Effects of Citrate Acid Concentrate (Citrasate®) on Heparin N Requirements and Hemodialysis Adequacy: A Multicenter, Prospective Noninferiority Trial

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Key Words

Citric acid dialysate • Heparin N • Hemodialysis • Dialysate

Abstract

Background: Citrasate®, citric acid dialysate (CD), contains 2.4 mEq of citric acid (citrate), instead of acetic acid (acetate) as in standard bicarbonate dialysate. Previous studies suggest CD may improve dialysis adequacy and decrease heparin requirements, presumably due to nonsystemic anticoagulant effects in the dialyzer. **Methods:** We prospectively evaluated 277 hemodialysis patients in eight outpatient facilities to determine if CD with reduced heparin N (HN) would maintain dialyzer clearance. Subjects progressed through four study periods [baseline (B): bicarbonate dialysate + 100% HN; period 1 (P1): CD + 100% HN; period 2 (P2): CD + 80% HN; period 3 (P3): CD + 66.7% HN]. The predefined primary endpoint was noninferiority (margin –8%) of the percent change in mean dialyzer conductivity clearance between baseline and P2. **Results:** Subjects were 57.4% male, 41.7% white, 54.3% black, and 44.4% diabetic; mean age was 59 ± 14.4 years; mean time on dialysis was 1,498 ± 1,165 days; 65.7% had arteriovenous fistula, 19.9% arteriovenous

graft, 14.4% catheters, and 27.8% used antiplatelet agents. Mean dialyzer clearance increased 0.9% (P1), 1.0% (P2), and 0.9% (P3) with CD despite heparin reduction. SpKt/V remained stable (B: 1.54 ± 0.29; P1: 1.54 ± 0.28; P2: 1.55 ± 0.27; P3: 1.54 ± 0.26). There was no significant difference in dialyzer/dialysis line thrombosis, post-HD time to hemostasis, percent of subjects with adverse events (AEs), or study-related AEs. **Conclusions:** CD was safe, effective, and met all study endpoints. Dialyzer clearance increased approximately 1% with CD despite 20–33% heparin reduction. Over 92% of P3 subjects demonstrated noninferiority of dialyzer clearance with CD and 33% HN reduction. There was no significant difference in dialyzer clotting, bleeding, or adverse events.

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Introduction

Citrasate®, citric acid dialysate (CD; Fresenius Medical Care NA, Waltham, Mass., USA), is a dialysis acid concentrate containing 2.4 mEq of citric acid (citrate) instead of acetic acid (acetate) as in standard bicarbonate

dialysate [1, 2]. Citrate is a short-acting anticoagulant due to its binding with calcium and is rapidly metabolized in the liver (half-life of 49 min) [3, 4]. CD, however, contains a much lower concentration of citric acid than required for regional citrate anticoagulation [1–4]. CD is FDA-approved [1] and has been demonstrated to be safe and effective [2]. Published reports suggest that CD may improve dialysis adequacy [Kt/V (K = clearance, t = time on dialysis and V = volume of distribution)] [2, 5, 6], decrease hemodialysis heparin requirements [7–9], and increase dialyzer reuse [10], presumably due to nonsystemic anticoagulant effects in the dialyzer. These studies, however, are limited by their small sample size and/or lack of adequate controls.

Subjects and Methods

We prospectively evaluated 277 hemodialysis patients in eight outpatient dialysis facilities (Renal Research Institute: 4; DaVita: 4) using Fresenius 2008K or 2008K² dialysis machines with on-line clearance monitors (OLC; Fresenius Medical Care NA, Waltham, Mass., USA) to determine if CD with reduced heparin N (HN) dosage would maintain dialyzer clearance (ClinicalTrials.gov identifier: NCT01092455). Subjects on thrice weekly HD with single bolus HN $\geq 2,000$ units/treatment and nonreuse of dialyzers were enrolled in an 8-week open-label sequential phase study including four study periods each comprising six HD treatments over 2 weeks: baseline (B) = standard bicarbonate dialysate + 100% of the subject's standard bolus HN dose; period 1 (P1) = CD + 100% of standard bolus HN; period 2 (P2) = CD + 80% of standard bolus HN; and period 3 (P3) = CD + 66.7% of standard bolus HN.

