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DIALYSIS / ORIGINAL ARTICLE

Timothy E. Bunchman · Norma J. Maxvold
Joni Barnett · Anne Hutchings · Mark R. Benfield

Pediatric hemofiltration: Normocarb dialysate solution with citrate anticoagulation

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Abstract Fourteen children, newborn to 17 years of age, underwent continuous veno-venous hemofiltration with dialysis (CVVHD), using a new FDA-approved bicarbonate-based calcium-free dialysis solution (Normocarb) in combination with citrate anticoagulation. Dialysis prescription included use of the PRISMA system (Gambro, Lakewood, Colo., USA), with ACD-A (Baxter, Deerfield, Ill., USA) for anticoagulation and Normocarb (Dialysis Solution, Richmond Hills, Ontario, Canada) for dialysate. Diagnosis included 11 children with sepsis and 3 children with tumor lysis syndrome. Mean weight was 31.6±4.7 kg (range 3.7–62 kg) and average length of therapy was 11.4±3.7 days (range 6 h to 67 days). Length of circuit patency was 71.3±7.2 h (range 6 h to 127 h), which was influenced in part by a decision to change circuits at 72 h as per manufacturer's recommendation. No bleeding occurred. This protocol utilizes industry-manufactured CVVHD machinery with both thermic and ultrafiltration control, with an effective anticoagulation protocol, and industry-produced bicarbonate dialysate. The use of industry machinery and solutions allows for consistent industrial quality assurance standards. This potentially may decrease the cost of therapy and minimize the risk of pharmacy errors that can occur with pharmacy-made dialysis solutions.

Keywords Hemofiltration · Citrate anticoagulation · Bicarbonate dialysis · Normocarb

T.E. Bunchman (✉) · J. Barnett · A. Hutchings · M.R. Benfield
Division of Pediatric Nephrology and Transplantation,
Children's Hospital of Alabama,
University of Alabama at Birmingham,
CHT 735, 1600 7th Avenue S, Birmingham, AL 35233, USA
e-mail: tbunchman@peds.uab.edu
Tel.: +1-205-9399781, Fax: +1-205-9757051

N.J. Maxvold
Division of Pediatric Critical Care,
Children's Hospital of Alabama,
University of Alabama at Birmingham,
Birmingham, Alabama, USA

Introduction

Hemofiltration (HF) is commonly used for the treatment of acute renal failure in the pediatric population [1, 2]. HF allows for care of the hemodynamically unstable child requiring renal replacement therapy and is effective in enhancing medical therapies (e.g., maximizes nutrition) in the face of diminished renal function [3, 4].

From 1990 to 1999, transitioning from adaptive machinery to industry-produced machinery resulted in the use of warmers in order to maintain euthermia, as well as ultrafiltration controllers to maintain accurate fluid balances [5, 6]. What has continued to be lacking, however, are user-friendly anticoagulation protocols, as well as solutions that have industry standards, which allow for metabolic control with minimal pharmacy involvement and cost.

In the early 1990s Mehta et al. [7] championed the idea of citrate anticoagulation. In many adult programs, citrate anticoagulation was substituted for heparin as a means of achieving anticoagulation of the HF system without increasing the patient's risk of bleeding [8]. Many programs followed suit. However, due to the high sodium load of the citrate from the protocol of Mehta et al. [7], hospital pharmacies are required to make specialized low-sodium dialysis solutions in order to achieve sodium balance. Recently, lower sodium-containing citrate solutions have begun to be used, no longer requiring specialized pharmacy-made solutions. This then allows for industry-produced dialysis solutions resulting in reduced pharmacy time and, subsequently, cost.

