secondary to uremia. Sodium citrate 4% has been proposed as an alternative to heparin as a catheter lock solution.

Sodium citrate 4% acts as a local anticoagulant by chelating ionized calcium present in blood, resulting in the blockade of calcium-dependent clotting pathways and a reduction in fibrin formation. Sodium citrate has been advocated as a catheter lock solution because of its antimicrobial properties and the relatively lower risk, compared with heparin, of systemic anticoagulation. Possible mechanisms for sodium citrate's antimicrobial activity include hyperosmolality of the solution and binding of divalent cations.5 Previous studies have found a benefit with using sodium citrate 30% in decreasing infection rates, maintaining catheter patency, decreasing hospitalization length of stay, and decreasing systemic anticoagulation effects.6,11 In vitro, sodium citrate concentrations above 0.5% inhibit biofilm formation and growth of Staphylococcus aureus and Staphylococcus epidermidis.10 Other in vitro studies showed that the use of sodium citrate was effective in killing staphylococcal strains, and a concentration of 30% was effective in killing Pseudomonas aeruginosa and Escherichia coli.11 Alternatively, heparin has been shown to enhance S. aureus accumulation on polymer surfaces.19

We conducted a single-center, open cohort study to compare the effect of heparin versus sodium citrate 4% as a lock solution on CRIs, catheter patency, and hospitalizations in patients receiving long-term hemodialysis and having a permanent CVC.

Methods

Patients were included in the study if they were at least 18 years old, were receiving long-term hemodialysis, and had a CVC. All patients in the dialysis unit with a CVC in use during all or part of the study period were included in the analysis. Patients were excluded if they had a documented allergy to heparin or sodium citrate or used an arteriovenous fistula or graft for vascular access during hemodialysis.

Data collection and review were conducted during two time periods. Data for patients receiving heparin lock solutions were collected from July 2008 through July 2009. Data on patients receiving sodium citrate 4% lock solution were collected from September 2009 through December 2010. Patients who were receiving the heparin lock solution who continued to have a CVC in September 2009 were transitioned from heparin to sodium citrate catheter 4% lock solution. New patients with CVCs placed after September 2009 received sodium citrate 4% without a period of using heparin lock solution.

From July 2008 to July 2009, patients had 2–3 mL of heparin instilled into each of the venous and arterial catheter ports until the next hemodialysis session. The heparin concentration used for the lock solution was 5000 units/mL. During the period of September 2009 to December 2010, 2–3 mL of sodium citrate 4% solution was instilled after hemodialysis into the venous and arterial catheter ports until the next hemodialysis session. After the completion of each hemodialysis session, the catheter lumens were flushed with 10 mL of 0.9% sodium chloride injection, and then heparin 5000 units/mL or sodium citrate 4% was instilled into each lumen. The lock solution in each port was aspirated and discarded before the start of each hemodialysis session. The heparin lock solution was drawn from vials obtained from the manufacturer. Sodium citrate 4% was obtained commercially in 500–mL bags and placed in 3-mL unit-dose syringes by the pharmacy department. The change in lock solution was a unit policy, so no written consent from study patients was obtained. Approval for the study was obtained from the institutional review board.

When catheters were considered to be partially or fully clotted, alteplase 2 mg/2 mL was instilled into the catheter lumen.

The computerized patient medical record system was reviewed to obtain data pertinent to the study. Data collected included demographic information, alteplase use, concomitant medications, indication for long-term hemodialysis, documentation of CRI, incidence of hospitalization,
microbiological cultures, and antibiotics used to treat any CRI. Radiology and consultation reports were used to identify catheter exchanges that resulted from poor blood flow or CRIs. Catheter exchanges due to cuff exposure or concerns about catheter integrity were excluded. Data were collected retrospectively for the heparin group and prospectively for the sodium citrate group.

There were approximately 60 patients with CVCs at any given time during the study period. These patients comprised the eligible patients for study enrollment. Statistical analyses were conducted using Shapiro-Wilk’s test to test for normality of continuous data. In addition, the independent Student t test and the Mann-Whitney U test were performed. Categorical data was evaluated using Pearson’s chi-square test or Fisher’s exact test where appropriate. The a priori level of significance was 0.05. The sum of all patient-months for the treatment period was multiplied by 30 (average number of days per month) to calculate catheter-days. The incidence of CRIs was defined as the number of CRIs per 1000 catheter-days. The rate of catheter exchange was defined as the number of catheter line exchanges divided by the number of catheter-days. A CRI was defined as a fever (temperature of >38 °C or >101 °F) or chills during or after a hemodialysis session and at least one positive blood culture from the CVC with no other identifiable sources of infection.

Results

During the study period, 85 unique patients each had a CVC for hemodialysis access. There were 360 patient-months among 60 patients during the heparin treatment period, accounting for 10,800 catheter-days. In contrast, there were 451 patient-months among 58 patients during the sodium citrate period, accounting for 13,530 catheter-days, as a higher percentage of patients were using fistula or graft access during this time period. Thirty-three patients were common to both study groups.

The demographics and characteristics of the study population are shown in Table 1. There was no statistical difference in these characteristics between treatment groups.

There were significantly more CRIs and CRIs per 1000 catheter-days in the heparin than the sodium citrate treatment group (Table 2). In the heparin group, two patients had 2 CRIs, and one patient had 3. One patient in the sodium citrate group had 3 CRIs. Two patients common to both groups had a CRI during each study period. Of the documented CRIs, 16 of 20 in the heparin group and 9 of 11 in the sodium citrate group resulted in hospitalization.

The most commonly isolated organisms were Enterobacter species and Staphylococcus species in the heparin group and Enterobacter species in the sodium citrate cohort. Two patients in the heparin group had multiple organisms isolated per CRI. One CRI had isolates of Klebsiella species and Acinetobacter species. The other CRI had isolates of Pseudomonas species and Enterobacter species. Antibiotics were not commonly instilled into locks in either study period. Gentamicin was used in one heparin lock solution for a coagulase-negative Staphylococcus species infection, and ceftazidime was used in one heparin lock solution for a gram-negative infection. In both instances, the antibiotic lock instillations were discontinued after one hemodialysis session.

The frequency of catheter thrombosis did not differ significantly between groups. Alteplase was used in each of these cases to dissolve the thrombus before a catheter exchange was required. CRIs and thrombosis led to significantly more catheter exchanges or removals in the heparin group than the sodium citrate group. One patient in the heparin group required two catheter exchanges due to a CRI, and one patient in the sodium citrate group required three catheter exchanges due to a CRI.

Discussion

Heparin is widely accepted as the standard of practice for a catheter lock solution, with sodium citrate being reserved for patients who are unable to receive heparin. The re-

Table 1.
Characteristics of Patients Receiving Heparin or Sodium Citrate as a Lock Solution*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Heparin (n = 60)</th>
<th>Sodium Citrate (n = 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. catheter-months</td>
<td>360</td>
<td>451</td>
</tr>
<tr>
<td>Mean ± S.D. age, yr</td>
<td>64.3 ± 10.3</td>
<td>65.1 ± 11.5</td>
</tr>
<tr>
<td>Male, no. (%) pts</td>
<td>58 (97)</td>
<td>54 (93)</td>
</tr>
<tr>
<td>Ethnicity, no. (%) pts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>30 (50)</td>
<td>32 (55)</td>
</tr>
<tr>
<td>Black</td>
<td>14 (23)</td>
<td>11 (19)</td>
</tr>
<tr>
<td>Asian</td>
<td>5 (8)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Other</td>
<td>12 (20)</td>
<td>10 (17)</td>
</tr>
<tr>
<td>Indication for dialysis, no. (%) pts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>43 (72)</td>
<td>41 (71)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>43 (72)</td>
<td>42 (72)</td>
</tr>
<tr>
<td>Other</td>
<td>25 (42)</td>
<td>20 (34)</td>
</tr>
</tbody>
</table>

*Thirty-three patients were common to both groups. Differences between groups were not significant.
*One patient in the heparin group had two etiologies documented.
results of this study show that sodium citrate 4% was associated with a lower frequency of CRIs compared with heparin. In addition, sodium citrate 4% was as effective as heparin 5000 units/mL in the maintenance of catheter patency for long-term hemodialysis. The results of this study are consistent with those of other studies comparing sodium citrate with heparin.

Lok et al. compared the number of catheter exchanges in two study periods using heparin 5000 units/mL and sodium citrate 4% as lock solutions. The authors found that the sodium citrate group had a significantly lower incidence of CRIs versus the heparin group (0.2 CRI per 1000 catheter-days versus 1.7 CRIs per 1000 catheter-days, $p < 0.0001$). The number of catheter changes per 1000 catheter-days was also significantly lower in the sodium citrate group (1.65 versus 2.98 in the heparin group, $p = 0.01$). Alteplase use was significantly higher with heparin versus sodium citrate (5.49 treatments per 1000 catheter-days versus 3.3 treatments per 1000 catheter-days, $p = 0.002$). The CRIs from this study support our findings that the use of sodium citrate 4% is associated with fewer CRIs. However, the difference in the number of CRIs between the treatments should be cautiously interpreted, as the institution in the study by Lok et al. had implemented a policy of applying bacitracin-polymixin B ointment to the catheter site during the study period. This was not done in our study. The effects of the antibiotic ointment policy on the study's results and outcomes are unknown, and further investigation is needed to determine its effect on the incidence of CRIs.

Weijmer et al. compared heparin 5000 units/mL with sodium citrate 30% in an 18-month, prospective, randomized trial. A total of 16,547 catheter-days were analyzed. There were 33 CRIs in the heparin group, compared with 9 in the sodium citrate group ($p < 0.001$). This translates to 4.1 CRIs per 1000 catheter-days in the heparin group and 1.1 CRIs per 1000 catheter-days in the sodium citrate group. Twenty-nine catheters were removed due to thrombosis in the heparin group compared with 27 catheters in the sodium citrate group (3.6 per 1000 catheter-days versus 3.2 per 1000 catheter-days, respectively; $p = 0.75$). The total number of catheters removed was 8.1 per 1000 catheter-days in the heparin group versus 5.0 per 1000 catheter-days in the sodium citrate group ($p = 0.005$). Compared with sodium citrate, heparin was associated with significantly more episodes of persistent bleeding after insertion at the catheter site ($p = 0.005$), of major bleeding during follow-up ($p = 0.01$), of gastrointestinal bleeding ($p = 0.034$), and of exit-site bleeding ($p = 0.028$).

In 2000, the Food and Drug Administration issued a warning about cardiac-related fatalities associated
with sodium citrate concentrations as high as 46%\(^6\)\(^{14}\); however, an increased frequency of cardiac events was not reported by Weijmer et al.\(^4\) for the sodium citrate 30% group. There was a higher frequency of catheter exchanges in that study compared with ours, but reasons for exchange in the former included unintentional catheter removal, thrombosis, leakage, and concerns about catheter integrity.

The results of the study conducted by Weijmer et al. support the use of sodium citrate but differ in important ways from our study. First, our study protocol used the lower sodium citrate concentration of 4% rather than the 30% used by Weijmer et al. The 30% and 46.7% formulations of sodium citrate are no longer available because they were associated with adverse effects. Second, our study included catheter removals due only to infection or thrombosis, leading to a potential difference in catheter maintenance results.

Gruzdinski et al.\(^8\) compared sodium citrate 4% with heparin 10,000 units/mL in a retrospective, two-year, single-center study. The study evaluated a total of 36,925 and 37,139 catheter-days in the heparin and sodium citrate groups, respectively. These investigators found no significant difference in the frequency of bacteremia between groups (0.77 episode of bacteremia per 1000 catheter-days with heparin versus 0.36 per 1000 catheter-days with sodium citrate, \(p = 0.36\)). The number of catheter changes per 1000 catheter-days did not significantly differ between the heparin and sodium citrate groups (1.81 versus 1.88, respectively; \(p = 0.89\)). There was also no significant difference in the number of alteplase treatments per 1000 catheter-days between the two groups (4.1 in the heparin group versus 3.2 in the sodium citrate group, \(p = 0.07\)).

