Sodium citrate 4% locking solution for central venous dialysis catheters—an effective, more cost-efficient alternative to heparin

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Abstract

Background. Thrombosis of the central venous haemodialysis catheter compromises dialysis adequacy and catheter survival. Heparin containing catheter-locking solution has been associated with bleeding, interferes with INR (prothrombin time/international normalized ratio) measurements and is costly. Sodium citrate has been used successfully as a catheter-locking solution, but long-term experience with its use as the exclusive locking solution has not been published.

Methods. Our haemodialysis unit converted to locking all central venous haemodialysis catheters with sodium citrate 4% instead of heparin 10 000 U/ml. A retrospective analysis compared the outcomes of the year prior and after the conversion. Flow-related catheter exchange rate, prevalence of INR assay interference, tissue plasminogen activator (rt-PA) utilization rate, rate of bacteraemias and annual cost of locking agent were examined.

Results. During the study period, 30 925 and 37 139 catheter days were identified during the heparin and citrate years, respectively. The rate of flow-related catheter exchange was not different during the two periods (1.81 vs 1.88 per 1000 catheter days, \( P = 0.89 \)). Falsely elevated INR values were eliminated with citrate and the rate of rt-PA treatments was similar during the two periods (4.1 vs 3.23 per 1000 catheter days respectively, \( P = 0.07 \)). The number of bacteraemias was similar during the two periods (0.77 vs 0.94 per 1000 catheter days respectively, \( P = 0.36 \)). There was an 85% reduction in the costs associated with locking agent during the citrate period.

Conclusions. The pharmaco-economic benefits of sodium citrate 4% are well supported by this analysis. Furthermore, citrate offers several clinical advantages over concentrated heparin: citrate lock avoids heparin-associated bleeding complications, improves reliability of INR assays and provides an effective alternative for patients with suspected or confirmed heparin-induced thrombocytopenia.

Keywords: catheter; citrate; cost; haemodialysis; heparin

Introduction

The arteriovenous fistula or graft is well recognized as the preferred vascular access for patients receiving chronic haemodialysis. However, due to the explosive growth in the population of patients with end-stage renal disease (ESRD), an increasing number of haemodialysis patients are dialysed via an indwelling central venous catheter [1]. Partial or total thrombosis of the catheter is a major complication which potentially compromises dialysis adequacy and may limit catheter survival period [2]. Catheter malfunction due to occlusion can have a significant impact on patient quality of life, patient morbidity and dialysis resources, while thrombolytic and diagnostic interventions add additional financial burden to the already escalating costs of chronic haemodialysis therapy.

To promote catheter patency during the interdialytic period, many haemodialysis centres utilize heparin as a catheter-locking agent. Although currently accepted as a standard of practice in most haemodialysis units, there is a lack of evidence-based literature to support the efficacy and safety of heparin as a locking agent, and questions remain regarding its optimal concentration, pharmacological viability when in situ at body temperature and potential for adverse systemic effects [3,4]. In fact there has never been a randomized trial to determine the optimum heparin concentration for catheter locking, and widely varying concentrations (usually 1000–10 000 U/ml) are commonly used. Heparin, when used as a locking agent, has been documented to cause unintentional systemic anti-coagulation [5], interferes with specific lab studies,
such as INR (prothrombin time/international normalized ratio) [6] and may predispose patients to other complications such as heparin-induced thrombocytopenia (HIT) [7]. As uraemic patients are inherently at greater risk for coagulopathy and bleeding and are already exposed to systemic heparin as part of the dialysis procedure, the use of high concentrations of heparin, a potent anticoagulant as a locking solution, may not be the best choice [8,9]. Systemic administration of heparin locking solution (intentional or unintentional), as well as leaching of heparin from the catheter tip further increases patient risk for bleeding complications [3]. In addition, the recent increases in heparin pricing on the Canadian market necessitated the need to investigate alternative, more cost-effective options for haemodialysis catheter-locking solutions.

Sodium citrate has been successfully used as an anticoagulant for continuous renal replacement therapies for several years [9–11]. Sodium citrate functions as an anticoagulant via the chelation of ionized calcium in the blood and tissues by the citrate ion, which prevents activation of calcium-dependent pro-coagulants [12]. A few small trials have suggested that replacing heparin with sodium citrate results in comparable catheter patency rates while avoiding exposure to systemic heparin [13–15]. These studies included either a small number of patients or were conducted over a short period of time.

