Concentrated Sodium Citrate (23%) for Catheter Lock

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For chronic central venous dialysis catheters, the standard method for maintaining catheter patency between treatments is to instill (lock) catheters with 5000 – 10 000 units of heparin in each lumen. Sodium citrate (citrate) is an anticoagulant with intrinsic antibacterial activity (at 20% concentration or higher). Citrate has only transient anticoagulant effects if accidentally infused to the patient. Prior studies of citrate as a catheter lock solution have utilized citrate concentrations of 1% in combination with 27 mg/mL gentamicin. We changed clinical protocols for catheter locks using various solutions, including concentrated citrate, in a dialysis unit with 50% of patients having chronic central venous catheters [40 catheters total, mostly Ash Split Cath (Medcomp, Harleysville, PA, U.S.A.) but some Tesio (Medcomp) and Hickman (BARD, Salt Lake City, UT, U.S.A.) catheters]. At 3- to 4-month intervals, the standard catheter lock solution for the unit was varied on the following schedule: heparin; 10% citrate with 3 mg/mL gentamicin; 20% citrate with 3 mg/mL gentamicin; heparin; and 23% citrate. Catheters were not routinely removed during treatment of bacteremia.

Incidence of bacteremia in patients with catheters using heparin as catheter lock was 4.32 episodes per 3000 patient-days (equivalent to percent of patients with catheters having bacteremia per month). The incidence of bacteremia decreased to 1.68 using 20% citrate/gentamicin as catheter lock ($p < 0.05$*) and to 0% with 47% citrate (*$p < 0.05$*). Incidence of bacteremia increased on return to heparin and decreased again with use of 23% citrate to 1.79 (*$p < 0.05$*). Use of urokinase for occluded catheters also significantly decreased with citrate during the time that it was available (*$p = 0.02$*). Life table analysis indicated an 83% survival of Ash Split Cath catheters at 1 year, in this unit. Concentrated citrate is an effective catheter lock solution that may provide prolonged central venous catheter use with a diminution in catheter-related infections and occlusion.*

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Introduction

For short (≤ 4 hours), three-times-weekly hemodialysis (HD) to be effective, it is necessary to achieve blood flows in the adult patient of 300 mL/minute or more. The best long-term method for HD blood access is a forearm or upper arm fistula. Fistulas are considered "permanent" access devices, and their life span is about 4 years before loss due to stenosis near the anastomosis, aneurysm, or clotting [1]. An alternative, surgically created access is an arteriovenous graft interposed between a vein and an artery. The half-life of this form of "permanent" access is 1.5 – 2 years before irreparable stenosis or clotting [1]. After fistulas or grafts are placed, several weeks to months are required before they can be punctured by needles to perform HD.

In many of the diabetic and elderly patients developing end-stage renal disease (ESRD) today, the veins of the arms are too small or too damaged to allow creation of a suitable fistula or graft, or there is not sufficient time to allow development of a fistula or graft. For a growing number of patients, tunneled and cuffed catheters are the first chronic access devices used for dialysis. Currently, for 13% – 20% of ESRD patients, the tunneled catheter is the chronic dialysis access device both at the start of dialysis and 60 days later [1,2]. The optimal access route for tunneled chronic central venous catheters is the right internal jugular vein, since this provides a straight path toward the superior vena cava and right atrium. The Dacron cuff placed within the tunnel promotes ingrowth of fibrous tissue, fixes the catheter in position, and prevents bacterial migration around the catheter [1]. As catheter designs improved, the attainable initial blood flow improved to reach the 300 mL/min minimum needed for effective dialysis. The longevity of flow in these catheters is the real problem: clots or sheaths create a need for therapeutic intervention in a range of 73 – 84 days [1,2]. Nonetheless, with intervention, Tesio catheters (Medcomp, Harleysville, PA, U.S.A.) can last for 4 years or more in home HD patients [1]. The Ash Split Cath (Medcomp) allows measured flow rates of over 400 mL/min, and early experience indicates a very low rate of obstruction requiring intervention [1,3,4].

Infection is a major reason for removal of tunneled catheters [1]. In a large prospective trial, catheter-related bacteremia was determined to be 1 episode per 252 catheter-days, or 12 per 3000 patient-days (12% of patients with catheters infected each month) [5]. The major source of contamination appears to be contamination of the catheter hub or lumen during use, rather than at the time of placement or infection migration around the catheter from the exit [1,6]. The foreign surfaces of catheters have a smooth surface in which bacteria can grow and where white cells are unable to surround or phagocytize the bacteria. Further, the biofilm coating of proteins and glycocalyx on the catheters can protect bacteria from antibiotics and white cells. If there is bacteremia, then the catheter surfaces within the vein can become seeded with bacteria. Infection is also the major reason for removal of the smaller, cuffed central venous catheters used for infusion of drugs or total parenteral nutrition. Studies in patients in intensive care units (ICU) and cancer patients have shown that bacteria were demonstrable in the biofilm of 88% – 100% of acute central venous catheters [6,7]. A patient with septicemia and a central catheter is often hospitalized and given intravenous antibiotics. In spite of this care, the patient will sometimes remain ill until the infected catheter is removed. Often the catheter is removed or replaced over a guidewire if the patient remains ill after 24 – 48 hours of therapy, because it is impossible to confirm that the catheter is not the source of the infection.