Results from that study differed from ours in that we found a difference in the frequency of CRLs and catheter exchanges. It is unclear why Gruzdinski et al. found a very low frequency of CRLs and catheter exchanges, which are among the lowest CRI rates reported in the medical literature. It was not reported whether the study institution used antibiotic ointments or creams at the catheter site. In addition, Gruzdinski et al.'s study had a larger number of catheter-days compared with our study, which may contribute to the differences between the studies.

Power et al.\(^{13}\) compared CRI frequency, exit-site infections, and catheter thrombosis using sodium citrate 46.7% (\(n = 132\)) versus heparin 5% (heparin 5000 units/mL) (\(n = 100\)) as a catheter lock solution. The authors found no difference in the number of CRLs per 1000 catheter-days between the sodium citrate and heparin groups (0.7 in both groups, \(p = 0.9\)). There was also no significant difference in catheter exchanges between treatment groups (0.5 per 1000 catheter-days versus 0.7 per 1000 catheter-days, respectively; \(p = 0.4\)). In addition, the rates of hospitalization and mortality did not significantly differ (\(p = 0.4\) and \(p = 0.9\), respectively). The numbers of CRLs and catheter exchanges reported in both treatment groups were lower than in our study.

The results of our prospective cohort analysis with historical controls suggest that sodium citrate 4% is superior to heparin 5000 units/mL in the prevention of CRLs. Sodium citrate 4% also appeared as effective as heparin as an antithrombotic agent for catheter patency. There were no significant differences in the secondary outcomes of hospitalizations and catheter thrombosis. A major limitation of our study was its size. As this was a single-center study, there were only 360 patient-months in the heparin group and 451 patient-months in the sodium citrate group. Our study compared 12 months of heparin use with 15 months of sodium citrate use. The period during which sodium citrate was used was extended to help detect a statistically significant difference in the outcomes between the study groups. Another limitation of our study was the fact that the length of time the catheter had been in place and the time since initiation of hemodialysis for all patients were not known. Some of the patients evaluated in the study transferred hemodialysis care to our site or did not have their CVC placed at our site.

Our study found a significant difference in the frequency of CRLs and catheter exchange or removal rates, which could translate into cost savings with the use of sodium citrate 4% instead of heparin 5000 units/mL. At our study site, the sodium citrate 4% was batched and prepared as unit-dose syringes. This incurs costs for labor and materials over what is required when heparin is acquired in unit-dose vials directly from the manufacturer. However, the cost association with one CRI episode, which includes catheter exchange or removal, hospitalization, and antibiotic treatment, would most certainly offset the auxiliary costs associated with using sodium citrate 4% for a year. A reduction in the incidence of CRI is a significant clinical and economical outcome.

Conclusion

In patients with long-term hemodialysis catheters, a lock solution of sodium citrate 4% was associated with fewer CRLs and similar effectiveness when compared with heparin 5000 units/mL.

References


Superior antimicrobial activity of trisodium citrate over heparin for catheter locking

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Abstract

Background. Haemodialysis catheters used for vascular access are frequently complicated by infection and catheter-related thrombosis. Improvement of interdialytic locking solutions could reduce these problems. Trisodium citrate (TSC) has been advocated in recent years because it might have antimicrobial qualities.

Methods. Antimicrobial efficacy of four concentrations of TSC (2.2, 7.5, 15 and 30%) was compared with three equi-osmolal sodium chloride (NaCl) concentrations, unfractionated heparin 5000 IU/ml and a solution of gentamicin 1 mg/ml in TSC 7.5%. We analysed antimicrobial properties by two classical in vitro susceptibility tests. All tests were performed in triplicate by incubation of test fluids with Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli, Pseudomonas aeruginosa and Candida albicans.

Results. Increasing TSC concentrations effectively killed the staphylococcal strains in both assays. For E.coli and P.aeruginosa complete killing was achieved only with TSC 30%. TSC 30% was also the only solution that significantly inhibited growth of C.albicans. Heparin manifested no antimicrobial effect of any significance. Adding gentamicin to TSC provided superior bacterial growth inhibition but had no effect on yeast growth. TSC solutions manifested superior antimicrobial activity compared with iso-osmolar NaCl solutions in both assays.

Conclusion. This in vitro study demonstrates superior antimicrobial activity of TSC, especially in higher concentrations, in contrast to heparin. The mechanism seems to differ from hyperosmolality. Ca²⁺ and Mg²⁺ chelating effects are probably more important. Adding gentamicin provided the most potent antimicrobial solution. However, for reasons concerning development of bacterial resistance and sensitization of the patient, continuous exposition to aminoglycosides seems not advisable.

Keywords: bacteraemia; catheter; haemodialysis; heparin; trisodium citrate; vascular access

Introduction

Vascular access is a major factor of concern for patients on haemodialysis treatment. Despite the recommendations of the National Kidney Foundation–Dialysis Outcome Quality Initiative Clinical Practice Guidelines for Vascular Access that recommends placement of an arteriovenous access before initiation of chronic haemodialysis treatment, the use of catheters for haemodialysis access is substantial [1]. Stehman-Breen et al. [2] reported from the United States Renal Data System 1996 that 66% of patients with end-stage renal disease started haemodialysis treatment with a catheter for access to the blood stream. Twardowski [3] reported that 24.3% of almost 30 000 haemodialysis treatments in his outpatient facility in the period 1995–1997 were performed with a tunneled cuffed catheter. The use of haemodialysis catheters, however, is associated with an important risk for catheter-related infection and insufficient dialysis due to flow problems with or without intraluminal thrombosis [4]. Especially vascular access-related infections, mostly associated with haemodialysis catheters, have emerged as an important cause of morbidity and mortality in haemodialysis patients. From a prospective study in 796 haemodialysis patients performed in seven outpatient haemodialysis centres in 1998, Tokars et al. [5] calculated that over 92 000 episodes of vascular access infection occur annually among 220 000 prevalent haemodialysis patients in the US. A third of these patients had to be treated by hospitalization because of the infection. In addition, patients with a catheter had a relative risk for infection of 2.07
compared with patients with an arteriovenous fistula or graft.

It is recognized that microorganisms can adhere to the surface of a catheter. Contamination of the catheter hub, subsequent colonization of catheters with microbes and formation of a biofilm produced by bacteria are thought to be major risk factors for both catheter-related infections and intraluminal thrombosis [6]. It is, however, not elucidated whether the most important mechanism of catheter-related bacteremia is extraluminal or intraluminal colonization. If catheter-related blood stream infections are mainly secondary to intraluminal colonization, interdialytic catheter-related infections and intraluminal thrombosis are mainly caused by a haemodialysis catheter manufacturer (Medcomp, Basingstoke, Hampshire, UK) supplemented with 7% sheep blood (Bio Trading, Mijdrecht, The Netherlands). All tests and cultures were performed in triplicate.

The purpose of this study is to evaluate the in vitro antimicrobial activity of different concentrations of TSC and to compare them with heparin and isosmolar sodium chloride (NaCl) solutions. We employed two classical in vitro antimicrobial susceptibility tests and used four bacterial strains and one yeast strain commonly found in catheter-related bacteremia.

Subjects and methods

Antimicrobial efficacy of four concentrations of TSC, 2.2% (300 mosmol/kg H₂O), 7.5% (1020 mosmol/kg H₂O), 15% (2040 mosmol/kg H₂O), 30% (4080 mosmol/kg H₂O), NaCl 6.1% (2040 mosmol/kg H₂O) and NaCl 12.2% (4080 mosmol/kg H₂O). All solutions were manufactured from raw base by the Department of Pharmacy of the Vrije Universiteit Medical Center, Amsterdam, The Netherlands. The solutions were heat sterilized for 16 min at 121°C and the pH was controlled between 6.4 and 7.5. Gentamicin sulphate was obtained from commercial vials (Gentamicin CF, Centralfarm Services, Etten-Leur, The Netherlands). All tests were performed with five standardized reference strains from the American Type Culture Collection (ATCC, Manassas, VA); *Staphylococcus aureus* (ATCC 25923) *Staphylococcus epidermidis* (ATCC 12228), *Pseudomonas aeruginosa* (ATCC 25922), *Escherichia coli* (ATCC 27853) and *Candida albicans* (ATCC 90028).

The antimicrobial activity of the solutions was investigated by time-kill and agar diffusion methods, essentially performed according to National Committee for Clinical Laboratory Standards guidelines [10]. Briefly, logarithmic-phase bacterial and yeast cultures were used for the final inoculum of 10⁵ colony-forming units per ml (c.f.u./ml). Twenty microlitres of the microbial suspension was added to 200 µl of a suspension containing a 10:1 dilution of the test solution in trypticase soy base (TSB) broth (Difco Laboratories, Sparks, MD) to achieve a final bacterial concentration of 10⁴ c.f.u./µl. At this initial concentration, the comparison with time-kill curves of control solution was best feasible. Tubes were incubated at 37°C. At the start of the experiment (t = 0) and at 1, 2, 4 and 24 h, 50 µl of this suspension was plated on blood agar plates (BA) (Oxoid, Basingstoke, Hampshire, UK) supplemented with 7% sheep blood (Bio Trading, Mijdrecht, The Netherlands). Subsequently, plates were incubated for 24 h at 37°C. Afterwards colonies were counted and time-kill curves constructed from calculated c.f.u./µl. All tests and cultures were performed in triplicate.

The agar diffusion susceptibility test was carried out analogous to the disk diffusion test (Kirby-Bauer) [10]. BA and TSB plates were seeded with a bacterial solution with a final inoculum of 10⁶ c.f.u./ml. Separate plates were used for each of the five microbial strains. Instead of using disks impregnated with test solution, one well with a diameter of 8 mm was punched out of the agar at the centre of the plate. The well was filled with test solution and this was repeated every 2 h for the first 6 h of incubation. A total of 0.45 ml of test solution had to be added to the well to keep it filled. Plates were incubated at 37°C for 24 h. Afterwards, zones of inhibition around the well were measured. All tests were performed in triplicate with BA and TSB plates.

Statistical analysis was performed with SPSS software package 9.0 (SPSS Inc., Chicago, IL) with repeated-measurements analysis of variance for time-kill curves. χ² analysis was performed for means of bacterial c.f.u. at t = 24 h and for zones of inhibition achieved from the agar diffusion test. Significance of test results was based on P < 0.05 on a two-tailed test.

Results

Antimicrobial properties of different locking solutions

Time-kill studies. The time-kill curves for heparin, all concentrations of TSC and the combination of TSC
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with gentamicin are presented in Figure 1. Heparin showed some growth inhibition of \textit{S.aureus} and \textit{S.epidermidis} compared with control (NaCl 0.9%). However, after 24 h all strains showed increasing growth (upward directed slope) when incubated with heparin. Heparin had no significant effect on growth of Gram-negative bacteria and \textit{C.albicans} compared with control.

TSC 15% and TSC 30% reduced the number of c.f.u/ml of all strains over 24 h compared with the concentration at start of the experiment except for the yeast \textit{C.albicans} and except for \textit{P.aeruginosa} with TSC 15%. The citrate solutions inhibited growth of all strains compared with control (NaCl 0.9%), including Candida. The Gram-negative strains \textit{E.coli} and \textit{P.aeruginosa} were only adequately affected by the highest concentrations of TSC (15% and 30%) \((P<0.05\) for \(t=24\) h). There were no statistically significant differences between TSC 30% and TSC 15%. TSC 30% was more effective in growth reduction of \textit{E.coli}, \textit{P.aeruginosa} and \textit{C.albicans} than heparin \((P<0.05\) for \(t=24\) h).

\textit{Agar diffusion susceptibility test} (Figure 2). Studies using TSB plates and BA plates revealed similar results. The results for the zones of inhibition were therefore pooled for further analysis. Zones of inhibition are given in Figure 3. For all microbial strains no growth inhibition by the control solution (NaCl 0.9%) was found. Heparin also showed no effect at all. In general, higher concentrations of TSC demonstrated increasing inhibitory effect on all strains (Figure 3). TSC 30% was the only solution to inhibit growth of all tested microbes including \textit{C.albicans}.