In April 2003, our in-centre haemodialysis unit converted to locking all central venous haemodialysis catheters with sodium citrate 4% instead of heparin 10 000 U/ml. A retrospective analysis was conducted to evaluate whether replacing heparin with sodium citrate 4% would ensure cost-effective, long-term interdialytic anticoagulation and satisfactory catheter function without exposing patients to systemic heparinization. The outcomes reviewed in this analysis included the following: flow-related catheter exchange rate, prevalence of INR assay interference, bacteremia rates, tissue plasminogen activator (rt-PA, alteplase) utilization rate and annual cost per patient (based upon thrice-weekly dialysis) for heparin vs sodium citrate as a catheter-locking agent.

Subjects and methods

Two 12-month audit periods were selected for retrospective data collection and review. The heparin period included data from 1 April 2002 to 31 March 2003, while the citrate period included data from 1 April 2003 to 31 March 2004. Data sources utilized included the Canadian Organ Replacement Register (CORR), the Humber River Regional Hospital (Toronto, ON, Canada) Nephrology program continuous quality improvement (CQI) database, as well as the radiology/angiography, pharmacy, microbiology and laboratory databases of the hospital.

All the patients in whom a central venous haemodialysis catheter was used during at least part of each period were included in the analysis. Age, dialysis vintage, previous dialysis history, presence of diabetes mellitus and patient outcome during the study period were analysed.

Causes of death during the two periods were compared. Number of patients who were dialysed during part or the total duration of both periods was counted. Concomitant medications likely to affect anticoagulation were also included in the analysis. They included warfarin, aspirin and clopidogrel (Plavix®). The number of patients on warfarin for maintenance of haemodialysis catheter patency in the two groups was also compared.

In the heparin period, all catheters were locked with concentrated heparin 10 000 U/ml. In the citrate period, all catheters were locked with sodium citrate 4%. As the change in routine locking agent was a unit policy change, no written patient consent was obtained. Four models of catheters were used during the analysis periods; Boston Scientific (Vaxcel) (Boston Scientific, Natick, MA, USA), Cardiomed (Cardiomed, Gormley, ON, Canada), Ash Split (Medcomp, Harleysville, PA, USA) and Bard Optiflow (Bard Access systems, Murray Hill, NJ, USA). All catheters were permanent, tunneled and double lumen. The catheter lengths ranged from 15 to 22 cm, with filling volumes ranging from 1.9 to 2.8 ml.

The process for locking catheters with sodium citrate 4% in the citrate period was identical to the process previously used when catheters were locked with heparin 10 000 U/ml. At the completion of each haemodialysis session, the lumens of the catheter were flushed with 10 ml of normal saline. Next, sodium citrate was instilled into each lumen as a locking agent in volumes corresponding to luminal capacity. Sodium citrate 4% (Baxter, Mississauga, ON, Canada) was aseptically repackaged by the hospital pharmacy and supplied as sterile 5 ml aliquots in 10 ml syringes. Partially or fully clotted catheters were treated with rt-PA. Each treatment used to restore catheter patency consisted of 4 mg of rt-PA (2 mg instilled into each catheter lumen).

Radiology reports of all haemodialysis catheter exchanges were collected for each respective 12-month audit period. Only those exchanges related to poor flow were included in this analysis. Catheter exchanges related to infection, suspected superior vena cava stenosis, cuff extrusion and catheter integrity were excluded. The number of line exchanges divided by the number of catheter days was used to calculate the number of exchanges per 1000 catheter days. Flow-related catheter exchange rates for each of the heparin and citrate periods were compared.

The majority of patients with catheters during each of the audit periods were treated with oral warfarin therapy. Anticoagulation was adjusted using weekly measurement of INR (prothrombin time/international normalized ratio). INR targets were set by the treating nephrologists and varied according to therapeutic indication. All measurements of INR and concurrent partial thromboplastin time (PTT) were reviewed. All assays were performed using routine methodology by the haematology laboratory of Humber River Regional Hospital. For the purposes of this analysis, an INR value greater than three accompanied by a PTT greater than 100 was used as the parameter for defining a falsely elevated INR due to contamination...
of the sample with heparin. The INR value greater than three was selected specifically as this would represent the most common threshold for therapeutic intervention with respect to oral warfarin dosing. We selected a PTT value of greater than 100 in order to predict with great certainty the presence of heparin contamination. The number of falsely elevated INR assays in the two audit periods was compared. Obviously, the chosen parameters offer high specificity for heparin contamination, but low sensitivity.

Utilization reports of rt-PA were generated from our computer records (Meditech, Westwood, MA, USA) for both heparin and citrate audit periods. Utilization rates of rt-PA (number treatments per 1000 catheter days) were compared for each 12-month period.

