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Citrate Anticoagulation in Hemodialysis

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1. Introduction

In hemodialysis, the patient's blood is flown through an extracorporeal circuit containing a hemodialyzer. This process stimulates coagulation for several reasons, most notably the blood's contact with the artificial surfaces of the tubing and dialyzer membrane and with air in the venous bubble trap, turbulent and stagnant blood flow, shear stress and hemoconcentration during the treatment [1]. Technological advances, e.g., the development of air-free blood circuits and more biocompatible materials for both tubing and dialyzer membranes, may eventually help reduce thrombogenicity of the extracorporeal circuit but are unlikely to eliminate this problem anytime soon. As a result, anticoagulation is (and will be, for the years to come) generally required for hemodialysis in the vast majority of patients.

In most cases in the United States, unfractionated heparin is the agent of choice to provide dialysis anticoagulation. While this is usually well-tolerated and relatively safe, there are significant drawbacks. The most obvious of these is that the anticoagulation is systemic in nature, which translates into an increased bleeding risk. This is certainly undesirable in end-stage renal disease patients, who are already afflicted with uremic thrombocytopathy, and it is particularly dangerous for patients with additionally increased bleeding risk, e.g., patients after surgery or trauma, and patients with active (e.g., gastro-intestinal) bleeding. Another possible complication related to heparin use, albeit rare in dialysis patients, is heparin-induced thrombocytopenia (HIT) type II [2], a potentially life-threatening condition associated with a mortality rate of 8 to 20 percent. Other possible side-effects of heparin use include osteoporosis, hair loss, and hyperlipidemia. Starting in late 2007, a series of severe anaphylactoid reactions had caused serious injuries and deaths. These reactions were later linked to heparin contaminated with oversulfated chondroitin sulfate [3, 4].

Several alternatives to heparin anticoagulation are potentially available, each of them accompanied by specific disadvantages. Intermittent saline flushes, i.e., flushing of the extracorporeal circuit with 25 to 50 mL of 0.9% sodium chloride solution every 15 to 30 minutes, is often used during acute dialysis in patients with increased bleeding risk or in patients with HIT type II. Since the procedure, surprisingly, is not automated, it is very laborious. Furthermore, its capacity to prevent clotting is rather limited, with partial clotting occurring in approximately 20 percent, and complete clotting of the extracorporeal circuit in about 7 percent of treatments [1]. Clotting of the extracorporeal system, of course, is associated with blood loss to the patient, and even with partial clotting, solute clearances will be impaired. Other agents used for systemic anticoagulation in hemodialysis are fondaparinux, danaparoid, and direct thrombin inhibitors. These have other downsides,

such as long half-life, lack of an antidote, or high cost, and all of them increase the bleeding risk as they are administered systemically.

The primary purpose of anticoagulation during hemodialysis is to prevent clotting of the blood while it is traveling through the blood tubing and dialyzer. Against this background, the cornerstones of optimal anticoagulation for hemodialysis are complete suppression of the activation of the clotting cascade, strict limitation to the extracorporeal circuit, absence of serious side-effects, and low cost.

Limitation of anticoagulation to the extracorporeal circuit, also known as regional anticoagulation, is important because it eliminates the increased bleeding risk associated with systemic anticoagulation. Originally, this was accomplished by infusing heparin into the arterial line of the blood circuit and antagonizing its anticoagulant effect by infusing its antidote protamine into the venous line. Since protamine's half-life is shorter than heparin's, the anticoagulant effect may return after the dialysis procedure, increasing the bleeding risk. Also, this mode of anticoagulation is not suitable for HIT type II patients because of the heparin administration. Regional anticoagulation by infusing the arachidonic acid derivative prostacyclin into the arterial line is based on this molecule's inhibitory effect on thrombocyte aggregation and its short half-life of only a few minutes. The downsides are its vasodilatatory properties, which can cause significant hypotension during the treatment, and its prohibitive cost. Regional citrate anticoagulation is an alternative to these two methods that also confines anticoagulation to the extracorporeal circuit but does not come with the disadvantages mentioned above. In fact, it conveys a set of additional advantages that go above and beyond merely providing regional anticoagulation.