In order to prevent clotting of tunneled catheters between uses, they are usually filled with concentrated solution of heparin after each use (5000 – 10 000 units per catheter lumen) [1]. This solution must be withdrawn from the catheter before the next use or infusion, since this much heparin might result in bleeding if infused into the patient. Heparin exerts its anticoagulant activity mainly through activation of antithrombin III, and it is effective in concentrations as low as 1 unit/mL blood. However, between uses of a catheter, blood can slowly enter the tip of the catheter and wash out residual heparin, resulting in clotting in the catheter. Further, heparin has no ability to lyse preformed thrombi or fibrin sheaths; enzymes such as urokinase or tissue plasminogen activator (tPA) are required to open clotted catheters. Heparin has no antibacterial properties and, in fact, may help to promote the biofilm layer of protein on catheter surfaces in which bacteria are protected from antibodies and antibiotics; protamine has the opposite effect [8]. Also, in patients with preformed antibodies, heparin induces severe loss of platelets and paradoxical clotting (heparin-induced thrombocytopenia, or the "white clot" syndrome).

Sodium citrate (citrate) is an anticoagulant with an alternate method of action. Citrate (Fig. 1) works by binding calcium, removing it from the many enzymes of the coagulation system that require it as a cofactor. Citrate binds ionized calcium according to the citrate concentration, with nearly complete binding and inactivation of calcium with a 4:1 ratio of citrate to calcium (Fig. 2). Since sodium citrate is mostly dissociated at neutral pH, one mole of sodium citrate creates a four-osmolar solution. Citrate has negligible effects on cellular blood components such as platelets and white cells, and for this reason it is used in blue-topped tubes for collection of blood for complete blood counts. Citrate is routinely used for extracorporeal blood treatments, such as plasmapheresis or granulocytopheresis, where preservation of cell elements is important. Citrate metabolism by the liver is very rapid, so pheresis therapy can be performed without calcium infusion if the blood flow rate is less than 150 mL/min.

Sodium citrate at high concentration has been infused into patients for dialysis anticoagulation and used for catheter locks in the past (Table I). In 1986 and 1996, Flanigan and co-workers infused 47% citrate directly into the blood to provide anticoagulation for HD [10,12]. In spite of infusion of approximately 200 mL per treatment, there were no signs of hemolysis, and occasional hypocalcemic symptoms were similar to those during use of dilute citrate. In 1991, Purchase and Gault described the use of 47% citrate to open a thrombosed tunneled PermCath in a dialysis patient with heparin-induced thrombocytopenia, and also to maintain patency (the mild corrosive action of citrate probably helped lyse the clot) [11]. In 1997, Sodemann and co-workers described use of 1% citrate and 27 mg/mL gentamicin solution as an antibacterial and anticoagulant lock for chronic venous catheters for HD [13]. The use of this locking solution for an average of 264 days resulted in no episodes of septicemia and resolution of documented catheter infection in 4 patients. In 1998, Buturovic and co-workers utilized 4% citrate for maintaining patency of acute dialysis catheters and found essentially the same incidence of clotting and infection as when using heparin [14]. Ing tested the Sodemann citrate/gentamicin mixture in tunneled catheters and found clotting rates similar to outcomes using heparin (personal communication, T.S. Ing, 1999). Leray–Moragues *et al*. tested the same solution in tunneled catheters and found that septicemia rate was zero during the time of use [15].

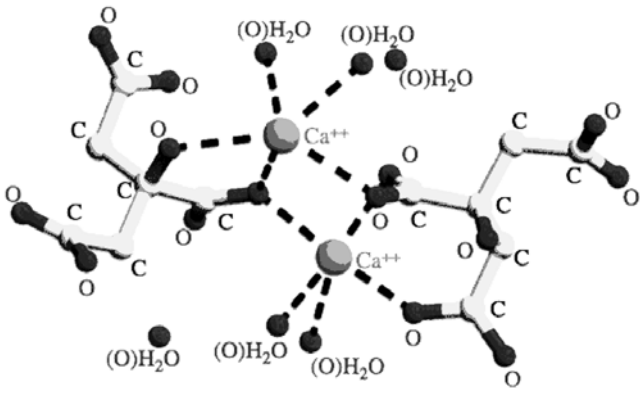

FIGURE 1 Structure of sodium citrate (calcium hydrogen citrate trihydrate) at slightly acidic pH and in presence of calcium.

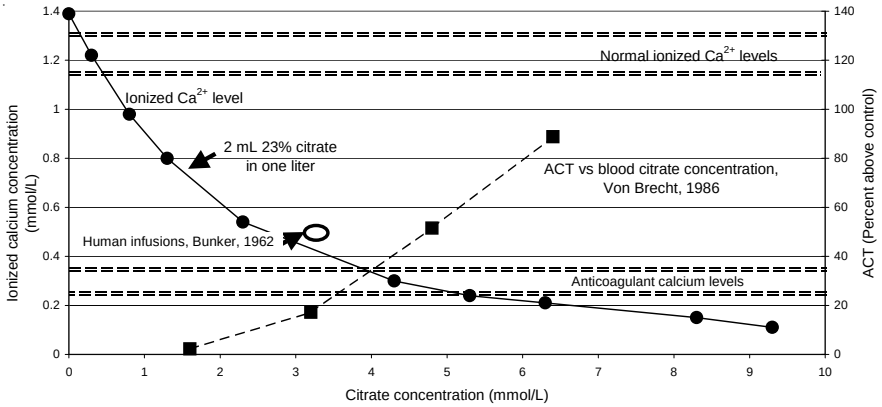

FIGURE 2 Ionized calcium levels versus citrate concentrations during titration in saline medium (pH 7.4). Circle represents ionized calcium levels and citrate levels during rapid infusion of citrate in normal volunteers (from Bunker, Ref. 9). Relationship of activated clotting time (ACT) to citrate level is in ESRD patients (from von Brecht, Ref. 10).