Dialysis solutions have also changed significantly in the last 20 years. In the 1970s and 1980s, the base used in hemodialysis changed from acetate to bicarbonate, resulting in improved quality of care and less hemodynamic instability [9]. The same trend towards bicarbonate-based solutions has begun in HF, with the initiation of Hemosol BO (Hospal, Lyon France) that is available outside the United States as a dialysis solution for continuous veno-venous hemofiltration with dialysis (CVVHD). Until recently, only lactate-based solutions

had FDA approval and, therefore, were predominantly used for dialysis solutions in HF in the United States when pharmacies were not supplying custom-made solutions. The primary reason for the use of lactate-based solutions is not because lactate is a superb buffer, but because of difficulties in maintaining bicarbonate-based solution in plastic bags. It is recognized that bicarbonate, over time, leeches out of the plastic bags, resulting in a lower bicarbonate level in a solution. Studies of HF have compared bicarbonate- and lactate-based dialysis solutions. Although the outcome appears to be similar, patients on bicarbonate-based solutions had improved pH and plasma bicarbonate levels, as well as lower plasma lactate levels during the bicarbonate portion of these studies [10, 11]. The recent FDA approval of a bicarbonate-based calcium-free dialysate solution (Normacarb, Dialysis Solutions, Richmond Hills, Ontario, Canada) has made available a bicarbonate-based dialysate for CVVHD in the United States.

As we rebuilt the HF program at the Children's Hospital of Alabama, we have combined industry standard machinery with thermo- and ultrafiltration control, industry standard bicarbonate-based dialysis solutions, and industry standard citrate anticoagulation protocols. The use of industry-produced equipment and solutions has allowed the program to rapidly expand with industry quality assurance, simultaneously cutting pharmacy time and cost and potentially cutting pharmacy errors.

Materials and methods

From November 2000 to March 2001, 14 children underwent HF. Diagnosis in these children included sepsis in 11 and tumor lysis syndrome in 3. Age varied from newborn to 17 years of age, and the mean weight was 31.6±4.7 kg (mean±SEM, range 3.7–62 kg). In November 2000 we implemented the use of citrate anticoagulation and, in December 2000, the use of Normocarb as the dialysate for CVVHD. Prior to the use of Normocarb we used pharmacy-made dialysis solution as previously described (Table 1).

The dialysis prescription is as follows. The PRISMA HF system is used (COBE, Lakewood, Colo., USA) with an attached Prismastherm for thermal control. At initiation, the machine is placed in the CVVHDF mode to allow for the addition of replacement fluid if needed, but the prescription is always CVVHD. Pre- or post-filter replacement fluid is not used other than what is given for routine patient management (e.g., IV fluids, nutrition, medications).

Access depends on the size of the patient, varying from the MedComp (Harleysville, Pa., USA) softline 7-Fr dual-lumen accesses to a triple-lumen 12-Fr access by Arrow International (Reading, Pa., USA).

Blood flow rate (BFR) is begun between 2 and 8 ml/kg per min and rarely exceeds 150 ml/min with the goal of maintaining sufficient BFR with minimal HF access alarms. Dialysis flow rate is set at 2,000 ml/1.73 m^2 per hour (2 l/1.73 m^2 per hour) as previously described [12] and recently validated by Ronco et al. [13].

The citrate solution used is the ACD-A (Baxter, Deerfield, Ill., USA) solution, placed on an IV pump and connected through a stop cock on the "arterial" part of the HF vascular access. Pharmacy-made calcium solution (8 g of calcium chloride per 1 l of saline) is placed on an IV pump and infused in a central line independent of the HF vascular access or in the "pig tail" of those vascular accesses that are triple lumen.

