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

Robert J Kossmann, MD1, Robin Callan, LLM2 and Suhail Ahmad, MD3; 1Nephrology, Nephrophiles, Santa Fe, New Mexico, United States; 3Nephrology/Medicine, University of Washington, Seattle, WA, United States.

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 ± 2179 (mean ± SD) units to 3165 ±1352 units, a 33.5% reduction for a 2 month period (1st reduction). After 2 months the heparin dose was further reduced to 2158 ± 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.

ASN's 39th Annual Renal Week Meeting

Presenting Author: Robert J Kossmann
Title: Increased Dialysis Dose and Decreased Concentration of Beta-2 Microglobulin with Citrate Dialysate

Robert J Kossmann, MD1, Robin Callan, LLM2 and Suhail Ahmad, MD3.
1Nephrology, Nephrophiles, Santa Fe, New Mexico, United States; And Nephrology/Medicine, University of Washington, Seattle, WA, United States.

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 (Citasate ) 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 + .20, Mean + 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 + 0.12 on NCD and on CD it increased to 1.34 + 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 as 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.

Heparin free citrate dialysis in end stage liver disease (ESLD) patients is well tolerated.

S. Ahmad1, A. Tu21Nephrology, Medicine, 2Nursing, University of Washington, Seattle, United States

Background: Heparin cannot be used for hemodialysis (HD) in patients at high risk of bleeding, but heparin-free dialysis is often associated with clotting, leading to early termination. Citrate- containing dialysate has been successfully used for dialysis without heparin in many acutely ill patients. CD differs from standard
dialysate only in containing 2.4 mEq/l citrate and 0.4 mEq/l acetate in the final dialysate. Since citrate is mainly metabolized in liver, the use of citrate is generally considered inadvisable in the presence of liver failure.

At our institution, acutely ill ESLD patients with renal failure require dialysis either in the intensive care unit or in the operating room during liver transplantation surgery. CD has routinely been used in these acutely ill patients in both settings.

**Objectives:** To study the safety and efficacy of CD in acutely ill patients with fulminant liver failure

**Methods:** We retrospectively analyzed the data in our five most recent patients with ESLD who used CD for their heparin-free HD. Three males and 2 females with average age of 57.8 years (range 32-68) used CD for 22 HD sessions (mean 4.4 treatments/patient), blood bilirubin 12.2 +/- 10.8 mg/dl. The length of dialysis ranged 3 to 6 hours (mean 4.12 hrs). Blood and dialysate flow ranged 200-400 (mean 288) and 300-500 (mean 468) ml/min, respectively.

**Results:** All treatments were well tolerated without any dialysis related complications including one 6hr session conducted during liver transplant surgery in the OR. No treatment was terminated due to clotting or increased bleeding. The pre- and post-dialysis blood values are given below:

Ionized Ca and magnesium declined but remained in the normal range. CD was not associated with hypernatremia or increase in anion gap. Thus there was no evidence of accumulation of citrate in these patients, probably because of the low citrate concentration coupled with citrate metabolism in the muscles. Significant increase in bicarbonate and decrease in blood urea nitrogen (BUN) was as expected with HD. In our experience CD is well tolerated in patients with advanced liver failure and bleeding risk and resolves the dilemma of anticoagulation in these patients.

**Title:** HEPARIN REDUCTION WITH CITRATE DIALYSATE

Suhail Ahmad1, Robin Callan2 and Robert Kossmann3. 1Nephrology, Medicine, University of Washington, Seattle, WA, United States; Nephrophiles, LLC, Santa Fe, New Mexico, United States.

**INTRODUCTION AND AIMS:** Systemic heparinization during hemodialysis (HD) is associated with significant clinical problems. Some patients despite receiving relatively small dose of heparin have constant oozing around the needles during the treatment and/or continue to bleed for a long time after the needles are removed. Citrate containing bicarbonate dialysate (Citrasate®, Advanced Renal Technologies, Bellevue, WA, USA) has been reported to have some anticoagulation properties. Regular bicarbonate dialysate contains acetic acid as acidifying agent (AD) whereas Citrasate contains citric acid with known anticoagulant properties.
The Aim of the study was to determine whether the use of citrate dialysate (CD) would permit a 30% reduction in heparin dose without increasing the risk of clotting of the dialyzer and dialysis set up and a decrease in the dialysis dose.