Patients with a hemoglobin (Hgb) <9.5 g/dl, eKt/V <1.0 (or spKt/V <1.2), on warfarin or low-molecular-weight heparin, history of HIT or other bleeding and/or thrombotic disorder, dialyzer or dialysis line clotting in the last 30 days requiring changing the dialyzer, bloodlines or terminating treatment, or with any medical condition which might jeopardize the subject were excluded.

Citrasate, citric acid 45 $\times$ -concentrate (Fresenius Medical Care NA) was utilized (P1, P2, P3) to provide final dialysate total calcium (Ca) of 2.5 mEq/l, magnesium (Mg) 1.00 mEq/l, chloride (Cl) 104.5 mEq/l, acetate 0.3 mEq/l, dextrose 100 mg/dl, and citrate 2.4 mEq/l. Dialysate potassium (K) concentration was 1–3 mEq/l and matched the subject's baseline. The effective conductivity clearance (mean KECN) and single pool Kt/V were measured for each treatment by ionic dialysance using the volume obtained from monthly kinetic modeling calculated with the mean KECN. All subjects were maintained on their same dialysis prescription throughout the study.

Subjects who developed thrombosis (significant clotting) defined as clotting in the dialyzer and/or bloodline which required dialyzer/dialysis line replacement or early treatment termination were withdrawn from the study after the clotting event to ensure patient safety. HN doses were rounded to the nearest 100 units to facilitate administration.

Endpoints

The predefined primary study endpoint was noninferiority (margin –8%) of the percent change in mean KECN between the baseline period and P2. To demonstrate noninferiority, the lower 95% CI must be greater than or equal to –8%. Secondary efficacy endpoints included the proportion of subjects with the percent change in the average of mean KECNs during P2 greater than or equal to –8% compared to baseline; the percent change in the average of mean KECNs in P3 greater than or equal to –8% compared to baseline; and the proportion of subjects with the percent change in the average of mean KECNs during P3 greater than or equal to –8% compared to baseline. Safety endpoints included the number and percentage of subjects with one treatment with significant clotting, the percent of subjects with reported adverse events (AEs), and the percent of subjects with study-related AEs.

Data Collection

Treatment mean KECN and spKt/V were measured by ionic dialysance. Thrombosis (significant clotting) was measured by the incidence of clotting requiring dialyzer and/or dialysis line replacement or treatment termination. Pre- and postdialysis blood urea nitrogen, predialysis Hgb, pre- and postdialysis serum total Ca and ionized calcium (iCa) were obtained weekly (midweek), and C-reactive protein was obtained once in each study period. Blood tubing and hemodialyzers were inspected for clotting at the beginning (30 min), middle (2 h), and end of each treatment, and patients were questioned for symptoms and/or anticipated or unanticipated AEs. Anticipated AEs potentially related to study participation included significant clotting (thrombosis), perioral numbness, numbness or paresthesias, dysgeusia, carpopedal spasm, tremor, and hypocalcemia (post-HD iCa <0.90 mmol/l or 3.6 mg/dl). All other AEs were reported as unanticipated AEs.

Statistical Analysis

One hundred subjects were required to conclude noninferiority with a –8% margin and achieve a power of 90% at $\alpha = 0.05$ (expected mean –5%; SD 10). Descriptive statistics (n, mean, SD) were performed for continuous endpoints and the frequency and percent of total subjects were calculated for categorical endpoints. For noninferiority, 95% CI were calculated using a t distribution. For continuous endpoints and tests between each period with baseline, a paired t test was employed. $p < 0.05$ was considered significant.

