PROTOCOL OF ANTICOAGULATION IN EXTRACORPOREAL PURIFICATION TECHNIQUES

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Method Article

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Abstract

The need for anticoagulation associated with the use of extracorporeal purification techniques is one of the main concerns regarding these techniques. Although we use sodium heparin (500 IU/h) as the main anticoagulant, we assess the presence of contraindications to it, mainly associated with bleeding risk (thrombocytopenia, coagulopathy). We consider alternatives such as the use of epoprostenol or citrate, or performing EPT without anticoagulation. Furthermore, when repeated hemofilter clotting occurs (>2 sets/day), we consider changing the anticoagulation system, preferably to citrate. While we need to monitor bleeding complications when using heparin or epoprostenol, these complications are minimized with citrate as it is a regional anticoagulation system. In the latter case, we need to monitor for ionic disturbances (mainly hypocalcemia and hypomagnesemia) and electrolyte imbalances (metabolic alkalosis or acidosis due to citrate accumulation) that may occur if adequate monitoring is not carried out.

Introduction

Extracorporeal purification techniques (EPT) are complex techniques with a growing application that can induce complications. One of the main concerns regarding these techniques is the need for anticoagulation to prevent blood coagulation as it passes through the extracorporeal circuit. This problem persists despite the existence of biocompatible membranes and the improvement of current hemofilters. Anticoagulation with sodium heparin has been the classical solution to this problem, but its use has limitations in certain situations, many of them specific to our critically ill patients: thrombocytopenia, coagulopathy, recent surgery, repeated coagulation of hemofilters despite adequate heparin doses, contraindication for the use of heparin, etc. Therefore, the search for alternative anticoagulation systems led to the initial use of epoprostenol as an alternative and the subsequent development of systems based on regional anticoagulation with citrate-calcium. These are based on the fact that ionic calcium is a fundamental element for clot formation and that Ca^{2+} levels below 0.5 mmol/L prevent coagulation. Citrate (C_{6}H_{5}O_{7}^{3-}) is a molecule capable of irreversibly chelating calcium, making it one of the most effective anticoagulants. It is metabolized in the Krebs cycle in the mitochondria of the liver, skeletal muscle, and renal cortex, generates bicarbonate (ratio 1:3), and has a short half-life in vivo (T/2 5 minutes). When metabolized, it releases the chelated calcium, and its anticoagulant effect is completely reversed, providing a rapidly reversible anticoagulation.

Numerous studies have shown the safety, efficacy, and efficiency of citrate anticoagulation, allowing for longer hemofilter duration, lower hemofilter clotting rates, and low complication rates even in demanding scenarios for Citrate-Calcium complex clearance such as sepsis or liver disease. However, this requires familiarity with the equipment and systematic monitoring and adjustment of ionized calcium levels in both the circuit and the patient.

Reagents
Equipment

1. **Hemofilter set**: the hemofilter sets that we mainly use in our units are PRISMAFLEX/PRISMAX System M100 set (Factory ID 8353520, Code No. 106697), PRISMAFLEX/PRISMAX System M150 set (Factory ID 8353584, Code No. 109990) and Oxiris Set.

2. **Bacteremia Zero Kit**.

3. **Double-lumen catheter**: we preferably use catheters of 13-14.5 Fr with a "shotgun barrel" geometry. The optimal length will be 24 cm for the femoral location, 15 cm for the right jugular-subclavian, and 20 cm if using the left jugular-subclavian.

4. **Extracorporeal depuration monitor**: we use Prismaflex\textsuperscript{R} or Prismax\textsuperscript{R}

5. **Dialysis and replacement fluids**: we use Phoxilium\textsuperscript{R} as the main dialysis and replacement fluid, and Prismasol\textsuperscript{R} in patients with hyperkalemia despite adequate therapy. If we use citrate anticoagulation, we employ Regioci\textsuperscript{R} (Citrate 18 mmol/L) on the PBP scale and Biphozy\textsuperscript{R} on the dialysis and replacement scales. The specific characteristics of the fluids that we use are detailed in Table 1.

6. **Corresponding anticoagulation system**: heparin, epoprostenol, or citrate and calcium.

Procedure

1. **Choose initial anticoagulation mode**: The decision algorithm for selecting the mode of anticoagulation is shown in Figure 1.

   · If anticoagulation is required due to underlying pathology we maintain the corresponding anticoagulation method according to the indication.

   · If anticoagulation is not required due to underlying pathology, the risk of bleeding is evaluated.

   · If there is not bleeding risk we initiate anticoagulation with our usual initial regimen: \textit{unfractionated sodium heparin}.