Table 1 Components of both a local pharmacy made solution and Normocarb

Electrolyte	Pharmacy made	Normocarb
Glucose	100 mg/dl	0
Na^+	140 mEq/l	140 mEq/l
Cl^-	95 mEq/l	105 mEq/l
HCO_3^-	40 mEq/l	35 mEq/l
Mg^{2+}	1 mEq/l	1.5 mEq/l
	If needed add:	If needed add to Normocarb
KCl	2 mEq/l	2 mEq/l
K_3PO_4[a]	2 mEq/l	2 mEq/l

[a] This equals 4 mEq/l of phosphorus

Table 2 Components needed for local Normocarb/citrate protocol

Components needed for citrate/Normocarb protocol
ACD-A (Baxter, Deerfield, Ill., USA)
$CaCl_2$ 8 g/l normal saline (pharmacy-made)
Normocarb (Dialysis Solution, Richmond Hills, Ontario, Canada)

The dialysate consists of Normocarb (Tables 1 and 2), which is a dialysate bath sodium of 140 mEq/l, bicarbonate 35 mEq/l, and magnesium 1.5 mEq/l. When indicated, we add to the Normocarb 2 mEq/l of potassium chloride and 2 mEq/l phosphorus (K_3PO_4).

At initiation, the ACD-A infusion rate (ml/h) began at 1.5 times the CVVHD system BFR (ml/min) with the calcium infusion rate running at 0.4 times the ACD-A rate in milliliters per hour. For example, in a 50-kg child the BFR would begin at 100 ml/min, the ACD-A rate would begin at 150 ml/h, and the calcium rate would begin at 60 ml/hr. The Normocarb dialysis flow rate is started at 2 l/1.73 m^2 per hour [e.g., in a 50-kg child (approximately 1.4 m^2) dialysis is at 1.6 l/h]. Two hours after beginning HF, the patient and the HF system ionized calcium (iCa^{2+}) are analyzed. The patient iCa^{2+} is assessed from an existing arterial line (or if an arterial access is not available the iCa^{2+} can be drawn from the HF "arterial" access that is post patient but prior to the infusion of the ACD-A) and targeted to the normal range of 1.1–1.3 mmol/l. The HF system iCa^{2+} is assessed from the blood sampling port that is at the post-filter site of the HF system and is targeted to a range of 0.35–0.5 mmol/l. Adjustment of the patient's iCa^{2+} is performed by increasing (in the face of a patient iCa^{2+} <1.1 mmol/l) or decreasing (if the patient's iCa^{2+} >1.3 mmol/l) the infusion rate of calcium chloride. Titration of the HF circuit's iCa^{2+} is performed by increasing (if HF iCa^{2+} >0.5 mmol/l) or decreasing (if HF iCa^{2+} <0.35 mmol/l) the ACD-A infusion rate (Fig. 1).

Results

The average length of HF therapy per patient was 11.4±3.7 days (range 6 h to 67 days) on therapy. Length of time of circuit patency was 71.3±7.2 h (range 6 h to 127 h). The length of circuit time was influenced in part by a decision to change circuits at 72 h as per manufacturer's recommendation. This varied based on the stability of the patient, as well as the decision of the nephrologist on service at the time.

No bleeding occurred at any time during these therapies using citrate anticoagulation. Electrolyte disturbances were primarily related to sodium, bicarbonate,