2. The principles and history of citrate anticoagulation in hemodialysis

The anticoagulant properties of citrate have been known since the late 1800s already and are based on its capacity to chelate calcium ions. Ionized calcium (iCa) is an important co-factor at several steps in the coagulation cascade and, in that role, was formerly called coagulation factor IV. Addition of citrate to whole blood leads to formation of stable calcium-citrate complexes, thereby lowering the concentration of ionized calcium. At iCa levels below 0.5 mmol/L, clotting becomes impaired; at levels below approximately 0.3 mmol/L, coagulation is virtually blocked. This principle has been applied for storage of red cells in transfusion medicine since the early 20th century and later on for blood cell apheresis and lipid apheresis. Citrate physiologically occurs in the human body. It is an intermediate metabolite in the mitochondrial Krebs cycle, and all human cells that possess mitochondria can generate and metabolize citrate, particularly those tissues that are rich in mitochondria, such as the liver.

The first mention of citrate for anticoagulation in hemodialysis dates back to 1961 [5]. Traditionally, regional citrate anticoagulation in hemodialysis involves infusion of trisodium citrate into the arterial line of the extracorporeal circuit in sufficient quantities to lower iCa levels to around 0.25 to 0.35 mmol/L in order to substantially inhibit coagulation. In the venous limb of the dialysis tubing, ideally close to the point of blood reinfusion into the patient, calcium is substituted in the form of a calcium chloride or calcium carbonate infusion. This calcium substitution primarily serves to raise the iCa concentration in the blood to safe levels before the blood re-enters the patient's circulation, but there is another aspect to it as we shall see later. Classically, a calcium-free dialysate is used in this setting so

as not to compromise anticoagulation due to calcium influx from the dialysate [6]. This setup of regional citrate anticoagulation is depicted in **Figure 1**.

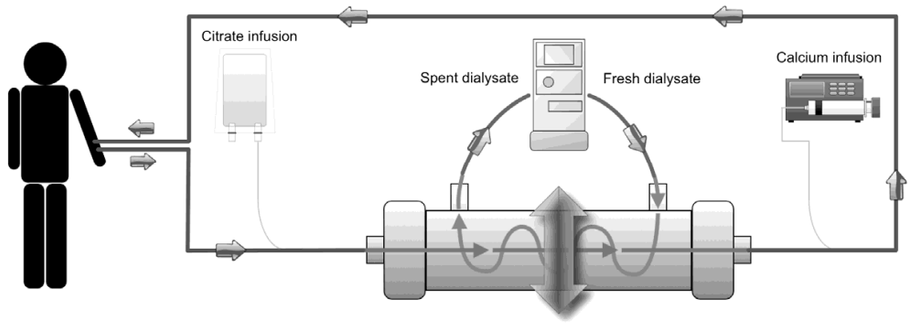

Fig. 1. Conventional setup of regional citrate anticoagulation in hemodialysis.