Concentrations used in various studies are listed in Table I and, for comparison, the concentration of citrate used in fresh frozen plasma is also listed.

Sodium citrate is antibacterial in hypertonic concentrations (such as 10% – 47%) and slightly acidic (pH 6.5). The osmolality of 47% citrate is 6400 mOsm, and it is well known that solutions of very high osmolality are, at least, bacteriostatic. Furthermore, high concentrations of citrate remove essential divalent cations from the bacteria. At high concentration, citrate is an effective anticoagulant, and its mild caustic action might diminish biofilm and lyse clots. We reasoned that if hypertonic citrate were used as a catheter lock, then a much lower concentration of antibiotic might be needed to disinfect contaminated catheters; at 23% – 47% citrate concentration, antibiotic might not be necessary to kill contaminating bacteria. Avoiding use of gentamicin or other antibiotic for catheter lock would prevent induction of resistant organisms, a growing concern with all antibiotics.

We performed *in vitro* studies demonstrating the bactericidal and fungicidal properties of concentrated citrate. We also changed clinical protocols, using various solutions, including concentrated citrate, for catheter locks in a dialysis unit with 50% of patients having chronic central venous catheters [40 catheters total, 90% Ash Split Cath and 10% Tesio or Hickman (Bard, Salt Lake City, UT, U.S.A.) catheters]. At 3- to 4-month intervals the procedures for catheter locks were changed as follows: heparin; 10% citrate with 3 mg/mL gentamicin; 20% citrate with 3 mg/mL gentamicin; heparin; and 23% citrate. We followed the overall incidence of bacteremia in the unit and use of urokinase to open occluded or catheters with low blood flow, and compared the results to incidence of bacteremia and use of urokinase before implementation of the citrate catheter lock.

Methods

In vitro *studies of bactericidal effects of citrate*

In vitro studies were performed with five organisms obtained from standard strains supplied to hospital laboratories. Strains included *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Candida albicans*, and *Aspergillus niger*. From a plate culture, a loopfull of organism was suspended in 1 mL of sterile saline and the saline mixed well. Then 20 µL of this organism suspension was diluted 1:100 with sterile saline and 20 µL of this diluted suspension was immediately plated on blood agar plates. The initial

TABLE I Concentrations of citrate used for anticoagulation or catheter lock

Author, date	*Sodium citrate* (%)	(mmol/L)	(mOsm)	*Purpose*
von Brecht *et al.*, 1986, Ref. 10	47	1600	6400	Dialysis anticoagulation
Purchase and Gault, 1991, Ref. 11	47	1600	6400	Tunneled catheter lock
Flanigan *et al.*, 1996, Ref. 12	47	1600	6400	Dialysis anticoagulation
Sodemann *et al.*, 1997, Ref. 13	1	34	136	Tunneled catheter lock, w/gentamicin
Buturovic, *et al.* 1998, Ref. 14	4	136	544	Acute catheter lock
Ing, 1999, personal communication	1	34	136	Tunneled catheter lock, with gentamicin
Leray–Moragues, *et al.*, 1999, Ref. 15	1	34	136	Tunneled catheter lock, with gentamicin
Product literature, VI Technologies, Melville, NY	0.3	10	40	Anticoagulant in fresh frozen plasma

concentration of organisms was determined by counting the number of colonies on this plate after 2 days.

Simultaneous to the initial plating experiment, 20 μL of the organism solution was added to 2-mL volumes of various catheter lock solutions, including 23% citrate. Each solution type was tested on one **(*one? or each? as on page 26*)** bacterial or fungal strain. The lock solutions were kept at 37°C for a period of 28 days. At the end of days 1, 7, 14, and 28, 20 μL of the lock solution was removed, diluted 1:100 with sterile saline, and 20 μL of the diluted solution was plated on blood agar plates. The concentration of organisms in each lock solution was calculated for various time periods after inoculation by counting the number of colonies on these plates after 2 days. The 1:100 dilution of the lock solution before plating assured that the organisms were not exposed to excessively high concentrations of the solutes as the 20 μL samples dried on the blood/agar plates. Bacteriology studies for 47% citrate were done in BEC Laboratories (Toledo, OH, U.S.A.); studies for 23% citrate were done at Toxicon, Bedford, MA, U.S.A.).