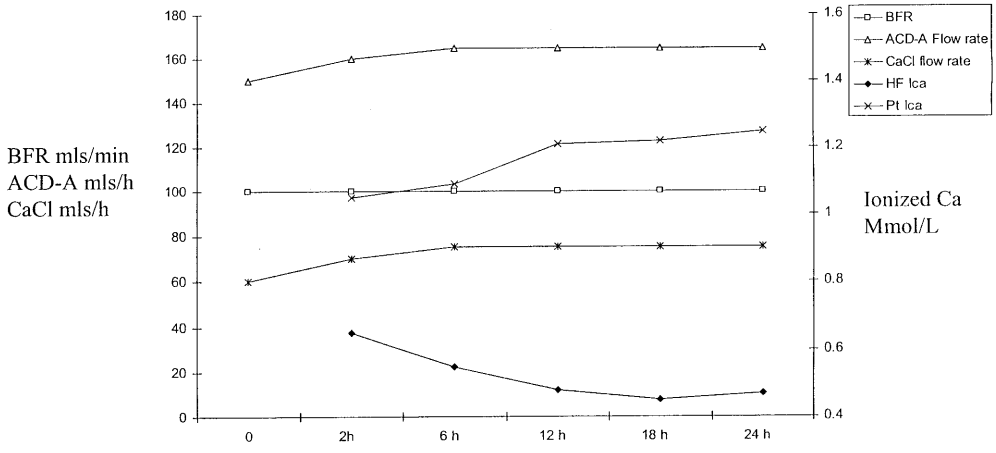

Fig. 1 Example of a 50-kg child at a blood flow rate (*BFR*) of 100 ml/min with ACD-A begun at 150 ml/h and adjusted based upon hemofiltration (*HF*) system ionized calcium and calcium chloride ($CaCl_2$) begun at 60 ml/h and adjusted based upon patient ionized calcium

and magnesium changes. One child had an acute drop in sodium (141 mEq/l to 121 mEq/l), over 6 h, resulting in a seizure. This was in retrospect related to a rapid free water infusion to the patient independent of the HF circuit. This was corrected with a 3% saline infusion and a halt in the free water infusion without long term sequelae. A second patient had a sodium level of 152 mEq/l, which was due to an accumulation of the sodium load from the total parenteral nutrition (TPN), the calcium chloride infusion in the saline, as well as IV antibiotics. This was corrected by lowering the sodium in the TPN and reducing the calcium chloride in the saline by half. Due to magnesium clearance, despite a magnesium concentration of 1.5 mEq/l in the Normocarb, hypomagnesia is often seen. This is easily corrected by either maximizing the TPN magnesium or adding up to 1.0 mEq/l additional magnesium sulfate to the Normocarb, which already has 1.5 mEq/L of magnesium sulfate.

All children who were on HF in excess of 7 days developed a metabolic alkalosis. Metabolic alkalosis is caused by many factors, including nasal gastric losses of the patient, the acetate base (that converts to bicarbonate) that is commonly used in TPN, bicarbonate from the Normocarb (35 mEq/l), and, most importantly, from hepatically produced bicarbonate, which is a direct result of citrate anticoagulation. In those patients that developed metabolic alkalosis, it was not uncommon for the plasma bicarbonate to become 35 and 40 mEq/l and at times pH in the 7.5 range. This is easily resolved by decreasing the Normocarb dialysate rate and adding normal saline as a replacement fluid at the same rate that the Normocarb is reduced. An example of this would be if a child's dialysate solution rate was 1,000 ml/h and a metabolic alkalosis occurred, then the dialysate solution would be decreased to 700 ml/h and normal saline as a replacement fluid (using the CVVHDF mode of the PRISMA system) would be begun at 300 ml/h. Therefore, the total exposure to dialysate and replacement solution remained constant, but the infusion of normal saline (pH 5.4) and reduction of bicarbonate exposure from the Normocarb resulted in improvement of the alkalemia.

A bradykinin release syndrome is commonly seen in adult patients on angiotensin-converting enzyme (ACE) inhibitors, but has been recently described by Brophy et al. in small children undergoing a blood-primed circuit when using an AN-69 membrane [14, 15]. In the 4 children (none of whom were on ACE inhibitors), who less than 6 kg, who underwent citrate anticoagulation, attention to the timing of citrate introduction with the PRISMA system is important. Brophy et al. [15] demonstrated that some children who require blood priming with an AN-69 membrane may have a bradykinin release syndrome due to plasma reaction to the AN-69 membrane in an acidotic environment. Because of this potential risk, in the PRISMA, a post-filter transfusion protocol was utilized that allows for a saline-primed circuit with a blood infusion post filter back to the patient. This results in an identical amount of blood exposure as with the blood-primed system. An average of 2–4 mEq/kg of bicarbonate is given pre filter directly into the PRISMA circuit. This seems to negate any side effects of hypotension from the acidotic environment of the banked blood associated with interactions with the AN-69 membrane. As the pH of the citrate solution is also quite low (pH<5), if one utilizes citrate anticoagulation from the start it may prolong the bradykinin release syndrome. In 1 child with sepsis we used citrate from the initiation of HF and found that the bradykinin release syndrome was prolonged. This was prevented subsequently by introduction of the citrate 5 min after the induction of the HF process. In theory, protein coating of the membrane, as well as normalization of the patient and HF system pH, prevents any untoward effect of the acidotic environment from the citrate. Therefore, in small children undergoing HF, care to maintain adequate flow without anticoagulation for the first 5–10 min prior to starting the citrate may be needed.

