Brief Communication

Continuous renal replacement therapy in children with severe sepsis and multiorgan dysfunction - A pilot study on timing of initiation

Krishna Mohan Gulla, Anil Sachdev, Dhiren Gupta, Neeraj Gupta, Kanav Anand[1], P. K. Pruthi[1]

Abstract

Objective: Scanty literature is available regarding continuous renal replacement therapy (CRRT) utility in severe sepsis with multiorgan dysfunction syndrome (MODS) from developing countries. Author unit's experience in pediatric CRRT is described and outcome of early initiation of CRRT with sepsis and MODS is assessed. **Materials and Methods:** Children aged <16 years with sepsis and MODS who required CRRT from September 2010 to February 2015 were analyzed on demographic factors, timing of initiation of CRRT, mode of CRRT, effect of CRRT onhemodynamics, oxygenation parameters, and outcome. **Results:** Twenty-seven children required CRRT (male - 16). The median age was 11 years (range 1.1–16). Twenty-one had severe sepsis with MODS. Eighteen patients were given CRRT within 48 h of admission to Intensive Care Unit (ICU). Statistically significant improvement in the P/F ratio, decrement in plateau pressure and vasoactive-inotropic score were noted in survivor group compared to nonsurvivor group (P = 0.022, 0.00, and 0.03, respectively). There was no statistically significant difference in duration of ICU stay, fluid overload, CRRT duration, PRISM score at 12 and 24 h, percentage of decrease in inotrope score, plateau pressure, and percentage of increase in P/F ratio in relation to timing of CRRT initiation. However, the survival rate was 61.1% (11/18) who received CRRT within 48 h of ICU admission compared to 33.3% (3/9) who received after 48 h (P = 0.0001). **Conclusion:** Our study emphasizes the CRRT role in improving the oxygenation status and hemodynamics. Survival benefit may be expected in those children who receive CRRT early in the course of sepsis. However, multicenter RCTs are required to prove mortality benefit.

Keywords: Humans, Intensive Care Units, multiple organ failure, pediatrics, renal replacement therapy, sepsis, treatment outcome

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Introduction

Continuous renal replacement therapy (CRRT) has become the preferred modality for the management of critically ill-children with acute kidney injury (AKI) and fluid overload (F.O), especially in developed countries because of the advances in technology allowing more accurate treatment delivery and better control of blood flow and fluid removal over extended period of time, especially in hemodynamically unstable patients.[1] CRRT eliminates the compulsion for fluid restriction and allows the provision of medications, blood products, and nutrition in critically ill-children with

From:
Division of Pediatric Emergency and Critical Care, [1]Division of Pediatric Nephrology, Institute of Child Health, Sir Ganga Ram Hospital, New Delhi, India

Correspondence:
Dr. Anil Sachdev, Division of Pediatric Emergency and Critical Care, Institute of Child Health, Sir Ganga Ram Hospital, Old Rajinder Nagar, New Delhi, India. E-mail: anilcriticare@gmail.com

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multiorgan failure. It has the capacity to provide more efficient clearance of solutes than standard peritoneal dialysis. Another potential use of CRRT is the removal of inflammatory cytokines and endotoxins in septic patients.[2] A descriptive study from India showed that, sepsis lead to 39.7% total multiorgan dysfunction syndrome (MODS) in a tertiary care pediatric Intensive Care Unit (PICU).[3] Data regarding the usage of CRRT is very limited from developing countries as compared to developed countries. The authors report their experience with CRRT in sepsis with MODS from a tertiary level PICU of a developing country.

Materials and Methods

In this retrospective descriptive study, data were collected from the patient case records who received CRRT for sepsis with MODS in a tertiary care PICU from September 2010 to February 2015 [Figure 1]. Children who received CRRT but excluded from the study were postoperative cardiac patients, children with inborn errors of metabolism, nonseptic MODS. Sepsis and multiorgan dysfunction were defined as per International Pediatric Sepsis Consensus Conference.[4] Information was obtained by a predesigned data collection sheet which included the following: Age, gender, primary disease leading to initiation of CRRT, relevant co-morbid illnesses, reason for CRRT initiation, time duration from ICU admission to CRRT initiation, fluid input from ICU admission to CRRT initiation (L/day), fluid output from ICU admission to CRRT initiation (L/day). F.O at the time of CRRT initiation was calculated using the formula:

F.O (%) = (Fluid in – fluid out)/PICU admission weight × 100%

Serum creatinine at the initiation of CRRT, PRISM score at 12 and 24 h, inotropic score (IS) at initiation and termination of CRRT were also noted. In this study, the IS was calculated as used by Gaies *et al*.[5] ([IS] = dopamine dose [mic/kg/min] + dobutamine [mic/kg/min] + 100 × epinephrine dose [mic/kg/min]). Vasoactive IS = IS + 10 × milrinone dose (mic/kg/min) + 10,000 × vasopressin dose (units/kg/min) + 100 × nor epinephrine dose (mic/kg/min).