Clinical observations

Greater Lafayette Healthcare Services (GLHS) operates three dialysis units in Northwest Indiana. In the GLHS units, the standard practice is to immediately obtain blood cultures for any patient with signs of septicemia, including fever, chills, rigors, or hypotension. If these blood cultures are positive, we consider this an episode of symptomatic bacteremia. As part of routine quality assurance procedures, all episodes of symptomatic bacteremia in the dialysis units are recorded and the incidence of bacteremia is calculated on a monthly basis for the total patient population and for patients with central venous catheters. In these dialysis units, central venous catheters have been the primary dialysis access for 50% of patients since 1998. The high rate of use of catheters in these units has been due to the long-term high flow rates provided by the Ash Split Cath and Tesio catheters. In these units, 90% of the chronic catheters are Split Cath catheters and 10% are Tesio or Hickman catheters. The rate of central venous catheters used for chronic access in this unit is higher than the 20% recommended by Dialysis Outcomes Quality Initiative (DOQI) standards [16]. However, these recommendations are based on the assumption that central venous catheters are short-lived and flow will be insufficient for long-term therapy. Using central venous catheters, many of our patients have blood flows that allow excellent dialysis efficiency and catheter longevity similar to the longevity of a graft. The most important DOQI standards are met.

The incidence of symptomatic bacteremia was calculated as the number of episodes per 3000 patient-days at risk. This incidence translates to the percent of patients with catheters developing symptomatic bacteremia in any one month. This is the same method used for expressing peritonitis rates in continuous ambulatory peritoneal dialysis patients; the inverse of this incidence of infection (expressed as a fraction rather than a percentage) is the number of months between infections for the population. The incidence of symptomatic bacteremia for patients with catheters was graphed for each month from January 1998 to March 2000.

In an effort to decrease the incidence of catheter infections, and to prevent more clotting within the catheter than with heparin, a number of clinical procedures, based on literature review and animal studies, were implemented from January 1998 through March 2000. Catheter lock solutions during this period, infused into each catheter lumen at the exact catheter volume were as follows:

1. 1/98–8/98: heparin 5000 units or 10 000 units;
2. 9/98–11/98: 10% sodium citrate (pH 6.5) with 3 mg/mL gentamicin;
3. 12/98–3/99: 20% sodium citrate with 3 mg/mL gentamicin;
4. 4/99–6/99: 47% sodium citrate;
5. 7/99–10/99: heparin 5000 or 10 000 units; and
6. 11/99–3/00: 23% sodium citrate.

The GLHS Pharmacy created solutions containing sodium citrate and gentamicin, and bags of 23% citrate using 47% solutions of triCitrasol. (46.7% trisodium citrate, triCitrasol, Citra Anticoagulants, Inc., distributed by Medcomp). Citrate 47%, was drawn directly from bottles of triCitrasol. In satellite units, 23% citrate was prepared by mixing an equal volume of 47% citrate, drawn from triCitrasol bottles, with normal saline.

Patients were closely monitored for any evidence of adverse reactions each time a catheter lock solution was infused to the catheter. Each reaction to the catheter lock was reported to physicians. The monthly incidence of symptomatic bacteremia for each of the observational periods was calculated and compared to the period of heparin use (1/98–8/98). The incidence was compared by two-tailed *t*-test assuming equal variances.

Also during this time period, the use of urokinase (Abbokinase, Abbott Laboratories, Abbot Park, IL, U.S.A.) to clear catheters with decreased flow rate was monitored in the local GLHS dialysis unit [Regional Treatment Center (RTC), Lafayette]. The routine practice in the unit at this time was to administer urokinase to any catheter in which flow rates of 250 mL/min could not be maintained. The number of vials of urokinase used by the RTC unit was calculated on a monthly basis. The number of vials ordered and used by the unit each month from January 1998 through August 1998 was compared to the number of vials used after the conversion to citrate, from September 1998 to June 1999. In June 1999, urokinase became unavailable in our unit due to a withdrawal of the product from the market. However, for the preceding 18-month time period it was possible to compare the use of urokinase during use of heparin as anticoagulant versus use of citrate as anticoagulant. These 18 months included four of the six catheter-locking protocol periods. After discontinuation of urokinase, tPA (Activase,

Genetech, Inc., South San Francisco, CA, U.S.A.) was used in therapy of catheters with diminished flow rates, but its use during this period was rare.

During these periods, the longevity of central vein catheters in ESRD patients was followed. Nurses and technicians in GLHS units use utmost care in opening the catheters and connecting to dialysis machines. The caps of the catheters are soaked in povidone iodine for 5 minutes before being removed. Nurses and technicians wear masks and nonsterile gloves, and the patient wears a mask while the catheter is opened. New sterile caps are placed on the catheter following each procedure. Catheters and connectors are inspected for leaks or evidence of damage during each treatment. Other than the changes in locking solutions, there were no changes in procedures for catheter use or care from January 1998 to March 2000.

Results

In vitro *studies of bactericidal effects*

In testing with a variety of bacteria and fungi injected into 47% citrate, in 7 days a 6-log kill was obtained for *P. aeruginosa*, and a 5-log kill was obtained for *E. coli*. In 21 days, a 5-log kill was obtained for *S. aureus* (Fig. 3). A longer period of exposure was necessary for killing *Aspergillus*. Bactericidal effects of 23% citrate are shown in Fig. 4. Further studies showed that 23% citrate is even more rapidly bactericidal and fungicidal when the pH is lowered to 4.5. The high concentration of citrate is the main bactericidal agent; lower concentration acid citrate dextrose (4% citrate, pH 4.5) has no bactericidal or fungicidal properties. Heparin also has no antibacterial properties for gram-positive organisms, in spite of the preservative agent included in multiple-use vials of heparin.

