CITRASATE®: EFFECTS ON HEMODIALYSIS ADEQUACY AND HEPARIN N REQUIREMENTS

Fresenius Medical Care

Jeffrey J. Sands, MD MMM [1]; Peter Kotanko MD[2]; Jonathan H. Segal MD[3]; Chiang-Hong Ho PhD[1]; Amy Young[4]; Mary Carter PhD[2]; Olga Sergeyeva MD[1]; Lisa Korth[4]; Eileen Maunsell[1]; Yueping Zhu[1]; Mahesh Krishnan MD FASN[4] and Jose A. Diaz-Buxo MD FACP[1]

Institutions: *[1]Fresenius Medical Care NA; [2]RRINY; [3]U. Michigan and [4]DaVita*

1. INTRODUCTION

Citrasate® (C) is a dialysis acid concentrate containing 2.4 mEq of citric acid, a known anticoagulant instead of acetic acid (acetate) as found in standard bicarbonate dialysate.[1] Previous reports suggest that Citrasate use may improve dialyzer clearance[2] and decrease hemodialysis heparin requirements[3-5] presumably due to non-systemic anticoagulant effects in the dialyzer. These studies however are limited by their small sample size and/or lack of adequate controls.

2. METHODS

We prospectively evaluated 277 hemodialysis patients to determine if the use of Citrasate with reduced Heparin N (H) dosage would maintain dialyzer clearance in an outpatient hemodialysis (HD) population. Consenting subjects maintained on thrice weekly HD with single bolus dose heparin N and non-reuse of dialyzers were evaluated over consecutive 2-week periods (P):

- Baseline (B): Standard bicarbonate dialysate + standard (100%) dose heparin N
- Period 1 (P1): Citrasate + 100% Heparin N
- Period 2 (P2): Citrasate + 80% Heparin N
- Period 3 (P3): Citrasate + 67% Heparin N

Dialyzer clearance (mean KECN) and spKt/V were measured by ionic dialysance and thrombosis was measured by the incidence of clotting requiring dialyzer and/or dialysis line replacement or treatment termination. The predefined primary study endpoint was non-inferiority (margin -8%) of the change in mean KECN between the baseline and Period 2 (Citrasate + 80 Heparin N). Power of 90% at α =0.05 required 100 pts to conclude non-inferiority with a -8% margin (expected mean -5%, SD=10%). Patients with clotting of their dialyzer or dialysis lines requiring replacement or treatment termination were withdrawn from the study after the clotting event to ensure patient safety.

3. RESULTS

The 277 subjects were 57.4% male 41.7% white, 54.3% black, 44.4% diabetic with a mean age of 59±14.4 years and a dialysis vintage of 1498±1165 days. Dialysis access included 65.7% AVF, 19.9% AVG and 14.4% catheters and 27.8% of subjects were maintained on antiplatelet agents.

Mean dialyzer clearance (Mean KECN) increased 0.9% in Period 1 (Citrasate + 100% Heparin N), 1.0% in Period 2 (Citrasate + 80% Heparin N) and 0.9% in Period 3 (Citrasate + 67% Heparin N) and achieved the primary predefined non-inferiority endpoint (Figure 1, 2) despite reduction in mean heparin dose from 3756±1506 u/treatment (Baseline) and 3753±1529 u/treatment in P1 to 3000±1227 u/treatment in P2 and 2551±1036 u/treatment in P3 (Table 1). Dialysis treatment parameters (Baseline Qb = 418±43, Qd = 520±122 mL/min, Td =220 ±26 min) remained unchanged. Post dialysis total and ionized calcium were lower by 5% and 10%, respectively, with Citrasate than with standard bicarbonate dialysate. There was no significant difference in dialyzer or dialysis line thrombosis, post dialysis time to hemostasis (Table 1), the percent of subjects with reported adverse events (AEs) (Baseline: 4.7%, (95%CI 2.5,7.9); P1: 8.7% (5.5,12.8); P2: 6.3% (3.5,10.3); P3: 6.2% (3.2,10.5)) or study related AEs (Baseline:4.7%, (95%CI 2.5,7.9); P1: 6.3% (3.6,10.0); P2:4.0% (1.9,7.5); P3: 5.1% (2.5,9.2)) with the use of Citrasate. There was one patient death which was unrelated to study participation and one reported episode of hypocalcemia related to the use of cinacalcet.

Figure 1.

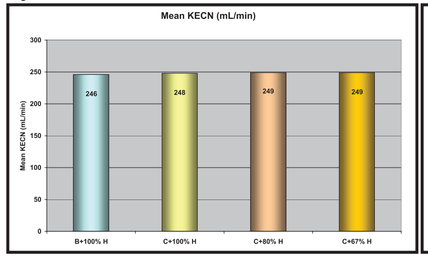

Figure 2.