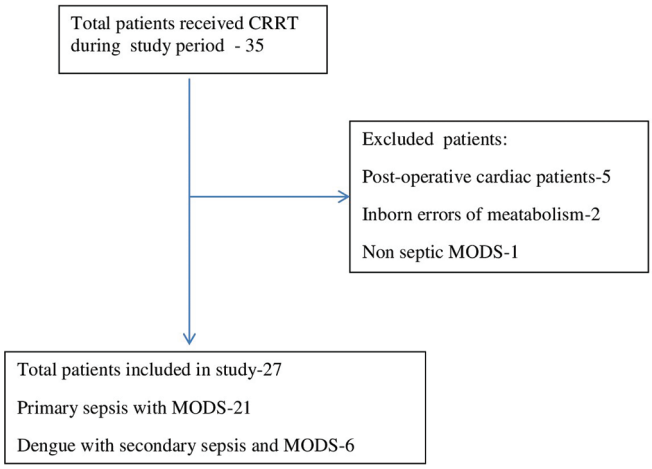

Figure 1: Study flow chart. Sepsis with multiorgan dysfunction syndrome

Plateau pressure required for mechanical ventilation at initiation and termination of CRRT, PaO_2/FiO_2 ratio at initiation and termination of CRRT, diuretic usage prior to CRRT initiation (yes/no), route of venous access, anticoagulation used, priming solution, CRRT modality used continuous venovenous hemodiafiltration (CVVHDF), continuous venovenous hemofiltration, continuous venovenous hemodialysis, complications during CRRT were also analyzed.

The primary outcome measured was survival. Secondary outcome measures were (a) change in fluid balance (b) percentage of change in IS, PaO_2/FiO_2 ratio and plateau pressure at the termination of CRRT, and (c) effect of timing of initiation of CRRT on survival.

Statistical analysis

Data were analyzed using SPSS (version 19, IBM-SPSS, SPSS Inc. New York, USA) software and significance was examined using *t*-test and Mann–Whitney test.

Results

Twenty-seven children were given CRRT during the study period. Median age and weight of subjects were 11 years (range 1.1–16) and 39 kg (range 7.5–65), respectively. Clinical profile of the patients is depicted in Table 1. All children had shock requiring ≥2 inotropes and were on mechanical ventilation support at the time of initiation of CRRT. Oligo-anuria and F.O (>10%) were presented in 90% and 48.1%, respectively. Chief indications for initiation of CRRT were AKI (88%), F.O (50%), as a part of MODS and anticipation of F.O. Total 34 CRRT sessions were given amounting to 1304.4 h with mean lifespan of each filter was 47.62 h. Femoral venous access, internal jugular venous access, and subclavian venous access were used in 23 (85%), 3 (11.1%), and 1 (3.7%) patients, respectively. Blood and 5% albumin were used for circuit priming in 15 (55.5%) and 12 (45.5%) patients, respectively. All patients were given CVVHDF as a modality of CRRT. Heparin was used as an anticoagulant in only 10 (37%) patients in view of coagulopathy. Manageable dyselectrolytemias namely hypokalemia, hypophosphatemia, hypomagnesemia, and hypocalcemia were observed in 21 (77.8%), 16 (59.2%), 13 (41.8%), and 7 (25.8%), respectively. Only one patient had major intracranial bleed secondary

to anticoagulation with heparin. Table 2 lists the data comparing clinical variables for survivors and nonsurvivors. Duration of ICU stay, time from admission to CRRT initiation, F.O, CRRT duration, PRISM score at 24 h, creatinine at CRRT initiation were not different between survivors and nonsurvivors. In contrast, percentage of decrease in inotrope score, plateau pressure, and percentage of increase in PaO_2/FiO_2 ratio were higher in survivor group compared to nonsurvivor group. The same clinical variables were compared between the children who received CRRT within 48 h of admission and those received after 48 h of admission and are depicted in Table 3. There was no difference in duration of ICU stay, time from admission to CRRT initiation, F.O, CRRT duration, PRISM score at 12 h, percentage of decrease in inotrope score, plateau pressure, and percentage of increase in PaO_2/FiO_2 ratios between the two groups. Creatinine at initiation of CRRT in children who received CRRT within 48 h of admission is significantly lower than those who received after 48 h. Fourteen patients of 27 patients (51.8%) were survived. Survival rate was 61.1% (11/18) in those patients who received CRRT within 48 h of admission and was 33.3% in those who received CRRT after 48 h of admission. Normalization of kidney function tests was observed in all patients.

