Dry-Citrasate® (Citrate Dialysate)

A Product of:

ART

Advanced Renal Technologies, USA

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POWDERED ACID CONCENTRATE

(More biocompatible and heparin saving)

Dialyse with Dry-Citrasate®

and draw the following benefits :

- Reduces metabolic acidosis.
- Increases reuse of Dialysers.
- Improves dose of Dialysis.
- Heparin can be reduced up to 55%
- Enables heparin-free dialysis of patients with antibodies to heparin (HIT) or those who are allergic to heparin.
- Enables heparin-free dialysis of patients with acute renal failure who are at risk of bleeding.
- Improves treatment to patients who are actively bleeding or who are at risk of hemorrhage.
- Improves dialysis in patients who are "dialyser clotters".
- Improves acid-base status.
- Less thrombogenic dialysis.
- Reduces inflammation.
- Improves tolerance to treatment.
- Improves operational efficiency.
- Saves huge storage space.

Dialysis Professionals

Health professionals responsible for the care of dialysis patients are well aware of the complex relationship between treatment variables and patient outcome. Much depends upon the interaction between the patient's blood and the extracorporeal circuit, especially within the hemodialyzer. Even with systemic heparin anticoagulation, clotting within the dialyzer reduces delivered "dose" of dialysis, increases blood loss, and limits dialyzer reuse. Dialyzer clotting is further accelerated in cases where heparin anticoagulation is contraindicated, for example, in patients with antibodies to this agent. These complications result in additional staff time required to treat the problems, as well as higher costs for additional supplies (dialyzers, blood lines, etc.).

Management of postsurgical and trauma a patient with increased risk of bleeding limits the use of heparin, making the dialysis especially challenging. The alternatives to heparin therapy in this group are limited to periodic flushes of the circuit or to regional citrate anticoagulation. Although widely used, line flushing is relatively ineffective and increases fluid load to the patient. The alternative, regional citrate anticoagulation, is difficult to deliver properly and expensive to set up and monitor. Both methods involve significant additional effort on the part of the staff.

Furthermore, in patients receiving uncomplicated, "routine dialysis," the goal is to optimize treatment by increasing the dose of dialysis within the constraints of available time and cost. Advanced Renal Technologies (ART) has developed a new dialysate formulation that addresses these problems and brings treatment to a more effective level. Containing citric acid as the acidifying agent, it is the first major change in dialysate formulation in over two decades, breaking away from traditional formulations that contain acetic acid. It is cleared for use by the FDA, and is already on the market and in use in clinics.

Citrate dialysate is not to be confused with regional citrate anticoagulation, in which high concentrations of citric acid are infused into the arterial blood line to bind calcium, and a corresponding infusion of calcium is delivered into the venous line or through the dialyzer to counteract hypocalcemia. Citrate dialysate has been used successfully in place of in-hospital regional citrate anticoagulation, and it is more effective than repeated saline flushing of the extracorporeal circuit. (ref. 1)

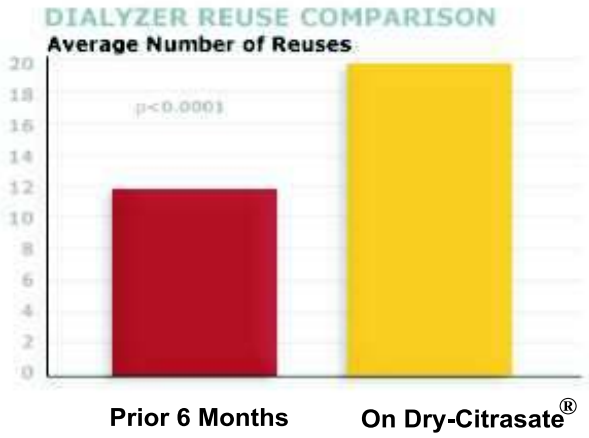
Citric acid content of both Citrasate® and Dry-Citrasate® is only 2.4 mEq/L in the final diluted concentration within the dialyzer, well below the 7-15 mEq/L threshold of true anticoagulation (ref. 2). Calcium levels in the patient remain within the normal range when citrate dialysate is used, and no supplemental calcium replacement measures are needed.

Making the conversion from conventional dialysate to citrate dialysate is effortless. The conversion is "transparent" for both staff and dialysis equipment.

- No adjustment in the dialysis system is required; simply substitute citrate concentrate for the A concentrate normally used.
- Additional staff training is unnecessary.
- There is no need to perform additional patient monitoring beyond ordinary measures. No blood tests are needed.

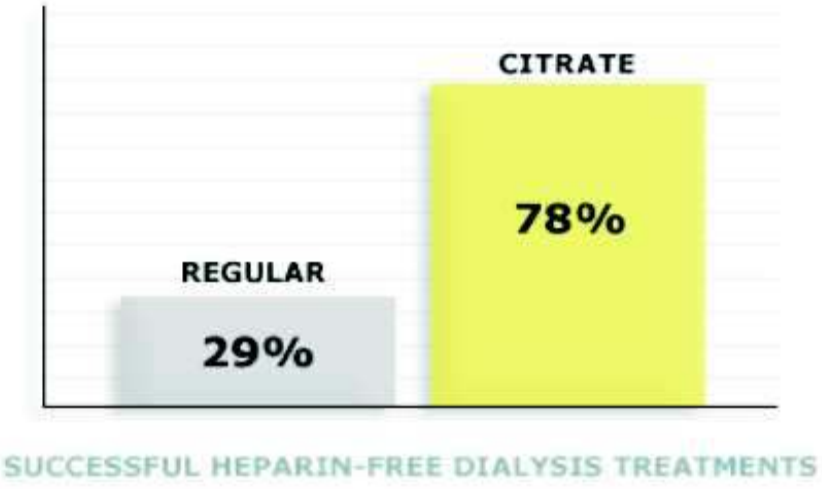
Clinical Use

- Compared with traditional acetic acid-containing dialysates, citrate dialysate has the following documented benefits:
- Citrate dialysate increases the delivered "dose" of dialysis for the patient, including improved Kt/V and URR and increased predialysis serum bicarbonate levels.
- Citrate dialysate can raise average dialyzer reuse by more than 60% on all patients, and by over 100% on patients considered "problem clotters." Consequently, for the facility seeking to cut operating costs, ART's citrate dialysate is an effective solution.



Citrate dialysate can be used for heparin-free dialysis of patients with antibodies to heparin.

- Where heparin anticoagulation is contraindicated, citrate dialysate can be used for dialysis of patients with acute renal failure who are at risk of bleeding. In most cases, citrate dialysate reduces or eliminates the need to flush the extracorporeal circuit with saline.



Citrate is a natural metabolite providing both energy and buffering capacity to the patients. In addition, citrate is a well known antioxidant and anticoagulant. Coagulation activation and oxidative stress leads to increased inflammation, and are identified risk factors for developing cardiovascular disease in dialysis patients.

55% HEPARIN REDUCTION USING CITRATE DIALYSATE (CITRASATE®)

Robert Kossmann[1], Robin Callan[2], Suhail Ahmad[3]

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ACKNOWLEDGEMENT: The authors wish to thank the management and staff of Fresenius Medical Care, NA for their help and assistance with this study.

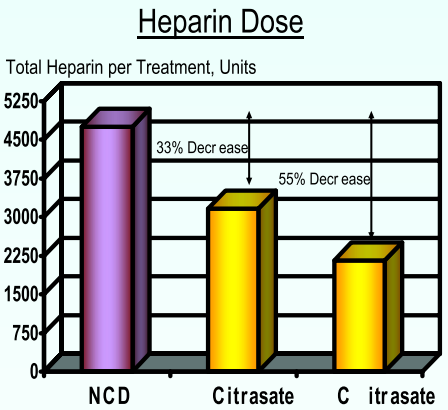
BACKGROUND AND AIMS:

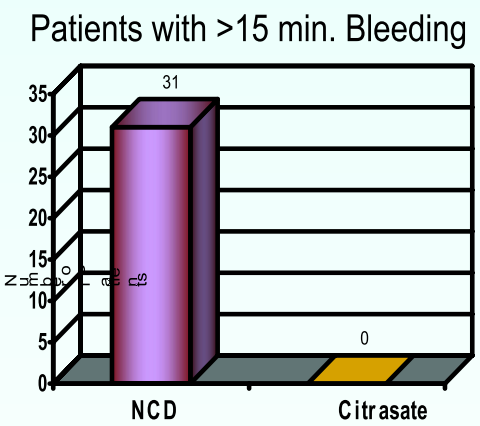
- Systemic heparinization in hemodialysis patients increases the risk of bleeding.
- Often manifesting as prolonged bleeding from access needle-sites after the removal of needles.
- Dialysate containing citrate, Citrasate® (CD) has been reported to prevent clotting of dialysis circuit (Tu et al Dialysis & Transplantation, 29: 620, 2000).
- Aim of the study was to assess whether CD would permit a **safe** reduction in heparin dose and would **reduce** bleeding episodes without increased clotting (maintaining the dose of dialysis)