Incidence of symptomatic bacteremia

The incidence of symptomatic bacteremia in patients with central line catheters was 4.32% of patients per month, from January through August 1998. During use of 10% citrate and gentamicin, the incidence of symptomatic bacteremia decreased to 2.74%; during use of 20% citrate and gentamicin, the incidence decreased to 1.68% (Fig. 5, $p < 0.05$ for each versus the initial heparin period). With the use of 47% citrate as catheter lock, the incidence of bacteremia was 0% ($p < 0.05$ versus the initial heparin period). On return to heparin as catheter lock, the incidence of symptomatic bacteremia increased to 4.13%, and with 23% citrate as catheter lock the incidence decreased to 1.79% ($p < 0.05$ for each versus the initial heparin period).

Utilization of urokinase

Usage of urokinase in the RTC dialysis unit during the initial heparin period was 41 vials per month, or approximately 1 vial per patient with tunneled catheter per month. After implementation of 20% citrate/gentamicin, the use of urokinase decreased to fewer than 20 vials per month in the unit, or less than one half vial per patient with tunneled catheter per month (Fig. 6, $p = 0.02$). During the 3-month period when 47% citrate was used to lock catheters (April – June 1999), no urokinase was used for any catheter. In July of 1999, urokinase became unavailable at the hospital. Since that time, tPA has been used for opening clotted catheters, but its usage has been, at most, 3 times per month.

Safety of citrate catheter lock

There were no patient symptoms during infusion of 10% or 20% citrate with 3 mg/mL gentamicin, or with 23% citrate alone, even with overfill of the catheter by 0.5 mL. When using 47% citrate at exactly the fill volume of the catheter,

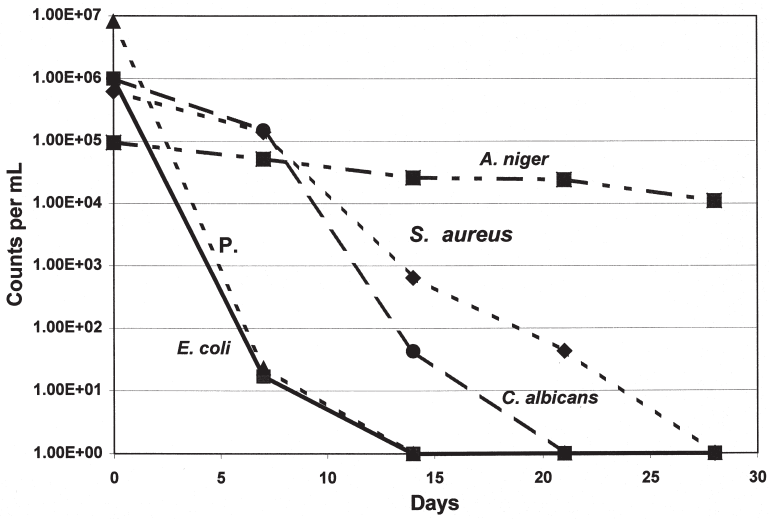

FIGURE 3 Counts of bacteria and fungi in 46.7% sodium citrate (pH 6.5) for varying periods of time after inoculation.

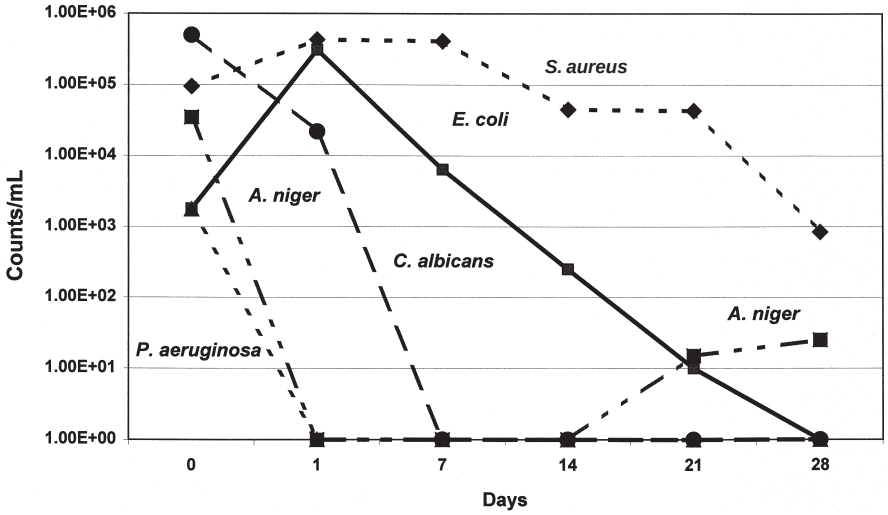

FIGURE 4 Counts of bacteria and fungi in 23% sodium citrate (pH 6.5) for varying periods of time after inoculation.

