Annie Tu, MS, ARNP, CNN; Suhail Ahmad, MD

Heparin-Free Hemodialysis with Citrate-Containing Dialysate in Intensive Care Patients

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.

Maintaining anticoagulation during hemodialysis in order to prevent the clotting of the extracorporeal system remains a challenge, particularly in acutely ill intensive care unit patients. Some of these patients have an increased risk of bleeding, which makes the use of heparin unsafe. In addition, patients will occasionally develop an antibody to heparin, which precludes its use. Without anticoagulation, the extracorporeal system frequently clots.

Alternatives to heparin are limited; the most commonly utilized methods include the use of regional citrate anticoagulation or periodic flushes of the system with normal saline.[1] Regional citrate anticoagulation requires the infusion of citrate in the arterial line proportional to the blood flow rate. This method is effective but has several disadvantages: It is expensive, the set-up is complex, and it requires additional staff involvement. Alternatively, the flushing of lines with saline is usually not very effective.

Recently, the use of citrate-containing dialysate has been described in chronic hemodialysis patients.[2] The authors proposed that the presence of citrate might prevent the clotting of dialyzer fibers, thereby accounting for an increase in dialysis dose. We were also aware of an increase in dialyzer reuse with the citrate dialysate.[3]

We have used citrate dialysate in acutely ill patients in whom heparin could not be used. The initial experience with this new alternative to heparin anticoagulation, as well as a comparison with the two more traditional methods of heparin-free dialysis, is reported in this manuscript.

Patients and Methods

Eleven acutely ill patients on the inpatient service at the University of Washington Medical Center who required hemodialysis but could not use heparin were dialyzed with the new citrate-containing dialysate, DRYalysate™ (Advanced Renal Technologies, Kirkland, WA). The composition of the two dialysates used in this study is described in *Table 1*.

A total of 43 hemodialysis treatments in the 11 patients were conducted. For comparison purposes, the data with regular

Annie Tu is a Renal Clinical Nurse Specialist, and 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.

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dialysate—either without anticoagulation (7 treatments) or utilizing modified intravenous regional citrate anticoagulation (4 treatments)—are also presented.

The regional citrate anticoagulation involved continuous infusion of one-half strength trisodium citrate (46.7% diluted with an equal volume of 5% dextrose in water) into the arterial line of the hemodialysis set-up; dialysate containing 3.0 mEq/L of calcium chloride was used. The citrate infusion was maintained at a rate equivalent to 0.5% of the blood flow rate. For 32 treatments, citrate dialysate without any anticoagulation was used. The reasons for not using heparin, as well as the types of dialyzers used, the types of access, and the types of dialysate, are shown in *Tables II* and *III*.

Results

Successful heparin-free dialysis was accomplished without clotting in 19 out of 32 treatments (59%) when using citrate dialysate. This compares to 1 out of 7 treatments (14%) using regular dialysate. Thus, 6 of 7 (86%) of the dialyses using regular dialysate, and 13 of 32 (41%) of dialyses using citrate dialysate, were associated with clotting of the system.

The dialysis sessions using citrate dialysate were associated with 78% completed treatments, while only 29% of the treatments were completed using regular dialysate ($p<0.0001$, citrate vs. regular dialysate). In other words, as shown in *Figure 1*, 5 of 7 (71%) of heparin-free treatments using regular dialysate had to be stopped because of clotting of the system. In contrast, only 7 of 32 (22%) heparin-free treatments using citrate dialysate had to be discontinued because the system clotted ($p<0.0001$, Fisher's Exact test, regular vs. citrate dialysate).

Additionally, 6 treatments with citrate dialysate and 1 with regular dialysate were associated with the presence of varying degrees of clotting in the system at the termination of dialysis. Three of 4 treatments using intravenous regional citrate anticoagulation were generally clot-free; 1 had a clotting problem.

The average treatment duration was significantly longer with the citrate dialysate than with the regular dialysate (*Figure 2*). Regional citrate anticoagulation was associated with a longer average dialysis treatment (5.75 hours) than the use of either regular or citrate dialysate.

No major changes in serum concentrations of bicarbonate or ionized calcium were noted with use of the citrate-containing dialysate. The average pre-dialysis ionized calcium level was 1.18 ± 0.08 mEq/L (mean ± std. dev.), and values obtained after dialysis (from immediately post-dialysis to up to 18 hours post-dialysis) remained essentially unchanged, at 1.18 ± 0.14 mEq/L (p = ns). During 1 regional citrate anticoagulation, intravenous calcium had to be used 3 times in order to treat hypocalcemia.

The average post-dialysis serum bicarbonate level was found to be higher than pre-dialysis values when using the citrate dialysate (26.3 ± 3.5 vs. 24.4 ± 3.4 mEq/L post-dialysis vs. pre-dialysis, respectively, $p = 0.008$). However, both values were in the normal range. There were no differences in serum bicarbonate values among the 3 types of treatments being evaluated.