Fig. 1. Time–kill curves for heparin, TSC and iso-osmolal NaCl solutions and the combination of TSC 7.5% with gentamicin. Tested microbial strains are \textit{S.aureus} (ATCC 25923), \textit{S.epidermidis} (ATCC 12228), \textit{P.aeruginosa} (ATCC 25922), \textit{E.coli} (ATCC 27853) and \textit{C.albicans} (ATCC 90028).
The inhibition zone was significantly larger for all strains compared with control (NaCl 0.9%) and heparin \((P<0.01\) for all comparisons).

Addition of gentamicin to TSC potentiated the effect of TSC on all bacterial strains in both the dilution and the diffusion test. Growth of \textit{C. albicans}, however, was not influenced.

\textbf{Antimicrobial properties of iso-osmolal solutions}

\textit{Time–kill studies}. Comparing the results of the time–kill curves of iso-osmolal solutions, it is clear that there are major differences (Figure 1). For the iso-osmolal solutions NaCl 0.9% and TSC 2.2%, TSC 2.2% provided stronger growth inhibition in \textit{S. epidermidis}, \textit{S. aureus} and \textit{C. albicans} \((P<0.05)\). The growth at 24 h was inhibited significantly better for \textit{S. epidermidis} and \textit{S. aureus} by TSC 15% compared with NaCl 6.1% and for \textit{S. epidermidis} and \textit{S. aureus} by TSC 30% compared with NaCl 12.2%. For the other strains the time–kill curves were not significantly different.

\textit{Agar diffusion susceptibility test}. The agar diffusion test also showed larger zones of inhibition for TSC compared with iso-osmolal NaCl solutions, especially when osmolality increased (Figure 3). NaCl 6.1% and NaCl 12.2% exhibited no significant effect on microbial growth over NaCl 0.9%. NaCl 0.9% did not inhibit growth of any microbial strain. In contrast, iso-osmolal TSC 2.2% inhibited growth of \textit{S. aureus} significantly. TSC 15% showed more antimicrobial effect compared with iso-osmolal NaCl 6.1% in all strains except for \textit{P. aeruginosa} \((P<0.05)\). For the iso-osmolal solutions with the highest osmolality, NaCl 12.2% and TSC 30%, superior growth inhibition of TSC 30% was found in all strains \((P<0.01)\).
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Discussion

In the present study we investigated the antimicrobial activity of TSC against five different microorganisms frequently encountered in catheter-related infections in haemodialysis patients using two standardized antimicrobial susceptibility tests. The antimicrobial activity was dose dependent with the highest efficacy for TSC 30%. In both tests the antimicrobial activity of TSC exceeded that of iso-osmolar NaCl concentrations, whereas heparin manifested only minimal antimicrobial activity. Thus, it can be concluded that the use of high concentrations of TSC for catheter locking could have an advantage over heparin. Adding gentamicin to TSC provided the most potent antibacterial solution. Lynn [11], however, showed that locking with a mixture containing an antibiotic, results in low systemic concentrations of the antibiotic resulting from diffusion from the tip of the catheter. The development of bacterial resistance and sensitization of the patient can be the consequence. Addition of aminoglycosides or other antibiotics to locking solutions for long-term use is therefore not advisable. Heparin revealed no relevant anti-microbial activity. This was recently also reported by Capdevila et al. [12] in vitro by means of the time–kill curves method and in vivo by implanting catheters in rabbits and inducing secondary infection but they only used one strain of S. aureus.

To investigate whether a locking solution can reduce complications, only a clinical study with large numbers of patients can provide definitive answers. The present study only provides in vitro data, but these studies have to be performed to give direction to which locking solution is most likely to reduce complications before conducting a clinical trial. No standardized methods are available for testing antimicrobial activity of catheter locking solutions. Although other in vitro methods have been advocated in the past, seldomly tests were performed using validated techniques with more then one microorganism and mainly established antibiotics were added to solutions for locking [12,13]. The methods we applied for this study consisted of two widely validated and recommended antimicrobial susceptibility tests. The tests were performed as recommended by the National Committee for Clinical Laboratory Standards [10,14]. Dilution tests are employed to provide more exact information on the concentrations of the antimicrobial solution that cause growth reduction and killing. However, the standardized disk diffusion test is the initial susceptibility test used in most laboratories because of its ease of performance, reproducibility, and proven value as a guide to antimicrobial therapy [15]. This test demonstrated the pronounced antimicrobial properties of TSC 30% most distinctly.

For the present study we selected both Gram-positive and Gram-negative bacteria frequently involved in catheter-related bacteraemia. S. aureus and S. epidermidis are the most common bacteria found in catheter-related bacteraemia. However, Gram-negative bacteria can be isolated in up to 45% of cultures and up to 21% of cultures reveal a polymicrobial infection [16]. We used reference microbial strains from the ATCC to minimize the variable microbial properties that may affect the results. Microorganisms were seeded on BA and TSB plates to investigate the influence of the growth medium. The results were very similar for both plates. Yeasts are not commonly involved in catheter-related infections. Nevertheless, we included a C. albicans strain in our study because of the high mortality of systemic yeast infection. Inhibition of growth of Candida spp. by a locking solution could therefore be of importance.

Both susceptibility tests showed clear differences in antimicrobial properties for iso-osmolar solutions. In 18 of 30 comparisons that could be made between iso-osmolar TSC and NaCl solutions, TSC exhibited significantly greater inhibitory effects on microbial growth. Therefore, the anti-microbial properties of higher concentrations of TSC cannot be attributed to hyperosmolality. It is likely that other effects of TSC like chelation of the divalent cations Ca2+ and Mg2+ are more important. From dentistry research it is known that Ca2+ and Mg2+ chelating agents like disodium-ethylenediaminetetraacetate (EDTA) and sodium citrate exhibit similar inhibition of growth and coaggregation of microorganisms. Root et al. [17] showed in an in vitro model with catheter segments incubated with 107 S. epidermidis that EDTA provided total killing of bacteria. They suggested that especially chelation of Mg2+ can interfere with cellular integrity by degradation of the bacterial cell wall membrane. Lipopolysaccharides in the bacterial cell wall are cross-linked with divalent cations, providing stability. Lowering the concentration of these cations can lead to disruption of the cell wall and increase permeability [15,18]. Consistent with these findings is the observation that sodium citrate proved to be a potent permeabilizer of the cell wall at millimolar concentrations in a model used for permeability changes in Gram-negative bacteria. The effect was partly (P. aeruginosa, S. typhimurium) or almost totally (E. coli O137) abolished by MgCl2, suggesting that part of the action occurs by chelation [18].

Apart from Mg2+ binding, removal of Ca2+ from the surrounding milieu can be an explanation for the antimicrobial properties of TSC. Ca2+ may regulate several genes responsible for growth and survival of microbes. Holland et al. [19] demonstrated that cell division in E. coli in particular appears to be very sensitive to the level of cellular Ca2+, with the frequency of division clearly reduced by incubation with EDTA and by verapamil, a Ca2+-channel inhibitor. The effect of EDTA was clearly correlated with depletion of cellular Ca2+. Biofilm formation, thought to be a key factor in catheter colonization and ultimately bacteraemia, is probably dependent on Ca2+. A biofilm consists of bacteria that attach to surfaces and aggregate in a hydrated polymeric glyco-calyx matrix of their own synthesis. Formation of these sessile communities and their inherent resistance
to antimicrobial agents allows microbes to survive in a hostile environment. Even in individuals with excellent cellular and humoral immune reactions, biofilm infections are rarely resolved by the host defense mechanisms. In addition, antibiotics are not very useful because they have been shown to penetrate poorly into a biofilm [20]. Furthermore, at least some of the microbial cells in a biofilm experience nutrient limitation and therefore exist in a slow-growing state. Slow-growing or non-growing microbial cells are not very susceptible to antimicrobial agents. Until recently, the bacterial glycocalyx was regarded as being homogeneous in construction and static in its structure. It is now recognized that glycocalyces are not structurally static, but rather responsive to the chemical composition of the surrounding milieu. An increasing environmental Ca$^{2+}$ concentration dramatically enhanced the survival of P. aeruginosa in biofilms upon a 12-h exposure to tobramycin in an in vitro experiment [21]. It was suggested that Ca$^{2+}$-induced crystallization of the glycocalyx resulted in decreased permeability of the biofilm for small molecules like aminoglycosides. In summary, chelation of Ca$^{2+}$ and Mg$^{2+}$ by TSC may prevent the formation of a biofilm that consists of microbes in a firm glycocalyx. Reduction of the incidence of catheter-related bacteraemia by the intraluminal route could be the result of this hypothesis was tested in some in vitro models with catheter segments but the constructions with catheters or fragments trying to imitate the clinical situation are artificial [22,23].

As stated before, this study only provides data from in vitro antimicrobial susceptibility tests. It is not clear if the results can be translated to general practice as numerous factors have been implicated in the pathogenesis of catheter-related bacteraemia. For that reason, locking solutions must be compared in a clinical study to confirm their benefit. So far, only a few comparative studies have been published showing no clear differences between TSC and heparin [8,24]. These studies, though, only accounted about 5000 catheter-days pooled data and mostly used lower concentrations TSC. With a rate of three to five infections per 1000 catheter-days it is obvious that larger studies are needed to find a significant difference.

Ash et al. [7] reported their experience in a haemodialysis patient cohort of 70 patients with 60% tunneled cuffed catheters. After introduction of TSC 23–47% for catheter locking they observed an average decline of 4.5% of all patients per month having a bacteraemia to zero percent. Recently, Stas et al. [8] reported a study comparing heparin 5000 IU/ml and TSC 30%. Thrombus formation in the catheter was evaluated after 201 interdialytic locking periods; no significant differences could be demonstrated. In both studies no clinically relevant side effects occurred during instillation of haemodialysis catheters with TSC. This is important, as concern has risen of using TSC for locking catheters after a fatal accident [25]. In this particular case, however, a large amount of TSC was injected in a previously unstable patient with severe electrolyte disturbances. It is clear that the use of these solutions should be restricted to authorized and skilled health care professionals.

We conclude that in our in vitro study using standardized antimicrobial susceptibility tests we demonstrated that TSC 30% was the most potent antimicrobial locking solution and that its hyperosmolality was of minor importance to explain the inhibitory effects of TSC on microbial growth. However, before introduction in practice, randomized clinical trials should confirm the benefit.

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Sodium citrate 4% locking solution for central venous dialysis catheters—an effective, more cost-efficient alternative to heparin

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Abstract

Background. Thrombosis of the central venous haemodialysis catheter compromises dialysis adequacy and catheter survival. Heparin containing catheter-locking solution has been associated with bleeding, interferes with INR (prothrombin time/international normalized ratio) measurements and is costly. Sodium citrate has been used successfully as a catheter-locking solution, but long-term experience with its use as the exclusive locking solution has not been published.

Methods. Our haemodialysis unit converted to locking all central venous haemodialysis catheters with sodium citrate 4% instead of heparin 10 000 U/ml. A retrospective analysis compared the outcomes of the year prior and after the conversion. Flow-related catheter exchange rate, prevalence of INR assay interference, tissue plasminogen activator (rt-PA) utilization rate, rate of bacteraemias and annual cost of locking agent were examined.

Results. During the study period, 30 925 and 37 139 catheter days were identified during the heparin and citrate years, respectively. The rate of flow-related catheter exchange was not different during the two periods (1.81 vs 1.88 per 1000 catheter days, \( P = 0.89 \)). Falsely elevated INR values were eliminated with citrate and the rate of rt-PA treatments was similar during the two periods (4.1 vs 3.23 per 1000 catheter days respectively, \( P = 0.07 \)). The number of bacteraemias was similar during the two periods (0.77 vs 0.94 per 1000 catheter days respectively, \( P = 0.36 \)). There was an 85% reduction in the costs associated with catheter-locking therapy during the citrate period.