   · If there is bleeding risk:

     o In cases of severe thrombocytopenia (<50,000) and/or high risk of bleeding, EPT can be performed \textit{without heparin} (in these cases, ensure that the filtration fraction does not exceed 10%-15%). It can also be performed directly with citrate.

     o If platelet count is between 50,000-75,000 and/or there is mild coagulopathy (PA<75\% and/or aPTT >45secs) EPT can be performed with epoprostenol or citrate.

     o If platelet count is above 75,000 and there is normal coagulation we can use sodium heparin.
· If two sets clot within 24 hours, we will follow the following sequential procedure: increase the dose of sodium heparin, add epoprostenol or switch to regional anticoagulation with citrate.

· The **indications for the use of citrate anticoagulation** would be:

  o Patients with thrombocytopenia <50,000.

  o Patients with high risk of bleeding (surgery in the previous 24 hours, recent or spontaneous bleeding, etc.)

  o Patients with thrombocytopenia between 50,000-70,000 and/or Prothrombin <75% and/or TTPA > 45 sec.

  o All patients with normal coagulation in whom filter durations are not achieved 24 hours with the usual protocol (heparin alone or in combination with epoprostenol).

  o Patients with contraindications for the use of heparin (induced antibodies, etc.) if the option of epoprostenol alone does not achieve filter durations >24 hours.

2. **Proceed according to the chosen anticoagulation system:**

   · **Sodium heparin:** dose of 500 IU/hour (10,000 IU in 40 ml of 0.9% Saline in a specific syringe for the Prismaflex/Prismax monitor). Set the heparin pump rate at 2 ml/h, which can be increased up to 3 ml/h.

   · **Epoprostenol:** the procedure for this anticoagulation is the following:

     o Dilute a vial of the new Epoprostenol in 250ml of 0.9% saline solution.

     o Place the saline with epoprostenol, with an infusion pump, in the afferent branch (arterial) of the circuit; as close as possible to the patient's outlet, and always pre-blood pump of the circuit (use the Y piece used for primming. NEVER use three-way valves).

     o Start at a rate of 5 mL/min, and increase by 5 mL every 5 minutes until reaching the treatment dose; usually 21 mL/h.

     o Since the saline with epoprostenol is introduced into the hemofilter circuit with an external pump, the volume provided (500ml, under normal conditions) must be considered in the patient's fluid balance.

   · **Citrate:**

     o It is based on the placement of a CITRATE infusion pump in the pre-pump arterial branch at a flow rate proportional to the blood flow, replenishing the decrease in ionic calcium by placing a second CALCIUM infusion pump in the venous branch (after the bubble catcher) at a flow rate proportional to the ultrafiltration.
A citrate concentration between 2.5 and 6 mmol/L is required to prolong coagulation time above 100%. We will achieve real regional anticoagulation of the EPT circuits by scheduling the infusion of citrate close to the arterial branch of the vascular access, which will be reversed when the blood returns from the patient and the citrate is metabolized. Currently, it can be done with the Prismaflex/Prismax monitors (all our monitors have updated software) using a specific line for calcium (from the syringe pump on the monitor itself).

The following parameters will be set:

- CITRATE FLOW: 2-4 mmol/L (we start at 3 by default).
- CALCIUM FLOW: 30-200% (we start at 100% by default).

The assembly scheme for citrate EPT is shown in Figure 2.

We will start with a blood flow of 140 ml/min; dialysis flow of 1500 ml/h; substitution fluid flow of 300 ml/h.

It should be noted that the dose of citrate used in each case is a substitution dose. Therefore, we usually only maintain a small dose to maintain fluid in the air/blood interface of the bubble catcher.

Calcium adjustment: ionic calcium in the circuit (post-filter venous sampling) must be determined 5 min after initiation (to confirm that the system is functioning correctly) and subsequently per shift, along with a blood gas test to assess the pH of the circuit and the patient (GEM). Corrections will be made based on the calcium levels of the circuit and the patient, according to Table 2.

Changes in blood flow and/or ultrafiltration will automatically vary the citrate and calcium flows to maintain the ratio. With Prismaflex-Prismax systems, the citrate infusion is done with the PBP pump. For calcium, which uses the monitor’s syringe pump, use the Y-piece used for primming; place it on the catheter return line (blue line).

We must use specific fluids for this therapy (specific palette instead of EDT fluid storage): Regiocit®(Citrate 18 mmol/L) on the PBP scale; and Biphozyl® (balanced fluid, calcium-free and with phosphate -2 mEq/L- and magnesium -1.5 mEq/L-) on the dialysis and replacement scales. The specific characteristics of the fluids that we use are detailed in Table 1.

