CONTINUOUS REPLACEMENT THERAPIES IN PEDIATRICS PATIENTS

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Abstract

At the middle of seventies the dialysis equipment starts to improve and new methods arrived in the field of replacement therapies (plasmapheresis, filtration). In recent years, the technique was modified and newer options were made available under the common name of Continuous Renal Replacement Therapies (CRRT).

We want to describe the newest technique for renal replacement and all the advantages and disadvantages for this machinery. We focused the presentation on pediatric CRRT and the advantages of these methods.

Hemofiltration is indicated in the pediatric population for hypervolemia, anuric, in acute renal failure, patients with sepsis, with electrolyte abnormalities, and for catabolic patients with increased nutritional needs, in some poisoning situations.

We need for Romanian children hospitals at least one machinery that can perform CRRT techniques and trained personnel for a performing intervention in emergency.

Key words: Replacement therapies, hemofiltration, children.

Introduction and history of CRRT

Renal replacement therapies applied to critically ill patients have been particularly designed to be simple and easy to be instituted and monitored. This is definitely a contradiction in terms and where the most sophisticated technology might be required for a very delicate task, primitive apparatus and supplies (Ronco et al). In 1977 Peter Kramer, to fulfill the requirement of simplicity, moved from the traditional intermittent hemodialysis to a newly designed treatment named Continuous arteriovenous hemofiltration (CAVH), and then newer options were made available under the common name of Continuous Renal Replacement Therapies (CRRT). The use of a blood pump with a veno-venous blood access became popular (CVVH) and the arterio-venous treatments were partially abandoned. All these modifications are today available as routine treatments.

The basic principles of continuous hemofiltration (HF) are similar for adults and children, but the application of these modalities in children require recognition of the unique properties for pediatric practice. Special attention to aspects such as, extracorporeal blood volume/blood priming (especially in patients < 10 kg), nutritional issues, etiological differences in disease processes (Inborn Errors of Metabolism), access, and line/membrane choice, must be given when dealing with problems in this population.

HF is indicated in the pediatric population for hypervolemic, anuric acute renal failure (ARF), electrolyte abnormalities, catabolic patients with increased nutritional needs, patients with sepsis, poisoning (occasionally in combination with hemodialysis - HD), inborn errors of metabolism, diuretic unresponsive hypervolemia, and hepatic or drug induced coma. Additionally, HF in conjunction with other therapies such as extracorporeal membranous oxygenation (ECMO), and the hepatic support therapies (MARS) has also proven to be quite useful (in Romania - in Iasi and Bucharest two medical teams already use this new method).

Equipment

In the past, blood pumps and fluid balancing systems have been borrowed from the standard hemodialysis technology, while only recently self standing machines have been specifically designed to perform continuous renal replacement therapies.

The simplest machinery often includes a blood pump segment with an air leak detector. What adaptive machinery does not include is the ability to regulate either ultrafiltration control or thermal control. The industry machinery (Gambro, Baxter, B. Braun Medical, Fresenius) offer a variety of warming systems, accurate ultrafiltration controllers, venous and arterial pressure monitor and blood leak detectors. In addition these allow for local prescriptions of HF including continuous veno-venous hemofiltration (CVVH), continuous veno-venous hemofiltration with dialysis (CVVHD), continuous veno-venous hemodiafiltration (CVVHDF (table 1).

Table 1 Available hemofiltration machines.

Company	Machine	Lines
GAMBRO	PRISMA	ADULT+/-PEDS
BAXTER	Accura, etc	ADULT/PEDS
FRESENIUS	2008	ADULT/PEDS
B BRAUN	Diapact	ADULT/PEDS

All systems can provide circuit volumes that offer the adaptability to sustain therapy for smaller and larger size individuals. The Baxter, Braun and the Fresenius machines allow for individual choice of hemofilter membrane while the PRISMA uses a single membrane (AN-69) that has been found in adult ARF data, to improve survival rate.

Vascular access

Standard vascular access utilized for acute dialysis is not adequate to perform high volume hemofiltration. In the majority of the cases, double lumen catheters are providing a large amount of recirculation and an insufficient blood flow. In hemofiltration, while transmembrane ultrafiltration represents the overall amount of fluid removed by the hemofilter, the "net" ultrafiltration represents the real amount of fluid removed from the patient after the re-infusion of the substitution fluid. When high blood flows are required, is recommended to use two separate catheters to permit a reduced resistance of the inflow and outflow, and to reduce the amount of access recirculation. These catheters may be positioned in the jugular and femoral veins without major complications. For pediatric patients the suggested selections for access are figurate in table 2.

Table 2 Size of HF Vascular Access for Pediatric Patients.