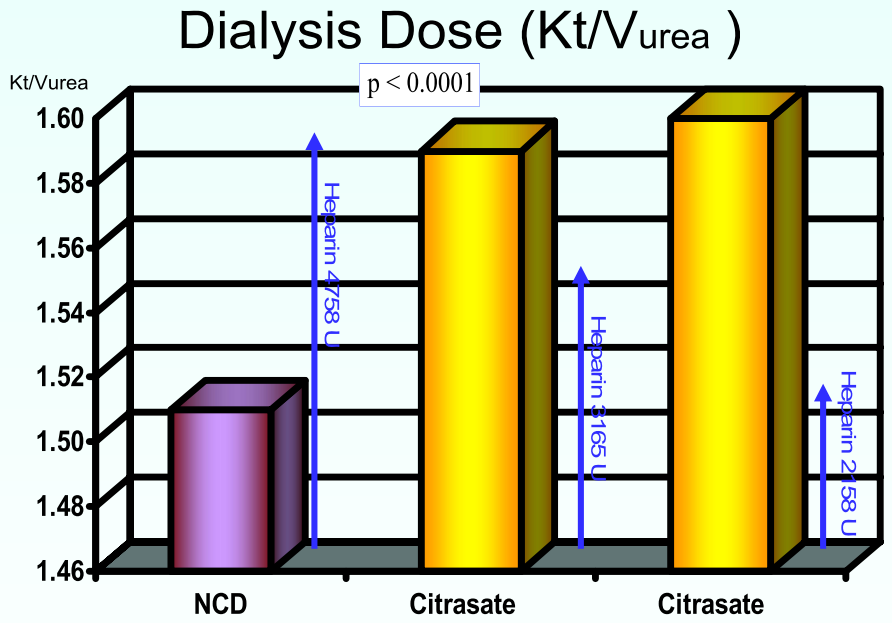
METHODS:

- Thirty one chronic HD patients were identified as having postdialysis bleeding for >15 minutes from needle sites.
- Using standard acetate containing bicarbonate non-citrate dialysate (NCD) with either Optiflux NR 160 or NR 180 dialyzers.
- All patients were switched to CD (Citrasate®, Advanced Renal Technologies, Belleveue, WA, USA) without changing Qb, Qd, treatment duration or other paramaters and followed for 2 months.
- After 2 months each patient's heparin dose was reduced by 33% for 3 months and, after assessing adequate dialysis, the dose was further reduced by another 33% (55% reduction from initial dose) for another 3 months.
- Dialyzer, tubings and air-traps were observed for clotting
- Patient observation was used to identify post-dilaysis bleeding from needle sites (>15 minutes)
- The adequacy of dialysis was measured by Kt/Vurea.

RESULTS:







SUMMARY & CONCLUSIONS:

1. Use of citrate dialysate permitted a 55% reduction in the dose of heparin during hemodialysis.
2. Reduction in Heparin resulted in a decrease in post-dialysis bleeding from needle site to less than 15 minutes in all 31 patients.
3. Heparin reduction (55%) was not associated with any clotting of dialysis circuit with Citrasate®.
4. Citrasate® was associated with an increase in the dose of dialysis despite a 55% decrease in heparin.

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Title	:	Fifty-five Percent Heparin Reduction is Safe with Citrate Dialysate in Chronic Dialysis Patients

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Citrate containing dialysate (CD) has been reported to have anticoagulation effect (Tu et al, D T, 29:620, 2000). Systemic heperinizaton during hemodialysis (HD) is associated with multiple risks including bleeding complications. The purpose of the study was to determine whether heparin can be safely reduced in chronic HD patients using CD. Thirty-one patients from 3 New Mexico FMC dialysis units were identified as having prolonged (>15 minutes) bleeding from needle sites at the end of dialysis when using regular dialysate. These patients were switched to CD and 2 months later their heparin dose was reduced from an average of 4758 $\pm$ 2179 (mean $\pm$ SD) units to 3165 $\pm$ 1352 units, a 33.5% reduction for a 2 month period (1st reduction). After 2 months the heparin dose was further reduced to 2158 $\pm$ 1362 units, another 32% reduction (2nd reduction), a total 55% reduction from the baseline. After the 2nd reduction patients were followed for another 3 months. Single use dialyzers (Optiflux NR160 or NR180) were used and the duration of dialysis, blood and dialysate flow remained unchanged.

After switching the patients to CD and reducing their heparin dose, prolonged bleeding reduced with no reported instances of bleeding.

Throughout the heparin reduction periods the dialyzer and blood tubing remained free of clots. After a total 55% reduction in heparin the Kt/V did not decrease, in fact it increased, as shown in the Table.

Despite a 55% reduction in heparin pre-dialysis Beta-2 microglobulin levels were lower during the CD, Pre CD 26.1 Vs 2nd reduction 24.0, p=0.08.

The use of citrate dialysate along with a 55% reduction in heparin was successful in decreasing the episodes of prolonged bleeding, was not associated with clotting of the system and an adequate dose of dialysis was maintained.

Kt/V values, mean (SD), during regular and citrate dialysate before and during heparin reductions

Pre CD	1.51 (0.21)
Baseline CD	1.55 (0.18)
1st Reduction	1.59 (0.18)
2nd Reduction	1.60 (0.16)*

*p=0.05 Pre CD Vs 2nd Reduction

INCREASED Kt/V AND DECREASED BETA-2 WITH CITRATE DIALYSATE

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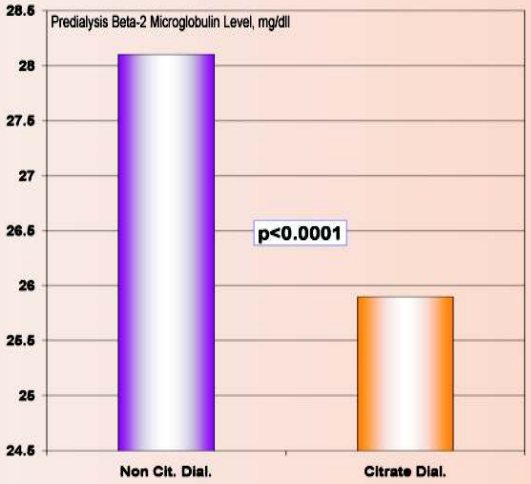
ACKNOWLEDGEMENT: The authors wish to thank the management and staff of Fresenius Medical Care, NA for their help and assistance with this study.

BACKGROUND & PURPOSE

- Clotting of dialyzer often occurs during dialysis and is a major cause of reduced delivered dose of dialysis.
- Citrate Dialysate has been reported to have anticoagulant properties (Tu et al Dial & Transpl, 29: 620, 2000).
- In a small number of patients over short study period, the dialysis dose increased with CD (Ahmad et al, AJKD, 35:493, 2000).
- The effect of Citrate D Dialysate on the dose was evaluated in a larger number of patients (n=142), over longer duration (6 months) and utilizing single use dialyzers (F160 NR & F180 NR).

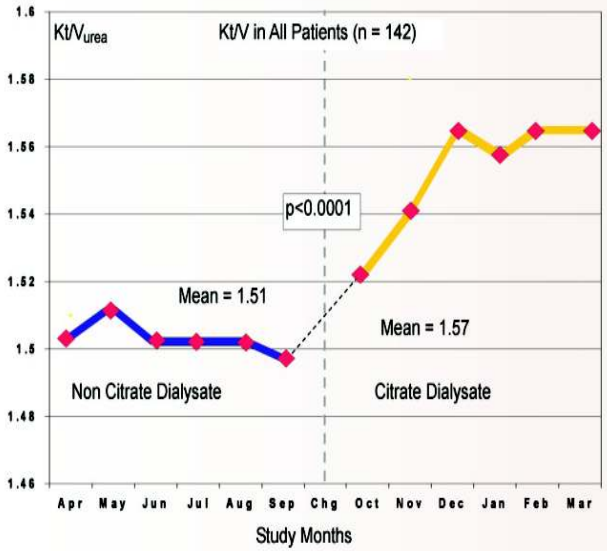
METHODS:

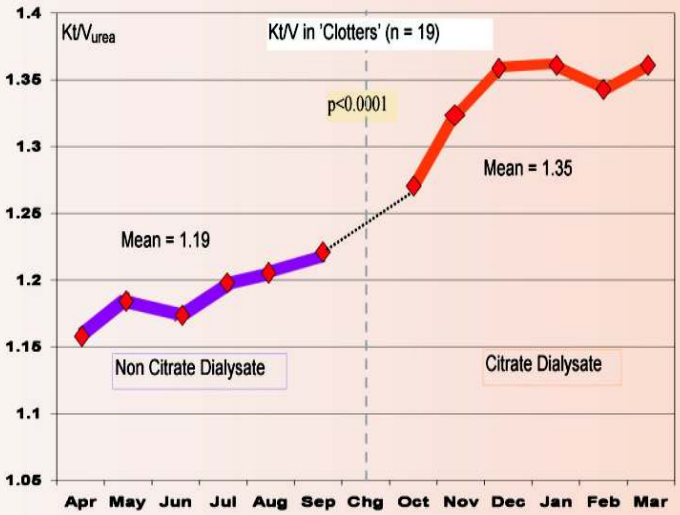
- Three FMC dialysis units in New Mexico were switched from regular bicarbonate non citrate dialysate (Naturalyte® & Granuflo®, "NCD") to Citrate Dialysate (Citrasate®,"CD") for 6 months.
- During the study dialysis time, dialyzer type, blood and dialysate flow remained unchanged.
- The dialysis dose in terms of Kt/Vurea was measured monthly on NCD and CD.
- Pre-dialysis Beta-2 microglobulin (B2Mg) was also measured at the beginning and end of CD use.
- Patients with Kt/V being 1 SD below average during the 6 months of NCD were labelled as "clotters".
- Predialysis Beta-2 microglobulin was measured twice; at the end of NCD and CD use.