Once the prescription is established, the patient's BFR, dialysate flow rate, the ACD-A infusion rate, the system's ionized calcium, the calcium infusion back to the patient, and the patient's ionized calcium should be monitored. Typically, within 12 h, steady state is reached, with very little adjustment required beyond this time point (Fig. 1).

Discussion

When commencing HF one often considers whether continuous veno-venous HF (CVVH) is equal or superior to CVVHD. Data to date have shown that, in studies comparing CVVH and CVVHD, urea clearance is identical when the total solution exposure is identical. These results have been consistent in other studies [12, 16, 17].

Data suggest that CVVH may be superior to CVVHD for sepsis syndrome. What at first glance was thought to be an improvement of cytokine clearance appears to be cytokine absorption. Therefore, if a convective mode (CVVH) of HF for sepsis is to be utilized it is clear that, because cytokines are absorbed and not significantly removed, frequent changes of the membrane are necessary over time [18, 19].

A replacement fluid is used in CVVH; if an industry-produced solution is required, then either normal saline or lactated Ringer's is used, but both of these may result in an acid load to a patient. If a pharmacy-made solution is required then solutions can be custom made according to the patient's special needs (as shown in Table 1). However, this lacks industry standard and increases pharmacy time and cost, with potential risk of compounding error.

In the United States, for CVVHD, a commercially available lactate- and calcium-containing solution (Hemofiltration Solution, Baxter) or a commercially available bicarbonate- and calcium-free solution (Normocarb, Dialysis Solutions) can be used. Outside the United States, Hemosol B0 (Hospal), which is a bicarbonate base containing calcium, is available. All of these solutions appear to be effective for overall urea clearance and reasonable as dialysate solutions. The Baxter solution, due to its lactate base, may result in higher plasma lactate levels in patients compared with bicarbonate-based solutions. The question of whether lactate or bicarbonate is better has been addressed in different studies. In an adult cross-over study Zimmerman et al. [11] showed that at 48-h increments lactate levels were less in the bicarbonate base solutions than in the lactate-based solutions. Further work by Maxvold et al. [10], a pediatric crossover study, showed similar differences at 24 h. Neither of these studies demonstrated outcome differences, but both studies showed that lactate-based solutions result in higher plasma lactate levels in the patient. Although this may itself not be detrimental, high patient plasma lactate levels may affect decision making by the intensivist looking for causes of lactic acidosis. This would include evaluation of poor tissue perfusion, splanchnic bed hypoperfusion with possible necrosis, as well as a sign of early sepsis.

Each of these solutions (Baxter, Dialysis Solution, Hospal) offers industry standards. Certainly a pharmacy can produce a solution to specification, but a pharmacy cannot offer industry standard and industry quality assurance. Programs have reported pharmacy errors resulting in untoward patient outcome. Thus, by using an industry standard solution for dialysate, the pharmacy no longer needs to double-check the components of the locally produced solution, potentially saving time and liability.

When comparing costs of industry standard solutions and pharmacy solutions, not only the cost of raw materials, but also technician time, pharmacist time, and potential liability due to lack of quality control should be considered. When we analyzed the financial cost of moving from pharmacy-made dialysis solutions to industry-produced solutions, we observed a reduction in pharmacy cost. Thus, an industry-made solution not only allows for industry standards with less potential liability to the hospital, but also at overall less expense to the program.