METHODS: Twenty chronic HD patients (11 females) from Fresenius Medical Care Santa Fe Dialysis Center, Santa Fe, NM, USA were identified to have excessive bleeding problems. These patients took more than 15 minutes to stop bleeding after the needles were removed and two patients also developed sub-conjunctival hemorrhage in addition to prolonged bleeding. They were switched from AD to CD and their heparin dose was reduced by an average of 30%. The AD contained either 4 mEq/l acetate (19 patients) or 8 mEq/l acetate (1 patient). CD contains 2.4 mEq/l citrate and 0.3 mEq/l acetate. The clotting assessed by the examination of the dialyzer and the set up. The dialyzer clotting was further measured by the urea reduction during the treatment and is expressed as Kt/Vurea. The data for two months on AD is compared with data for two months on CD.

RESULTS: The reduction in the heparin dose averaged 30% from 4275 + 1758 (mean + SD) during AD to 2970 + 1322 units/treatment during CD. No clotting of dialysis set up was noted on reduced heparin and CD treatments. The Kt/V for the two months on AD and usual heparin were 1.61 + .15 and 1.62 + .15, this remained unchanged during the two months on 30% less heparin on CD, 1.62 + .19 and 1.59 + .17, all p values ns. With a 30% reduction in the heparin dose bleeding episodes decreased.

CONCLUSIONS: The use of CD permitted a significant reduction in heparin without any increase in clotting during the treatment, and without any decrease in the dose of dialysis as determined by Kt/Vurea. Based on these results a larger reduction in heparin dose will be studied.

Acknowledgement: The study was supported by Fresenius Medical Care, NA

---

**Citrate vs. Acetate In Bicarbonate-Based Dialysis Fluid – What Does it Mean Clinically?**

*Prepared by Lars-Göran Nilsson*  
*Medical Strategy Director at Gambro Medical & Safety Office*

**Introduction**

One objective of dialysis is to provide buffer base to neutralize the acids that accumulate in body fluids between dialysis sessions. Today the dominating buffer in dialysis fluid is bicarbonate, which is also the most abundant physiological buffer in plasma [1]. The use of bicarbonate in hemodialysis (HD) fluid is technically challenging as carbonate, the base form of bicarbonate, easily forms precipitates with calcium and magnesium ions that also are present in dialysis fluid.
To minimize the risk of precipitate formation sodium bicarbonate is kept separate (B-concentrate) and not mixed with the divalent cations until immediately before use. In addition, the cation-containing concentrate solution (A-concentrate) is acidified to ensure that the prepared dialysis fluid gets a neutral pH that limits the presence of carbonate.

Today, acetic acid is commonly used to acidify the A-concentrate. When such an A-concentrate is mixed with water and B-concentrate in the fluid path of the dialysis machine acetic acid reacts with bicarbonate to form carbon dioxide and acetate.

Thus, bicarbonate-based dialysis fluid generally contains acetate.

In Europe, it is common to use A-concentrates that give 3–5 mmol/l of acetate in the prepared dialysis fluid, while dialysis fluid in Japan may contain 8–11 mmol/l of acetate.

Alternatives to acidify the A-concentrate have recently become available, responding to reports on acetate intolerance. Citric acid is attractive as replacement for acetic acid as it leads to dialysis fluid containing citrate. Several clinical studies have been conducted with citrate-containing dialysis fluid, showing results that indicate significant patient benefits. In addition, therapy alternatives like acetate-free biofiltration (AFB) have been developed to eliminate the need for acidifier by keeping bicarbonate separate from the dialysis fluid [2].

This paper deals primarily with potential issues of acetate in dialysis fluid and the benefits of substituting citrate for acetate.