A question of central importance is how plasma citrate concentrations relate to iCa concentrations. We analyzed the data from 21 regional citrate anticoagulation treatments performed at Renal Research Institute facilities in New York, USA, in 10 patients, during which 4% trisodium citrate (136 mmol/L) was infused into the arterial line and iCa measured before the dialyzer. Blood flow rates were 350 mL/min in 4 treatments, 400 mL/min in 13 treatments, and 450 mL/min in 4 treatments. Hematocrit and iCa were measured 13 minutes into the treatment using an Abbott i-Stat point-of-care analyzer. Hematocrits ranged from 28% to 39% (average, 33.6%). Citrate infusion rates ranged from 140 to 480 mL/h, and iCa ranged from 0.27 to 0.68 mmol/L (average, 0.38 mmol/L). Plasma citrate concentrations were calculated based on citrate infusion rates and calculated plasma flow rates. **Figure 2** illustrates the relationship between pre-dialyzer blood iCa activity and plasma citrate concentration. As can be seen, a plasma citrate concentration of >3.5 mmol/L is typically required to bring iCa levels to below 0.3 mmol/L. The exact citrate concentration necessary depends mainly on the individual patient's plasma calcium and protein (primarily albumin) concentrations. Total calcium in the serum comprises a protein-bound and a free (ionized) fraction, and the equilibrium concentrations of each can be estimated based on the respective dissociation constant [7-10]. Likewise, free citrate reacts with free calcium to form calcium-citrate complexes, again with a known dissociation constant [11]. Strictly, the multi-ionic milieu of the plasma should be considered, but reducing the relationships to calcium, protein, and citrate is a fair approximation. In clinical practice, these relationships are, however, not calculated. Instead, the citrate infusion rate is generally based on empirical knowledge and in most cases only tailored to the patient's blood flow rate. As can be expected, this may occasionally lead to citrate concentrations that are either too low to provide sufficient anticoagulation, or unnecessarily high. To assess the individual situation, pre-dialyzer (some groups use post-dialyzer) iCa levels can be measured in the plasma to ascertain that they are within the desired target range of approximately 0.25 to 0.35 mmol/L. If they are not, adjustments to the citrate infusion rate can be implemented and the iCa levels reassessed. Likewise, the post-dialyzer iCa concentrations are not known in clinical practice, and the rate of calcium substitution is based on empirical knowledge. Routinely, systemic iCa levels are measured in the patient at multiple time points during the treatment, and the calcium substitution rate is adjusted to counter drops or rises in systemic iCa concentration. Each adjustment usually necessitates a reassessment of iCa levels after 15 to 30 minutes to monitor its effect.

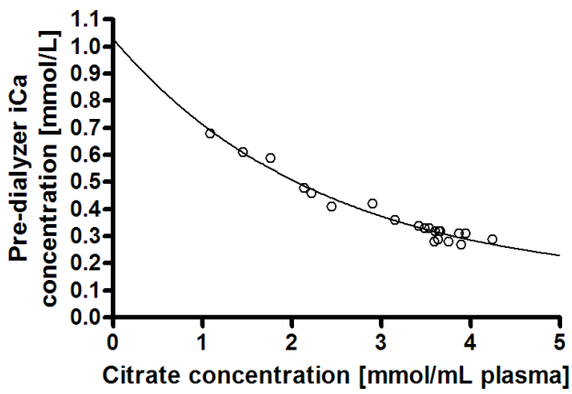

Fig. 2. Pre-dialyzer ionized calcium (iCa) concentration plotted against plasma citrate concentration.

During regional citrate anticoagulation, citrate enters the body in the form of both free citrate and calcium-citrate complexes. When this citrate is metabolized, each molecule yields three molecules of bicarbonate, which will have an impact on the acid-base status. Also, calcium is released from calcium-citrate complexes as they are metabolized, which impacts serum calcium concentration. The use of trisodium citrate or Acid Citrate Dextrose (ACD) solution further entails an additional sodium load to the patient that should be taken into account. In clinical practice, the dialysis prescriptions for regional citrate anticoagulation typically incorporate reduced sodium (by about 2 mmol/L) and bicarbonate (by about 5 mmol/L) concentrations. Magnesium concentration in the dialysate may be increased since citrate also complexes magnesium, leading to increased magnesium losses across the dialyzer.

Over the years, different algorithms for the administration of regional citrate anticoagulation have been suggested and studied, both for intermittent as well as continuous hemodialysis. These algorithms usually define blood and dialysate flow rates, the starting rates for citrate infusion and calcium substitution, rules on how these rates should be adjusted in case of iCa deviations from the specified circuit or systemic target ranges, time points for monitoring iCa, and downward adjustments for sodium and bicarbonate in the dialysate. Since citrate and calcium kinetics during dialysis depend on many factors, including the type of dialyzer used and the blood and dialysate flow rates, such algorithms generally are only applicable to the particular dialysis setting for which they have been validated. The purpose of all these algorithms is always to make the administration of regional citrate anticoagulation as safe and simple as possible, i.e. to minimize the risk for calcium or acid-base derangements, circuit clotting or other complications while requiring as little monitoring or intervention by the staff as possible.