The microbiology reports from blood cultures taken through the dialysis catheters during the heparin and citrate years were reviewed from the microbiology computer database (Meditech, Westwood, MA, USA). A positive blood culture was considered to represent a new infection after a previous positive blood culture if a new organism was grown or if the culture was positive at least 1 month after the previous positive culture and completion of the antibiotic treatment.

Finally, the annual cost per patient for each respective catheter-locking agent was calculated and included the price of locking solution, materials for repackaging and any associated labour costs. This financial data was compared for each of the audit periods.

Statistical analysis

The chi-square test (with Yates correction) was used to compare the rates in the parameters under review. A two-sided \( P \)-value of \(<0.05\) was considered statistically significant. The GraphPad InStat Ver 3.06 computer program for Windows (GraphPad Software Inc., San Diego, CA, USA) was used for the statistical analysis.

Results

Out of 286 patients on haemodialysis during the heparin period, 146 (51%) were dialysed using central venous haemodialysis catheters. The total number of catheter days was 30 925. Correspondingly, during the first 12-month period of citrate use, out of 321 patients on haemodialysis, 161 (50%) were dialysed using central venous haemodialysis catheters. The total number of catheter days was 37 139.

Table 1 includes the characteristics of patients with central haemodialysis catheters (age, dialysis vintage, presence of diabetes, previous dialysis history, outcomes and causes of death). There was no significant difference between the two groups. This is not surprising as 118 patients included in the analysis partially overlapped and 78 fully overlapped the two audit periods.

Table 2 includes the concomitant medications including use of warfarin, aspirin and clopidogrel during the two comparison periods. The indication for the use of warfarin is also included. There were no differences in the use of these medications in the two groups. Most patients on warfarin were being treated for maintenance of haemodialysis catheter patency (81% vs 88%) and this was similar during both periods.

Catheter exchanges

Table 3 includes the number of catheter exchanges per 1000 catheter days during the two audit periods. Fifty-six catheters were exchanged during the heparin period (1.81 exchanges per 1000 catheter days), while 70 were exchanged during the citrate period (1.88 exchanges per 1000 catheter years) (NS, \( P = 0.89 \)).

Prevalence of INR assay interference

Average INR and PTT were higher in the heparin group (1.7 ± 1.19 vs 1.6 ± 0.9 and 59.3 ± 38.3
were encountered during the citrate period while 35 bacteraemias (0.94 per 1000 catheter days) were encountered during the heparin period, Twenty-four bacteraemias (0.77 per 1000 catheter days) were associated with catheter-locking therapy. The realized annual cost savings for our haemodialysis unit totalled $861.12 CAD per patient. This reflects an 85% reduction in the costs associated with catheter-locking therapy. The realized cost savings for our haemodialysis unit totalled $112 000 CAD in the 12-month citrate period (1 April 2003–31 March 2004).

**Discussion**

Despite the K/DOQI guidelines and evidence regarding the poorer outcomes of patients dialysed through central venous catheters, their utilization remains high [2,16]. Our centre was no exception and the 50% catheter prevalence rate is actually higher than the average use as reported by the DOPPS data for Canada [17]. In addition to infection, catheter thrombosis and associated malfunction are among the primary complications associated with central venous haemodialysis catheters [11]. Although heparin, in varying concentrations, remains the accepted standard of practice as a catheter-locking agent in most dialysis centres, there is little evidence to confirm its safety and efficacy, and even less supporting documentation regarding its superiority over other alternative locking agents. Sodium citrate 4% has generally been reserved as a locking agent for patients with suspected or confirmed HIT, or other relative contraindications to heparin exposure.

Citrate 4% as a catheter-locking solution was proposed in a small feasibility study by Buturovic et al. [11] and Michaud et al. [9] in a case report. In a prospective randomized study, Hendrickx et al. [15] randomized 19 patients into two groups using heparin vs citrate 4% in single lumen catheters. Although the citrate group had a higher number of clot formation, there were no differences in the use of thrombolytic therapy. Meeus et al. [18] used citrate in 18 patients in a crossover study comparing 5% to 10% citrate. There were no significant differences in the measured outcomes in the two groups. High concentration of citrate at 30% or 46.7% has also been used for both anticoagulation as well as for antibacterial action [3,19]. Furthermore, citrate in combination with gentamicin or taurolidine has been shown to decrease the rate of catheter-related infections [20–22]. In 2000, the US Food and Drug Administration (FDA) issued a warning that concentrated trisodium citrate (46.7%) should not be used as a catheter-locking solution as a result of a reported death due to cardiac arrest, after mistaken bolus injection of 46.7% citrate systemically. The FDA talk paper also advised that 4% solutions of citrate were alternatively available for use in these settings [23]. Citrate 4% is safe even if the total amount of citrate in both catheter lumens is injected rapidly intravenously. If one assumes only intravascular distribution and no compensation from dissociation of bound calcium, in an average size patient the serum ionized calcium will decrease by only 10%, which is extremely unlikely to have any physiological effect [24,25]. To minimize any potential risk, the volume of sodium citrate 4% for locking should be limited to lumen volume, and the locking agent should be aspirated prior to dialysis [19]. To our knowledge, there is no published long-term experience with the use of low citrate concentration in a large number of patients as a routine catheter-locking solution.