Conclusions. The pharmaco-economic benefits of sodium citrate 4% are well supported by this analysis. Furthermore, citrate offers several clinical advantages over concentrated heparin: citrate lock avoids heparin-associated bleeding complications, improves reliability of INR assays and provides an effective alternative for patients with suspected or confirmed heparin-induced thrombocytopenia.

Keywords: catheter; citrate; cost; haemodialysis; heparin

Introduction

The arteriovenous fistula or graft is well recognized as the preferred vascular access for patients receiving chronic haemodialysis. However, due to the explosive growth in the population of patients with end-stage renal disease (ESRD), an increasing number of haemodialysis patients are dialysed via an indwelling central venous catheter [1]. Partial or total thrombosis of the catheter is a major complication which potentially compromises dialysis adequacy and may limit catheter survival period [2]. Catheter malfunction due to occlusion can have a significant impact on patient quality of life, patient morbidity and dialysis resources, while thrombolytic and diagnostic interventions add additional financial burden to the already escalating costs of chronic haemodialysis therapy.

To promote catheter patency during the interdialytic period, many haemodialysis centres utilize heparin as a catheter-locking agent. Although currently accepted as a standard of practice in most haemodialysis units, there is a lack of evidence-based literature to support the efficacy and safety of heparin as a locking agent, and questions remain regarding its optimal concentration, pharmacological viability when in situ at body temperature and potential for adverse systemic effects [3,4]. In fact there has never been a randomized trial to determine the optimum heparin concentration for catheter locking, and widely varying concentrations (usually 1000–10 000 U/ml) are commonly used.

Heparin, when used as a locking agent, has been documented to cause unintentional systemic anticoagulation [5], interferes with specific lab studies,
such as INR (prothrombin time/international normalized ratio) [6] and may predispose patients to other complications such as heparin-induced thrombocytopenia (HIT) [7]. As ureaemic patients are inherently at greater risk for coagulopathy and bleeding and are already exposed to systemic heparin as part of the dialysis procedure, the use of high concentrations of heparin, a potent anticoagulant as a locking solution, may not be the best choice [8,9]. Systemic administration of heparin locking solution (intentional or unintentional), as well as leaching of heparin from the catheter tip further increases patient risk for bleeding complications [3]. In addition, the recent increases in heparin pricing on the Canadian market necessitated the need to investigate alternative, more cost-effective options for haemodialysis catheter-locking solutions.

Sodium citrate has been successfully used as an anticoagulant for continuous renal replacement therapies for several years [9–11]. Sodium citrate functions as an anticoagulant via the chelation of ionized calcium in the blood and tissues by the citrate ion, which prevents activation of calcium-dependent pro-coagulants [12]. A few small trials have suggested that replacing heparin with sodium citrate results in comparable catheter patency rates while avoiding exposure to systemic heparin [13–15]. These studies included either a small number of patients or were conducted over a short period of time.

In April 2003, our in-centre haemodialysis unit converted to locking all central venous haemodialysis catheters with sodium citrate 4% instead of heparin 10 000 U/ml. A retrospective analysis was conducted to evaluate whether replacing heparin with sodium citrate 4% would ensure cost-effective, long-term interdialytic anticoagulation and satisfactory catheter function without exposing patients to systemic heparinization. The outcomes reviewed in this analysis included the following: flow-related catheter exchange rate, prevalence of INR assay interference, bacteremia rates, tissue plasminogen activator (rt-PA, alteplase) utilization rate and annual cost per patient (based upon thrice-weekly dialysis) for heparin vs sodium citrate as a catheter-locking agent.

Subjects and methods

Two 12-month audit periods were selected for retrospective data collection and review. The heparin period included data from 1 April 2002 to 31 March 2003, while the citrate period included data from 1 April 2003 to 31 March 2004. Data sources utilized included the Canadian Organ Replacement Register (CORR), the Humber River Regional Hospital (Toronto, ON, Canada) Nephrology program continuous quality improvement (CQI) database, as well as the radiology/angiography, pharmacy, microbiology and laboratory databases of the hospital.

All the patients in whom a central venous haemodialysis catheter was used during at least part of each period were included in the analysis. Age, dialysis vintage, previous dialysis history, presence of diabetes mellitus and patient outcome during the study period were analysed.

Causes of death during the two periods were compared. Number of patients who were dialysed during part or the total duration of both periods was counted. Concomitant medications likely to affect anticoagulation were also included in the analysis. They included warfarin, aspirin and clopidogrel (Plavix®). The number of patients on warfarin for maintenance of haemodialysis catheter patency in the two groups was also compared.

In the heparin period, all catheters were locked with concentrated heparin 10 000 U/ml. In the citrate period, all catheters were locked with sodium citrate 4%. As the change in routine locking agent was a unit policy change, no written patient consent was obtained. Four models of catheters were used during the analysis periods; Boston Scientific (Vaxcel) (Boston Scientific, Natick, MA, USA), Cardiomed (Cardiomed, Gormley, ON, Canada), Ash Split (Medcomp, Harleysville, PA, USA) and Bard Optiflow (Bard Access systems, Murray Hill, NJ, USA). All catheters were permanent, tunneled and double lumen. The catheter lengths ranged from 15 to 22 cm, with filling volumes ranging from 1.9 to 2.8 ml.

The process for locking catheters with sodium citrate 4% in the citrate period was identical to the process previously used when catheters were locked with heparin 10 000 U/ml. At the completion of each haemodialysis session, the lumens of the catheter were flushed with 10 ml of normal saline. Next, sodium citrate was instilled into each lumen as a locking agent in volumes corresponding to luminal capacity. Sodium citrate 4% (Baxter, Mississauga, ON, Canada) was aseptically repackaged by the hospital pharmacy and supplied as sterile 5 ml aliquots in 10 ml syringes. Partially or fully clotted catheters were treated with rt-PA. Each treatment used to restore catheter patency consisted of 4 mg of rt-PA (2 mg instilled into each catheter lumen).

Radiology reports of all haemodialysis catheter exchanges were collected for each respective 12-month audit period. Only those exchanges related to poor flow were included in this analysis. Catheter exchanges related to infection, suspected superior vena cava stenosis, cuff extrusion and catheter integrity were excluded. The number of line exchanges divided by the number of catheter days was used to calculate the number of exchanges per 1000 catheter days. Flow-related catheter exchange rates for each of the heparin and citrate periods were compared.

The majority of patients with catheters during each of the audit periods were treated with oral warfarin therapy. Anticoagulation was adjusted using weekly measurement of INR (prothrombin time/international normalized ratio). INR targets were set by the treating nephrologists and varied according to therapeutic indication. All measurements of INR and concurrent partial thromboplastin time (PTT) were reviewed. All assays were performed using routine methodology by the haematology laboratory of Humber River Regional Hospital. For the purposes of this analysis, an INR value greater than three accompanied by a PTT greater than 100 was used as the parameter for defining a falsely elevated INR due to contamination
of the sample with heparin. The INR value greater than three was selected specifically as this would represent the most common threshold for therapeutic intervention with respect to oral warfarin dosing. We selected a PTT value of greater than 100 in order to predict with great certainty the presence of heparin contamination. The number of falsely elevated INR assays in the two audit periods was compared. Obviously, the chosen parameters offer high specificity for heparin contamination, but low sensitivity.

Utilization reports of rt-PA were generated from our computer records (Meditech, Westwood, MA, USA) for both heparin and citrate audit periods. Utilization rates of rt-PA (number treatments per 1000 catheter days) were compared for each 12-month period.

The microbiology reports from blood cultures taken through the dialysis catheters during the heparin and citrate years were reviewed from the microbiology computer database (Meditech, Westwood, MA, USA). A positive blood culture was considered to represent a new infection after a previous positive blood culture if a new organism was grown or if the culture was positive at least 1 month after the previous positive culture and completion of the antibiotic treatment.

Finally, the annual cost per patient for each respective catheter-locking agent was calculated and included the price of locking solution, materials for repackaging and any associated labour costs. This financial data was compared for each of the audit periods.

Statistical analysis

The chi-square test (with Yates correction) was used to compare the rates in the parameters under review. A two-sided $P$-value of $<0.05$ was considered statistically significant. The GraphPad InStat Ver 3.06 computer program for Windows (GraphPad Software Inc., San Diego, CA, USA) was used for the statistical analysis.

Results

Out of 286 patients on haemodialysis during the heparin period, 146 (51%) were dialysed using central venous haemodialysis catheters. The total number of catheter days was 30,925. Correspondingly, during the first 12-month period of citrate use, out of 321 patients on haemodialysis, 161 (50%) were dialysed using central venous haemodialysis catheters. The total number of catheter days was 37,139.

Table 1 includes the characteristics of patients with central haemodialysis catheters (age, dialysis vintage, presence of diabetes, previous dialysis history, outcomes and causes of death). There was no significant difference between the two groups. This is not surprising as 118 patients included in the analysis partially overlapped and 78 fully overlapped the two audit periods.

Table 2 includes the concomitant medications including use of warfarin, aspirin and clopidogrel during the two comparison periods. The indication for the use of warfarin is also included. There were no differences in the use of these medications in the two groups. Most patients on warfarin were being treated for maintenance of haemodialysis catheter patency (81% vs 88%) and this was similar during both periods.

Catheter exchanges

Table 3 includes the number of catheter exchanges per 1000 catheter days during the two audit periods. Fifty-six catheters were exchanged during the heparin period (1.81 exchanges per 1000 catheter days), while 70 were exchanged during the citrate period (1.88 exchanges per 1000 catheter years) (NS, $P=0.89$).

Prevalence of INR assay interference

Average INR and PTT were higher in the heparin group ($1.7\pm1.19$ vs $1.6\pm0.9$ and $59.3\pm38.3$...
were encountered during the citrate period (4.1 and 3.2 treatments per 1000 catheter days, respectively; NS, $P<0.003$ and $P<0.001$, respectively) likely as a result of sample contamination with heparin during the heparin period. Out of 3744 INR measurements, 31 were clearly contaminated (INR > 3 and PTT > 100) during the heparin period, while none of the 3973 measurements had similar values in the citrate period ($P<0.0001$). 

**rt-PA (alteplase) utilization rate**

Table 3 illustrates the number of treatments with rt-PA per 1000 catheter days during the two audit periods. The number of rt-PA treatments was 127 and 120 during the heparin and citrate period (4.1 and 3.2 treatments per 1000 catheter days, respectively; NS, $P=0.07$). The cost per standard treatment of rt-PA (2 mg per each catheter lumen) used to restore catheter patency was $108 Canadian dollars (CAD).

**Bacteraemias**

Table 3 illustrates the number of treatments with rt-PA per 1000 catheter days during the two audit periods. Twenty-four bacteraemias (0.77 per 1000 catheter days) were encountered during the heparin period, while 35 bacteraemias (0.94 per 1000 catheter days) were encountered during the citrate period (NS, $P=0.5$).

**Annual cost of catheter-locking agent**

The cost of locking catheters with heparin 10 000 U/ml was calculated at $6.46 CAD per treatment, whereas the cost of using sodium citrate 4% was only $0.94 CAD. This translates to an actualized annual cost savings (based upon a thrice-weekly catheter-locking schedule) of $861.12 CAD per patient. This reflects an 85% reduction in the costs associated with catheter-locking therapy. The realized cost savings for our haemodialysis unit totalled $112 000 CAD in the 12-month citrate period (1 April 2003–31 March 2004).

**Discussion**

Despite the K/DOQI guidelines and evidence regarding the poorer outcomes of patients dialysed through central venous catheters, their utilization remains high [2,16]. Our centre was no exception and the 50% catheter prevalence rate is actually higher than the average use as reported by the DOPPS data for Canada [17]. In addition to infection, catheter thrombosis and associated malfunction are among the primary complications associated with central venous haemodialysis catheters [11]. Although heparin, in varying concentrations, remains the accepted standard of practice as a catheter-locking agent in most dialysis centres, there is little evidence to confirm its safety and efficacy, and even less supporting documentation regarding its superiority over other alternative locking agents. Sodium citrate 4% has generally been reserved as a locking agent for patients with suspected or confirmed HIT, or other relative contraindications to heparin exposure.