Data, to date, have not identified whether citrate or heparin results in a difference in patient or HF system outcome. Certainly the use of citrate allows for HF system anticoagulation without patient anticoagulation. If one uses citrate anticoagulation, calcium-free or minimal calcium dialysate solution is preferred, in order to minimize the amount of citrate and calcium binding at the level of the HF membrane. By using the ACD-A solutions there is a lower sodium exposure compared with the protocol of Mehta et al. [7], therefore allowing a standard 140 mEq/l sodium bath for dialysate solution. This results in a no-net-positive sodium level to the patient. Normocarb is calcium free, whereas the HF solutions of Baxter or Hospal Hemosol B0 contain calcium. Although comparative data are lacking, in theory both the Baxter-based solutions and the Hemosol B0, which contains calcium, could result in citrate and calcium binding at the HF membrane. Therefore, if citrate anticoagulation is used with the Hospal or Baxter solutions, a greater citrate infusion may be required to maintain the same degree of anticoagulation due to calcium and citrate binding at the membrane level.

The bedside nursing needs to be considered with all protocols. Citrate anticoagulation requires ionized calcium monitoring, while heparin anticoagulation requires monitoring of clotting time. The frequency of monitoring along with the extent of HF clotting from either anticoagulation protocol results in nursing burden. No data to date have evaluated the bedside work and circuit life with the HF protocol compared with heparin protocols. Historically, this program used heparin and followed bedside-activated clotting times (ACTs) every 2–4 h for heparinized patients. We are currently measuring ionized calcium of the HF system and the patient at 6-h increments. Cost of measurement of ACTs is influenced by the ACT tube, nursing personnel time, as well as the cost of the blood gas used for the iCa^{2+} analysis. When these components are considered, the overall cost appears to be similar for the two protocols. This is due, in part, to the fact that the ionized calcium performed for the patient is part of the blood gas used for ventilator management.

In prior work we have reported an average life of the HF system with heparin of approximately 67 h [20]. The citrate protocol results in an average HF circuit life of 71 h. These data are influenced by the fact that we at-

tempted to follow the manufacturer's recommendations and changed the HF circuit at 72-h intervals. Each time a circuit is changed there is the cost of the disposables and (potential) blood exposure. Therefore, if citrate allows for a longer circuit life than heparin, this may result in additional cost reduction.

One side effect of the use of Normocarb with the citrate solution, over time, is a resultant metabolic alkalosis that occurs in 100% of children beyond 7 days on HF [7, 8]. This is easily prevented or can be easily remedied.

The laboratory findings of rising total calcium and falling ionized calcium are referred to as "citrate lock," which can occur in patients on citrate anticoagulation. This occurs when the citrate (ACD-A) rate exceeds the hepatic metabolism and dialysate clearance of citrate. Stopping the citrate infusion for 2–4 h and then re-instituting the ACD-A at a rate of 70% of the previous rate easily treats this. During this time the patient ionized calcium needs to be frequently monitored and the calcium infusion rate adjusted appropriately.

In summary, with the use of industry standard machinery with warmers and ultrafiltration monitors, the use of industry standard citrate anticoagulation solution, and the use of industry standard dialysis solution, minimal pharmacy input is needed for the care of pediatric HF patients. Pharmacies are still necessary for the calcium in normal saline and for some potential additives to the Normocarb, but our procedure results in less pharmacy time, less risk of pharmacy error, a reduction in pharmacy cost, and less hospital liability. These children are critically ill, therefore minimizing the risk of complications is important for outcome. Normocarb removes the risk of error from the pharmacy and citrate removes the risk of bleeding from heparinization.

This work does not indicate whether bicarbonate or lactate affects outcomes or whether heparin or citrate affects the life of the HF system, but allows a basic design of what we feel is a simple and safe HF prescription for children.

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