The patients included in our analysis dialysed during the two periods were similar in terms of age, dialysis vintage and the presence of diabetes mellitus. The number of prevalent vs incident patients was
also similar. The similarity of the two patient groups is also supported by the fact that 118 out of the 161 patients of the citrate year were converted from heparin to citrate and 78 of these patients were dialysed throughout both years with the use of catheters. The number of patient exits and the outcomes were also similar including the causes of death (Table 1). The concomitant medications that were likely to affect the catheter outcomes including warfarin, aspirin and clopidogrel were similar including the percentage of patients who were on coumadin, in order to preserve catheter patency (Table 2).

Our retrospective analysis appears to indicate that replacing heparin 10 000 U/ml with sodium citrate 4% resulted in similar exchange rates for central venous haemodialysis catheters (Table 3). Our analysis confirms that heparin contamination of blood samples collected via the haemodialysis catheter can result in falsely elevated INR assays, which can compromise therapeutic interventions regarding oral anticoagulation treatment, and may potentially contribute to patient morbidity. Residual heparin contamination and resultant inaccuracy of the INR assay can, in most cases, be suspected from the presence of a simultaneously elevated PTT result but until the test is repeated, usually prior to the following dialysis treatment, an erroneous or no therapeutic decision can be made [6]. Leaching of concentrated heparin from the catheter tip can result in systemic heparinization and associated bleeding risks [4]. Citrate provides local anticoagulation without exposing the patient to the risks of systemic heparinization. In addition, citrate can also be used in the case of confirmed or suspected HIT [15], or where the use of heparin could be potentially dangerous. Prevalence rates for post-catheter-insertion bleeding for each of the treatment periods could not be reviewed in our study as data was not collected prospectively and chart documentation of bleeding events was incomplete. However, clinical observations reported by both the angiography department and haemodialysis unit suggest a dramatic decrease in the occurrence of insertion-related catheter bleeding episodes after converting to sodium citrate. In patients at high risk for bleeding, citrate may provide a valuable therapeutic alternative to heparin for catheter locking.

RT-PA is a thrombolytic agent routinely administered to restore catheter patency when partial or total occlusion has occurred, or when flows are inadequate. The total rt-PA utilization rates were comparable for both the heparin and citrate periods. Although there was a trend towards fewer treatments with rt-PA when expressed per 1000 catheter days, it did not reach statistical significance and therefore one has to conclude that the change to citrate did not have an effect on rt-PA utilization.

One would not expect that the change in locking solution would have any effect on the bacteraemia rates of the dialysis patients as neither low-concentration citrate 4% or heparin have antimicrobial activity. Indeed, the number of bacteraemias during each of the 2 years under observation were not significantly different.

The financial impact of the conversion from heparin 10 000 U/ml to sodium citrate 4% as a catheter-locking agent is very significant. Sodium citrate 4% is considerably more economical than full strength heparin, generating annual cost savings of $861.12 CAD per patient (based upon thrice-weekly dialysis), which translates to an 85% cost reduction for interdialytic anticoagulation of haemodialysis catheters. Actual realized cost savings for the 1-year citrate audit period for our haemodialysis unit totalled $112 000, which is quite substantial.

We now have over 3 years of clinical experience with sodium citrate 4%, and it appears to be a cost-effective agent for the maintenance of long-term interdialytic patency of central venous haemodialysis catheters. To our knowledge, this is the first report of complete conversion from heparin to citrate on all patients with dialysis catheters in a large dialysis unit. We acknowledge that the retrospective nature of the study is a weakness and that a prospective randomized study is needed for confirmation of the results. Despite this weakness, the continued, successful use of citrate as a routine locking solution in our unit is quite encouraging.

In conclusion, sodium citrate 4% does not appear to be inferior in efficacy to heparin 10 000 U/ml for the maintenance of long-term interdialytic patency of central venous haemodialysis catheters. Furthermore, sodium citrate 4% offers several potential clinical advantages over concentrated heparin. Use of citrate avoids patient exposure to the risks of systemic heparinization and associated bleeding complications, improves reliability of reported INR assays and is significantly more cost efficient from a pharmaco-economic perspective.

Conflict of interest statement. None declared.

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