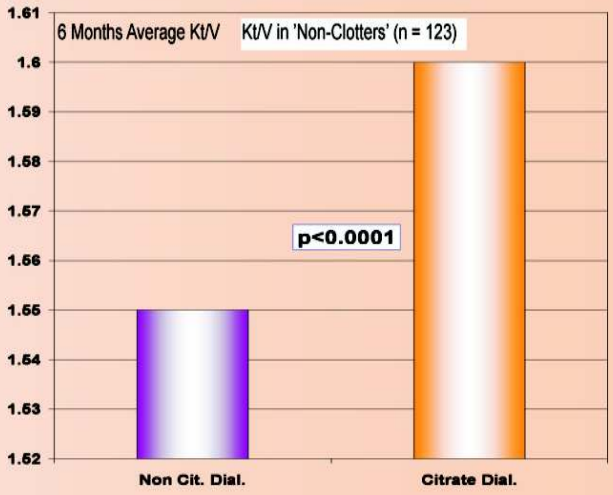


RESULTS & CONCLUSIONS:

- Six months of Citrate Dialysate was associated with a significant increase in the dose of dialysis as measured by Kt/Vurea.
- This increase was particularly significant in 19 patients whose baseline (NCD) Kt/Vurea was <1.20 (1 Std.Dev. < population mean).
- In the remaining 123 patients, with mean Kt/V of 1.55, the Kt/V also increased significantly to 1.60 with Citrate Dialysate (p<0.0001).
- Associated with increase in Kt/V was a significant decrease in pre dialysis BUN and creatinine concentrations (p<0.008).
- Predialysis blood concentration of beta-2 microglobulin also declined significantly with 6 months of citrate dialysate.
- It is postulated that anticoagulation property of CD kept the dialyzer fibers and its pores open resulting in better removal of both small (urea, creatinine) and middle molecules (beta-2 microglobulin).
- CD anticoagulation caused an increase in the dose of dialysis.







ASN's 39th Annual Renal Week Meeting

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Title : Increased Dialysis Dose and Decreased Concentration of Beta-2 Microglobulin with Citrate Dialysate

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Increase in Kt/V was earlier reported with citrate dialysate in 22 patients using reprocessed dialyzers (Ahmad et al, AJKD, 35:493, 2000). The purpose of the present prospective study was to evaluate the effect of citrate dialysate (CD) on Kt/V in a larger number of patients (n=142), on single use dialyzers (Optiflux 180NR and 160NR) and over a longer period (6 months). The Kt/V was compared on regular non-citrate (NCD) dialysate for 6 months (Naturalyte and Granuflo) with CD (Citrasate) for following 6 months. During the study the dialyzers and dialysis treatment remained unchanged. Patients, 60 F and 82 M, were 63 +/- 14 years old (mean + SD) and had been on dialysis for 35 + 29 months.

As shown in Figure 1 the Kt/V increased significantly during the CD use compared to NCD (1.57 + .20 Vs 1.51 $\pm$ .20, Mean $\pm$ SD, CD Vs NCD respectively, $p < 0.0001$). Over the 6 months of CD use there was a decline in predialysis beta-2 microglobulin concentration (28.1 to 25.9, $p=0.0001$). Kt/V in 19 patients was one SD below the population average on NCD. The Kt/V in this group was 1.19 $\pm$ 0.12 on NCD and on CD it increased to 1.34 $\pm$ 0.16 ($p<0.0001$). The remaining 123 patients the Kt/V values were 1.55 and 1.60 on NCD and CD respectively ($p<0.0001$).

The Kt/V remained unchanged during the 6 months on NCD. The switch to CD was associated with increase in Kt/V, apparent in the first 3 month of CD. The increase in the dose was larger in those patients who had lower Kt/V before the switch.

This study suggests that the anticoagulation effect of citrate keeps the dialyzer fibers and pores open and is responsible for the increased removal of urea and beta-2 microglobulin

CITRATE DIALYSATE IN ADVANCED LIVER FAILURE

Annie Tu, MS, ARNP, CNN and Suhail Ahmad, MD University of Washington, Seattle, Washington, USA

BACKGROUND:

Anticoagulation for continuous dialysis therapies is particularly challenging in patients with increased risk of bleeding. Systemic anticoagulation is unsafe, regional citrate increases the risk of citrate accumulation and its toxicity along with hypo-calcemia, alkalosis and hypernatremia.
Citrate containing dialysate (CD) has been safely and effectively used for heparin free intermittent hemodialysis and CRRT. Since the liver is a major site of citrate metabolism, the safety of CD in liver failure patients needed to be evaluated.

PATIENTS & METHODS:

During 2005, Twenty-three hemodynamically unstable ICU patients at the University of Washington Medical Center had advanced liver failure and also had a risk of bleeding thus requiring heparin free CRRT (Slow Low Efficiency Dialysis or SLED).
These patients underwent 77 heparin free SLED treatments using CD (Citrasate®, Advanced Renal Technologies, Bellevue, WA).

UNDERLYING CONDITIONS:

Most patients in addition to Advanced Liver Failure and/or liver transplantation had additional underlying conditions such as sepsis, hypotension, or other than liver transplantation, such as stem cell transplant : in addition to the co-morbidities of Multiple Organ Failures, HIT and Sepsis.

SLED TREATMENT HIGHLIGHTS:

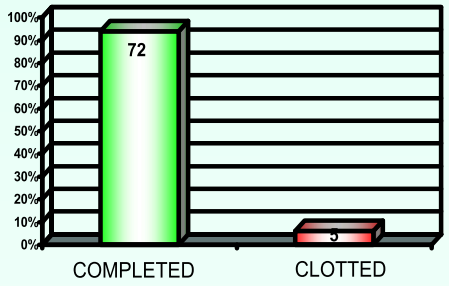
Blood Flow Rate: 201 ± 70 ml/min.
Dialysate Flow Rate: 269 ±139 ml/min.
Dialyzers used: Polyflux 6L, 8L & 10L and F– 5.
Duration: 2 - 24 hours; average 9.5 ± 4.4 hours

COMPLETED TREATMENTS is defined as completion of treatment duration as ordered or ≥ 6 hours.

CLOTTED TREATMENTS is defined as treatment stopped due to clots before the completion of ordered duration.

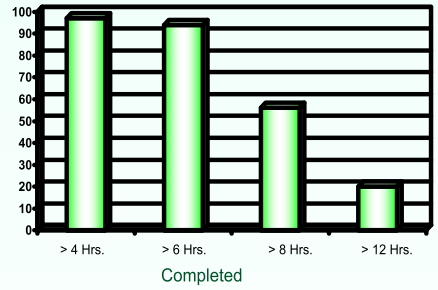
Clot Free SLED With No Heparin

TREATMENTS, % for SLED as ordered or duration of ≥ 6 hours

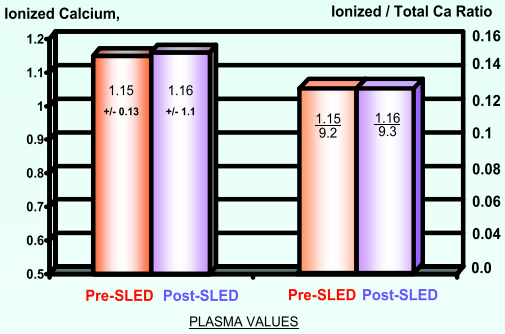


Clot Free Treatments

Treatment %



Ionized Ca & Ionized to Total Ca Ratio



Blood Concentrations

	iCa	Mg	HCO3	Anion Gap
PRE-SLED	1.14	2.0	22.5	14.8
Post-SLED	1.15	1.8	26.0	12.6
p	NS	0.001	0.008	0.007

Normal Range: 1.18 – 1.38 1.3 – 2.1 22 - 29 10 - 12

SUMMARY & CONCLUSIONS:

- During 2005 all UWMC patients requiring CRRT received SLED dialysis treatments.
- Patients with a contraindication to heparin used CD for heparin free SLED treatments.
- Twenty three patients had significantly compro-mised liver function and, even in these acutely ill patients, the CD was well tolerated without any adverse events.
- Ninety-four percent of SLED treatments were successfully completed (>6 hrs.) with CD.
- The CD for long treatments was well tolerated with no adverse events noted.
- Even with non-functioning livers the use of CD was not associated with accumulation of citrate as judged by both the ionized to total calcium ratio. as well as the decrease in the anion gap.
- No hypocalcemia or hypernatremia was noted.
- A significant decline in magnesium and increase in bicarbonate were seen but both values remained in the normal ranges.
- Long slow SLED dialysis using CD is a viable alternative for heparin free treatment of acutely ill patients, even those with liver failure.
- Extended SLED treatments of as long as 24 hours showed no evidence of citrate accumulation or hypocalcemia despite hepatic failure.