3. The benefits of regional citrate anticoagulation

Regional citrate anticoagulation does not increase the patient's bleeding risk and is, therefore, not only an ideal mode of anticoagulation in any patient with high bleeding risk or active bleeding but also for the average hemodialysis patient. Furthermore, citrate anticoagulation avoids all the other potential side effects of heparin use noted above, which also makes it a choice mode of anticoagulation in patients with HIT type II. Aside from these

obvious advantages, however, there are several additional benefits to using regional citrate anticoagulation. One of these appears to be improved biocompatibility of the dialysis procedure: comparing heparin anticoagulation with citrate anticoagulation, Böhler et al. found that citrate anticoagulation reduced complement activation, neutropenia and lactoferrin release with the use of cuprophane dialyzers, and significantly inhibited neutrophil degranulation with the use of polymethyl methacrylate membranes [12]. Likewise, Gritters and colleagues compared anticoagulation using unfractionated heparin, low molecular weight heparin and citrate in a randomized crossover trial and found that citrate anticoagulation suppressed the dialysis-associated degranulation of polymorphonuclear cells and platelets. Furthermore, pro-atherogenic oxidized low-density lipoprotein levels were reduced by a median of 26% after only one week on citrate anticoagulation [13]. In view of the heightened inflammatory state of chronic hemodialysis patients, the reduction of oxidative stress, complement and cell activation associated with citrate dialysis may be a relevant benefit with regard to reducing the high cardiovascular morbidity in these patients. Hofbauer et al. compared anticoagulation with unfractionated heparin, low molecular weight heparin and citrate during dialysis with a single-use polysulfone dialyzer and used scanning electron microscopy to quantify the degree of membrane-associated clotting [14]. The highest degree of cell adhesion and thrombus formation was observed with unfractionated heparin, and it was only slightly reduced with the use of low molecular weight heparin. With regional citrate anticoagulation, on the other hand, thrombus formation was found to be negligible, indicating a far superior anticoagulation using citrate compared to both unfractionated and fractionated heparin. Gabutti et al. employed a randomized controlled cross-over design to compare standard heparin dialysis with regional citrate anticoagulation, dosed to achieve a similar degree of coagulation activation, and study the effects on complement activation and interleukin-1 beta release. In this setting, complement activation was slightly but significantly higher in the citrate dialysis group, but at the same time, interleukin-1 beta release was markedly reduced. Citrate can, and often is, dosed higher in regional citrate anticoagulation than was done in this study, and it stands to reason that with such higher citrate concentrations, complement activation would have been lower than with standard heparin dialysis, associated perhaps with a further decrease in interleukin-1 beta secretion. In line with Hofbauer's results mentioned above, regional citrate anticoagulation appears to allow for markedly prolonged filter patency times in continuous dialysis [15-18]. Lastly, a recent study by Oudemans-van Straaten and colleagues found higher patient and kidney survival in critically ill patients on citrate versus low-molecular weight heparin [19]. On top of these benefits, citrate is a relatively inexpensive compound compared to heparin.

4. The downsides of regional citrate anticoagulation

The single biggest concern with regional citrate anticoagulation is the development of potentially life-threatening systemic calcium derangements. Acute changes in systemic iCa can develop quickly when calcium elimination across the dialyzer (in the form of free calcium and calcium-citrate complexes), calcium release from the metabolism of calcium-citrate complexes, and calcium substitution (from the calcium infusion and/or the dialysate, if a calcium-containing dialysate is used) are mismatched. From this concern springs the need to monitor, at least initially, systemic iCa levels fairly closely during regional citrate anticoagulation. This, along with the more complex setup, presents a significant strain on