3. Monitoring of complications: This topic will be further discussed in the Troubleshooting section.

Troubleshooting

Potential complications of anticoagulation systems:

1. Heparin: if any of these complications occur, it will be necessary to suspend heparin anticoagulation and initiate citrate anticoagulation.
1. Hemorrhage
2. Heparin-induced thrombocytopenia

2. Epoprostenol: if any of these complications occur, it will be necessary to suspend epoprostenol anticoagulation and initiate citrate anticoagulation

- Hemorrhage
- Hypotension
- Arrhythmias: bradycardia, tachycardia
- Severe Headache
- Gastrointestinal disorders

3. Citrate:

a) Acid-base balance disorder:

a. As each molecule of citrate has the same buffering effect as 3 molecules of bicarbonate, metabolic alkalosis can occur. Dialysis fluids with low or no bicarbonate concentration are required.

b. In citrate metabolism disorders (liver failure, severe shock with tissue hypoperfusion, etc.) the risk of citrate accumulation will be increased and metabolic acidosis may occur. The best parameter to avoid this complication is to monitor the $\text{TOTAL Ca}/\text{Ca}^{2+}$ ratio daily. When this ratio reaches a value of 2.1, the possibility of citrate accumulation begins to be high. At this point, measures should be taken to avoid further citrate loading on the patient.

**Solution: in this situation, we should decrease the total citrate load (increase dialysis, decrease blood flow, etc.) and monitor the clinical response, considering interrupting the therapy if metabolic impairment persists.

b) Hydro-electrolyte disorders:

a. The citrate complexes resulting from the binding of citrate to Ca$^{2+}$ (Ci-Ca) are easily removed by diffusion and convection ($\text{Sc Ci-Ca} > 0.85$), therefore it will be necessary to replace it to avoid hypocalcemia.

b. Citrate also chelates magnesium and must be supplemented (use dialysis and/or replacement fluids or supplement it externally).

c. Likewise, when trisodium citrate is used, we administer 3 mmol of Na$^+$ for each mmol of citrate, and low sodium dialysis or substitution fluids should be used.
**Solution: to avoid ionic disturbances derived from the application of the therapy, we should monitor sodium, potassium, calcium, phosphorus, and magnesium daily and make the necessary adjustments in therapy and supplementation based on their results.**

c) **Balance adjustment mistakes:**

a. The need for a citrate solution (prefilter) and a calcium solution (postfilter) will result in a volume load indirectly proportional to the concentration of the solutions used.

**Solution: to avoid inadvertent overhydration we will have to compensate for the volume load. Any monitor with the option of regional anticoagulation with citrate should do this compensation automatically.**

d) **Inadvertent overdosage of the connective clearance:**

a. The citrate solution works as a pre-filter replacement and the calcium solution as a post-filter. As the volume provided by these therapies has to be eliminated by ultrafiltration, continuous hemofiltration is performed.

b. The amount of "extra" dose of connective clearance we provide will depend on the concentration of the solutions we use. With diluted citrate (trisodium citrate 0.5%-18mmol/L) the concentration is very low, so the volume administered to avoid coagulation of the circuit ranges between 1L/h and 2L/h. This volume will be considered as convective clearance (prefilter replacement) and depending on the patient's weight, it may represent >2/3 of the usual dose (in AKI of 20-40ml/kg/h). Regarding calcium, due to the usual doses needed for replacement, the volumes are negligible, ranging from 5ml/h to 100ml/h depending on concentrated or diluted calcium.

**Time Taken**

- Preparation of the hemofilter: 15-20 minutes
- Selection of vascular access and catheter insertion: 15 minutes
- Decisions regarding the selection of the anticoagulation mode, the monitoring of its complications, and their resolution require a variable amount of time.

**Anticipated Results**

The standardized management of extracorporeal depuration techniques allows for a systematic approach and minimizes the rate of associated complications. In a complex aspect such as anticoagulation, having a specific anticoagulation protocol for extracorporeal depuration techniques provides professionals with tools to aid in the selection of the most appropriate anticoagulation system for the patient and its management. Furthermore, since citrate anticoagulation is an effective and
efficient technique that requires a learning curve for implementation and has complex management aspects, the availability of such a protocol can facilitate its application and development. All of this is analyzed through data collection via the DIALYREG registry to analyze our practices and identify areas for improvement. It has been demonstrated through our DIALYREG study.

References


**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- ACOTable1.pdf
- ACOTable2.pdf
- ACOFigure1.pdf
- ACOFigure2.pdf