Nephrol Dial Transplant (2010) 1 of 6
doi: 10.1093/ndt/gfq396

Original Article

Anticoagulation during haemodialysis using a citrate-enriched dialysate: a feasibility study
Yuk-Lun Cheng1, Alex W. Yu1, Kwong-Yuen Tsang1, Dilip H. Shah2, Carl M. Kjellstrand2,
Siu-Man Wong1, Wai-Yan Lau1, Lap-Man Hau1 and Todd S. Ing2
1Department of Medicine, Alice Ho Miu Ling Nethersole Hospital, Chinese University of Hong Kong, Hong Kong, China and
2Department of Medicine, Hines Veterans Affairs Hospital/Loyola University Medical Center, Hines, IL, USA
Correspondence and reprint requests to: Yuk-Lun Cheng; E-mail: chengyl11@ha.org.hk

Abstract Background. The feasibility of anticoagulating the extracorporeal circuit during haemodialysis using a simple citrate-enriched dialysate was evaluated in a prospective, randomised, cross-over study of 24 patients who were at high risk for bleeding.
Methods. A dialysate, with a citrate level of 3 mEq/L (1 mmol/L), was generated by adding citrate to the conventional liquid ‘bicarbonate concentrate’ of a regular, dual-concentrate, bicarbonate-buffered dialysate delivery system. Each of the 24 patients received two dialysis treatments. For anticoagulation of the extracorporeal circuit, one treatment used the citrate-enriched dialysate (Citrate Group), while the other treatment used conventional saline flushing (Saline Group). The order of the two treatments was randomised.

With either method, a heparinized, saline-rinsed dialyser was used, and no heparin was administered during dialysis.

Results. Ninety-two per cent (22 out of 24) and 100% of patients tolerated the procedure well in the Citrate Group and the Saline Group, respectively. Eight per cent (two out of 24) of the treatments in each group had to be abandoned because of clotting in the extracorporeal circuit. Significantly less thrombus formation in the venous air traps was detected in the Citrate Group. No patients from either group suffered from hypocalcaemic or bleeding complications, but the immediate post-dialysis and 0.5-h post-dialysis plasma levels of ionised calcium and of magnesium were slightly lower in the Citrate Group than in the Saline Group.

Conclusions. Our findings suggest that it is feasible to use the present simple citrate-enriched dialysate to dialyse patients safely and effectively. Furthermore, the approach is much simpler than a conventional, intermittent, saline-flushing method.

Keywords: anticoagulation; bicarbonate concentrate; citrate; dialysate; Haemodialysis.

BMC Nephrology
Citrate- vs. acetate-based dialysate in bicarbonate haemodialysis: consequences on haemodynamics, coagulation, acid-base status, and electrolytes
Luca Gabutti*1, Barbara Lucchini2, Claudio Marone3, Lorenzo Alberio4 and Michel Burnier5
Address: 1Division of Nephrology, Ospedale la Carità, Via Ospedale, 6600 Locarno, Switzerland, 2Department of Internal Medicine, Ospedale la Carità, Locarno, Switzerland, 3Department of Internal Medicine, Ospedale San Giovanni, Bellinzona, Switzerland, 4Department of Hematology, University Hospital of Bern, Bern, Switzerland and 5Division of Nephrology, University Hospital of Lausanne, Lausanne, Switzerland
Email: Luca Gabutti* - luca.gabutti@eoc.ch; Barbara Lucchini - lucchinib@hotmail.com; Claudio Marone - claudio.marone@eoc.ch; Lorenzo Alberio - lorenzo.alberio@insel.ch; Michel Burnier - michel.burnier@chuv.ch* Corresponding author

Abstract Background: A concentrate for bicarbonate haemodialysis acidified with citrate instead of acetate has been marketed in recent years. The small amount of
citrate used (one-fifth of the concentration adopted in regional anticoagulation) protects against intradialyser clotting while minimally affecting the calcium concentration. The aim of this study was to compare the impact of citrate- and acetate-based dialysates on systemic haemodynamics, coagulation, acid-base status, calcium balance and dialysis efficiency.

Methods: In 25 patients who underwent a total of 375 dialysis sessions, an acetate dialysate (A) was compared with a citrate dialysate with (C+) or without (C) calcium supplementation (0.25 mmol/L) in a randomised single-blind cross-over study. Systemic haemodynamics were evaluated using pulse-wave analysis.

Coagulation, acid-base status, calcium balance and dialysis efficiency were assessed using standard biochemical markers.