Table 1: Clinical profile of the patients underwent CRRT

Diagnoses	No. of patients
Gut associated sepsis with MODS	2
Severe Dengue with secondary sepsis and AKI	6
Diabetic Keto Acidosis with sepsis	1
Post liver transplant with sepsis and F.O	2
Secondary Hemophagocytosis	3
Severe Combined Immunodeficiency - post Bone Marrow Transplant with sepsis	1
Burkitt's lymphoma with sepsis	1
Chronic Kidney Disease with peritonitis with sepsis	2
Propionic acidemia with sepsis	1
Pneumonia with sepsis	2
Culture negative sepsis with MODS	6

MODS: Multiorgan dysfunction syndrome; CRRT: Continuous renal replacement therapy; AKI: Acute kidney injury

Table 2: Comparison of the parameters between survivors and non survivors

Parameter measured	Median (P25-P75)		*P* value
	Survivors (*n*=14)	Non survivors (*n*=13)	
Age (years)	10 (3-15)	9 (1.1-16)	0.872
Duration of ICU stay (days)	11.5 (3-60)	10 (1-49)	0.662
Time from admission to CRRT initiation	34.5 (10-432)	48 (8-136)	0.544
Fluid over load (%)	9.8 (2.1-21.5)	10.2 (−1.7-19)	0.645
% decrease in inotropic score	37.5 (15.4-100)	14.1 (−20-83.4)	0.022
% decrease in Plateau pressure	16.3 (0-46.7)	3.57 (−100-24)	0.00
%Increase in P/F ratio	44.4 (−27-118)	5.26 (−72-44)	0.03
CRRT duration	60 (24-129)	54 (12-104)	0.396
PRISM score at 24 hours of admission	19 (7-28)	22 (7-39)	0.243
Creatinine at initiation of CRRT	2.8 (1.9-3.85)	3.7 (2-3.95)	0.636

CRRT: Continuous renal replacement therapy

Table 3: Comparison of the parameters between patients received CRRT within 48 hours of admission and after 48 hours of admission to PICU

Parameter measured	Median (P25-P75)		*P* value
	CRRT initiation within 48 hours of admission to PICU (*n*=18)	CRRT initiation after 48 hours of admission to PICU (*n*=9)	
Age (years)	10.5 (3-16)	11 (1.1-15)	0.853
Duration of ICU stay (days)	11.5 (2-48)	10 (1-60)	0.837
CRRT duration (hours)	54.5 (16-97)	68 (12-129)	0.368
Fluid over load (%)	5 (−1.7-21.4)	11.5 (2.5-19)	0.173
% decrease in inotropic score	21.6 (−20-100)	21.05 (−5.56-100)	0.926
% decrease in Plateau pressure	9.8 (−100-46.6)	9.37 (−25-32.4)	0.504
% increase in PaO_2/FiO_2 ratio	32.5 (−72-118)	11.1 (−24-52)	0.304
PRISM score at 24 hours of admission	18.5 (7-26)	18 (11-31)	0.918
Creatinine at initiation of CRRT	2.1 (1.9-3.85)	3.7 (2-3.95)	0.03
Survival	11/18 (61.1%)	3/9 (33%)	0.0001

CRRT: Continuous renal replacement therapy; PICU: Pediatric intensive care unit

Discussion

Sepsis is a major contributor for MODS in PICU constituting 39.2% of MODS etiology as reported by Khilnani *et al*.[3] from India. Most pediatric centers from developed nations use CRRT as an initial mode of renal replacement therapy (RRT) for critically ill-children with MODS. Unfortunately, scanty literature is available from developing nations regarding CRRT usage. Recently, Khandelwal *et al.* from India, reported their experience of pediatric CRRT in which 15 out of 17 patients (88.2%) had sepsis with MODS at the time of initiation of CRRT.[6] In this study, comparison of relevant clinical and laboratory parameters between survivors and nonsurvivors who received CRRT. The same parameters were also compared in those patients who were given CRRT within 48 h of ICU admission to after 48 h of admission. F.O was one of the major indication for initiation of CRRT in our study population as it is an independent risk factor for poor outcome in critically ill-patients.[7-9] One study found that survivors of acute respiratory distress syndrome had a net negative fluid balance as compared with nonsurvivors in an ICU.[10] We took the advantage of CRRT to provide adequate nutrition, to transfuse blood and plasma products transfusion without much hesitancy.[11] Assessment of F.O in critically ill-patients is multidimensional such as clinical examination (edema, hepatomegaly, bilateral basal lung crepitations), serial weight measurement, cumulative fluid balance (mL fluid in - mL fluid out from