Results

Two hundred eighty-seven subjects consented to the study and 277 subjects had at least one study treatment. The population was 57.4% male, 41.7% white, 54.3% black, and 44.4% diabetic; and had a mean age of 59 ± 14.4 years and dialysis vintage of $1,498 \pm 1,165$ days. Dialysis access included 65.7% arteriovenous fistula, 19.9% arteriovenous graft, and 14.4% catheters; 27.8% of subjects were maintained on antiplatelet agents. Dialysis was

Table 1. Heparin doses, measures of dialysis adequacy, and dialyzer thrombosis

	B: standard dialysate + 100% HN	P1: CD + 100% HN	P2: CD + 80% HN	P3: CD + 67% HN
n	277	254	224	195
Heparin N, U	3,756 ± 1,506	3,753 ± 1,529	3,000 ± 1,227	2,551 ± 1,036
Change from baseline		0 ± 0	-743 ± 305	-1,265 ± 505
% change		0.0 ± 0.0	-19.9 ± 1.0	-33.2 ± 1.5
p value vs. B			<0.001	<0.001
Heparin N, U/kg	47.3 ± 16.7	47.2 ± 16.4	38.0 ± 13.2	31.9 ± 11.1
Change from baseline		-0.1 ± 0.5	-9.5 ± 3.5	-16.0 ± 5.5
% change		-0.1 ± 0.9	-20.1 ± 1.5	-33.5 ± 1.9
p value vs. B		0.107	<0.001	<0.001
Mean KECN, ml/min	246 ± 29	248 ± 28	249 ± 27	249 ± 26
p value vs. B		0.052	0.062	0.196
% change mean KECN		0.9 ± 6.6	1.0 ± 6.4	0.9 ± 7.2
95% CI		0.1, 1.7	0.1, 1.8	-0.2, 1.9
% subjects with decrease in mean KECN >8%		5.5	5.8	7.7
95% CI		3.1, 9.1	3.1, 9.7	4.4, 12.4
spKt/V by OLC	1.54 ± 0.29	1.54 ± 0.28	1.55 ± 0.27	1.54 ± 0.26
p value vs. B		0.596	0.915	0.716
% subjects with spKt/V <1.2 by OLC	7.6	7.5	7.6	6.7
95% CI	4.8, 11.4	4.6, 11.4	4.5, 11.9	3.6, 11.1
spKt/V by Daugirdas 2	1.56 ± 0.24	1.56 ± 0.28	1.56 ± 0.22	1.56 ± 0.30
p value vs. B		0.415	0.232	0.361
% subjects with spKt/V <1.2	5.9	5.4	4.1	7.3
95% CI	3.42, 9.45	2.92, 9.08	1.91, 7.73	4.02, 11.87
% subjects with clotted dialyzer/lines	4.7	3.1	3.1	5.1
95% CI	2.5, 7.9	1.4, 6.1	1.3, 6.3	2.5, 9.2
Time to hemostasis, min	10.7 ± 3.7	10.9 ± 4.4	10.3 ± 3.1	10.8 ± 3.5
p value vs. B		0.519	0.129	0.660

performed using Fresenius Optiflux® dialyzers (18.8% F160 NRE, 50.5% F180 NRE, 7.2% F200 NRE), Gambro Polyflux® (18.4% 170H, 4.7% 210H), or Gambro Polyflux® Revaclear (0.4%) dialyzers.

Mean KECN increased 0.9% in P1 (CD + 100% HN), 1.0% in P2 (CD + 80% HN) and 0.9% in P3 (CD + 67% HN) with 95% CI (0.1, 1.7), (0.1, 1.8), and (-0.2, 1.9), respectively (table 1). The lower limit of the 95% CI for each period was greater than -8%. This demonstrated noninferiority despite a reduction in mean HN dose from 3,756 ± 1,506 units/treatment (baseline) and 3,753 ± 1,529 units/treatment in P1 to 3,000 ± 1,227 units/treatment in P2 and 2,551 ± 1,036 units/treatment in P3. The percentage of subjects with spKt/V by OLC <1.2 was similar in each period [B: 7.6% (95% CI 4.8, 11.4); P1: 7.5% (4.6, 11.4); P2: 7.6% (4.5, 11.9); P3: 6.7% (3.6, 11.1)] and over 92% of the subjects achieved a spKT/V ≥ 1.2 by OLC. There was no significant difference in dialyzer/dialysis line thrombosis or postdialysis time to hemostasis (table 1).