Discussion

Prevention of blood clotting in the extracorporeal system is one of the requirements of a successful hemodialysis treatment. Traditionally, this is achieved by the use of heparin anticoagulation. However, the systemic nature of heparin anticoagulation increases the risk of bleeding complications and, therefore, cannot be safely used in post-surgical patients or in those who

Table I. Chemical composition of regular bicarbonate and citrate bicarbonate dialysates.

	Regular Dialysate	Citric Acid Dialysate
sodium (mEq/L)	137	137.3
potassium (mEq/L)	0–4	0–4
calcium (mEq/L)	2.5 or 3.0	2.5 or 3.0
magnesium (mEq/L)	0.75	0.75
chloride (mEq/L)	103–107	103–107
bicarbonate (mEq/L)	37	37
acetic acid (mEq/L)	4	0.3
citric acid (mEq/L)	0	2.4
dextrose (g/L)	2	2

Table II. Characteristics of the study patients (n = 11).

	No. of Patients
Reasons for not using heparin	
post-surgery	5
active bleeding	3
heparin antibody	2
thrombocytopenia	1
Access type	
femoral catheter	5
AV fistula	1
subclavian catheter	3
internal jugular catheter	2

are actively bleeding.[4] Some acutely ill patients develop severe thrombocytopenia with the use of heparin.[5] In these patient groups, if hemodialysis is needed, heparin cannot be safely used, and successful completion of the hemodialysis procedure can often become quite challenging, since without anticoagulation the system frequently clots.

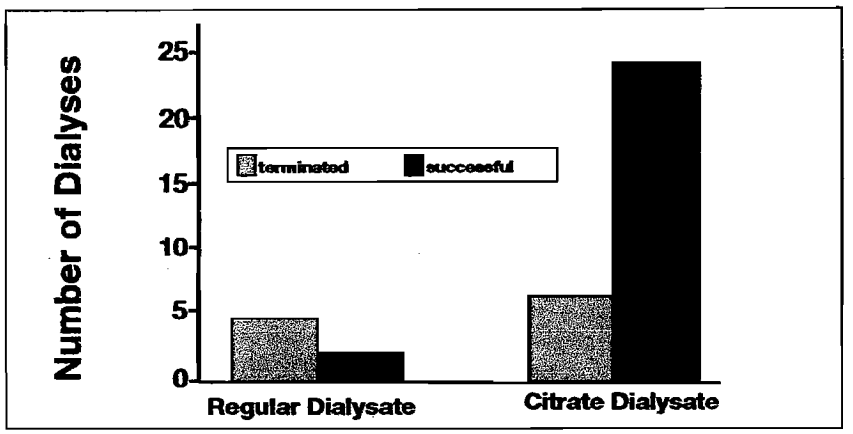

Figure 1. Number of hemodialysis treatments successfully completed or terminated early due to clotting, comparing regular dialysate with citric acid dialysate. Only 7 of 32 (22%) heparin-free treatments using citric acid dialysate had to be discontinued due to clotting of the extracorporeal system. This compares with 5 of 7 (71%) of heparin-free treatments using regular dialysate ($p<0.0001$).

Hemodialysis without any anticoagulation—using, instead, frequent flushing of the system with saline—has been used to prevent clotting.[6] However, this method has limited efficacy, and clotting of the extracorporeal system is noted quite frequently. Additionally, the frequent disruption of dialysis in order to perform the flushing requires an increase in dialysis (and staff) time. The additional saline used to flush the system also needs to be accounted for in the calculation of the total amount of ultrafiltration.

Regional citrate anticoagulation is one of the most useful and effective heparin-free anticoagulation methods. With citrate infusion, either calcium-free dialysate is used with a corresponding infusion of calcium in the venous line (the traditional method),[4] or calcium-containing dialysate is used and a venous line calcium infusion is administered on an as-needed basis (modified citrate method).[7]

Regional anticoagulation has been quite safe, even in patients with active bleeding.[4] However, regional citrate anticoagulation is complex, expensive, and labor-intensive, often requiring frequent monitoring and administration of calcium. With prolonged citrate infusion, metabolic alkalosis and hypocalcemia have been reported.[8]

Use of citric acid as an acidifying agent for the acid concentrate of dialysate has recently been described.[2] Increased delivered dose of dialysis was noted with the use of the new dialysate, and it was proposed to be related to the presence of citric acid which could have prevented the clotting of dialyzer fibers. We were also aware of additional data showing an increase in the reuse of dialyzers when the new dialysate was being used.[3] The new dialysate has been as well tolerated by the chronic patients as has been the regular dialysate, and the switch to the new dialysate has been totally uneventful.