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Keywords: haemodialysis	:	Technique, liver calcium, haemodialysis: outcome.
Title	:	Citrate Dialysate in Advanced Liver Failure

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INTRODUCTION AND AIMS: Citrate dialysate (CD) has been safely used for both acute and chronic dialysis. It has also been reported to be safe for use in both traditional intermittent and Slow Low Efficiency Diffusion Dialysis (SLEDD) in acutely ill patients. However, since the liver is a major site of citrate metabolism the safety of CD in liver failure patients needs to be evaluated. At University of Washington CD is routinely used for heparin free dialysis. The aim of the this study was to assess the safety and efficacy of CD used for SLEDD in the presence of severe liver failure.

METHODS: CD was used 23 patients (average age 53.6 $\pm$ 13.6 years, 14 male and 9 females) with advanced liver failure requiring heparin free SLEDD. The average pre-Sledd INR and total bilirubin levels were 2.8 $\pm$ 1.2 and 26.3 $\pm$ 17.2 mg/dl, respectively. The patients underwent a total of 77 SLEDD treatments; the average blood and dialysate flows were 201 $\pm$ 70 and 269 $\pm$+ 139 ml/min. (mean $\pm$ SD), respectively. The average duration of SLEDD was 9.5 $\pm$ 4.4 hours and ranged between 2 and 24 hours. Vascular access was through central venous catheters. Anion gap (increases with citrate accumulation) as well as the ratio of ionized calcium (iCa) to total calcium (tCa) were both used to assess the accumulation of citrate in blood; the latter has been reported to be a sensitive measure for citrate accumulation, the ratio declining as citrate increases.

RESULTS: Heparin free SLEDD was well tolerated by all patients and no complications related to CD were observed. Clot free treatments were completed for >4, >6, >8 and >12 hours for 98%, 94%, 64% and 25% of the treatments, respectively. Pre-SLEDD iCa and tCa and iCa to tCa ratios were 1.15 + 0.13, 9.2 + 1.2 (mg/dl), and 0.12 $\pm$ 0.01, respectively and remained unchanged. Post-SLEDD values were 1.16 $\pm$ 1.1, 9.3 $\pm$ 1.1, and 0.12 $\pm$ 0.007, respectively (mean + SD, p=ns). Similarly the anion gap decreased from pre-SLEDD to post-SLEDD, 14.8 to 12.6, respectively (p=0.007).

CONCLUSIONS: Long slow dialysis using CD was successfully completed in 94% of the treatments for at least 6 hours without clots despite using no heparin. CD used for extended SLEDD treatments of as long as 24 hours duration was safe without any evidence of citrate accumulation or development of hypocalcemia in hepatic failure. Thus CD in SLEDD is safe and effective in presence of severe liver dysfunction.

ALTERNATIVES TO HEPARIN ANTICOAGULATION DURING SLOW EXTENDED DAILY DIALYSIS IN THE ICU

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BACKGROUND

- Slow Extended Daily Dialysis (SLEDD) is a well tolerated method of Renal Replacement Therapy in ICU patients
- Concern exists about the amount of heparin that is used to maintain the dialysis circuit in most critically ill patients. This is particularly true when a patient has antibodies to heparin.
- Alternative methods utilized to perform dialysis in these situations include, frequent saline flushes, citrate based dialysate (Citrasate®), and regional citrate anticoagulation
- *In this report, we review our experience with alternatives to heparin-based anticoagulation during SLEDD treatments among the critically ill admitted to UC Davis Medical Center*

METHODS

- Patients receiving SLEDD in the Intensive Care Units, 2005-2006.
- For inclusion, patients were = 18 years, on no systemic anticoagulation, and on SLEDD without heparin use.
- Alternatives to heparin included:
  1. ***Saline flushes*** with 200 cc at least every hour
  2. ***Citrasate®:*** (2.5meq/L) citrate-based dialysate
  3. ***Regional citrate: ACD-A*** (0.113 mol/L) & Calcium gluconate (40mg/ml)
- Clotting was defined as early discontinuation of dialysis, greater than 30 minutes prior to prescribed time because of circuit clotting in lines, chambers, or dialyzer.
- Data was abstracted by chart review and groups were compared using Chi-Square, T-test and ANOVA

Slow Extended Daily Dialysis Technique

SLEDD Prescription: 6-8 hours, Qb=200 ml/min, Qd=400 ml/min, with either standard acid dialysate or Citrasate® 30 brand dialysate.

ACD-A Protocol: Goals - pt's iCa^{2+} [1.11-1.31], Circuit iCa^{2+} [0.35-0.50]. ACD-A (citrate) infused proximally in the circuit, calcium gluconate in separate central venous access.

Data collected: Record any dialysis related adverse event, continuous cardiac monitoring, mean arterial pressure, ionized Ca^{2+} when indicated, and any chamber, circuit or dialyzer clotting.

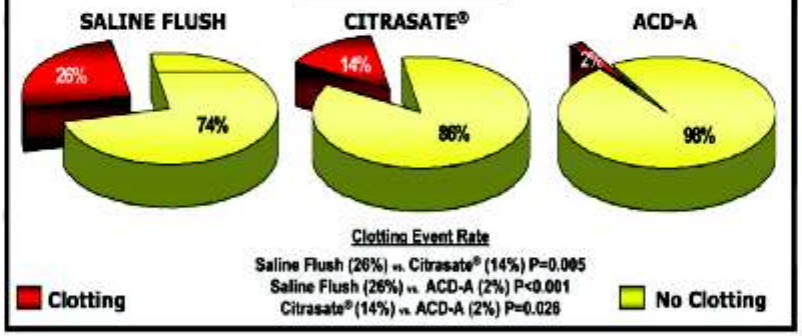
RESULTS

Baseline Characteristics

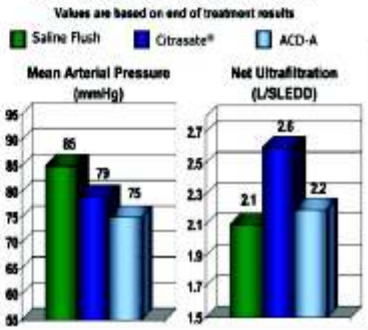
	Saline Flush (n=97 pts) 336 treatments	Citrasate® (n=19 pts) 72 treatments	ACD-A (n=16 pts) 87 treatments	P value
Age (yrs)*	56 (± 16)	50 (± 14)	57 (± 14)	<0.01
Women (%)	36	81	23	<0.01
Pressors (%)	16	28	34	<0.01
SLEDD treatment per pt†	3.5 (1-20)	3.8 (1-14)	5.4 (1-34)	0.01
Actual treatment time (hr)*	5.8 (± 1.34)	5.9 (± 1.22)	6.1 (± 1.1)	0.11 ns
Average Starting BP (mmHg)	136/60	126/52	122/58	0.35 ns

*Values expressed as means (±SD), or † expressed as means (ranges)

Clotting Episodes



Treatment Observations



Regional Citrate Management

Initial ACD-A Infusion
176 (±40) cc/hr
47% required adjustments, only 3% required 3 or more

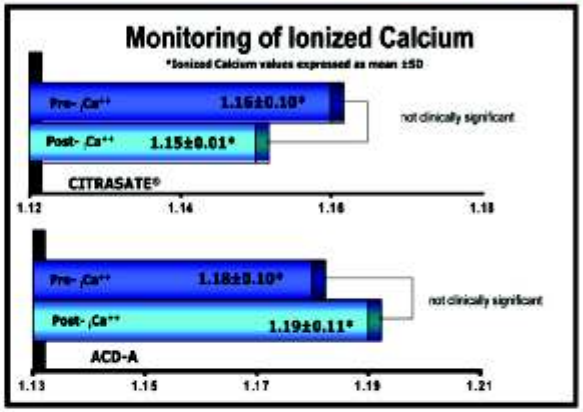
Achieved mean sys-iCa
0.42 (±0.07) mmol/L

Initial Calcium gluconate Infusion
112 (±31) cc/hr
55% required adjustments, only 16% required 3 or more

Achieved Pt-iCa, Post- SLEDD
1.19 (±0.11) mmol/L

RESULTS - CONTINUED

Monitoring of Ionized Calcium



DISCUSSION

- SLEDD was a safe, effective and well-tolerated method of renal replacement therapy in all ICU patients in this study
- Saline flushes, the most commonly employed alternative to heparin, was least effective at preventing circuit clotting
- Citrasate® was more effective in maintaining the circuit than saline flushes, and appears to safe for use in SLEDD
- We observed no clinically significant hypocalcemia events using either Citrasate® or regional citrate
- Regional citrate, using our protocol, was the superior method to keep the dialysis circuit from clotting.
- Our regional citrate protocol was safe and required limited adjustments in about half of all treatments
- It appears that regional citrate and Citrasate® can safely be used for SLEDD treatments in critically ill patients

LIMITATIONS

- Retrospective, observational, single center Review
- Small cohorts, non-randomized

Slow, Low, Efficient, Daily Dialysis (SLEDD) in the Critically Ill Patient

By Pat Isaacs, MSN, CS, CNN, NP

April 24, 2006

Slow, low, efficient, daily dialysis (SLEDD) is a form of renal replacement therapy for the critical care setting.