Hgb decreased modestly, serum albumin increased, and C-reactive protein was unchanged (table 2). Pre- and postdialysis total Ca and iCa were lower with CD than with standard dialysate, and both Ca and iCa decreased intradialytically (post-/pre-HD) with CD (table 2). Dialysis treatment parameters (baseline Qb: 418 ± 45; Qd: 520 ± 122 ml/min; Td: 220 ± 25 min) remained essentially unchanged throughout.

There was no difference in the percent of subjects with reported AEs with CD [B: 5.1% (95% CI: 2.8, 8.3); P1: 9.1% (5.8, 13.3); P2: 8.0% (4.8, 12.4); P3: 7.2% (4.0, 11.8)] or study-related AEs [B: 5.1% (95% CI: 2.8, 8.3); P1: 6.7% (3.9, 10.5); P2: 6.3% (3.5, 10.3); P3: 6.7% (3.6, 11.1)]. There was a higher incidence of reported carpopedal spasm during the CD periods [B: 0%; P1: 2.4% (95% CI: 0.9, 5.1); P2: 0.9% (0.1, 3.2); P3: 0.5% (0.0, 2.8)]. These events were not associated with low post-HD serum iCa, which remained ≥ 3.9 mg/dl in all of the affected subjects. There was 1 patient death (from cardiac disease) which was unrelated