In the present study, attempts to dialyze patients without any anticoagulation and using the regular dialysate were generally not successful. Regional anticoagulation was successful in 3 of 4 treatments, but it required calcium monitoring during all of those treatments, and frequent calcium administration during 1 of those treatments.

One of the study patients could not use heparin because of the risk of bleeding immediately after surgery. Without anticoagulation, he clotted the system in 2 hours. Two attempts to use regional anticoagulation required calcium infusion during one of the treatments, and changing of the blood lines at 2 hours into the other treatment. Two additional attempts, involving the use of low-dose heparin (700 units/hr), also resulted in clotting of the system. This patient received five treatments, each with an average duration of 4.75 hr, without anticoagulation

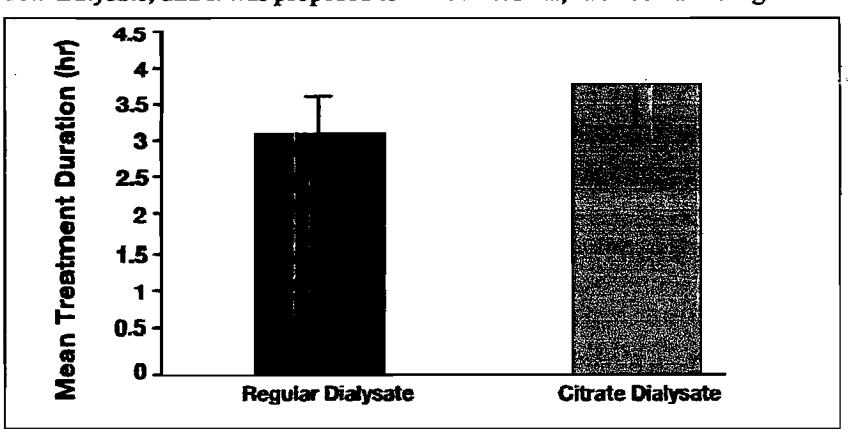

Figure 2. Completed treatment times, in hours, using regular vs. citric acid dialysate ($p = 0.05$).

when citrate dialysate was used.

Similarly, because of the clotting problems encountered without anticoagulation in the remaining patients, and because of the complexity of regional anticoagulation, the new citrate-containing dialysate (DRYalysate) was used and was found to be more effective than the regular dialysate.

magnesium was seen. There were no toxic effects of citrate noted, and no cardiac arrhythmias were observed.

Most recently, in April of this year, the U.S. Food and Drug Administration (FDA) issued a warning to all hospital pharmacies and hemodialysis units regarding the use of the 46.7% concentration of sodium citrate as a dialysis

Table III. Characteristics of the dialysis treatments (n = 43).

Dialyzer Type	Regional Citrate	Regular Dialysate*	Citrate Dialysate*	Total No. of Dialyses
F-8	2	3	16	21
B3-2.0 A	1	2	11	14
B2-2.0 A	0	0	3	3
B2-1.3 A	0	1	2	3
B3-1.3 A	1	1	0	2
Total	4	7	32	43

**with no anticoagulation*

The occurrence of clotting was significantly lower with the use of citrate dialysate than with the use of regular dialysate. Not only was the citrate dialysate associated with less clotting, it was also associated with a longer average dialysis time (*Figure 2*). However, because of the problems associated with anticoagulation-free dialysis using regular dialysate vs. the relatively problem-free dialysis with the citrate dialysate, the number of treatments conducted using each method were not similar for the three types of treatments. We should, therefore, be careful in evaluating the statistical results.

Citrate freely binds with calcium and magnesium, and is associated with hypocalcemia and hypomagnesemia. With the citrate dialysate, no significant decline in calcium or

catheter anticoagulant (especially at full-strength), stating that rapid or excessive infusion of citrate solutions can cause fatal heart arrhythmias, seizures, or bleeding due to hypocalcemia.[9] The use of citrate at lower concentrations has traditionally been safe, both in dialysis as well as blood banking.

Citrate is metabolized in liver and muscles. Three patients who had undergone liver transplants were placed on citrate dialysate for 6 treatments and had no apparent problem in metabolizing the citrate.

The use of citrate dialysate was not completely free of clotting problems; some clotting was encountered during 41% of the treatments. This may be related to the relatively lower concentration of the citrate in the dialysate compared with that typically used for regional citrate anticoagulation. The citrate concentration in the dialysate was 2.4 mEq/L, and the reported blood anticoagulation concentration ranges from about 7 to 15 mEq/L.[4]

Conclusion

Despite the small concentration of citrate in the dialysate, its presence appears to be effective in significantly reducing the clotting of the extracorporeal hemodialysis system.

Regional anticoagulation was associated with a longer dialysis time than was citrate dialysate. Again, this may reflect the relatively lower concentration of citrate in the dialysate. Future studies are planned using higher concentrations of citrate in the dialysate.

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