The slow continous removal of solute and water tends to offer greater hemodynamic stability than a conventional hemodialysis treatment. SLEDD is a newer technique of renal replacement therapy that utilizes conventional hemodialysis equipment, but with similar therapeutic goals as Continous Renal replacement Therapy (CRRT).

SLEDD techniques combine the advantages of CRRT and Intermittent Hemodialysis (IHD) by using conventional hemodialysis machines with blood flow rated (BFR) between 50-200 and dialysate flow rates (DSF) of 200-400. Dialysis time varies anywhere from 6 to 12 hours or can be done continuously. The possible varations and adaptations of blood flow, hemofiltration rate and duration of dialysis time as a function of needs of the patient are practically unlimited, which makes SLEDD applicable to the critically ill patient. Clinical trials comparing SLEDD to CRRT have failed to demonstrate a survival difference when adjusting for disease severity. The benefit is in being able to use one type of machine for any renal replacement therapy, instead of one machine for hemodialysis and a different machine for CRRT.

Several economic evaluations have shown SLEDD to be less expensive than CRRT. The main source of savings in in convention dialysis supplies, versus CRRT equipment supplies, i.e. bloodlines, kidneys and dialysate, versus industrially produced sterile substitution fluid. A hospital did a cost analysis of a CRRT treatment for an episode of acute renal failure, lasting an average of 9.3 days with a replacement of the extracorporeal circuit every 2.5 days. The cost of consumables (hemofilter, blood and fluid lines and replacement fluid) per episode (9.3 days) of acute renal failure was $1,614. The replacement fluid alone cost $880.00. The equivalent cost for treatment with conventional dialysis machines was $672.00, assuming 10 daily treatments.

In CRRT, when unable to use heparin, regional citrate (RC) used to be the anticoagulant of choice Citrate acts as an anticoagulant by binding the calcium. RC anticoagulation requires the infusion of citrate into the arterial line. RC is costly, the set-up is complex and it requires the infusion of citrate into the arterial line. RC is costly, the set-up is complex and it requires additional staff involvement. Calcium needs to be replaced via the venous line and ionized calcium need to be closely followed. With prolonged RC infusion, metabolic alkalosis and hypocalcaemia have been reposted.

Citrasate®, a new acid bath/concentrate, matches very well with SLEDD as the renal replacement therapy of choice for the critically ill patient. Citrasate® contains a small amount of citrate, which anti-coagulates the extracorporeal circuit. Citrasate® causes no significant decline in calcium or magnesium. The half-life of citrate is very short, which allows it to be quickly metabolized by the liver. Citrasate® has also been successfully used on liver transplant patients with no metabolization problems. Citrasate® can provide a better dialysis treatment, reduced blood loss and a reduction in acidosis.

The use of Citrasate® in SLEDD or conventional hemodialysis treatments is an excellent alternative for an anticoagulant when heparin cannot be utilized, i.e. heparin-induced thrombocytopenia (HIT) bleeding risks, trauma and impending/post surgery procedures.

In summary, SLEDD is an increasingly utilized renal replacement therapy that facilitates efficient detoxification and has a favorable cardio-vascular tolerability profile for the critically ill patient. The technically simple, conventional, hemodialysis equipment is easier to operate, supplies are less expensive and one has more flexibility in planning patient patient therapies.

HEPARIN FREE SLOW LOW EFFICIENCY DIALYSIS (SLED) USING CITRATE DIALYSATE (CD) IS SAFE AND EFFECTIVE

Annie Tu, MS, ARNP, CNN and Suhail Ahmad, MD University of Washington, Seattle, Washington, USA

BACKGROUND:

Anticoagulation for continuous therapies (CRRT) is particularly challenging in patients with increased risk of bleeding.
Systemic anticoagulation is unsafe, regional citrate increases the risk of citrate accumulation and its toxicity, hypocalcemia, alkalosis & hypernatremia.
Citrate containing dialysate (CD) has been safely and effectively used for heparin free intermittent hemodialysis, however its use in CRRT has not been as well documented.

PATIENTS & METHODS:

During 2005, Forty-seven hemodynamically unstable ICU patients at the University of Washington Medical Center needed CRRT but the use of heparin was unsafe:

- HIT - 6 patients
- Active bleeding - 41 patients

These patients underwent 117 heparin free SLED treatments using CD (Citrasate®, Advanced Renal Technologies, Bellevue, WA).

UNDERLYING CONDITIONS

Advanced Liver Failure / liver transplant: 25
Stem Cell Transplant: 10
Solid organ transplants: 6
Others: 6
COMORBIDITIES: Multi-organ failures: 25
Sepsis:29

SLED

Blood Flow Rate: 198 ± 71 ml/min.
Dialysate Flow Rate: 287 ±85 ml/min.
Dialyzers: Polyflux 6L, 8L & 10L - 85%
F– 5 dialyzers - 15%
Duration: 6 - 24 hours; average 9.6 ± 4.3 hours

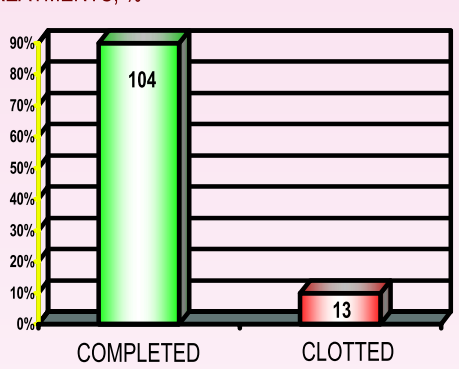
COMPLETED TREATMENTS:

Completion of treatment duration as ordered (≥ 6 hours) or clot free for ≥ 12 hour duration.

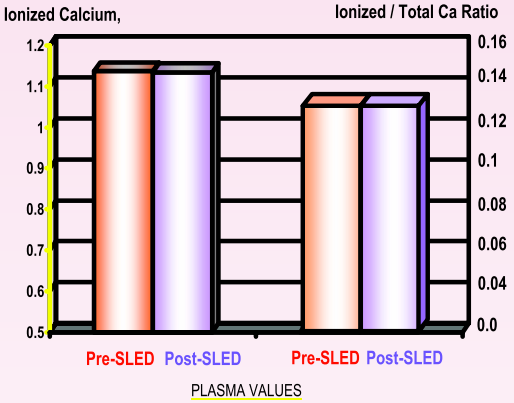
CLOTTED TREATMENTS:

Treatment stopped due to clots either before the completion of ordered duration or before 12 hours.

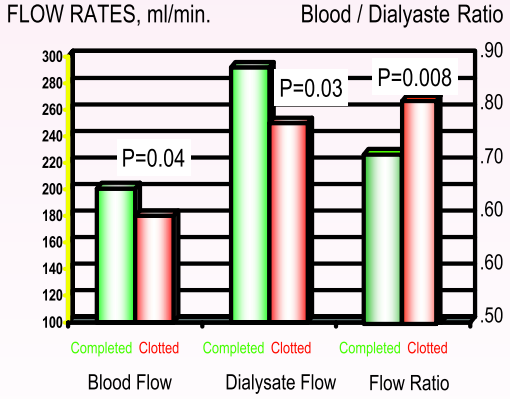
Success of Heparin Free SLED



Ionized Ca & Ionized to Total Ca Ratio



Blood & Dialysate Flows



Blood Concentrations

Draw Time	Na	Mg	HCO3	Anion Gap
PRE-SLED	135 (4.7)	2.0 (0.3)	22.9 (5.8)	13.9 (3.2)
Post-SLED	134 (2.9)	1.8 (0.3)	26.1 (4.4)	11.9 (4.5)
p	NS	<0.0001	<0.0001	NS

SUMMARY & CONCLUSIONS:

- All patients during 2005 requiring CRRT at the UWMC received SLED.
- Patients with contraindication to heparin used CD for heparin free SLED treatments.
- Ninety percent of SLED treatments were successfully completed.
- The dialysate flow to blood flow ratio was found to be lower for unsuccessful treatments compared to the successful treatments. It is possible that the citrate delivery rate is one variable affecting the clotting of dialyzers.
- The CD for long treatments was well tolerated with no adverse events noted.
- Even prolonged use of CD was not associated with accumulation of citrate as judged by the ionized to total calcium ratio. No hypocalcemia, hypernatremia or increase in anion gap was noted. A significant decline in magnesium and an increase in bicarbonate were seen, and all values remained in normal ranges.
- Many patients had significantly compromised liver function and, even in these acutely ill patients, the CD was well tolerated without any adverse events.
- CD is a viable alternative to heparin in acutely ill patients requiring SLED.

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Heparin Free Acute Dialysis Using Citrate Dialysate

Annie Tu MS, ARNP, CNN, Suhail Ahmad MD. Scribner Kidney Center, Division of Nephrology, University of Washington, Seattle, WA, USA

Background:

Heparin Antibody

A hospital patient, with an antibody to heparin, received acute dialysis using regional citrate anticoagulation. Outpatient dialysis with regional citrate was unavailable. A newly approved citrate dialysate (DRYalysate, Advanced Renal Technologies, Kirkland, WA) was successfully used for heparin free dialysis. Subsequently, eleven acutely ill patients with bleeding risk, who generally clotted when using regular dialysate without heparin, were switched to citrate dialysate. Data is presented here comparing the treatment results.