Table 2. Laboratory values

	B: standard dialysate + 100% HN	P1: CD + 100% HN	P2: CD + 80% HN	P3: CD + 67% HN
n	277	254	224	195
WBC, 100/ μ l	6.77 $\pm$ 2.13	6.80 $\pm$ 2.20	6.68 $\pm$ 2.00	6.85 $\pm$ 2.28
p value vs. B		0.761	0.912	0.314
Hgb, g/dl	11.81 $\pm$ 1.15	11.70 $\pm$ 1.08	11.65 $\pm$ 1.09	11.61 $\pm$ 1.12
p value vs. B		0.006	0.040	0.016
Pre-HD Ca, mg/dl	8.85 $\pm$ 0.74	8.78 $\pm$ 0.76	8.78 $\pm$ 0.70	8.77 $\pm$ 0.72
p value vs. B		<0.001	0.124	0.007
% change pre-HD Ca ¹		-1.18 $\pm$ 4.56	-0.87 $\pm$ 4.56	-1.03 $\pm$ 5.13
p value vs. B		<0.001	0.005	0.006
Post-HD Ca, mg/dl	8.99 $\pm$ 0.57	8.52 $\pm$ 0.45	8.55 $\pm$ 0.50	8.57 $\pm$ 0.47
p value vs. B		<0.001	<0.001	<0.001
% change post HD Ca ¹		-5.09 $\pm$ 4.71	-4.79 $\pm$ 5.75	-4.59 $\pm$ 5.39
p value vs. B		<0.001	<0.001	<0.001
Intradialytic change (post-/pre-HD) in Ca, mg/dl	0.14 $\pm$ 0.63	-0.25 $\pm$ 0.62	-0.23 $\pm$ 0.57	-0.20 $\pm$ 0.56
p value vs. B		<0.001	<0.001	<0.001
% intradialytic change in Ca	1.96 $\pm$ 7.39	-2.35 $\pm$ 7.41	-2.24 $\pm$ 6.56	-1.88 $\pm$ 6.43
p value vs. B		<0.001	<0.001	<0.001
Pre-HD iCa, mg/dl	4.71 $\pm$ 0.45	4.69 $\pm$ 0.43	4.68 $\pm$ 0.41	4.70 $\pm$ 0.42
p value vs. B		0.002	0.084	0.064
% change pre-HD iCa ¹		-0.73 $\pm$ 6.62	-0.51 $\pm$ 6.27	-0.35 $\pm$ 6.86
p value vs. B		0.088	0.234	0.482
Post-HD iCa, mg/dl	4.81 $\pm$ 0.34	4.35 $\pm$ 0.28	4.26 $\pm$ 0.26	4.28 $\pm$ 0.26
p value vs. B		<0.001	<0.001	<0.001
% change post-HD iCa ¹		-9.55 $\pm$ 4.93	-11.13 $\pm$ 5.43	-10.83 $\pm$ 5.13
p value vs. B		<0.001	<0.001	<0.001
Intradialytic change (post-/pre-HD) in iCa, mg/dl	0.09 $\pm$ 0.39	-0.34 $\pm$ 0.37	-0.41 $\pm$ 0.35	-0.41 $\pm$ 0.35
p value vs. B		<0.001	<0.001	<0.001
% intradialytic change in iCa	2.5 $\pm$ 9.0	-6.8 $\pm$ 7.5	-8.3 $\pm$ 7.3	-8.3 $\pm$ 6.9
p value vs. B		<0.001	<0.001	<0.001
Serum albumin, g/dl	3.94 $\pm$ 0.36	3.97 $\pm$ 0.36	3.97 $\pm$ 0.35	4.00 $\pm$ 0.34
p value vs. B		0.012	0.058	<0.001
C-reactive protein, mg/l	12.19 $\pm$ 18.57	12.40 $\pm$ 17.60	10.59 $\pm$ 14.08	11.46 $\pm$ 24.55
p value vs. B		0.161	1.000	0.936
Epogen, units/treatment	5,127.0 (4,398.1)	4,713.6 $\pm$ 3,999.3	4,744.1 $\pm$ 3,929.9	4,725.2 $\pm$ 3,926.5
p value vs. B		0.016	0.107	0.196
% change in Epogen ¹ dose		-1.17 $\pm$ 23.77	2.89 $\pm$ 38.40	6.53 $\pm$ 55.57
p value vs. B		0.475	0.316	0.143

Conversion factors for units: Hgb in g/dl to g/l $\times$ 10; Ca (or iCa) in mg/dl to mmol/l $\times$ 0.2495; albumin in g/dl to g/l $\times$ 10.

¹ % change from the baseline period (B).

to study participation and 8 reported episodes (7 with CD) of asymptomatic post-HD hypocalcemia. The study withdrawal rate was 36.2% [B: 8.3% (95% CI: 5.3, 12.2); P1: 11.8% (8.1, 16.4); P2: 12.9% (8.8, 18.1); P3: 6.2% (3.2, 10.5)]. The most common reasons for withdrawal were clotting of the dialyzer or dialysis lines (9.0%, 25/277), withdrawal of informed consent (7.6%, 21/277), and hospitalization unrelated to study participation (6.1%, 17/277).

Discussion

This study demonstrated the ability to reduce HN doses up to 33% while maintaining dialysis adequacy, and met all predefined study endpoints in a large prospective cohort of HD patients dialyzed with CD. Dialyzer clearance increased approximately 1% and superiority of clearance was demonstrated with CD + 100% HN (P1)

and CD + 80% HN (P2). Over 94% (211/224) of the subjects in P2 and over 92% (180/195) of the subjects in P3 (CD + 66.7% HN) demonstrated noninferiority of dialyzer clearance (margin greater than -8%) with no increase in dialyzer/dialysis line clotting or postdialysis time to hemostasis. These data confirm earlier reports of improved dialyzer clearance and heparin reduction with the use of CD [2, 5, 10–12]. Heparin use is associated with significant risks including the possibility of bleeding, HIT, and contamination [11–14]. Thus, reducing heparin dose is clinically attractive and may offer significant benefits [14].