Citrate 4% as a catheter-locking solution was proposed in a small feasibility study by Buturovic et al. [11] and Michaud et al. [9] in a case report. In a prospective randomized study, Hendrickx et al. [15] randomized 19 patients into two groups using heparin vs citrate 4% in single lumen catheters. Although the citrate group had a higher number of clot formation, there were no differences in the use of thrombolytic therapy. Meeus et al. [18] used citrate in 18 patients in a crossover study comparing 5% to 10% citrate. There were no significant differences in the measured outcomes in the two groups. High concentration of citrate at 30% or 46.7% has also been used for both anticoagulation as well as for antibacterial action [3,19]. Furthermore, citrate in combination with gentamicin or taurolidine has been shown to decrease the rate of catheter-related infections [20–22]. In 2000, the US Food and Drug Administration (FDA) issued a warning that concentrated trisodium citrate (46.7%) should not be used as a catheter-locking solution as a result of a reported death due to cardiac arrest, after mistaken bolus injection of 46.7% citrate systemically. The FDA talk paper also advised that 4% solutions of citrate were alternatively available for use in these settings [23]. Citrate 4% is safe even if the total amount of citrate in both catheter lumens is injected rapidly intravenously. If one assumes only intravascular distribution and no compensation from dissociation of bound calcium, in an average size patient the serum ionized calcium will decrease by only 10%, which is extremely unlikely to have any physiological effect [24,25]. To minimize any potential risk, the volume of sodium citrate 4% for locking should be limited to lumen volume, and the locking agent should be aspirated prior to dialysis [19]. To our knowledge, there is no published long-term experience with the use of low citrate concentration in a large number of patients as a routine catheter-locking solution.

The patients included in our analysis dialysed during the two periods were similar in terms of age, dialysis vintage and the presence of diabetes mellitus. The number of prevalent vs incident patients was
also similar. The similarity of the two patient groups is also supported by the fact that 118 out of the 161 patients of the citrate year were converted from heparin to citrate and 78 of these patients were dialysed throughout both years with the use of catheters. The number of patient exits and the outcomes were also similar including the causes of death (Table 1). The concomitant medications that were likely to affect the catheter outcomes including warfarin, aspirin and clopidogrel were similar including the percentage of patients who were on coumadin, in order to preserve catheter patency (Table 2).

Our retrospective analysis appears to indicate that replacing heparin 10 000 U/ml with sodium citrate 4% resulted in similar exchange rates for central venous haemodialysis catheters (Table 3). Our analysis confirms that heparin contamination of blood samples collected via the haemodialysis catheter can result in falsely elevated INR assays, which can compromise therapeutic interventions regarding oral anticoagulation treatment, and may potentially contribute to patient morbidity. Residual heparin contamination and resultant inaccuracy of the INR assay can, in most cases, be suspected from the presence of a simultaneously elevated PTT result but until the test is repeated, usually prior to the following dialysis treatment, an erroneous or no therapeutic decision can be made [6]. Leaching of concentrated heparin from the catheter tip can result in systemic heparinization and associated bleeding risks [4]. Citrate provides local anticoagulation without exposing the patient to the risks of systemic heparinization. In addition, citrate can also be used in the case of confirmed or suspected HIT [15], or where the use of heparin could be potentially dangerous. Prevalence rates for post-catheter-insertion bleeding for each of the treatment periods could not be reviewed in our study as data was not collected prospectively and chart documentation of bleeding events was incomplete. However, clinical observations reported by both the angiography department and haemodialysis unit suggest a dramatic decrease in the occurrence of insertion-related catheter bleeding episodes after converting to sodium citrate. In patients at high risk for bleeding, citrate may provide a valuable therapeutic alternative to heparin for catheter locking.

RT-PA is a thrombolytic agent routinely administered to restore catheter patency when partial or total occlusion has occurred, or when flows are inadequate. The total rt-PA utilization rates were comparable for both the heparin and citrate periods. Although there was a trend towards fewer treatments with rt-PA when expressed per 1000 catheter days, it did not reach statistical significance and therefore one has to conclude that the change to citrate did not have an effect on rt-PA utilization.

One would not expect that the change in locking solution would have any effect on the bacteraemia rates of the dialysis patients as neither low-concentration citrate 4% or heparin have antimicrobial activity. Indeed, the number of bacteraemias during each of the 2 years under observation were not significantly different.

The financial impact of the conversion from heparin 10 000 U/ml to sodium citrate 4% as a catheter-locking agent is very significant. Sodium citrate 4% is considerably more economical than full strength heparin, generating annual cost savings of $861.12 CAD per patient (based upon thrice-weekly dialysis), which translates to an 85% cost reduction for interdialytic anticoagulation of haemodialysis catheters. Actual realized cost savings for the 1-year citrate audit period for our haemodialysis unit totalled $112 000, which is quite substantial.

We now have over 3 years of clinical experience with sodium citrate 4%, and it appears to be a cost-effective agent for the maintenance of long-term interdialytic patency of central venous haemodialysis catheters. To our knowledge, this is the first report of complete conversion from heparin to citrate on all patients with dialysis catheters in a large dialysis unit. We acknowledge that the retrospective nature of the study is a weakness and that a prospective randomized study is needed for confirmation of the results. Despite this weakness, the continued, successful use of citrate as a routine locking solution in our unit is quite encouraging.

In conclusion, sodium citrate 4% does not appear to be inferior in efficacy to heparin 10 000 U/ml for the maintenance of long-term interdialytic patency of central venous haemodialysis catheters. Furthermore, sodium citrate 4% offers several potential clinical advantages over concentrated heparin. Use of citrate avoids patient exposure to the risks of systemic heparinization and associated bleeding complications, improves reliability of reported INR assays and is significantly more cost effective from a pharmaco-economic perspective.

Conflict of interest statement. None declared.

References


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Citrate 4% versus Heparin and the Reduction of Thrombosis Study (CHARTS)

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Background and objectives: Citrate 4% has antithrombotic and antibacterial properties, which makes it a potentially superior alternative to heparin as an indwelling intraluminal locking agent.

Design, setting, participants, and measurements: Sixty-one prevalent hemodialysis (HD) patients dialyzing with a tunneled cuffed HD catheter were randomized in a pilot study to receive either heparin 5000 U/ml or citrate 4% as a locking agent after HD. The primary outcomes were the development of catheter dysfunction (defined as a blood pump speed <250 ml/min or the use of tissue plasminogen activator) and catheter-associated bacteremia. The secondary outcomes were the development of an exit-site infection or bleeding complications (either local or systemic).

Results: Citrate had comparable catheter dysfunction episodes to heparin (13/32 [41%] cases versus 12/29 [41%] cases, respectively). There were no differences in the development of catheter-associated bacteremia (2.2/1000 catheter days citrate versus 3.3/1000 catheter days heparin group; P = 0.607) or exit-site infection (2.2/1000 catheter days for both groups).

Conclusions: The preliminary findings from our pilot study demonstrate that 4% citrate is effective in maintaining catheter patency and does not appear to have any increased incidence of infections. Because citrate is significantly cheaper and has a more favorable side effect profile than heparin, it can be considered a potentially better locking agent in HD catheters.


Catheter use among hemodialysis (HD) patients continues to be high; in fact, recent data indicates that up to 33% of patients in Canada are dialyzing with a catheter (1). Complications of catheters are well known and include catheter dysfunction (CD), infection, and central vein stenosis. The burden of catheter-associated infections contributes to morbidity and subsequent mortality in HD patients. Catheter-related infections may start with bacterial colonization of the catheter hub or exit site and lead to subsequent exit-site infection (ESI) with or without bacteremia.

The use of a catheter and all of its associated complications significantly increases the cost of care in these patients as compared with a native arteriovenous fistula (2). There is a renewed interest in citrate as an alternate to heparin as a locking solution in HD catheters because of its antithrombotic and antibacterial properties and the reduced costs relative to heparin. Furthermore, complications of heparin include local and systemic bleeding events as well as the potential for thrombocytopenia (3). Citrate may be a useful alternative to heparin because it is not known to produce the complications of thrombocytopenia or bleeding.

Despite the use of citrate 4% in many HD units there is only one published randomized trial that compares citrate 4% and heparin in the HD catheter population (4). This study allocated 30 patients with temporary catheters to citrate 4% and heparin 5000 U/ml or polygeline (4). Unfortunately this study was not designed to compare outcomes of infection or thrombosis and the main outcome (i.e., visible clot formation in the catheter) is of questionable clinical relevance. Two prospective observational trials (5,6) recently examined the rate of catheter exchange, tissue plasminogen activator (TPA) use, and bacteremias in a HD population who were converted from heparin to citrate 4%. These studies gave conflicting results, with Lok et al. demonstrating significant reductions in catheter exchange rates, TPA use, and bacteremias in the citrate group whereas Grudzinski et al. found no reduction in catheter exchanges or bacteremias.

Weijmer et al. performed a randomized trial involving 210 patients (98 tunneled cuffed catheters and 193 uncuffed catheters) who received either heparin 5000 U/ml or citrate 43% (7). There was a significant reduction in catheter-associated bacteremia (CAB): 1.1/1000 catheter days for citrate and 4.1 catheter days in the heparin group (P < 0.01) but no difference in the CD episodes.

Initial studies of citrate were halted because of cardiac toxicity of 43% solutions (8); recent advances have demonstrated that 4% solutions are safe and effective, but direct comparisons of citrate to heparin are limited and have been performed in variable populations with different outcomes (9,10). We con-
ducted a pilot study using a randomized design to compare the effect of citrate 4% and 5000 U/ml heparin in terms of CAB, ESI, and thrombotic episodes in a Canadian cohort of prevalent dialysis patients with cuffed catheters. The purpose of this pilot study is to assess the feasibility of pursuing a large, multicenter, quasi-randomized trial by exploring the resources and recruitment methods required.

Study Population and Methods
This study was carried out at St. Paul’s Hospital, a tertiary-care facility situated in Vancouver, Canada. All patients receiving chronic HD three times a week, 4 h/session, at the in-center Hemodialysis Unit with cuffed catheters as primary vascular access were eligible for the trial. Patients were enrolled in the study until their catheters were removed or until the study completion date. All patients were dialyzed on Gambro Integra machines using Gambro tubing and Fresenius F80 dialyzers. Patients were excluded if they had been previously randomized to the study, if their arteriovenous fistula or arteriovenous graft was already in use at the time of the study, if they were currently on antibiotics, or if they were unable or unwilling to give informed consent. The study was approved by the Ethics Board of St. Paul’s Hospital and University of British Columbia, and informed consent was obtained. The study duration was from December 2004 to June 2005.

Study Design and Details
This was a prospective, randomized, nonblinded study. Patients were randomized according to their last name. Patient last names A to L were randomized to receive citrate 4% and patient last names M to Z received heparin 5000 U/ml. This randomization method was chosen to ensure simple logistics for the dialysis staff and to eliminate protocol violations. The citrate was provided prepackaged by the manufacturer (MED-XL, Montreal, Quebec, Canada) in a 5-ml syringe containing citrate 4% per patient per dialysis run (one syringe for both venous and arterial lumen). From these prefilled syringes, citrate was instilled at a volume determined by the manufacturer specifications of the lumen volume. For the heparin group, the nurses aspirated 1 ml of 10,000 U/ml of heparin into a 2-ml syringe and added 1 ml of sterile normal saline to produce 2 ml of heparin 5000 U/ml as per the current standard of care (one syringe per catheter lumen). The locking agent remained in the catheter lumen until the next HD run, and at the beginning of the next run the solution was withdrawn and discarded.

Catheter Care Protocols
Usual care of all catheters involved application of Amuchina (Alcavis, Gaithersburg, MD) to clean the hub, exit site, and limbs of the catheter and then application of a nontransparent Mepore (Direct Medical, Houston, TX) 2.5 × 3 inch dressing at each dialysis run. Catheter manipulations and exit-site dressing changes were performed by dialysis nurses wearing masks and gloves using sterile technique. Topical exit-site prophylaxis is not used in this HD unit. At every dialysis run the catheter exit site is examined, and if there are any concerns regarding possible exit-site infection (erythema, exudate, or tenderness at exit site) a swab is sent for culture and sensitivity.