Anticoagulation In Acute Hemodialysis

Acute dialysis patients with
active bleeding,
a high risk of bleeding, or
with a heparin antibody
present a major treatment challenge because heparin free dialysis is frequently complicated by clotting.

The most prevalent alternative methods in clinical practice when heparin is contraindicated include;

1) Regional citrate anticoagulation is effective and well tolerated. It is expensive and complex, requiring close monitoring by the dialysis staff. This method is not compared here.
2) Periodic rinsing of the extra-corporeal system with saline has limited efficacy, generally increases the patients fluid load and extends the time required for dialysis.

Since DRYalysate contains citric acid, an anticoagulant, we wanted to assess its effectiveness in conducting heparin free dialysis.

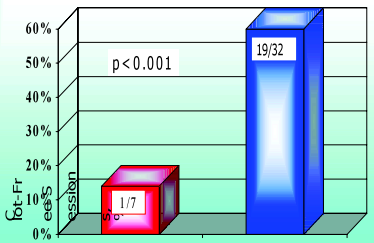
Subjects & Methods:

N = 11, Acutely ill ICU patients:

- Heparin Antibody 3
- Risk of /Active Bleeding 8

Regular Dialysate, N = 7
Citrate Dialysate, N = 32

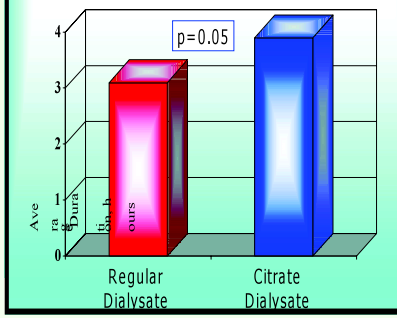
Clot-Free Treatments



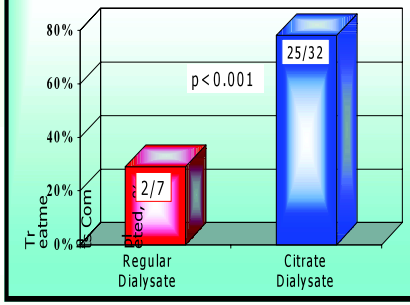
Composition of Two Dialysates
(Differences Highlighted)

Chemicals	Regular	DRYalysate
Na (mEq/l)	137	137
K	0-4	0-4
Ca	2.5/3.0	2.5/3.0
Mg	0.75	1.0
Cl	~105	~105
Dextrose	200	200
Citrate	0	2.4
Acetate	4	0.3
HCO3	37	37

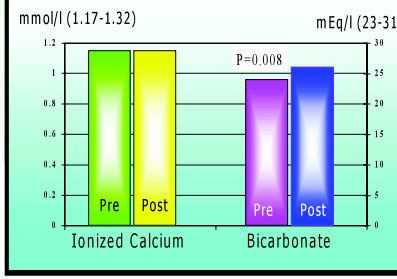
Duration of Treatments



Completed Treatments



Pre- & Post-dialysis Serum Concentrations When Using Citrate Dialysate



Summary:

Most heparin free dialyses with regular dialysate could not be completed.

In the same patients, dialyses with citrate dialysate were significantly more successful (p=0.001).

Citrate dialysate was associated with less clotting.

Dialyses with citrate dialysate were of longer duration than with regular dialysate.

No complications were noted with citrate dialysate, even in patients with poor liver function (transplantation).

There was no decline in serum calcium.

Conclusions:

Citrate dialysate was significantly better than regular dialysate for heparin free hemodialysis in acute patients.

Citrate dialysate was well tolerated and no side effects were noted.

The presence of citrate in dialysate may help prevent the clotting of dialyzer fibers.

Citrate dialysate appears to be a safe and effective alternative when heparin cannot be used in high-risk acute patients.

Presented at the American Society of Nephrology meeting in Toronto, Ontario October 2000

INCREASED DIALYZER EFFICIENCY USING A DIALYSATE CONTAINING CITRIC ACID IN PLACE OF ACETIC ACID

Suhail Ahmad, Robin Callan, James J. Cole, Christopher R. Blagg
University of Washington, Seattle and Advanced Renal Technologies, Kirkland, Washington

Hemodialysate

Dialysate: Last Major Modification In 1970s – Bicarbonate Dialysate

Bicarbonate Dialysate: Two Concentrates
- Acid Concentrate – All Electrolytes
- Bicarbonate Concentrate – Sodium Bicarbonate

Acid Concentrate Contains Acidifying Agent To Control Dialysate pH

12-Week Study

RESULTS

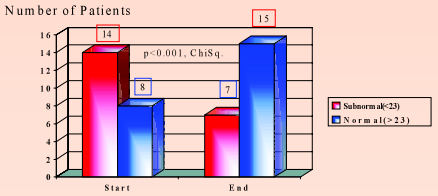
DRYalysate Treatment Well Tolerated, No Unexpected Symptoms Observed

No Bleeding Problems Observed, ACT In 4 Patients Checked & Unchanged From Usual

Staff Noted Increase In Number of Reuses

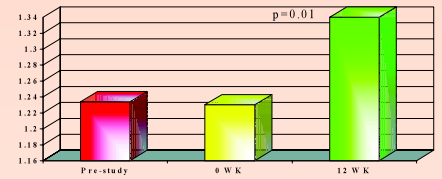
Several Positive Effects Noted

Predialysis Serum Bicarbonate



Delivered Kt/V

(Daugirdas Formula)



	Pre-study	0 WK	12 WK	
Qb (ml/min)	370 ± 49	368 + _ 48	375 ± 42	NS
Time (hrs)	3.9 ± 0.41	3.9 + _ 0.39	3.9 + _ 0.48	NS

No Changes In Dialyzers

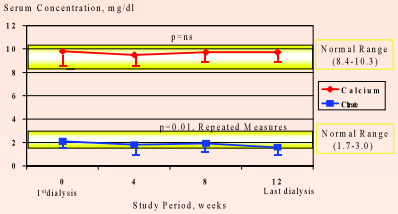
Acid Concentrate

Current Acid Concentrate Contains **Acetic Acid** to Lower pH of Final Dialysate

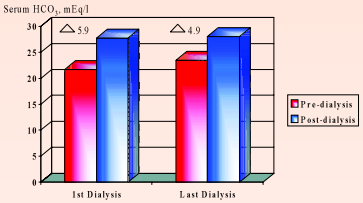
New Acid Concentrate (DRYalysate™) Contains **Citric Acid** As Acidifying Agent

Citric Acid Allows Acid Concentrate To Be Dry Powder

Predilaysis Serum Calcium & Citrate Concentrations, mg/dl

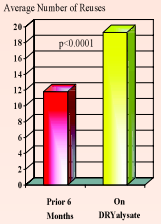


Pre- And Post-dialysis Serum Bicarbonate During The Study

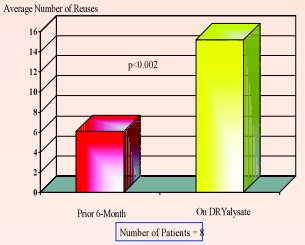


Dialyzer Reuse Comparison

Twenty patients exclusively used DRYalysate >3 months (starting with new dialyzers). Average dialyzer reuse during this period is compared to average reuse during previous 6 months on regular dialysate. (Maximum Reuse = 25)

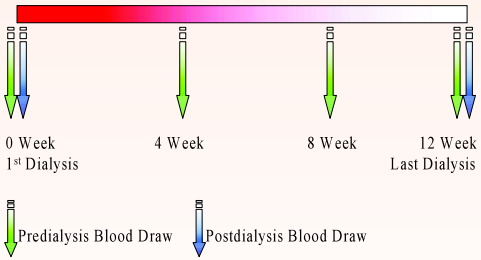


Patients With <10 Reuse Before DRYalysate

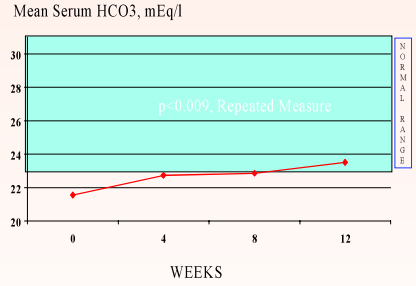


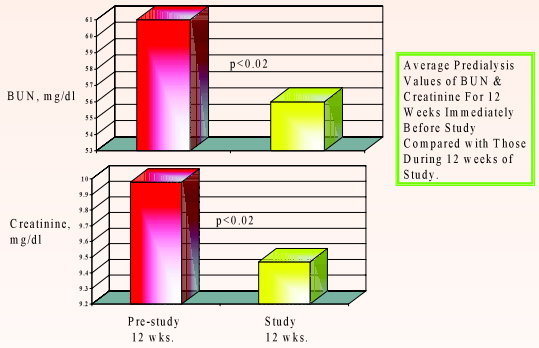
Study Design

Twenty two stable hemodialysis patients used DRYalysate exclusively for 12 weeks.



Predialysis Serum Bicarbonate





Average Predialysis Values of BUN & Creatinine For 12 Weeks Immediately Before Study Compared with Those During 12 weeks of Study.