Results: Patients receiving the citrate dialysate had significantly lower systolic blood pressure (BP) (-4.3 mmHg, p < 0.01) and peripheral resistances (PR) (-51 dyne.sec.cm-5, p < 0.001) while stroke volume was not increased. In hypertensive patients there was a substantial reduction in BP (-7.8 mmHg, p < 0.01). With the C+ dialysate the BP gap was less pronounced but the reduction in PR was even greater (-226 dyne.sec.cm-5, p < .001). Analyses of the fluctuations in PR and of subjective tolerance suggested improved haemodynamic stability with the citrate dialysate.

Furthermore, an increase in pre-dialysis bicarbonate and a decrease in pre-dialysis BUN, postdialysis phosphate and ionised calcium were noted. Systemic coagulation activation was not influenced by citrate.

Conclusion: The positive impact on dialysis efficiency, acid-base status and haemodynamics, as well as the subjective tolerance, together indicate that citrate dialysate can significantly contribute to improving haemodialysis in selected patients.

Trial registration: ClinicalTrials.gov NCT00718289
Published: 5 March 2009
Received: 1 June 2008
Accepted: 5 March 2009
This article is available from: http://www.biomedcentral.com/1471-2369/10/7
© 2009 Gabutti et al; licensee BioMed Central Ltd.
This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
Heparin-Free Hemodialysis with Citrate-Containing Dialysate in Intensive Care Patients

Dr. Ahmad is Associate Professor, Department of Medicine, Division of Nephrology, at the University of Washington, Seattle, Washington. Dr. Ahmad is also Medical Director of the Scribner Kidney Center, Seattle.

In 11 acutely ill hemodialysis patients, heparin could not be used for the dialysis treatment.

Over the course of 43 treatments, 3 different methods of heparin-free dialysis were performed and compared.

Dialysis without anticoagulation using “regular” (acetic acid-containing) bicarbonate dialysate was associated with clotting in 6 of 7 treatments (86%), and 5 treatments (71%) had to be discontinued due to clots. A new dialysate (DRYalysate™) containing citric acid as an acidifying agent has recently become available commercially. When the citric acid (citrate) bicarbonate dialysate was used, 13 of 32 treatments (40%) were associated with clots, and only 7 (22%) had to be stopped due to clots (p<0.0001, regular vs. citrate dialysate). The use of regional citrate anticoagulation was successful in 3 of 4 treatments (75%), and treatments were able to be continued for a longer time. The use of citrate dialysate was associated with significantly less clotting than the regular dialysate, and can be a safe alternative to heparin in patients with high bleeding risk or who are intolerant to heparin.

Myeloperoxidase up-regulation during haemodialysis: is heparin the missing link?

Jacek Borawski, Beata Naumnik, Alicja Rydzewska-Rosołowska and Michał Myśliwiec + Author Affiliations Department of Nephrology and Transplantology with Dialysis Unit Medical University Białystok, Poland Email: jborawski@post.pl

Sir,

We read with interest the recent series of articles showing a striking increase in blood myeloperoxidase (MPO) levels during haemodialysis (HD) sessions [1–3]. In this setting, the enzyme is traditionally regarded as a marker of neutrophil degranulation and thus, of dialyser membrane biocompatibility, as well as generation of oxidative stress [1–5]. Some results of the above studies and their interpretations seem, however, not to be corroborated enough and indicate the existence of other unrecognized factors responsible for MPO up-regulation during HD [1,2]. For example, in the study by Wu et al. [1] the increase in plasma MPO was as much as 3-fold vs baseline with a biocompatible polysulfone membrane, occurring as early as 15 min from the start of HD and, surprisingly, was not accompanied by a fall in circulating neutrophil counts. In the study by Gritters et al. [2] serum MPO levels almost doubled after the first passage of blood through the
high-flux polysulfone dialyser. Notably, the effect was only observed when either unfractionated heparin or low-molecular-weight heparin dalteparin was used for temporary HD anticoagulation, and then disappeared with regional trisodium citrate anticoagulation [2]. The authors ascribed the latter absence of MPO release to the calcium-free environment created within the dialyser, and suggested that it could be a valuable approach to avoid overdialytic neutrophil degranulation. They seem, however, to have overlooked the previous report indicating no MPO up-regulation during HD treatments anticoagulated with nafamostate mesylate instead of heparin [4]. In the most recent trial, Krieter et al. [3] showed a remarkable, 6-fold rise in blood MPO levels taking place 5 min after the start of HD. They also revealed a small (~9%) but significant difference between MPO levels in blood leaving vs entering the filter, which confirms the actual but negligible intra-dialyser neutrophil degranulation. On the basis of the early high MPO levels in the pre-dialyser blood, the authors attentively concluded that the contact of blood with the filter membrane could not be the only cause of MPO generation [3]. Unfortunately, both Wu et al. [1,5] and Krieter et al. [3] failed to specify the anticoagulation strategy used in their HD patients, ascribed the very early MPO upregulation to either ‘the dialysis per se and dialysate contaminants’ [5] or ‘shear forces through the blood pump’ [3] and prematurely ended with the statement that MPO is a useful and reliable marker of HD-induced oxidative stress.