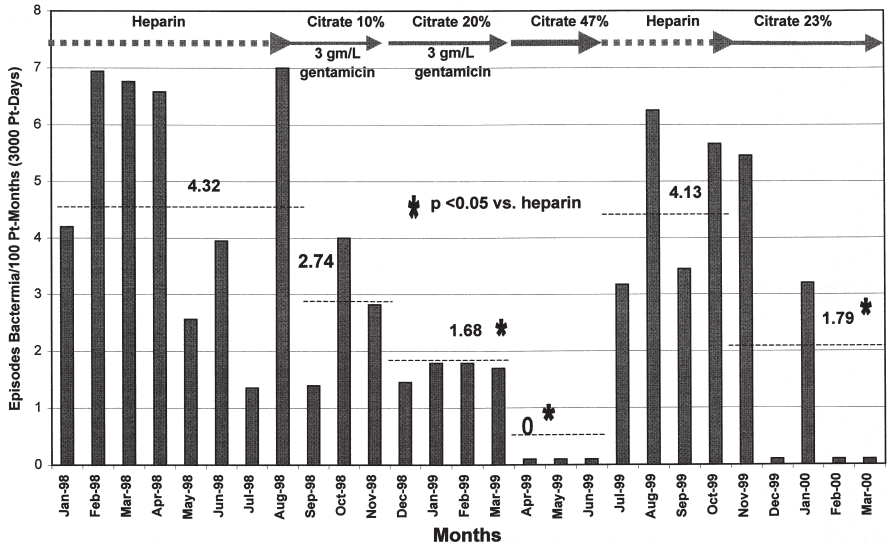

FIGURE 5 Monthly incidence of symptomatic bacteremia in patients with central venous catheters, during use of the following catheter lock solutions: heparin; 10% citrate with 3 mg/mL gentamicin; 20% citrate with 3 mg/mL gentamicin; 47% citrate; heparin; 23% citrate. Incidence is expressed in number of episodes per 3000 patient-days, equivalent to the percent of patients with symptomatic bacteremia per month. *p* values compare rates of infection to the first period of heparin use.

about 10% of patients commented that they had a "metallic" taste shortly after injection, or complained of transient tingling of the fingers. Also, in some active patients, a small amount of blood was noted in the external tubing of the catheter after 2 or 3 days. Laboratory tests indicated that the density of 47% citrate caused the citrate to drip slowly out of some catheters when hanging perfectly vertical in water, but that this did not happen with 23% citrate. Therefore, we later accepted 23% citrate as our standard locking solution.

The safety of 23% citrate as catheter lock is as expected from clinical data and basic pharmacology. We performed an *in vitro* investigation to study the relationship between ionized calcium levels and citrate concentrations. The study demonstrated that an infusion of 2 mL 23% sodium citrate should not result in even transient anticoagulation if infused rapidly (Fig. 2). The amount of citrate in 2 mL of 23% citrate is 1.6 mmol/L, or 300 mg (about 2 mg/lb body weight). If this amount of citrate were injected over 12 seconds, and

diluted into 1 L blood, the resulting citrate concentration would be enough to decrease ionized calcium slightly, and not enough to anticoagulate the blood.

The 1.6 mmol/L of citrate in 2 mL of 23% catheter lock solution is less citrate than is included in many blood products (Fig. 7). Animal studies have demonstrated that over 20 times the volume of 23% citrate used for catheter lock would be required to cause death or a serious adverse event, when calculated by the dose of citrate per pound body weight (Fig. 8).

A considerable number of human studies of citrate toxicity have been performed to determine tolerance of patients to citrate. In one study by Bunker *et al*. [9], an average of 100 mg/lb body weight was infused in an average of 13 min, with a 50% decrease in ionized calcium level. This decrease in ionized calcium level caused no symptoms or side effects. This rate of citrate infusion would be equivalent to infusing 2 mL of 23% citrate to the patient four times per minute for 13 minutes [9,10,13,17,18] (Fig. 9).

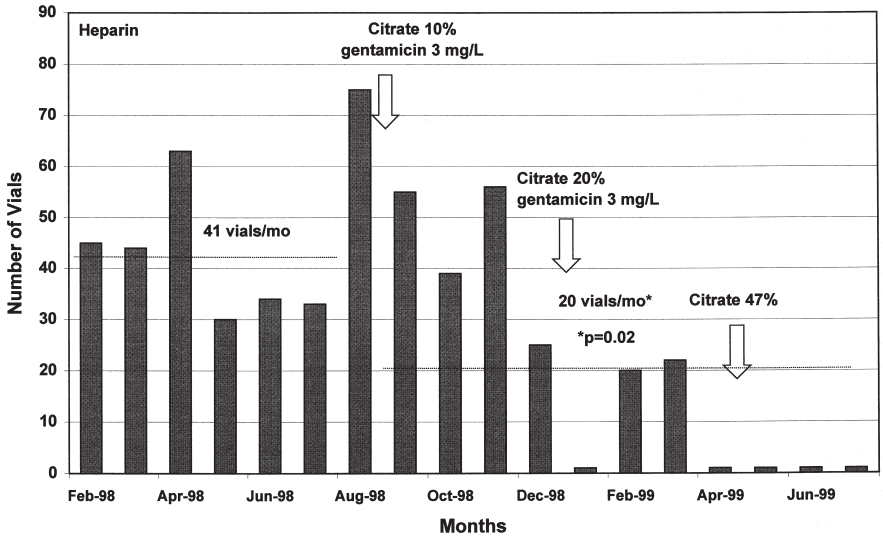

FIGURE 6 Vials of urokinase used for catheter occlusion in RTC Dialysis Unit, before and after implementation of hypertonic citrate/gentamicin, then 47% citrate. Number of patients in the Unit with catheters was stable during this period (70 patients total, 60% with tunneled catheters for chronic vascular access). Urokinase became unavailable in the Unit in June 1999.