Summary & Conclusion

With DRYalysate Use:
- No Decline in Serum Calcium was Noted
- No Increase in Predialysis Serum Citrate Concentration was Observed

DRYalysate Use Associated with Decreased Acidosis

DRYalysate Use Increased Dose of Dialysis (Higher Kt/V, Lower BUN & Creatinine)

DRYalysate Use Increased Dialyzer Reuse

Presented at the American Society of Nephrology meeting in Miami, Florida November 1999

What is the mechanism of Dry-Citrasate® inside the dialyser?

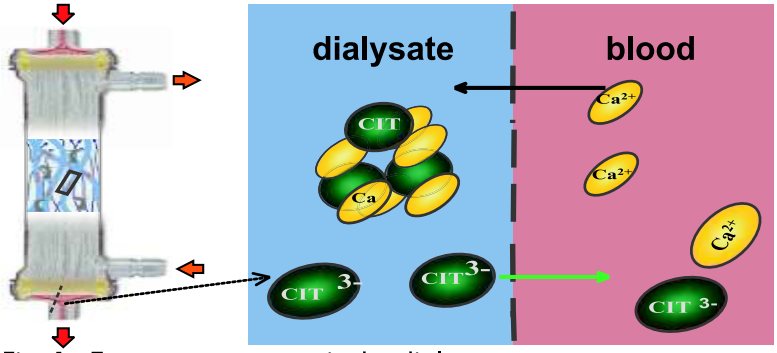


Fig. 1 : Transport processes in the dialyser

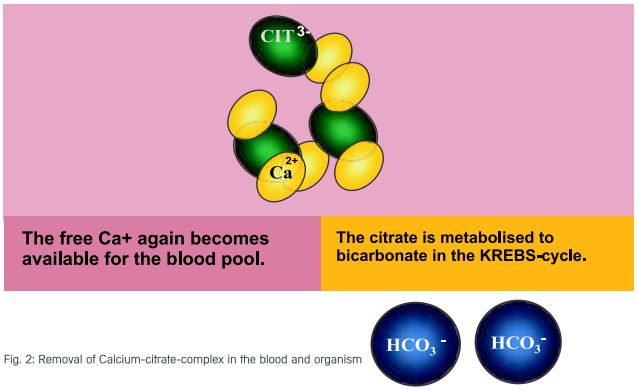


Fig. 2: Removal of Calcium-citrate-complex in the blood and organism

Step 1

At pH 1.9 of Dry-Citrasate® the calcium and citrate ions do not form a complex. The formation of Ca-citrate-compiex takes place during mixing of A-and B-component inside the dialysis machine producing the final dialysis fluid.

- As a result of the concentration gradients in the dialyser, free citrate ions diffuse into the blood and bind free calcium ions there to form a Ca-citrate complex.
- At the same time, free calcium ions diffuse from the blood to the dialysate side, because the ionised calcium has been reduced there as a result of the Ca-citrate complex formation.

Both transport processes lead to a reduction of concentration of the free calcium ions in the blood and cause therefore a local anticoagulatory effect inside the dialyser.

Step 2

The Calcium-citrate complex in the blood will be transported and again dissociated into free Ca^{2+} and citrate ions, with the result that the free calcium ions are again available for the blood pool. The citrate ions are metabolised to bicarbonate in the KREBS-cycle. As citrate can also be metabolised by muscle cells, Dry-Citrasate® can also be used for patients with liver insufficiency.

Reduction of thrombus formation in the dialyser as a result of citrate

Citrate versus heparin after 4 h of hemodialysis.

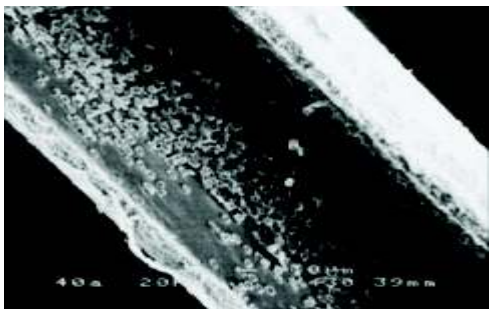


Fig. 13 Polysulfon membrane + low molecular weight heparin (14)

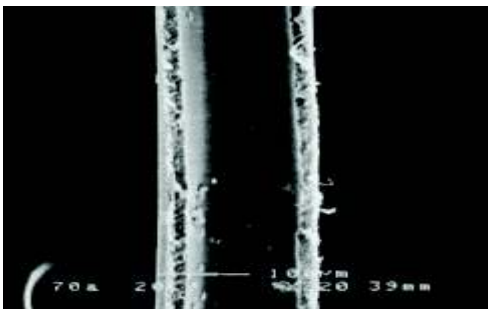


Fig. 14 Polysulfon membrane + citrate (14)

Fig. 15 Dialyser after rinseback, following 4 h of hemodialysis with dialysate containing acetate (15)

Fig. 16 Dialyser after rinseback, following 4 h of hemodialysis with Citrasate® (15)

The influence of Dry-Citrasate® on biocompatibiiity

Myeloperoxidase (MPO) is considered as a marker for oxidative stress and as parameter of inflammation in patients (6) suffering from kidney disease or to be treated with extracorporea! blood purification (17).

MPO induces vascular complications via various mechanisms:

- Inhibition of NO-dependent vasorelaxation
- Production of endogenous NO-inhibitors
- Oxidation of LDL with consecutive increased reception in local macrophages
- Production of reactive species.

The plasma levels of MPO are associated with the extent of atherosclerotic complications and mortality of patients with acute renal failure (17).

Heparin was shown to stimulate the release of MPO from atherosclerotic vessels and to stimulate the activation of leukocytes (18), independently from the stimulation by the membrane material (19).

MPO and platelet factor 4 will be released immediately after starting dialysis treatment (20).

Using citrate for the regional anticoagulation, however, the release of MPO could be inhibited totally (20). By means of the regional citrate anticoagulation for critical ill acute patients the significant decrease of mortality could shown (21) using CWH as treatment mode. A better recovery of kidney function was supposed as reason,

Ahrenholz and Winkler (10) examined the MPO plasma levels and the leukocyte numbers pre-and posf-dialytic and also 15 min alter the start of dialysis in accordance with the following study protocol;

Patients and Method		
8 patients were treated with High- flux dialysis No change of their treatment parameters (duration of session, blood and dialysate flow, kind of cllalyser)		
Weeks 1 + 2	:	Treatment with the previous dialysate and the previous amount
Weeks 3 -6	:	Change to Citrate without any change of the other conditions
Weeks 7 – 10	:	Dialysis with Dry-Citrasate® and reduction of the amount of heparin in the bolus by 50%
Weeks 11-14	:	Dialysis with Dry-Citrasate® and reduction of the amount of heparin in the bolus by 50% and in the continuous dosage by 50%, resulting in a total reduction of 50%

In fig. 18 it is shown that no significant changes of leucocyte numbers could be observed as function of used dialysate or used amount of heparin.

After 15 min dialysis time, however, a significant drop of MPO-plasma levels could be observed between acetate-containing dialysate and Dry-Citrasate® dialysate with reduced amount of heparin (Fig. 19),

These results can be considered as the first proof that dialysis with Dry-Citrasate® seems to be more biocompatibie for chronic diaiysis patients, because the reduction of acetate and heparin concentration in dialysate diminishes obviously the inflammatoric and oxidative potential in the blood. The question whether the mortality of chronic dialysis patients can be reduced by Dry-Citrasate® dialysis remains reserved for long-term examinations with larger numbers of patients.

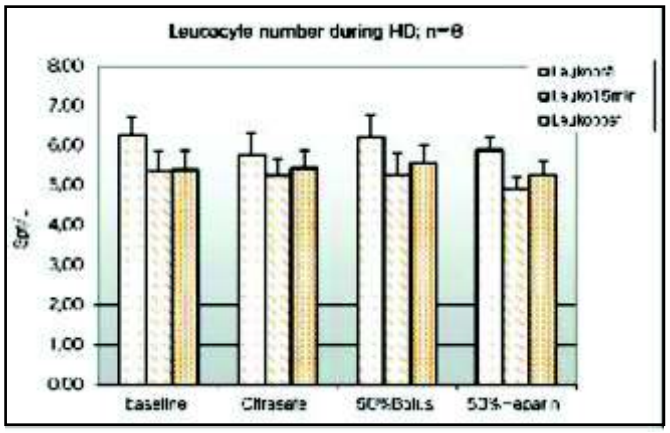


Fig. 18 Leucocyte number during dialysis with acetate-containing dialysate or Dry-Citrasate® dialysate with stepwise heparin reduction.