PATIENT SIZE	CATHETER SIZE + comp.	SITE / INSERTION
NEONATE	Single-lumen 5 Fr (COOK)	Femoral artery or vein
3-6 Kg	Dual-Lumen 7.0 French (COOK)	Internal/External-Jugular, Subclavian or Femoral vein
	Triple-Lumen 7.0 Fr (MEDCOMP, ARROW)	Internal/External-Jugular, Subclavian or Femoral vein
6-15 Kg	Dual-Lumen 8.0 French (ARROW, KENDALL)	Internal/External-Jugular, Subclavian or Femoral vein
>15-Kg	Dual-Lumen 9.0 French	Internal/External-Jugular, Subclavian or Femoral vein
>30 Kg	Dual-Lumen 10.0 French (ARROW, KENDALL)	Internal/External-Jugular, Subclavian or Femoral vein
	Triple-Lumen 12.5 French	Internal/External-Jugular, Subclavian or Femoral vein

Solutions

The Zimmerman et al studies with adult patients demonstrated that both lactate as well as the bicarbonate based solutions result in the same degree of effective clearance, but plasma lactate levels are higher in patients on lactate-based solutions. Elevated lactate levels may offer mystifying information to the clinician, especially in the setting of sepsis and organ perfusion. Patients with hepatic failure may not be able to convert lactate to bicarbonate, and use of lactate based dialysis solution may produce or exacerbate lactic acidosis, thus bicarbonate buffered dialysis solutions are therefore preferred for patients with hepatic failure. Barenbrock et al demonstrated an improved care of the patient when receiving bicarbonate based solutions when compared to lactate, but the overall data are controversial. Essentially with the use of these products the use of lactate based solutions should be considered historical and potentially detrimental to the child needed CRRT.

Solutions for CVVH can be as uncomplicated as normal saline, lactated ringers, total parenteral nutrition (TPN), routine intravenous fluids or pharmacy made solutions (tables 4 and 5) or other. Many doctors will use saline or lactate of ringers as a relatively inexpensive form of replacement fluid in those patients who are having excessive ultrafiltration. The decision to use replacement fluid is often based on the overall solute and ultrafiltration clearance requirements of the patient as well as the local standard of care. Additionally, pharmacies made customized solutions (usually bicarbonate based) are also available. Some are calcium free dialysate solutions, providing a venue for the provision of either citrate or alternate anticoagulation.

Finally, while it is still controversial whether the substitution fluid should be warmed in standard CVVH, the warming procedure in HVHF is practically mandatory since severe hypothermia may fatally occur when high volumes of fluid are exchanged in a short period of time.

Anticoagulation

If we use high blood flows, anticoagulation becomes less critical since the time of contact between blood and the artificial surfaces is reduced. It should however be remembered that blood viscosity and hematocrit may significantly increase within the filter once high filtration fractions are achieved. In these circumstances, adequate anticoagulation is essential to avoid clots formation. Anticoagulation should be thought about in three different ways. Patients with multi-organ system failure have a natural anticoagulation due to the underlying disease (e.g. sepsis with intravascular coagulation). Those patients may have a natural anticoagulation that may be in the range whereby anticoagulation is not necessary. In those patients obtaining a high blood flow rate with a large size access may be sufficient to maintain HF without the use of anticoagulation, but is not easy to take the decision. Bleeding secondary to systemic heparinization is always a potential complication.

The majority of studies have shown that heparin is efficient in children. The use of heparin loading at 10-20 units/kg as an initial bolus and then 10-20 units/kg/h maintaining an anticoagulation usually adequate in most patients.

Citrate anticoagulation is performed by adding citrate to the blood as it leaves the patient and returns to the machine. The principle is the same that we usually use in plasmapheresis. The result is an ionized calcium of 0.35 to 0.45 mmol/l within the circuit. Citrate anticoagulation requires a calcium free dialysis bath in order to prevent any potential binding of calcium and any potential risk of coagulation in the HF system.

Citrate also requires a separate central line for calcium replacement

Indications

Prescriptions for acute HF have been for the treatment of acute renal failure (ARF). If one were to suggest a standard prescription, then a blood flow for CVVH would be in the range of 4-6 ml/kg/min trying to keep a venous return pressure of less than 200 mm Hg. Further there is no absolute data to date on the rate of replacement fluid or dialysate fluid. Historically we have used rate of 2000 per 1.73 m^2 /hr for this allows us to compare pediatric data based on body surface area to adult data. Thus in an 11 kilo child who has a $0.5m^2$ body surface area, the dialysate or replacement fluid prescribed would be roughly in the 700 ml/hr. The standardization of flow rate as well as ones replacement or dialysate rates allows a better appreciation of steady state drug kinetics, clearance and toxic removal.