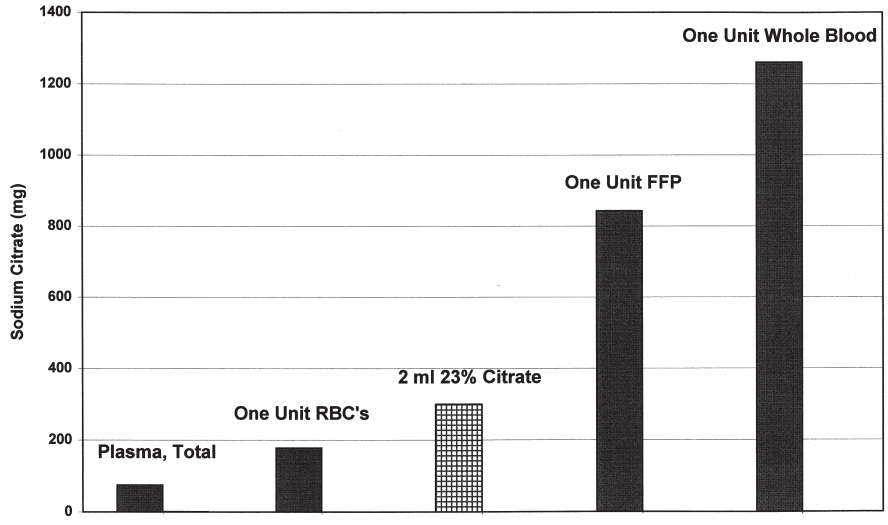

FIGURE 7 Comparative citrate content (in milligrams) in plasma, blood products, and 2 mL of 23% citrate as catheter lock. RBC = red blood cells; FFP = fresh frozen plasma.

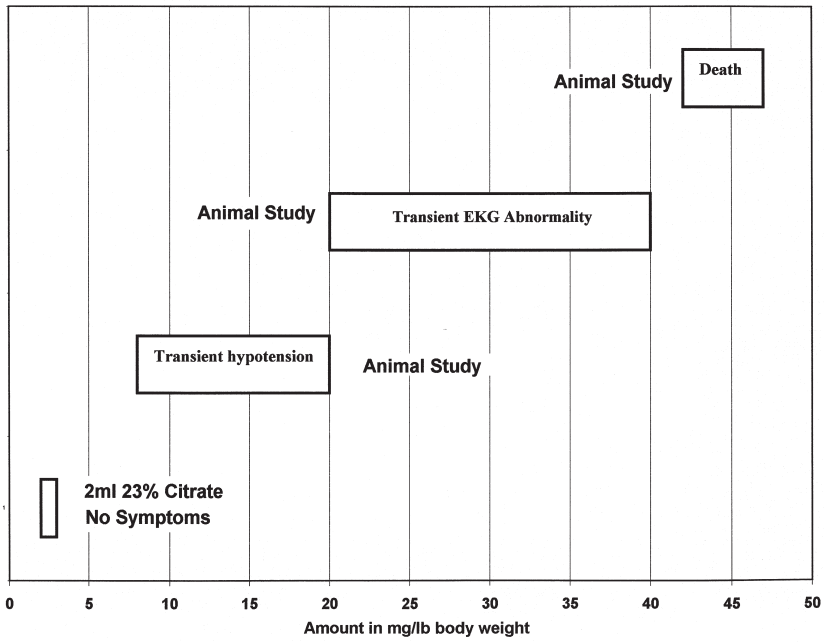

FIGURE 8 Results of a study of safety of bolus intravenous citrate in dogs, with data expressed as milligrams of citrate injected per pound of animal weight (personal communication, Mr. Frank Prosl, Biolink Corporation, Middleboro, MA, U.S.A.). For comparison, the amount of citrate in 2 mL of 23% catheter lock is indicated and expressed per pound for a 150-pound patient.

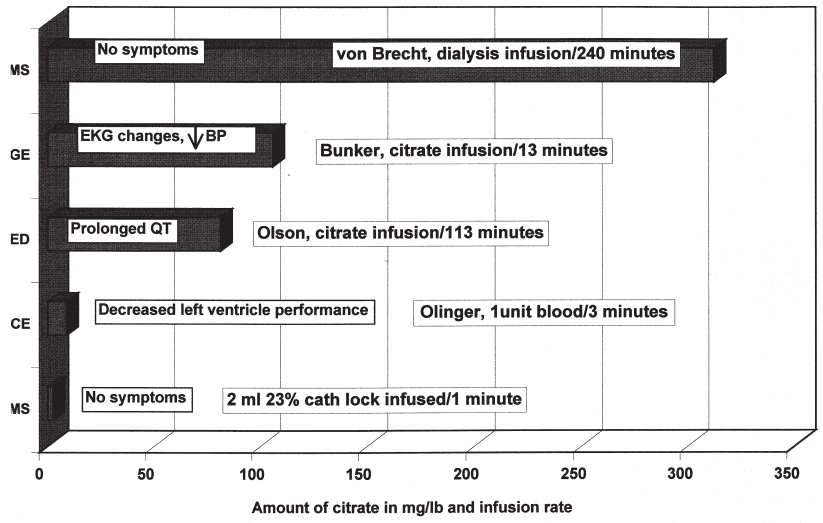

FIGURE 9 Human studies relating patient symptoms versus amount and rate of citrate infusions without concomitant calcium reinfusion (data from References 9, 10, 17,18). QT = QT interval; BP = blood pressure.