Data Tracking
Using a standardized tracking form, events, complications, and regular assessment of the catheter site integrity and catheter function was undertaken. All patients were assessed for infection at each dialysis run, where the patient’s temperature was recorded and they were asked about symptoms of chills, rigors, or sweats between the last dialysis. If patients had temperatures >37.8°C, blood cultures ≥2 were drawn and sent to the hospital laboratory for culture and sensitivity data as part of the standard care in this dialysis unit. The nephrologist on rounds was informed of all possible infections and a clinical assessment of the patient was made. All patients had documentation made by the nurses with respect to bleeding or bruising complications at the catheter exit site and evidence of exit-site infection (defined below). The dialysis nurse recorded the presence or absence of any bleeding or bruising events such as gastrointestinal bleed, epistaxis, heavy menorrhage, prolonged hemostasis, bruising, or bleeding from the fistula or graft. Regular, independent review of all charts, study tracking sheets, and lab culture data (blood and exit site swabs) was conducted on a weekly basis by the study coordinator during the course of the study period.

Outcomes
The primary outcomes were CAB and CD. CAB was defined as two sets of positive blood cultures ≥ fever >37.8°C in the absence of other causes as determined by the clinical assessment of the nephrologist on rounds. CD was defined as the use of TPA (Alteplase; Roche, East Sussex, UK) for mean blood pump speeds that were <250 ml/min on two or more consecutive dialysis occasions.

The secondary outcomes were episodes of ESI, local and systemic bleeding complications, and thrombocytopenia. Local bleeding was defined as visible bleeding and or bruising at the catheter exit site. Systemic bleeding was defined as epistaxis, fistula hematoma, prolonged fistula bleeding >30 min, hemarthrosis, gastrointestinal bleed, hemoptyisis, and intracerebral hemorrhage. A major systemic bleed was defined as a decrease in hemoglobin of ≥10g/L or an intracerebral hemorrhage. The absence or presence of these events was recorded on the standardized study tracking forms. ESI was defined as erythema, tenderness, induration (two of three catheters) at exit site ± positive exit-site cultures in the absence of other causes. Thrombocytopenia was defined as the platelet count of <100 on two consecutive occasions. All patients had platelet counts done every 6 wk as part of the protocol for standard blood work in this dialysis unit. Baseline data included demographic information, cause of ESRD, as well the presence of co-morbidities including coronary artery disease, peripheral vascular disease, and diabetes. Current use and dose of antiplatelet drugs, warfarin, immune suppressives, and antibiotics within the last month were recorded. Baseline laboratory data obtained from the hospital laboratory included platelet count and activated partial thromboplastin time. Detailed information was collected with regard to the type of catheter, original insertion date, catheter location, site, and number of previous HD catheters. Use of TPA or antibiotics in the past month and a previous history of CAB or ESI was recorded.

Statistical Analyses
Patient demographic, clinical, and laboratory data were described using mean (±SD) or median (range), depending on the underlying distribution, for continuous variables, or frequencies (percent) for categorical variables. Continuous variables were compared using the t test or the Wilcoxon rank sum test where appropriate. Categorical variables were compared using the χ2 test. A P value <0.05 for two-sided univariate tests was considered statistically significant.

Associations between patient and catheter characteristics and the development of CAB or CD on the next HD run were analyzed by use of logistic regression modeling. Catheter survival was determined from the time of randomization to the next catheter dysfunction event by use of the Kaplan-Meier method. Patients were censored in cases of unre-
lated catheter interventions such as switching to an arteriovenous fistula, planned conversion to peritoneal dialysis, transplantation, or death. Differences between catheter survival times for the citrate and heparin groups were compared by use of the log-rank test. The Cox proportional hazards regression model was used to determine predictors of time to next catheter dysfunction.

A recent randomized controlled trial comparing heparin 1:5000 units and 30% citrate had an incidence of 23% CAB episodes in the heparin group (7). In this study by Weijmer et al., the 30% citrate resulted in a reduction of CAB events by 74% (event rate was 6% in citrate 30% group) (7). We estimate that the effectiveness of 4% citrate is probably less and we expect that it will achieve a reduction of CAB events by 25% (from 20% to 15%). If we assume a power of 0.80 and two-tailed alpha of 0.05, the required sample size is estimated to be 906 patients per treatment arm. Given that we only have a pool of 80 patients with a HD catheter, the intention of this trial was to function as a pilot study for a multicenter trial to test the feasibility of patient recruitment and study design.

Results

The trial was conducted over 6 mo with a median length of follow up of 64 d (25th to 75th percentile: 32 to 132 d). During the study period, 61 patients were recruited to the study: 29 patients to the heparin group and 32 patients to the citrate group.

Baseline Patient Characteristics

The characteristics of the study population are shown in Table 1 and are in keeping with provincial and national demographics. The 61 patients recruited represent 73% of the possible patients eligible for the study in the unit. There were no differences between those randomized and those with catheters who declined to participate. The causes of ESRD were diabetes mellitus (39%), hypertension (13%), glomerulonephritis (28%), and other (20%).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Heparin (n = 29)</th>
<th>Citrate (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr, mean (SD)</td>
<td>69 ± 15</td>
<td>63 ± 16</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>14 (48.3)</td>
<td>21 (65.6)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>14 (48.3)</td>
<td>18 (56.3)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>white, n (%)</td>
<td>16 (55.2)</td>
<td>20 (62.5)</td>
</tr>
<tr>
<td>Asian Oriental, n (%)</td>
<td>12 (41.4)</td>
<td>8 (25.0)</td>
</tr>
<tr>
<td>other, n (%)</td>
<td>1 (3.5)</td>
<td>4 (12.5)</td>
</tr>
<tr>
<td>Duration on HD, mo (25th to 75th percentile)</td>
<td>9.0 (3.0 to 33.0)</td>
<td>10.5 (3.5 to 25.0)</td>
</tr>
<tr>
<td>Current catheter duration, d (25th to 75th percentile)</td>
<td>105 (23 to 176)</td>
<td>92 (29 to 215)</td>
</tr>
<tr>
<td>CAB History, n</td>
<td>12 (41.4)</td>
<td>14 (43.8)</td>
</tr>
<tr>
<td>TPA used in past month, n (%)</td>
<td>9 (31)</td>
<td>13 (40.6)</td>
</tr>
<tr>
<td>ESI History, n (%)</td>
<td>10 (34.5)</td>
<td>12 (37.5)</td>
</tr>
<tr>
<td>APTT, mean (SD)</td>
<td>31.1 ± 4.4</td>
<td>32.7 ± 9.0</td>
</tr>
<tr>
<td>Platelet count, mean (SD)</td>
<td>214 ± 72</td>
<td>226 ± 107</td>
</tr>
<tr>
<td>Warfarin use, n (%)</td>
<td>5 (17.2)</td>
<td>6 (18.8)</td>
</tr>
</tbody>
</table>

There were no significant differences between the two groups for the above baseline characteristics. HD, hemodialysis; CAB, catheter-associated bacteremia; TPA, tissue plasminogen activator; ESI, exit-site infection; APTT, activated partial thromboplastin time.

The most frequent site of catheter placement was the right internal jugular (84%), followed by the left internal jugular (8%) and subclavian (8%). No study patients had femoral lines. All of the catheters were tunneled cuffed catheters (Permcat, Quinton Instruments Co., Seattle, WA). The median catheter duration at study entry was 99 d (25th to 75th percentile: 25 to 182 d), and the distribution of catheter duration was similar between the two groups.

Catheter Dysfunction

Table 2 summarizes the primary and secondary outcomes of the study. Catheter dysfunction, as defined by the use of TPA, occurred in 44.8% of patients in the heparin group and 40.6% in the citrate group ($P = 0.799$).

Catheter-Associated Infections

A total of 18% of the study patients developed CAB: six episodes of CAB in the heparin and five episodes in citrate group. One patient in the citrate group had three episodes of CAB and one patient in the heparin group had two episodes of CAB. This translates into 3.3 episodes of CAB per 1000 catheter days in the heparin group and 2.2 episodes of CAB per 1000 catheter days for the citrate group. In the heparin group, one of six CAB episodes was preceded by an ESI, whereas no CAB episodes were preceded by an ESI in the citrate group.

Six patients in the heparin group developed an ESI, one of whom subsequently developed CAB. Five patients in the citrate group developed an ESI, none of whom developed CAB.

Catheter-Associated Bleeding

There was no difference in the number of overall bleeding episodes between the heparin and citrate groups (37 total bleeding events in heparin versus 25 bleeding events in citrate;
There was no significant difference in the number of local bleeds between the two groups (16 events in heparin versus 18 in citrate; P = 1.0). There were two major systemic bleeds in the heparin group (one gastrointestinal bleed, one intracerebral hemorrhage) and one major systemic bleed (gastrointestinal bleed) in the citrate group. Only 20 patients had platelet counts checked at least twice during the study period. Of these patients, two in the heparin group (25.0%) had a platelet count of <100 on two consecutive occasions during the study versus one patient in the citrate group (8.3%; P = 0.537).

**Table 2. Primary and secondary outcome results**

<table>
<thead>
<tr>
<th></th>
<th>Heparin (n = 29)</th>
<th>Citrate (n = 32)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catheter dysfunction, n (%)</td>
<td>13 (44.8)</td>
<td>13 (40.6)</td>
<td>0.799</td>
</tr>
<tr>
<td>CAB, n (%)</td>
<td>6 (20.7)</td>
<td>5 (15.6)</td>
<td>0.743</td>
</tr>
<tr>
<td>Catheter dysfunction or CAB, n (%)</td>
<td>17 (58.6)</td>
<td>17 (53.1)</td>
<td>0.797</td>
</tr>
<tr>
<td>ESI, n (%)</td>
<td>6 (20.7)</td>
<td>5 (15.6)</td>
<td>0.743</td>
</tr>
<tr>
<td>Total patients with a bleeding event, n³</td>
<td>20</td>
<td>14</td>
<td>0.048</td>
</tr>
<tr>
<td>systemic bleed, n</td>
<td>11</td>
<td>6</td>
<td>0.095</td>
</tr>
<tr>
<td>local bleed, n</td>
<td>9</td>
<td>8</td>
<td>0.600</td>
</tr>
<tr>
<td>Platelet count &lt;100 on two consecutive occasions, n (%)</td>
<td>2/8 (25.0)</td>
<td>1/12 (8.3)</td>
<td>0.537</td>
</tr>
</tbody>
</table>

³Some patients had multiple bleeding events. Overall there were 37 bleeding events in heparin and 25 in citrate patients (P = 0.48). Of these, there were 21 systemic bleeding events in the heparin group and 7 in the citrate group (P = 0.035).

The multivariate proportional hazards modeling (Table 3), after adjusting for age, gender, race, and diabetic status, revealed that use of TPA in past month (HR 8.38, 95% CI 3.37 to 20.87) and catheter duration of <1 mo (HR 4.17, 95% CI 1.70 to 10.19) were statistically significantly associated with increased risk of primary outcome (bacteremia or new TPA).

**Catheter and Patient Survival**

Of the 61 patients that were recruited in the study, 6 patients (20.7%) in the heparin group and 5 patients (15.6%) in the citrate group (P = 0.743) completed the full 6 mo of the study duration with a functioning catheter (Figure 2). Fifteen patients (51.7%) had their catheters removed in the heparin group versus 20 patients (65.5%) in the citrate group. Reasons for catheter removal were CD (17.2% in the heparin group versus 25.0% in the citrate group), infection (10.3% in the heparin groups versus 9.3% in the citrate group), and transfer to peritoneal dialysis or to arteriovenous fistula or graft (24.1% in the heparin group versus 28.1% in the citrate group). Two patients from the citrate group and two patients from the heparin group were transferred to other dialysis centers, and one patient in the heparin group was excluded from the study because of protocol violation. One patient in the heparin group and two patients in the citrate group withdrew from dialysis. Five patients died in the heparin group and four patients died in the citrate group (two withdrew from dialysis, two suffered cardiac arrest, three developed infection/sepsis, one experienced intracranial hemorrhage, and one from unknown causes). The median catheter/patient survival time was 90 d (95% CI 47 to 129 d) in the heparin group versus 55 d (95% CI 32 to 93 d) in the citrate group (P = 0.208).

