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%, 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 lumens). 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 menstruation, 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, hemorrhathosis, gastrointestinal bleed, hemoptyisis, and intracerebral hemorrhage. A major systemic bleed was defined as a decrease in hemoglobin of ≥100/ 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%).

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;

<table>
<thead>
<tr>
<th>Table 1. Patient baseline characteristics</th>
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<tr>
<td>Variable</td>
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<tr>
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<tr>
<td>Age, yr, mean (SD)</td>
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<tr>
<td>Male, n (%)</td>
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<tr>
<td>Diabetes, n (%)</td>
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<tr>
<td>Race</td>
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<tr>
<td>white, n (%)</td>
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<tr>
<td>Asian Oriental, n (%)</td>
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<tr>
<td>other, n (%)</td>
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<tr>
<td>Duration on HD, mo (25th to 75th percentile)</td>
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<tr>
<td>Current catheter duration, d (25th to 75th percentile)</td>
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<tr>
<td>CAB History, n</td>
</tr>
<tr>
<td>TPA used in past month, n (%)</td>
</tr>
<tr>
<td>ESI History, n (%)</td>
</tr>
<tr>
<td>APTT, mean (SD)</td>
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<tr>
<td>Platelet count, mean (SD)</td>
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<td>Warfarin use, n (%)</td>
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</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.
Table 2. Primary and secondary outcome results

<table>
<thead>
<tr>
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<th>Heparin (n = 29)</th>
<th>Citrate (n = 32)</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Catheter dysfunction, n (%)</td>
<td>13 (44.8)</td>
<td>13 (40.6)</td>
<td>0.799</td>
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<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, n&lt;sup&gt;a&lt;/sup&gt;</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>

<sup>a</sup>Some 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).

There were significantly more systemic bleeding events in the heparin group, 21 compared with 7 systemic bleeds in the citrate group (P = 0.035). 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).

**Time to Primary Outcome**

Figure 1 demonstrates bacteremia-free catheter survival as determined from the time of randomization until the next CAB. There is no difference in bacteremia-free catheter survival between the heparin and citrate groups (25th percentiles: 175 d versus 133 d, respectively; P = 0.930). Also, there is no statistically significant difference in dysfunction-free catheter survival between the heparin and citrate groups (25th percentiles: 16 d versus 15 d, respectively; P = 0.867; data not shown). Both groups demonstrated similar time to combined primary outcome (CD or CAB): median event-free catheter survival was 55 d in the heparin group versus 54 d in the citrate group (P = 0.912).

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

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![Figure 1. Kaplan-Meier survival curve for time to catheter dysfunction.](image-url)
($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.

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Disclosures
None.

References