In recent years, compelling evidence has accumulated to show that MPO is not only a neutrophil secretagogue but also an abundant constituent of vascular wall, from which it can be easily and extensively mobilized into circulating blood by exogenous heparin (for review, refer [6]). This mechanism very likely underlies the marked MPO upregulation encountered during heparin-anticoagulated HD procedures [6]. In this clinical setting, heparin should be viewed as an agent protecting the atherosclerotic arteries from oxidative stress (because of endothelial MPO depletion) rather than being harmful to them, as prematurely judged on the basis of marked plasma MPO elevations. Unfortunately, this relatively novel link between MPO and heparin [6] seems to have been either overlooked [1,3] or understudied [2] in the recent trials in HD patients, while it could clarify their results, as well as improve or call into question their meanings.

Conflict of interest statement. None declared.

© The Author [2006]. Published by Oxford University Press on behalf of ERA-EDTA. All rights reserved. For Permissions, please email: journals.permissions@oxfordjournals.org

References


Abstract/FREE Full Text

Abstract/FREE Full Text

Krieter DH, Lemke HD, Wanner C. Myeloperoxidase serves as a marker of oxidative stress during single haemodialysis session using two different biocompatible membranes. Nephrol Dial Transplant 2006; 21: 546

FREE Full Text


MedlineWeb of Science


FREE Full Text


Citrate dialysate (CD) is well tolerated in patients with advanced liver failure and bleeding risk, and CD resolves the dilemma of anticoagulation in these patients. Ahmad, S., Tu, A., Division of Nephrology, University of Washington, Seattle Wash. Heparin-free citrate dialysis in end stage liver disease (ESLD) patients is well tolerated. Presented at the European Dialysis and Transplant Nurses Association congress, Madrid, Spain, September 2006.

The use of citrate dialysate (CD) permitted a significant reduction in heparin (30% reduction) without any increase in clotting during the treatment, and without any decrease in the dose of dialysis as determined by Kt/V (urea). Ahmad, S., Division of Nephrology, University of Washington, Seattle Wash.; Callan, R., Advanced Renal Technologies, Bellevue, Wash.; Kossmann, R., Nephrophiles, LLC (Fresenius Medical Care), Santa Fe, New Mexico, USA. Heparin reduction with citrate dialysate. Presented at the European Renal Association – European Dialysis and Transplant Association congress, Glasgow, Scotland, July 2006, and published in Nephrology Dialysis Transplantation, Volume 21 Supplement 4 2006.

Stated conclusion: “The results from this study show that citric acid-containing dialysate is associated with increase in dialyzer reuse and appears to be related to reduced clotting.” Ahmad S, Callan R, Cole JJ, Blagg CR. Increased dialyzer reuse with citrate dialysate. Hemodialysis International 2005; 9: 264-267

Stated conclusion: "The use of citrate dialysate was associated with significantly less clotting than the regular dialysate, and can be a safe alternative to heparin in patients with high bleeding risk or who are intolerant to heparin." Tu A, Ahmad S. Heparin-free hemodialysis with citrate-containing dialysate in intensive care patients. Dial Transplant. 29(10):620-626, 2000

Heparin-free acute dialysis using citrate dialysate--this experience with citrate dialysate suggests it to be superior to regular dialysate in patients with a high risk of bleeding. Tu A, Ahmad S. Div. of Nephrology, University of Washington, Seattle, Wash. Presented at the meeting of the American Society of Nephrology, Toronto, Ontario, Canada, October 2000.