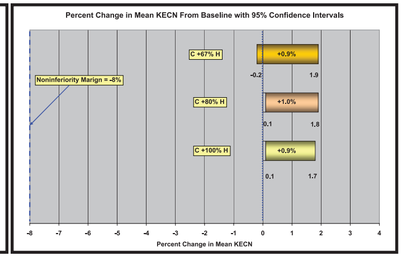

Table 1.

	B: Standard dialysate +100% H	P1: Citrasate +100% H	P2: Citrasate +80% H	P3: Citrasate +67% H
N	277	254	224	195
Heparin N (u)	3756±1506	3753±1529	3000±1227	2551±1036
Change from Baseline			-742±304.8**	-1265±504.7**
% Change		0%	-19.9%	-33.2%
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%	-20%	-33.3%
Mean KECN (mL/min)	246±29	248±28	249±27	249±26
% Change Mean KECN 95% CI		0.9%* (0.1, 1.7)	1.0%* (0.1, 1.8)	0.9% (-0.2, 1.9)
% Subjects ↓ KECN > 8% 95% CI		5.5% (3.1,9.1)	5.8% (3.1,9.7)	7.7% (4.4,12.4)
spKt/V by OLC	1.54±0.29	1.54±0.28	1.55±0.27	1.54±0.26
% Change in spKt/V		0.04±8.3	0.35±9.3	0.14±10.7
% Subjects spKt/V < 1.2 95% CI	7.6% (4.8,11.4)	7.5% (4.6,11.4)	7.6% (4.5,11.9)	6.7% (3.5,11.1)
% Subjects with clotted dialyzer/lines 95% CI	4.7 (2.5,7.9)	3.1 (1.4,6.1)	3.1 (1.3,6.3)	5.1 (2.5,9.2)
Time to hemostasis (min)	10.7±3.70	10.9±4.36	10.3±3.09	10.8±3.46
Pre HD Ca	8.85±0.74	8.78±0.76	8.78±0.70	8.77±0.72
% Change pre-HD Ca		-1.18±4.56**	-0.87±4.56**	-1.03±5.13**
Post HD Ca	8.99±0.57	8.52±0.45	8.55±0.50	8.57±0.47
% Change post HD Ca		-5.09±4.71**	-4.79±5.75**	-4.59±5.39**
Pre-HD iCa	4.71±0.45	4.69±0.43	4.68±0.41	4.70±0.42
%Change Pre-HD iCa		-0.73±6.62	-0.51±6.27	-0.35±6.86
Post HD iCa	4.81±0.34	4.35±0.28	4.26±0.26	4.28±0.26
%Change post HD iCa		-9.55±4.93**	-11.13±5.43**	-10.83±5.13**

* $p < 0.05$ compared to the baseline period

** $p < 0.01$ compared to the baseline period

4. DISCUSSION

This study demonstrated the ability to decrease heparin N doses by up to 33% in a cohort of hemodialysis patients dialyzed with Citrasate dialysate and met the predefined dialyzer clearance non-inferiority endpoint. Dialyzer clearance increased ~1% and superiority of clearance was demonstrated with Citrasate and 100% (P1) and 80% Heparin N (P2). Over 92% of the subjects completing the trial demonstrated non-inferiority of dialyzer clearance despite a 33% heparin N reduction. In addition, there was no increase in dialyzer/ dialysis line clotting or in post dialysis time to hemostasis. This confirms earlier reports by Koosman et al[2, 3] that both improved dialyzer clearance and heparin reduction were possible with the use of Citrasate.

There was no difference in AEs and the reported AEs also did not correlate with measurements of serum calcium. Although post dialysis serum total and ionized calcium was lower with the use of Citrasate, these values remained within physiologic range and did not decrease to levels required for systemic anticoagulation or known to cause symptoms.

The study can not totally eliminate the possibility that patients were over heparinized at baseline. This however appears unlikely. At baseline, patients were receiving ~47u Heparin N/Kg which is consistent with the general guideline for bolus heparin of 50u/Kg and the US standard of care. In addition, all patients had been switched to heparin N prior to the initiation of the study with adjustments in heparin dose only in the event of clotting. This would have decreased their effective heparin dose ~10% prior to the onset of 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-heparinzed at baseline.

5. CONCLUSIONS

- Patients dialyzed with Citrasate + 80% heparin N maintained HD adequacy and met the primary endpoint of non-inferiority of mean KECN compared to bicarbonate dialysis with standard dose heparin
- Dialyzer clearance increased ~1% with the use of Citrasate despite 20% to 33% heparin N reduction
- There was no significant difference in clotting of dialyzers/dialysis lines between the 4 periods and no evidence of increased bleeding

6. REFERENCES

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Jeffrey J. Sands MD MMM | Abstract #992 | Poster #F-P01416
Direct tel: 407 566-0683 | e-mail: jeffrey.sands@fmc-na.com