**Costs**

The cost of the 5-ml citrate syringe is $1.07 (CDN) and one syringe between the ports was used. Alternatively, for HD units that require two separate citrate syringes, the cost is $1.80 for the two syringes. Heparin cost is $1.10 for 10,000 units/5 ml, of which the nurses aspirated 1 ml in a 2-ml syringe ($0.11) using an 18-gauge needle (0.02) and 1 ml of sterile normal saline.
($0.55) to produce 2 ml of heparin 5000 U/ml. This procedure is repeated to produce two 2-ml syringes of heparin, because one syringe per catheter port is used. The total cost of heparin not including nursing time is $3.78 ($1.10 + $0.22 + $0.02 + $0.55 saline = $1.89 × 2 = $3.78). In Canadian dollars, the total yearly cost of citrate for a HD patient is $166.92 (or $280.80 if two separate citrate syringes are used), whereas the total yearly cost for heparin 5000 U/ml is more than three times as expensive at $589.68.

**Discussion**

Although our study is a pilot trial, it is noteworthy in that it compares citrate 4% to heparin 5000 U/ml as catheter locking agents in a randomized design using a sample size >30 patients and as such adds to the current citrate literature. Other studies involving citrate 4% or 5% either had very small sample sizes (n = 19 [10], n = 30 [9]) or were focused on the primary outcome of clot formation (4). Of the large cohort studies, (one prospective, n = 129, and one retrospective, n = 189) (5,6), the data were obtained during the time that the HD unit practice changed from heparin to citrate 4%. Changes in catheter care were not controlled during these studies and may have changed between the heparin and citrate study periods. Methodology issues related to pre- and post-study design are applicable to these studies and may introduce a survivor bias that favors the citrate group. Ideally, the best way to avoid these methodology issues is to perform a randomized trial with large numbers. The study by Weijmer et al. (7) had a large study population of 291 patients who were randomized to high-concentration citrate (30%). However, given the safety concerns of 43% citrate (11), it is unlikely that the 30% citrate solution will be widely adopted in North America HD units because of persistent fears of myocardial toxicity from hypocalcemia.

Our study size of 61 patients was too small to demonstrate significant differences with respect to CAB or ESI. Future studies using a larger sample size may demonstrate a benefit of citrate 4% over heparin, but our study does not provide this evidence. Unfortunately, we had to stop the study after exhausting all eligible HD patients (80 patients in our HD unit) and receiving suboptimal interest from other centers to pursue a multicenter trial. We felt that, because of our low CAB infection rate (18% or 2.7/1000 catheter days) and the unrealistic target of 906 patients per treatment arm, it was not feasible to continue as the only single center in the absence of a large multicenter trial. Nonetheless we present data regarding the two treatments that is of value for a future meta-analysis study.

Our pilot study was underpowered to demonstrate significant differences between citrate 4% and heparin 5000 U/ml as catheter locking agents. Nonetheless, we found that the side effect profile of citrate is superior in terms of systemic bleeding complications as compared with heparin; these findings are consistent with bleeding complications reported elsewhere in the literature (3). We also found, as has been previously demonstrated (12), that a recent history of CD was associated with the development of subsequent TPA use. In addition, the placement of a catheter within the previous month was also associated with subsequent bacteremia or CD. This finding may reflect inadequate treatment of the infection or thrombus that led to the catheter removal in the first place. An alternate explanation for this finding is that perhaps there is a survival bias effect whereby the time of highest risk for CD or infection...
is within the first month of catheter placement and if patients can survive beyond this time their risk of complications may decrease. Our study findings need to be confirmed in incident patients with newly placed catheters to determine the reproducibility of this finding.

There is a significant cost difference between citrate and heparin, with citrate being almost 300% cheaper without factoring in the additional nursing required to dilute the heparin. This equates to a cost difference of $33,820.80 (CDN) over 12 mo with 80 catheter dependent patients.

Citrate is available in a range of concentrations: 4%, 7%, 15%, 30%, and 43%. The use of citrate 43% is limited by the potential for cardiac arrest as a result of hypocalcemia. The lower citrate concentrations are safe and do not have the cardiac toxicity profile of higher concentrations. Higher concentrations of citrate are effective at lowering CAB and prevent thrombosis, but these citrate concentrations are not used in North America because of persistent fears of an adverse side effect profile.

Citrate 4% has been reported to have weak antibacterial properties against gram-positive organisms; however, we could not detect a difference with respect to the number of infections when compared with heparin. Clearly, a large multicenter study is required to determine whether citrate 4% is superior to heparin. It is possible that higher citrate concentrations such as 10% and 15% have stronger antibacterial properties, without the adverse effects of cardiac toxicity associated with the 43% solution. Future studies may consider studying those concentrations. Given the cost differential and the significant reduction in major systemic bleeding events, it may be appropriate to substitute citrate 4% for heparin. Alternatively, comparing an incident catheter population for a randomized trial may also be worthwhile. Furthermore, a future trial should be large enough to include patients with temporary uncuffed catheters and stratify the results according to catheter type (uncuffed versus cuffed).

The limitations of this study include the relatively small sample size and the fact that prevalent catheters instead of incident catheters were included. This latter point is worth expanding upon. Given that the majority of catheter patients that entered into this study were those that had survived for a period of time, the strictest interpretation of our data would be that in those patients with functional catheters initially locked with heparin, who had maintained catheter integrity on that regimen for a mean of 149 d, conversion to a cheaper lock solution results in comparable outcomes. Thus, the next study to be undertaken will be a multicenter trial to compare incident catheter patients who are randomized at the time of catheter insertion to receive one or the other agent. In this way, the issue of survivor bias may be better addressed. Despite these acknowledged limitations, the findings from this randomized pilot study are useful to future meta-analysis studies comparing heparin and 4% citrate and for the design of large randomized multicenter trials.

Conclusions

Citrate 4% is associated with significantly fewer systemic bleeding complications and lower costs than heparin making it a potentially better locking agent in HD catheters. Future studies should explore the utility of the citrate 4% as well as higher doses of citrate in both incident and prevalent catheter patients so as to increase the generalizability of these findings.

Acknowledgments

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Disclosures

None.

References

CRITICAL APPRAISAL TO THE COUNCIL DIRECTIVE 2010/32/EU:

This directive is valid since 10 May 2010.

According to clause 6 of the directive the unnecessary use of sharps should be eliminated by implementing changes in practice on the basis of the results of the risk assessment.

Assessment of the risk should include

a) Effectivity of the product:
   4% citrate can not reduce catheter related infection as it is not antimicrobial
   Heparin containing lock solutions are superior regarding patency.

b) The risk of sharps (ampoules) can be reduced by using vials or using ampoule breakers

c) The risk of blood infection of nurses is low since the needle is only used during filling the syringe. Prefilling of the syringe with TauroLock could be done remote from the patient.

d) Multidose containers can be used to prefill syringes remote from the patient using spikes.
   This means there is no danger of getting in contact with contaminated blood.

e) Sharps are still considered as necessary work equipment (see clause 7).

Conclusion: The EU-Directive 2010/32/EU refers to measures to reduce the risk of sharps of needles.
It does not give priority to needle free application over the quality of the product. Only in case of identical products the needle free application should be clearly given priority to other needlefree solutions.
DIRECTIVES

COUNCIL DIRECTIVE 2010/32/EU
of 10 May 2010
implementing the Framework Agreement on prevention from sharp injuries in the hospital and healthcare sector concluded by HOSPEEM and EPSU

(Text with EEA relevance)

THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Article 155(2) thereof;

Having regard to the proposal from the European Commission,

Whereas:

(1) The social partners may, in accordance with Article 155(2) of the Treaty on the Functioning of the European Union (the TFEU), jointly request that agreements concluded by them at the level of the Union in matters covered by Article 153 of the TFEU be implemented by a Council decision on a proposal from the Commission.

(2) By letter of 17 November 2008, the European social partner organisations HOSPEEM (the European Hospital and Healthcare Employers’ Association, a sectoral organisation representing employers) and EPSU (the European Federation of Public Services Unions, a European trade union organisation) informed the Commission of their wish to enter into negotiations in accordance with Article 138(4) and Article 139 of the Treaty establishing the European Community (the EC Treaty) (1) with a view to concluding a Framework Agreement on prevention from sharp injuries in the hospital and healthcare sector.

(3) On 17 July 2009 the European social partners signed the text of a Framework Agreement on prevention from sharp injuries in the hospital and healthcare sector.

(4) Since the objectives of the Directive, namely to achieve the safest possible working environment by preventing injuries to workers caused by all medical sharps (including needle-sticks) and protecting workers at risk in the hospital and healthcare sector, cannot be sufficiently achieved by the Member States and can therefore be better achieved at the level of the Union, the Union may adopt measures in accordance with the principle of subsidiarity as set out in Article 5 of the Treaty on European Union. In accordance with the principle of proportionality, as set out in that Article, this Directive does not go beyond what is necessary in order to achieve those objectives.

(5) When drafting its proposal for a Directive, the Commission took account of the representativeness of the signatory parties, having regard to the scope of the Agreement, for the hospital and healthcare sector, their mandate and the legality of the clauses in the Framework Agreement and its compliance with the relevant provisions concerning small and medium-sized undertakings.


(7) The European Parliament adopted on 11 February 2010 a resolution on the proposal.

(8) The purpose of the Framework Agreement as set out in Clause 1 thereof is to further the achievement of one of the objectives of social policy, namely the improvement of working conditions.

(9) Clause 11 allows the Member States and the Community (since 1 December 2009 replaced by the Union) to maintain and introduce provisions which are more favourable to workers’ protection from injuries caused by medical sharps.

(10) The Member States should provide for effective, proportionate and dissuasive penalties in the event of any breach of the obligations under this Directive.

(1) Renumbered: Articles 154(4) and 155 of the TFEU.
(11) The Member States may entrust the social partners, at their joint request, with the implementation of this Directive, as long as they take all the steps necessary to ensure that they can at all times guarantee the results imposed by this Directive.

(12) In accordance with point 34 of the Interinstitutional agreement on better law-making (\(^\text{(*)}\)), Member States are encouraged to draw up, for themselves and in the interests of the Union, their own tables which will, as far as possible, illustrate the correlation between this Directive and the transposition measures, and to make them public.

HAS ADOPTED THIS DIRECTIVE:

Article 1
This Directive implements the Framework Agreement on prevention from sharp injuries in the hospital and healthcare sector signed by the European social partners HOSPEEM and EPSU on 17 July 2009, as set out in the Annex.

Article 2
Member States shall determine what penalties are applicable when national provisions enacted pursuant to this Directive are infringed. The penalties shall be effective, proportionate and dissuasive.

Article 3
1. The Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive or shall ensure that the social partners have introduced the necessary measures by agreement by 11 May 2013 at the latest. They shall forthwith inform the Commission thereof.

When the Member States adopt those provisions, they shall contain a reference to this Directive or shall be accompanied by such reference on the occasion of their official publication. The Member States shall determine how such reference is to be made.

2. The Member States shall communicate to the Commission the text of the main provisions of national law which they adopt in the field covered by this Directive.

Article 4
This Directive shall enter into force on the 20th day following its publication in the Official Journal of the European Union.

Article 5
This Directive is addressed to the Member States.

Done at Brussels, 10 May 2010.