staff resources and, consequently, can make citrate dialysis more costly than standard heparin dialysis. The prolonged filter patency times seen with citrate anticoagulation, however, may also introduce cost savings compared to heparin dialysis in continuous dialysis therapies [20]. The administration of buffer base in the form of citrate can further lead to metabolic alkalosis [20-22]. Hypernatremia can occur secondary to the additional sodium load administered with the citrate infusion (e.g., in the form of trisodium citrate, which carries 3 moles of sodium for each mole of citrate) [5, 21]. With high citrate infusion rates and/or in patients with impaired liver function (liver failure, cirrhosis), systemic citrate accumulation may occur. Measurements of plasma citrate concentrations are not usually readily available in clinical laboratories, but citrate accumulation may be detected by looking for its effects on calcium levels: citrate accumulation traps calcium in the form of calcium-citrate complexes. The growing plasma pool of calcium-citrate complexes and the insufficient release of calcium from this pool via citrate metabolism lead to a drop in systemic iCa which is spotted in systemic iCa measurements and countered by an increase in the calcium substitution rate in order to restore systemic iCa to physiologic levels. Under such conditions, the amounts of free calcium, calcium-protein complexes and the increased amount of calcium-citrate complexes add up to an increased total calcium concentration. Therefore, citrate accumulation may be detected by an increased total calcium concentration or an increased ratio of total to ionized serum calcium concentration [23]. An increased anion gap may also point towards citrate accumulation [24].

5. The future of citrate anticoagulation in hemodialysis

The fundamental roadblocks to widespread implementation of regional citrate anticoagulation are fear of electrolyte or metabolic disturbances and the relative laboriousness of this mode of anticoagulation. These two domains are interconnected. What current citrate dialysis algorithms have in common is that they are empiric. There is some degree of individualization, but only on a relatively low level. As a consequence, while these algorithms may work for the average patient, or even a majority of patients, there will always be the concern that the characteristics of a particular patient situation are not captured adequately, leading to unexpected and possibly dangerous changes in electrolyte or acid-base parameters. And for this very reason, these algorithms will never help eliminate the intensive laboratory monitoring that, at least initially, is currently required for regional citrate anticoagulation.

Tailoring the citrate infusion rate to the blood flow rate alone is a crude oversimplification. Anticoagulation along the extracorporeal circuit depends on a myriad things, such as the hematocrit, the void volume fraction, the plasma water calcium concentration, the composition of the other ionic species in the multi-ionic milieu of the plasma, the ultrafiltration rate, the type, size and geometry of the dialyzer used and, consequently, its solute removal characteristics, the blood and dialysate flow rates, the concentration of the citrate infusion (high concentrations entail low infusion rates, which may cause mixing issues or discontinuous, pulsatile flow), the dialysate composition (e.g., in terms or calcium, magnesium and citrate concentration), the plasma protein concentration, the rates of citrate generation and metabolism, the systemic citrate levels, the degree of access recirculation, the patient's capacity to buffer changes in extracellular calcium concentration, and so on, to name but a few. Some of these have greater impact than others; some are easier to model than others. But if the kinetics of calcium and citrate are to be predicted (not on average, but

for a particular patient) with any degree of reliability, then these factors must be taken into account. Needless to say, the interactions between all these factors cannot possibly be assessed (let alone integrated over an entire treatment and beyond) based on intuition or clinical experience. Computer-aided calcium and citrate kinetic modeling is the only way to simulate in detail the processes during regional citrate anticoagulation. We have recently published a comprehensive, yet versatile, mathematical model for citrate dialysis [25]. A refinement of this model (comprised of our original model combined with a statistical correction component), recently presented as a talk at the XLVII ERA-EDTA conference in Munich, Germany, showed excellent prediction quality [26]. When applied to 120 patients on pure dialysate-side citrate dialysis (dialysate containing 2.4 mEq/L citrate and 2.25 mEq/L calcium), the model overestimated end-dialysis ionized calcium levels by only 0.026 mmol/L on average. While current clinical citrate dialysis algorithms are only applicable to a rather narrow setting for which they have been developed, computer-aided calcium and citrate kinetic modeling affords much greater flexibility and could possibly even be adapted on-the-fly to different conditions.