Ahmad et al. [2] demonstrated improved dialysis adequacy in a 12-week study with 25 patients with the use of CD containing 2.5 or 3.0 mEq/l calcium, resulting in the urea reduction ratio (68 ± 5.9 to $73 \pm 5.3\%$; $p < 0.03$) and spKt/V increasing (1.23 ± 0.19 to 1.34 ± 0.20 ; $p = 0.01$). Kossmann et al. [5] also demonstrated improved adequacy in 146 subjects following conversion from standard dialysate to CD containing 2.4 mEq/l citrate and 2.0 or 2.5 mEq/l calcium. eKt/V increased from 1.51 ± 0.01 to 1.57 ± 0.01 with CD ($p < 0.0001$) and β_2 -microglobulin declined (28.1 ± 10.0 to 25.9 ± 10.0 mg/l; $p = 0.0001$). In the poststudy period, eKt/V for subjects remaining on CD was unchanged (1.60 ± 0.17 vs. 1.59 ± 0.18 ; $p = \text{NS}$), but decreased from 1.55 ± 0.20 to 1.52 ± 0.17 ($p < 0.0001$) in the patients returning to standard dialysate.

CD has also been reported to have a positive impact on hemodynamics. Gabutti et al. [6] demonstrated significant reduction in systolic blood pressure (SBP) and peripheral resistance with the use of CD (2.4 mEq/l citrate, 0.3 mEq/l acetate) when compared to standard acetate containing bicarbonate dialysate (0 mEq/l citrate, 3.0 mEq/l acetate) in a randomized single blind crossover study of 25 patients. SBP decreased 4.3 mm Hg ($p < 0.01$), peripheral resistance decreased $51 \text{ dyn} \cdot \text{s} \cdot \text{cm}^{-5}$, and stroke volume remained stable. Predialysis serum bicarbonate increased 0.9 mEq/l with CD (20.6 ± 2.5 mEq/l standard dialysate; 21.5 ± 2.8 mEq/l CD; $p < 0.01$). These data suggest that CD is more biocompatible and physiologic than standard acetate containing bicarbonate dialysate, with positive effects on hemodynamics and acid-base balance in addition to improved dialysis efficacy [6] and heparin reduction.

There have been no safety issues reported with CD [2, 5, 6]. The major potential concern is the possibility of decreasing iCa. In this study, mean total Ca and iCa decreased modestly during dialysis (approximately 2.35 and 8.3%, respectively), mean postdialysis total Ca remained

>8.5 mg/dl, and mean postdialysis iCa was >4.25 mg/dl. These values are within physiologic range and did not decrease to levels required for systemic anticoagulation or known to cause symptoms. There were eight reported instances (7 with CD) of asymptomatic post-HD hypocalcaemia, which is consistent with previous data [2, 5, 6]. There was no difference in reported AEs or study-related AEs with CD. There was, however, a higher incidence of reported carpopedal spasm during the use of CD. The reason for these reports remains unclear. These events were not associated with low post-HD iCa, which remained ≥ 3.9 mg/dl in all affected subjects and none of the subjects were treated with Ca administration. Rather, during each of the study treatments where subjects reported carpopedal spasm, they were either unable to achieve their written target weight, or had an aggressive ultrafiltration goal. This suggests that many of these reported symptoms may represent volume-mediated cramping rather than true hypocalcemic carpopedal spasm.

This study has several limitations. We cannot wholly eliminate the possibility that patients were over-heparinized at baseline due to the study's sequential design. This, however, appears unlikely. At baseline, patients received approximately 47 U HN/kg, which is consistent with the general guideline for bolus heparin administration (50 U/kg) and the current US standard of care. In addition, all patients had been switched to HN prior to the initiation of the study with adjustments in HN dose only in the event of clotting. This would have decreased subjects' effective heparin dose by approximately 10% prior to the baseline period. Lastly, 4.7% of patients clotted their dialyzer or dialysis lines during the baseline period. This would not be expected if the patients were over-heparinized at baseline.