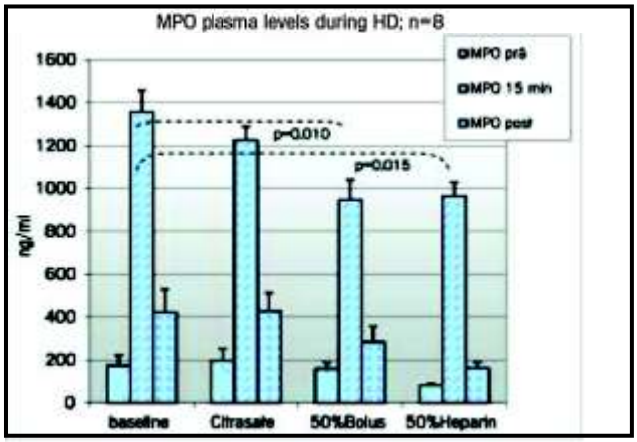


Fig. 19 Change of MPO-plasma levels during dialysis with acetate-containing dialysate or Dry-Citrasate® dialysate with stepwise heparin recution

Which types of dialysis modes can be applied with Dry-Citrasate®?

- The results presented in this brochure relate exclusively to High-flux dialysis with Dry-Citrasate® for which most results are available.
- First results for the application of Dry-Citrasate® in online hemodiafiltration are available from Polakovic et al. (22) for 2 patients in pre-dilution and 1 patient in post-dilution mode after 2 weeks of treatment.
- However, no statistically relevant statements can be made yet on the basis of this low number of patients and treatments.
- Kron et al. (23) successfully carried out a heparin-free hemodiafiltration in pre-dilution mode with calcium-free Dry-Citrasate® as dialysate and substitution fluid in HIT II patients and patients with bleeding risk. The 32 treatments were free of clotting problems. However, calcium chloride solution was infused behind the dialyser in order to maintain a constant level of Ionised calcium in the blood.
- The successful use of Dry-Citrasate® for heparin-free "slow efficiency" dialysis (SLED) for the acute treatment of critically ill patients with multiorgan failure or liver failure has been described by Ahmad and Tu (24)

Dry-Citrasta® is applicable for most of all conventional dialysis machines.

Machines and Methods

Polakovic et al, (25) carried out double measurements with A concentrate with acetic acid (AA) or Polakovic et al, (25) carried out double measurements with A concentrate with acetic acid (AA) or citric acid (CA) with ? types of HD machines from 4 manufacturers (Dialog - BBraun, 4008/5008 - Fresenlus, AK 100/200/200S - Sambro, DB805 -Nikkiso), Ail machines were preset for conventional acetate, containing A-concentrates.

Concentrations of NaS K+-, Ca2* in final diafysate were measured by ion selective electrodes. The bicarbonate concentration was calculated from measured pH- and pC02 – values.

The measurements were performed for 4 different combinations of sodium and bicarbonate set values covering the whole range of practically used settings (132/28,132/39, 148/28 and 148/39 mmol/i)

Results of the in vitro measurements (25)

1. Performance of all tested dialysis machine types was problem-free without any alarms.
2. Control of Na+ und HC03~ - concentration worked over the whole concentration range for all machines tested.
3. The concentration of ionized calcium was found to be 0.35 - 0.55 mmol/l lower in the citrate-containing dialysate.
4. Bicarbonate concentration exhibited tendency towards slightly higher values (0.5 – 2.5 mmel/0) when used Dry-Citrasate® concentrate as compared to dialysate to conventional acidified type, depending on the type of mixing system (volumetric or conductometric) of the HD machine.

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Frequently Asked Questions

Q: Is citrate dialysate the same as regional citrate anticoagulation?
A: No. Performing citrate dialysis is no different operationally than doing regular dialysis. There is no regional infusion of citric acid employed. "It's all in the dialysate."

Q: Is it necessary to do continuous calcium infusions into the venous blood line, as is done for regional citrate anticoagulation, in order to avoid problems associated with hypocalcemia?
A: No. Calcium binding by dialysate citrate is so small that no significant alteration in calcium occurs during dialysis (ref. 3). The citrate content of the dialysate is only 2.4 mEq/L.

Q: How does citrate dialysate provide the noted patient benefits?
A: As you know, citric acid is an anticoagulant. Its presence in the dialysate is 2.4 mEq/L concentration provides some anticoagulation effect in the dialyzer and venous blood line that is quickly neutralized upon reentry into the systemic circulation.

Q: Is it necessary to check clotting times when citrate dialysate is used?
A: No.

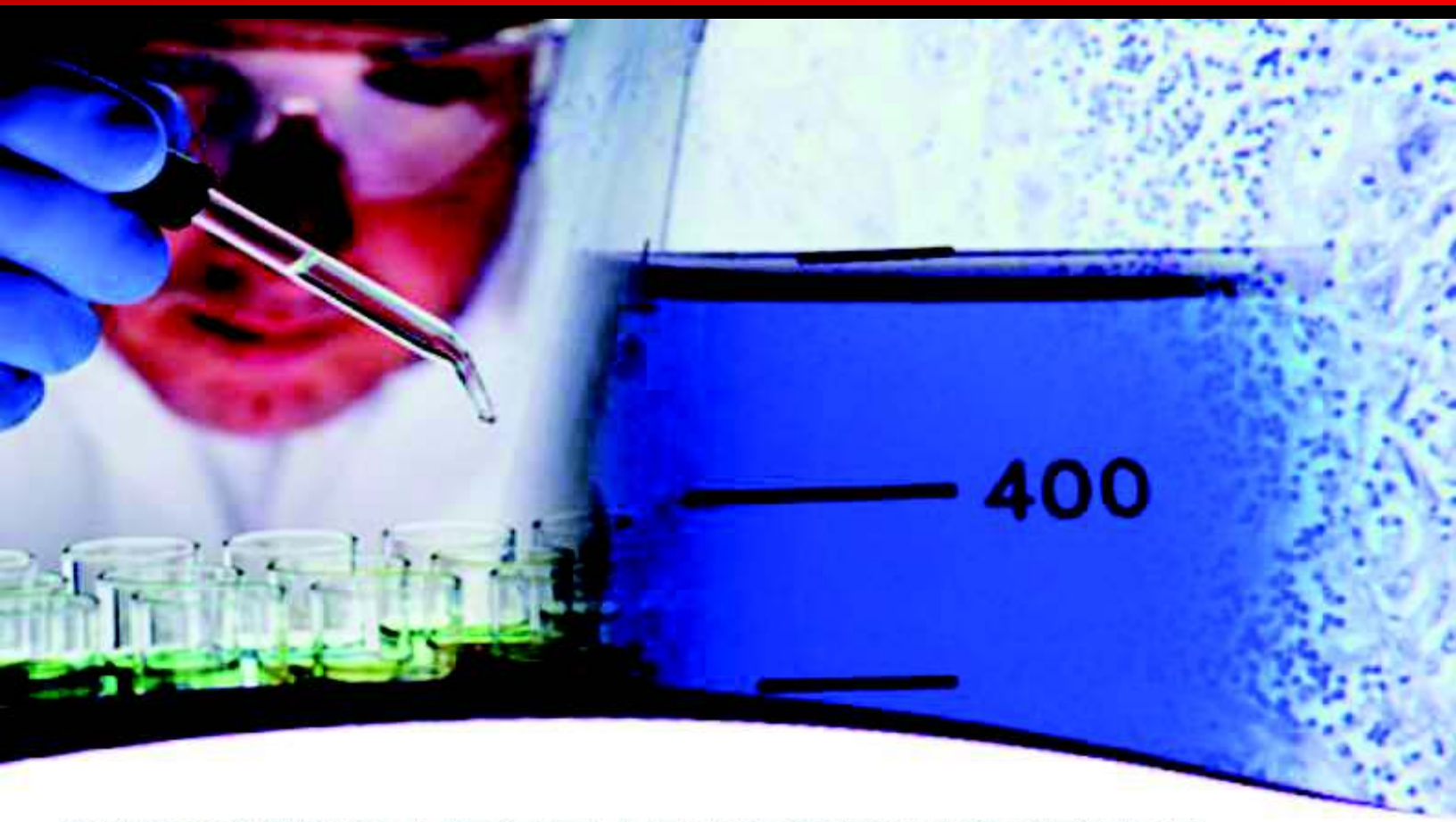
Q: Is there reason to be concerned about bleeding risk, hypocalcemia, or hypomagnesemia when treating patients with citrate dialysate?
A: No. Because the concentration of citrate in the dialysate is well below the level needed to produce anticoagulation of the patient's blood, there is no risk of bleeding or low blood mineral levels from citrate use.

Q: Are Citrasate® and Dry-Citrasate® cleared for clinical use by the FDA?
A: Yes.

Q: How do I adapt my present dialysis system to allow the use of Citrasate® or Dry-Citrasate® ?
A: You don't need to adapt your system to the new dialysate formulation. No changes are necessary. Citrasate® concentrate is available in all the standard concentrations and formulations. You simply pour it into your standard A concentrate container and attach it to your dialysis system as you always do. If you prefer to mix A concentrate from powder, Dry-Citrasate® is available for this purpose, and it can be mixed in your facility to make concentrate.

Q: What steps are necessary before citrate dialysis can be started?
A: Both Citrasate® and Dry-Citrasate® may be used in existing dialysis systems without altering them. Also, there is no additional patient or system monitoring needed beyond that normally employed in treatment with standard dialysate formulations. Consequently, no staff training is necessary for the conversion to citrate dialysate.

Q: Can citrate dialysate be "spiked" with potassium or calcium?
A: Yes, it can be spiked just as you do with traditional dialysate concentrates



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Dry-Citrasate® (Citrate Dialysate) is available in india with..

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