Complications of the CRRT

The same complications that occur in other replacement therapies are present in applying hemofiltration. Jenkins et al demonstrated up to a 30% ultrafiltration error rate when using intravenous pumps to regulate ultrafiltration. The only way to avoid the ultrafiltration error is to use industry made equipment that has been purposefully made for ultrafiltration regulation. This will not affect the individual IV pump error rate, but will minimize most of the error seen at bedside.

One of the more biocompatible membranes has been shown to cause a bradykinin release syndrome in patients who are acidotic at the onset of HF or in children who require a "blood prime" in the setting of one of these membranes. These membranes, in the face of interacting with an acidotic plasma environment generate bradykinin which may result in reactions from minor nausea to clinical anaphylaxis.

Children nutrition

For these children it is imperative to understand that HF prescriptions will result in significant amino acid loss across the hemofilter. Data by Davies et al in adults, Maxvold et al in pediatrics and by Zobel et al in neonates has showed that whether one does CVVH or CVVHD, one need to consider the amount of protein calories given to a patient. In non-dialytic setting of ARF the standard recommendation for protein requirements is in the range of 1.5 grams/kilo/day. In patients on HF, in order to maintain adequate nitrogen balance, protein administration may be in the range of 3-4 grams/kg/day. Further in phosphorous deficient dialysate solutions, hypophosphatemia occurs frequently, requiring either a separate phosphorous infusion or additional phosphorous.

Discussion

A retrospective study by Goldstein et al examined outcome in 22 pediatric patients receiving CVVH (D) and controlled for patient severity of illness using the Pediatric Risk of Mortality score. Of the clinical variables studied (glomerular filtration rate, mean airway pressure, patient size or % fluid overload), only the degree of % fluid overload at the time of CRRT initiation differed between survivors (16.4% +/- 13.8%) and non-survivors (34.0% +/- 21.0%, p =0.03), even when controlled for severity of illness by PRISM score using a multiple regression model. This supports earlier data by Fargason et al suggesting that the PRISM score may not be predictive.

A database (Bunchman et al) examined 226 children treated with replacement therapies (HF, HD and PD) looking at predictors of outcome. Diagnosis in these groups varied from ARF to inborn error of metabolism, to intoxications. Similar to adult data, outcome appears to be related not to age, not to modality but to severity of illness and underlying cause of need for RRT. This points out that it is not the modality, but rather the underlying cause of the need for HF, as well as the overall hemodynamic status of the patient (including the presence or absence of vasopressor agents) that affects outcome. Prospective data by the Prospective Pediatric Continuous Renal Replacement Therapy database validates Goldstein's work showing that early intervention with less fluid overload at the time of beginning CRRT improves survival.

In our country in some centers these methods have been were applied, but in few cases, thus no conclusion can be made. In the near future we hope that all the decision making factors can understand that life can be saved with high performance machines and using expensive methods.

The ideal machine should have a small volume, an easy interface and high flexibility (i.e. the ability of performing all types of treatments). The machine must be a self standing equipment, easily transportable at the bedside. Recently, new machines for CRRT have been designed with 4 to 5 pumps. Such machines are not utilized on daily basis, and in some cases the training of the personnel becomes difficult or prolonged. Furthermore, such machines are frequently big, difficult to move and require costly maintenance. The cost of the lines and the entire treatment, including the machine, may significantly increase. In Romania even the commonest machinery performing CRRT is an luxurious one.

Conclusion

Continuous renal replacement therapies appear to be the appropriate treatment in patients with ARF complicated by different clinical problems and other critical situations. In children patients with ARF and other organ system failure, or in patients with a septic syndrome, high volume hemofiltration may be indicated.

For our emergency cases in pediatric units this hemofiltration equipment is mandatory to perform a modern treatment in some desperate situations.