The study also had a high drop-out rate. This was primarily due to the fact that patients who clotted a dialyzer or lines (9.0%, 25/277) were removed from the study to decrease the potential risk of blood loss in patients to be treated with reduced heparin. Additionally, a significant number of subjects were withdrawn due to nonstudy-related hospitalization (6.1%, 17/277). Lastly, 7.6% (21/277) of subjects withdrew their informed consent. The reasons for these withdrawals do not appear related to AEs and may reflect the increased time requirements due to the use of nonformulary dialysate.

Conclusion

CD was safe, effective and allowed significant heparin reduction while maintaining dialysis adequacy and achieved all predefined study endpoints. Dialyzer clearance increased approximately 1% with CD despite 20–33% HN reduction, and over 92% of the subjects in P3 demonstrated noninferiority of dialyzer clearance despite a 33% HN reduction. There was no significant difference in clotting of dialyzers/dialysis lines, no evidence of increased bleeding and no significant difference in AEs.

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Disclosure Statement

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References

- 1 510(K) Summaries or 510(K) Statements for Final Decisions Rendered during the Period June 1, 2000 through June 30, 2000;510(k) No. K000792. http://www.accessdata.fda.gov/cdrh_docs/pdf/k000792.pdf.
- 2 Ahmad S, Callan R, Cole JJ, Blagg CR: Dialysate made from dry chemicals using citric acid increases dialysis dose. *Am J Kidney Dis* 2000;35:493–499.
- 3 Bauer E, Derfler K, Joukhadar C, Druml W: Citrate kinetics in patients receiving long-term hemodialysis therapy. *Am J Kidney Dis* 2005;46:903–907.
- 4 O'Shea SI, Ortel TL, Kovalik EC: Alternative methods of anticoagulation for dialysis-dependent patients with heparin-induced thrombocytopenia. *Semin Dial* 2003;16:61–67.
- 5 Kossmann RJ, Gonzales A, Callan R, Ahmad S: Increased efficiency of hemodialysis with citrate dialysate: a prospective controlled study. *Clin J Am Soc Nephrol* 2009;4:1459–1464.
- 6 Gabutti L, Lucchini B, Marone C, Alberio L, Burnier M: Citrate- vs. acetate-based dialysate in bicarbonate haemodialysis: consequences on haemodynamics, coagulation, acid-base status, and electrolytes. *BMC Nephrol* 2009;10:7.
- 7 Tu A, Ahmad S: Heparin-free hemodialysis with citrate-containing dialysate in intensive care patients. *Dial Transplant* 2000;29:620–626.
- 8 Kossmann, R, Callan R, Ahmed S: Fifty-five percent heparin reduction is safe with citrate dialysate in chronic dialysis patients (abstract). *J Am Soc Nephrol* 2006;17:109–110.
- 9 Dittrich M, Callan R, Ahmad S: High citrate dialysate is safe and permits heparin free chronic hemodialysis (abstract). *J Am Soc Nephrol* 2008;19:461.
- 10 Ahmad S, Callan R, Cole JJ, Blagg CR: Increased dialyzer reuse with citrate bicarbonate dialysate. *Hemodial Int* 2005;9:264–267.
- 11 Valentine KA, Hull RD: Therapeutic use of heparin and low molecular weight heparin; in Leung LK, Landaw SA (eds): *UpToDate for Medicine v 17.2*. www.uptodate.com, 2009.
- 12 Lohr JW, Schwab SJ: Minimizing hemorrhagic complications in dialysis patients. *J Am Soc Nephrol* 1991;2:961–975.
- 13 Kishimoto TK, Viswanathan K, Ganguly T, et al: Contaminated heparin associated with adverse clinical events and activation of the contact system. *N Engl J Med* 2008;358:2457–2467.
- 14 Golper TA, Ward RA: Dialysate... Ho-Hum! *Clin J Am Soc Nephrol* 2009;4:1403–1404.