For the Council
The President
Á. GONZÁLEZ-SINDE REIG

ANNEX

FRAMEWORK AGREEMENT ON PREVENTION FROM SHARP INJURIES IN THE HOSPITAL AND HEALTHCARE SECTOR

Preamble

1. Health and safety at work is an issue, which should be important to everyone in the hospital and healthcare sector. Taking action to prevent and protect against unnecessary injuries if properly carried out, will have a positive effect on resources;

2. Health and safety of workers is paramount and is closely linked to the health of patients. This underpins the quality of care;

3. The process of policy making and implementation in relation to medical sharps should be the result of social dialogue;

4. HOSPEEM (European Hospital and Healthcare Employers’ Association) and EPSU (European Public Services Union), the recognised European Social partners in the hospital and healthcare sector, have agreed the following:

General considerations

1. Having regard to the Treaty establishing the European Community and in particular Articles 138 and 139 (2) thereof (1);


3. Having regard to Council Directive 89/655/EEC of 30 November 1989 concerning the minimum safety and health requirements for the use of work equipment by workers at work (3);

4. Having regard to Directive 2000/54/EC of the European Parliament and of the Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work (4);

5. Having regard to the Community strategy 2007-2012 on health and safety at work (5);


7. Having regard to the resolution of the European Parliament of 6 July 2006 on protecting European healthcare workers from blood-borne infections due to needle-stick injuries (2006/2015(INI));

8. Having regard to the first and second stage consultation of the European Commission on protecting European healthcare workers from blood-borne infections due to needle-stick injuries;

9. Having regard to the outcomes of the EPSU-HOSPEEM technical seminar on needle-stick injuries of 7 February 2008;

10. Having regard to the hierarchy of general principles of prevention laid down in Article 6 of Directive 89/391/EEC as well as to the preventative measures defined in Articles 3, 5 and 6 of Directive 2000/54/EC;

11. Having regard to the joint ILO/WHO guidelines on health services and HIV/AIDS and to the joint ILO/WHO guidelines on post-exposure prophylaxis to prevent HIV infection;

12. With full respect to existing national legislation and collective agreements;

13. Whereas action needs to be taken to assess the extent of the incidence of sharp injuries in the hospital and healthcare sector, scientific evidence shows that preventive and protection measures can significantly reduce the occurrence of accidents and infections;

(1) Renumbered: Articles 154 and 155(2) of the TFEU.
14. Whereas a full risk-assessment process is a precondition to take appropriate action to prevent injuries and infections;

15. Whereas the employers, and workers' health and safety representatives need to cooperate to prevent and protect workers against injuries and infections from medical sharps;

16. Whereas healthcare workers are primarily but not exclusively concerned by sharp injuries;

17. Whereas students undertaking clinical training, as part of their education, are not considered as workers under this agreement, they should be covered by the prevention and protection measures outlined in this agreement, with liabilities being regulated according to national legislation and practice;

Clause 1: Purpose
The purpose of this framework agreement is:

— to achieve the safest possible working environment,

— to prevent workers' injuries caused by all medical sharps (including needle-sticks),

— to protect workers at risk,

— to set up an integrated approach establishing policies in risk assessment, risk prevention, training, information, awareness raising and monitoring,

— to put in place response and follow-up procedures.

Clause 2: Scope
This agreement applies to all workers in the hospital and healthcare sector, and all who are under the managerial authority and supervision of the employers. Employers should deploy efforts to ensure that subcontractors follow the provisions laid down in this agreement.

Clause 3: Definitions
Within the meaning of this agreement:

1. Workers: any persons employed by an employer including trainees and apprentices in the hospital and healthcare sector—directly related services and activities. Workers who are employed by temporary employment business within the meaning of Council Directive 91/388/EEC supplementing the measures to encourage improvements in the safety and health at work of workers with fixed-duration employment relationship or a temporary employment relationship (1) fall within the scope of the agreement;

2. Workplaces covered: healthcare organisations/services in public and private sectors, and every other place where healthcare services/activities are undertaken and delivered, under the managerial authority and supervision of the employer;

3. Employers: natural/legal persons/organisations having an employment relationship with workers. They are responsible for managing, organising and providing healthcare and directly related services/activities delivered by workers;

4. Sharps: objects or instruments necessary for the exercise of specific healthcare activities, which are able to cut, prick, cause injury and/or infection. Sharps are considered as work equipment within the meaning of Directive 89/655/EEC on work equipment;

5. Hierarchy of measures: is defined in order of effectiveness to avoid, eliminate and reduce risks as defined in Article 6 of Directive 89/391/EEC and Articles 3, 5 and 6 of Directive 2000/54/EC;

6. Specific preventative measures: measures taken to prevent injury and/or transmission of infection in the provision of hospital and healthcare directly related services and activities, including the use of the safest equipment needed, based on the risk assessment and safe methods of handling the disposal of medical sharps;

7. Workers' representatives: any person elected, chosen or designated in accordance with national law and/or practice to represent workers.

8. Worker's health and safety representatives are defined in accordance with Article 3(c) of Directive 89/391/EEC as any person elected, chosen or designated in accordance with national law and/or practice to represent workers where problems arise relating to health and protection of workers at work.

9. Subcontractor: any person who takes action in hospital and healthcare directly related services and activities within the framework of working contractual relations established with the employer.

Clause 4: Principles

1. A well trained, adequately resourced and secure health service workforce is essential to prevent the risk of injuries and infections from medical sharps. Exposure prevention is the key strategy for eliminating and minimising the risk of occupationally acquired injuries or infections.

2. The role of health and safety representatives is key in risk prevention and protection.

3. The employer has a duty to ensure the safety and health of workers in every aspect related to the work, including psycho-social factors and work organisation.

4. It shall be the responsibility of each worker to take care — as far as possible — of their own safety and health and that of other persons affected by their actions at work, in accordance with their training and the instructions given by their employer.

5. The employer shall develop an environment where workers and their representatives are participating in the development of health and safety policies and practices.

6. The principle of the following specific preventative measures indicated in clauses 5 to 10 of the present agreement shall never assume that there is no risk. The hierarchy of general principles of prevention according to Article 6 of Directive 89/391/EEC and Articles 3, 5 and 6 of Directive 2000/54/EC is applicable:

7. Employers and workers' representatives shall work together at the appropriate level to eliminate and prevent risks, protect workers' health and safety, and create a safe working environment, including consultation on the choice and use of safe equipment, identifying how best to carry out training, information and awareness-raising processes.

8. Action needs to be taken through a process of information and consultation, in accordance with national laws and/or collective agreements.

9. The effectiveness of awareness-raising measures entails shared obligations of the employers, the workers and their representatives.

10. In achieving the safest possible workplace a combination of planning, awareness-raising, information, training, prevention and monitoring measures is essential.

11. Promote a 'no blame' culture. Incident reporting procedure should focus on systemic factors rather than individual mistakes. Systematic reporting must be considered as accepted procedure.

Clause 5: Risk assessment

1. Risk-assessment procedures shall be conducted in compliance with Articles 3 and 6 of Directive 2000/54/EC, and Articles 6 and 9 of Directive 89/391/EEC.

2. Risk assessment shall include an exposure determination, understanding the importance of a well resourced and organised working environment and shall cover all situations where there is injury, blood or other potentially infectious material.

3. Risk assessments shall take into account technology, organisation of work, working conditions, level of qualifications, work-related psycho-social factors and the influence of factors related to the working environment. This will:
   — identify how exposure could be eliminated,
   — consider possible alternative systems.

Clause 6: Elimination, prevention and protection

1. Where the results of the risk assessment reveal a risk of injuries with a sharp and/or infection, workers' exposure must be eliminated by taking the following measures, without prejudice to their order:
   — specifying and implementing safe procedures for using and disposing of sharp medical instruments and contaminated waste. These procedures shall be regularly reassessed and shall form an integral part of the measures for the information and training of workers referred in clause 8,
— eliminating the unnecessary use of sharps by implementing changes in practice and on the basis of the results of the risk assessment, providing medical devices incorporating safety-engineered protection mechanisms,
— the practice of recapping shall be banned with immediate effect;

2. Having regard to the activity and the risk assessment, the risk of exposure must be reduced to as low a level as necessary in order to protect adequately the safety and health of the workers concerned. The following measures are to be applied in the light of the results of the risk assessment:
— place effective disposal procedures and clearly marked and technically safe containers for the handling of disposable sharps and injection equipment as close as possible to the assessed areas where sharps are being used or to be found,
— prevent the risk of infections by implementing safe systems of work, by:
(a) developing a coherent overall prevention policy, which covers technology, organisation of work, working conditions, work-related psycho-social factors and the influence of factors related to the working environment;
(b) training;
(c) conducting health surveillance procedures, in compliance with Article 14 of Directive 2000/54/EC;
— use of personal protective equipment;

3. If the assessment referred to in clause 5 reveals that there is a risk to the safety and health of workers due to their exposure to biological agents for which effective vaccines exist, workers shall be offered vaccination;

4. Vaccination and, if necessary, revaccination shall be carried out in accordance with national law and/or practice, including the determination of the type of vaccines:
— workers shall be informed of the benefits and drawbacks of both vaccination and non-vaccination,
— vaccination must be offered free of charge to all workers and students delivering healthcare and related activities at the workplace.

Clause 7: Information and awareness-raising
As sharps are considered as work equipment within the meaning of Directive 89/655/EEC (1), in addition to information and written instructions to be provided to workers specified in Article 6 of Directive 89/655/EEC, the employer shall take the following appropriate measures:
— to highlight the different risks,
— to give guidance on existing legislation,
— to promote good practices regarding the prevention and recording of incidents/accidents,
— to raise awareness by developing activities and promotional materials in partnership with representative trade unions and/or workers’ representatives,
— to provide information on support programmes available.

Clause 8: Training
In addition to measures established by Article 9 of Directive 2000/54/EC, appropriate training shall be made available on policies and procedures associated with sharps injuries, including:
— the correct use of medical devices incorporating sharps protection mechanisms,
— induction for all new and temporary staff,
— the risk associated with blood and body fluid exposures,
— preventive measures including standard precautions, safe systems of work, the correct use and disposal procedures, the importance of immunisation, according to the procedures at the workplace,
— the reporting, response and monitoring procedures and their importance,
— measures to be taken in case of injuries.

(1) Subsequently the Directive has been codified into Directive 2009/104/EC.
Employers must organise and provide training which is mandatory for workers. Employers must release workers who are required to attend training. This training shall be made available on a regular basis taking into account results of monitoring, modernisation and improvements.

Clause 9: Reporting

1. This includes the revision of the reporting procedures in place with health and safety representatives and/or appropriate employers/workers representatives. Reporting mechanisms should include local, national and European-wide systems.

2. Workers shall immediately report any accident or incident involving sharps to the employers and/or the person in charge, and/or to the person responsible for safety and health at work.

Clause 10: Response and follow-up

Policies and procedures shall be in place where a sharp injury occurs. All workers must be made aware of these policies and procedures. These should be in accordance with European, national/regional legislation and collective agreements, as appropriate.

In particular the following action shall be taken:

— the employer takes the immediate steps for the care of the injured worker, including the provision of post-exposure prophylaxis and the necessary medical tests where indicated for medical reasons, and appropriate health surveillance in accordance with clause 6(2)(c),

— the employer investigates the causes and circumstances and records the accident/incident, taking — where appropriate — the necessary action. The worker must provide the relevant information at the appropriate time to complete the details of the accident or incident,

— the employer shall, in cases of injury, consider the following steps including counselling of workers where appropriate and guaranteed medical treatment. Rehabilitation, continued employment and access to compensation shall be in accordance with national and/or sectoral agreements or legislation.

Confidentiality of injury, diagnosis and treatment is paramount and must be respected.

Clause 11: Implementation

This agreement will be without prejudice to existing, future national and Community(1) provisions which are more favourable to workers' protection from medical sharps' injuries.

The signatory parties request the Commission to submit this framework agreement to the Council for a decision in order to make this agreement binding in the Member States of the European Union.

If implemented through Council decision, at European level and without prejudice to the respective role of the Commission, national courts and the European Court of Justice, the interpretation of this agreement, could be referred by the Commission to the signatory parties who will give their opinion.

The signatory parties shall review the application of this agreement five years after the date of the Council decision if requested by one of the parties to the agreement.


For EPSU
Karen JENNINGS
For HOSPEEM
Godfrey PERERA

(1) "Community" has been replaced since 1 December 2009 by "Union".