As was mentioned above, the calcium substitution in regional citrate anticoagulation is currently dosed empirically and adjusted so as to keep systemic iCa within the physiologic range. However, it must be born in mind that this approach pays no heed to the question of calcium mass balance. This is, of course, not done deliberately but simply from necessity, because clinicians have no way of assessing intradialytic calcium mass balance reliably, let alone under such complex conditions as occur in regional citrate anticoagulation. The difference between calcium substitution and calcium loss across the dialyzer membrane determines the intradialytic calcium mass balance, and from this perspective, the calcium substitution should be chosen so as to effect the desired mass balance. The challenges with determining what calcium mass balance is required for a given patient is a related but separate issue and shall not be discussed here. With higher citrate infusion rates, and accompanying citrate accumulation and calcium "trapped" systemically in the form of calcium-citrate complexes, calcium mass balances can easily become positive. In practice, this point is often dismissed and calcium substitution rates justified with reference to the need to maintain serum ionized calcium within the normal range. What becomes clear, however, when simulating citrate dialysis is that many roads lead to Rome, and, within limits, different calcium mass balances can be achieved without compromising the extracorporeal anticoagulation by modifying parameters such as dialysate calcium and citrate concentrations and blood and dialysate flow rates. Dialysis dose issues certainly have to be considered, and the combination of calcium and citrate kinetic modeling with urea kinetic modeling would be a particularly powerful tool. Conversely, the same calcium mass balance can be achieved in different ways, potentially allowing for individualization of the citrate dialysis prescription according to particular patient characteristics, such as impaired liver function or reduced calcium buffering capacity. In view of the ever-increasing awareness of the potential importance of calcium mass balance for long-term outcomes in hemodialysis patients, calcium and citrate kinetic modeling offers a unique opportunity for actively incorporating this parameter into the dialysis prescription. This may turn out to be crucial for translating the compelling short-term benefits associated with regional citrate anticoagulation into long-term improvements in cardiovascular outcomes and ultimately survival. Currently, this mode of anticoagulation is thoroughly ignoring this aspect and is lagging behind the trend towards neutral calcium mass balance seen in standard heparin hemodialysis. Similar to calcium mass balance considerations, dialysis-related sodium

loading is another topic that has been receiving more and more attention in recent years and is another domain of solute kinetic modeling that should ultimately be integrated into citrate dialysis modeling, particularly given the additional sodium load administered with the use of regional citrate anticoagulation.

The use of dialysate-side citrate anticoagulation (i.e., the use of a citrate- and calcium-containing dialysate without arterial citrate infusion or venous calcium substitution) has sparked interest recently for its alleged heparin-sparing potential and its safety and ease of use [27-29]. At unchanged heparin doses, using citrate-containing dialysate (instead of bicarbonate dialysate acidified with acetate) appears to improve solute removal [30].

Citrate anticoagulation holds great promises for improving the outcomes of hemodialysis patients. Ultimately, kinetic modeling will be essential for taking this therapy to the next level (i.e., a high degree of individualization and increased safety through accurate prediction of electrolyte and acid-base kinetics) and to facilitate its widespread use in routine clinical practice.

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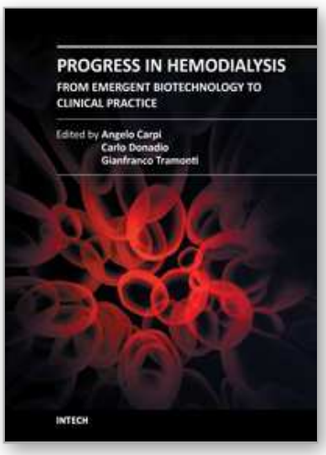

Progress in Hemodialysis - From Emergent Biotechnology to Clinical Practice

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Hemodialysis (HD) represents the first successful long-term substitutive therapy with an artificial organ for severe failure of a vital organ. Because HD was started many decades ago, a book on HD may not appear to be up-to-date. Indeed, HD covers many basic and clinical aspects and this book reflects the rapid expansion of new and controversial aspects either in the biotechnological or in the clinical field. This book revises new technologies and therapeutic options to improve dialysis treatment of uremic patients. This book consists of three parts: modeling, methods and technique, prognosis and complications.

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