References

1. Barenbrock M, et al. Effects of bicarbonate- and lactate- buffered replacement fluids on cardiovascular outcome in CVVH patients, Kidney Int 2000, 58:1751-1757
2. Bellomo, R. Choosing a Therapeutic Modality: Hemofiltration vs. Hemodialysis vs. Hemodialfiltration, Seminars in Dial, 1996; 9
3. Braun, M C et al. Continuous Venovenous Am J Nephrol, 1998; 18: 531-533
4. Brophy PD, et al. Access for Pediatric CRRT, presented at the 8th CRRT, March 6-8, 2003, San Diego
5. Brunet S, Leblanc M, et al. Diffusive and Convective Solute Clearances During Continuous Renal Replacement Therapy at Various Dialysate and Ultrafiltration Flow Rates, Am J Kid Dis 1999; 34:486-492
6. Bunchman TE, et al. Vascular access for hemodialysis or CVVH (D) in infants and children, Dial Transplant. 1994; 23:314-317
7. Bunchman TE, McBryde KD, Mottes TE, Gardner JJ, Maxvold NJ, Brophy PD: Pediatric acute renal failure: outcome by modality and disease Pediatr Nephrol 16 (2001) 12, 1067-1071
8. Chadha V, et al. Citrate clearance in children receiving continuous venovenous renal replacement therapy, Pediatric Nephrology 2002, 17:819-824
9. Davies SP, Reaveley DA, Brown EA, Kox WJ: Amino acid clearance and daily losses in patients with acute renal failure treated by continuous arteriovenous hemodialysis, Critical Care Med 1991 19:
10. Fargason CA, Langman CB: Limitations of the pediatric risk of mortality score in assessing children with acute renal failure. Pediatr Nephrol 1994; 7:703-7
11. Flynn JT. Choice of dialysis modality for management of pediatric acute renal failure. Pediatr Nephrol 2002 17:61-9
12. Gardner JJ, et al. Flow characteristics of a new pediatric continuous renal replacement therapy catheter for acute renal failure management. Blood Purif 1997; 15, abstr 33
13. Geary DF, et al. Low dose and heparin free hemodialysis in children, Pediatr. Nephrol. 1991; 5:220, 1991.
14. Goldstein SL, Currier H, Graf JM, Cosio CC, Brewer ED, Sachdeva R: Outcome in children receiving continuous hemofiltration . Pediatrics 2001 Jun;107(6):1309-12
15. Goldstein SL, Somers MJG, Symons JM, Brophy PD, Baum M, Bunchman TE. Anticoagulation for Pediatric CRRT: A Report from the ppCRRT Registry Group, presented at the 8th CRRT, March 6-8, 2003, San Diego
16. Jenkins R, Harrison H, Chen B. Arnold D. Funk J: Accuracy of intravenous infusion pumps in continuous renal replacement therapies, Trans Am Soc Artif Intern Organs J 1992;38:808-811
17. Jenkins RD, Kuhn RJ, Funk JE: Clinical implications of catheter variability on neonatal continuous hemofiltration, Trans Am Soc Artif Intern Organs 1998; 34:108-111
18. Lacour F, Maheut H: AN-69 membrane and conversion enzyme inhibitors: prevention of anaphylactic shock by alkaline rinsing? Nephrologie 1992; 13:135-136
19. Lane PH, Mauer SM, Blazar BR, Ramsey NK, Kashtan CE. Outcome of dialysis for acute renal failure in pediatric bone marrow transplant patients, Bone Marrow Transplantation 1994 13:613-7
20. Macdonald D, Martin R: Use of Sodium Citrate Anticoagulation in a Pediatric Continuous Venovenous Hemodialysis Patient ANNA Journal 1995; 22: 21-24
21. Maxvold NJ, Flynn JT, Brophy PD, et al. Prospective, crossover comparison of bicarbonate vs lactate-based dialysate for pediatric CVVHD, Blood Purif 1999; 17; abst :27
22. Maxvold NJ, Smoyer WE, Custer JR, Bunchman TE. Amino acid loss and nitrogen balance in critically ill children with acute renal failure: A comparison between CVVH and CVVHD therapies. Crit Care Med, 2000; 28:1161-1165
23. Mehta RL, McDonald B, Gabbai FB et al; A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure Kid Intern 2001 60:1154-116
24. Meyer RJ, Brophy PD, Bunchman TE et al, Survival and renal function in pediatric patients following extracorporeal life support with hemofiltration. Pediatric Critical Care Medicine 2001; 2:238-242.
25. Parekh RS, Bunchman TE: Dialysis support in the pediatric intensive care unit. Adv Ren Replace Ther 1996 3:326-3.
26. Ronco C, Kellum JA, Mehta RL: Nephrol Dial Transplant (2001) 16:1555-1558
27. Ronco C, Parenzan L Acute renal failure in infancy: Treatment by continuous renal replacement therapy Inten Care Med 1995; 21: 490 – 499
28. Ronco et al, Hemofiltration on www.hemofiltration.org
29. Roy, D., et al Continuous veno-venous hemodiafiltration using bicarbonate dialysate Pediatr Nephrol, 1997; 11:680-683
30. Symons JM, et al, Techincal Characteristics of Pediatric CRRT :A Report from the ppCRRT Registry Group -presented at the 8th CRRT, March 6-8, 2003, San Diego, Ca

31. Williams DM, et al: Acute kidney failure: a pediatric experience over 20 years. Arch Pediatr Adol Med 2002 156:893-90
32. Zimmerman D, Cotman P, Ting R, Karanicolas S, Tobe SW: Continuous veno-venous haemodialysis with a novel bicarbonate dialysis solution: prospective cross-over comparison with a lactate buggered solution, Nephrol Dial Transplant 1999 14:2387-2391
33. Zobel G, et al. Prognosis in Pediatric Patients with Multiple Organ System Failure and Continuous Extracorporeal Renal Support Contrib to Nephrol Basel, Karger, 1995, Vol. 116, pp 163-168.

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