Catheter survival

For Ash Split Cath catheters, the catheter survival rate was 83% at 1 year. This surprisingly high survival of these catheters may be partly attributable to the use of citrate-based catheter lock solutions during many of the dialysis procedures using this catheter.

Discussion and conclusions

In this evaluation of clinical procedures for locking tunneled catheters, in a single dialysis unit, it appears that hypertonic citrate (10% – 47%) is at least as effective as heparin in preventing clotting of catheters. The use of urokinase to open these tunneled catheters did not increase and, in fact,

significantly decreased after implementation of citrate catheter lock solutions.

Hypertonic citrate as a catheter locking solution appears to decrease the incidence of symptomatic bacteremia in a dialysis unit with a high percentage of patients with tunneled catheters. When catheters were locked with 10% or 20% citrate containing 3 mg/mL gentamicin, the incidence of symptomatic bacteremia decreased significantly. An even greater decrease in incidence of symptomatic bacteremia appears to occur with use of 47% citrate alone (without gentamicin). Effectiveness of 23% citrate appears to be better than heparin in prevention of symptomatic bacteremia and catheter clotting. Through a variety of actions, concentrated citrate is bactericidal and sporicidal when tested *in vitro*. Therefore, it is expected that it would diminish the bacterial content of catheters after chance contamination of the catheter hub. On the other hand, a similar antibacterial effect could be obtained through the effect of citrate on biofilm: if the mild corrosive action of citrate helps to eliminate the biofilm, it would also eliminate bacteria trapped within the biofilm. The effect of citrate on bacterial contamination of catheters may decrease the risk of symptomatic bacteremia in patients with catheters, without the risk of developing resistant strains of the bacteria (as will occur with antibiotic lock solutions).

Of course, with proper care it is possible to utilize tunneled catheters for dialysis without an antibacterial solution infused. A satellite unit of GLHS is in Frankfort, Indiana, at Clinton County Hospital. In this unit, 20 stable ESRD patients are dialyzed; the percentage and types of catheters (50% of patients, mostly having Ash Split Cath and some Tesio catheters) are similar to those at the RTC unit. The unit uses the same procedures as the RTC unit in handling tunneled catheters. As opposed to the RTC, this unit has traditionally had a very low to zero incidence of symptomatic bacteremia from any cause. In the period of January 1998 to December 1999, this unit continued to use heparin as a catheter lock solution and had only 1 patient with symptomatic bacteremia during this period (representing 5% of all patients, for 1 month). Urokinase use also remained low during the entire period.

In this evaluation of clinical procedures for locking tunneled cuffed catheters, the advantages of citrate versus heparin are not proven. A randomized, prospectively controlled study to compare heparin to concentrated citrate is scheduled to begin shortly under an Investigational Device Exemption (IDE) to determine whether citrate as catheter lock is beneficial versus heparin in preventing infectious and clotting complications of dialysis catheters.

Hypertonic citrate as catheter lock has certain safety advantages over heparin with respect to anticoagulation. If the citrate contained within the catheter is accidentally infused into a patient, the citrate will be rapidly inactivated by calcium in the blood or calcium derived from body stores. If infused very rapidly, this citrate might cause transient hypocalcemic symptoms, but would not cause peripheral anticoagulation. If a tunneled catheter is used, without removing the citrate lock, for fluid infusion for a patient in the emergency room or operating room, the patient will not become anticoagulated just at the time when blood coagulation is important.

As is obvious from the animal and human studies referenced above, from Figs. 2 and 7 – 9, and from common sense, there is some limit to the amount and rate at which citrate infusion is safe. The FDA has reported recently that an ESRD patient received a rapid injection of 5 mL 47% citrate into one lumen of a central vein, tunneled catheter, just after placement, for the purpose of anticoagulation. A second 5-mL injection was then performed through the other lumen [19]. Although details of the case are sketchy, the FDA claims that the patient "died of cardiac arrest shortly after" the injection. The Medical Device Report (MDR), however, indicates that the patient did not expire immediately, but more than 24 hours later. If the catheter volume was 2 mL, then 2 cc of the injected citrate would have remained in each lumen after injection. Therefore, the patient received about 6 mL of 47% citrate into the central vein (approximately 10 mmol/L). This represents a sixfold excess of citrate versus the amount contained in the standard catheter lock (2 mL of 23%). From animal studies displayed in Fig. 8, a sixfold excess of citrate in the catheter would be expected to cause only transient hypotension without arrhythmia. Immediate death should occur only after twentyfold excess of catheter citrate. Several factors may have increased this patient's sensitivity to the overdose of citrate: double amputation of the legs (decreasing extracellular space), hyperkalemia before surgery (due partly to diabetes), performance of an arteriovenous graft procedure before placing the central vein catheter (possibly further increasing plasma potassium levels), and general anesthesia (preventing patient complaint after the first injection). In ESRD patients without these additional risk factors, even this massive overinfusion of citrate should not have caused injury to the patient.

The problems of infection and occlusion of tunneled catheters for dialysis are even greater for central venous catheters used in hospitalized patients and home patients for long-term total parenteral nutrition, chemotherapy, and antibiotic administration. Citrate has an added advantage of being compatible with almost every type of antibiotic drug, even in high concentrations [20]. Concentrated citrate may provide significant advantages for catheter lock in patients with all types of central venous catheters, reducing catheter clotting, infection, and subsequent bacteremia.

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