PICU admission)/PICU admission weight in kg ×100%), chest X-ray, oxygenation indices, lung ultrasound, echocardiography, intra-abdominal pressure, and bio-impedance analysis of body composition.[12,13] These additional findings provide indications that prevention of excessive F.O may be a hallmark of optimal care for the pediatric patient with MODS. Hence, we assessed plateau pressure, PaO_2/FiO_2 ratio at the time of CRRT initiation and CRRT termination between the two groups. Percentage of decrease in plateau pressure ($P = 0.00$) and increase in PaO_2/FiO_2 ratio ($P = 0.03$) in survivors is significant compared to nonsurvivors. The severity of illness as measured by PRISM score at 12 and 24 h of admission to ICU is also similar between the two groups. In our cohort, survivor group had low serum creatinine at initiation of CRRT as compared to nonsurvivor group (2.8 mg/dl vs. 3.7 mg/dl) which may suggest that initiation of CRRT at early stage of AKI may give survival benefit. CRRT registry subgroup analysis on children with MODS receiving CRRT showed survival rate of 52%[14] which is similar to our cohort, that is, 51.8%. A study by Proulx *et al*. showed that severe and life-threatening MODS occur very early in pediatric patients during their ICU course. In their study, 87% of children developed the maximum number of organ failures within 72 h of PICU admission and 88.4% of deaths occurred within 7 days of MODS evolution.[15] Hence, early and appropriate aggressive supportive measures, including RRT to treat or prevent AKI sequelae, could conceivably improve patient outcome. Hence, we compared clinical parameters, laboratory parameters as well as mortality in those who were given CRRT within 48 (early initiation) hours of admission to those who were given CRRT after 48 h (late initiation) of admission to ICU. The survival rate in early initiation group (61.1%) is statistically significant compared to late initiation group (33%) ($P = 0.0001$). A recent retrospective study by Modem *et al*. also showed that early initiation of CRRT was associated with lower mortality in critically ill children requiring renal support for F.O or AKI.[16] A study in 2005, had shown that plasma endotoxin and cytokines (tumor necrosis factor-alpha, interleukin (IL)-1 beta, IL-6, and IL-8) can be removed effectively with CRRT in severely burned patients with sepsis.[2] Another animal study in 2014 showed that CRRT reduces the systemic and pulmonary inflammation induced by veno - venous extracorporeal membrane oxygenation in a porcine model.[17] Even though, there is no statistically significant difference in the F.O between the patients who received early CRRT and late CRRT in our cohort, the early removal of inflammatory cytokines may be the key factor for mortality benefit.

Disadvantages of CRRT are vascular access, requirement of technical expertise, vigilance over hemodynamic and coagulation parameters.[18] The cost of disposables per session in our setup ranges between Rs. 25,000 and 30,000.00 (400-450USD). Limitations of our study are its retrospective nature, small number. However, this is the first study done in children with severe sepsis and MODS from a developing country.

Conclusion

Our study emphasizes the role of CRRT in improving the oxygenation status and probably also the survival in children with severe sepsis with MODS who receive CRRT early in the course of illness.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Sutherland SM, Alexander SR. Continuous renal replacement therapy in children. Pediatr Nephrol 2012;27:2007-16.
2. Peng Y, Yuan Z, Li H. Removal of inflammatory cytokines and endotoxin by veno-venous continuous renal replacement therapy for burned patients with sepsis. Burns 2005;31:623-8.
3. Khilnani P, Sarma D, Zimmerman J. Epidemiology and peculiarities of pediatric multiple organ dysfunction syndrome in New Delhi. India. Intensive Care Med 2006;32:1856-62.
4. Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005;6:2-8.
5. Gaies MG, Jeffries HE, Niebler RA, Pasquali SK, Donohue JE, Yu S, *et al*. Vasoactive-inotropic score is associated with outcome after infant cardiac surgery: An analysis from the pediatric cardiac critical care consortium and virtual PICU system registries. Pediatr Crit Care Med 2014;15:529-37.
6. Khandelwal P, Sharma S, Bhardwaj S, Thergaonkar RW, Sinha A, Hari P, *et al*. Experience with continuous renal replacement therapy. Indian J Pediatr 2015;82:752-4.
7. Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, *et al*. Sepsis in European intensive care units: Results of the SOAP study. Crit Care Med 2006;34:344-53.
8. Bouchard J, Soroko SB, Chertow GM, Himmelfarb J, Ikizler TA, Paganini EP, *et al*. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. Kidney Int 2009;76:422-7.
9. Vaara ST, Korhonen AM, Kaukonen KM, Nisula S, Inkinen O, Hoppu S, *et al*. Fluid overload is associated with an increased risk for 90-day mortality in critically ill patients with renal replacement therapy: Data from the prospective FINNAKI study. Crit Care 2012;16:R197.
10. Sakr Y, Vincent JL, Reinhart K, Groeneveld J, Michalopoulos A, Sprung CL, *et al*. High tidal volume and positive fluid balance are associated with worse outcome in acute lung injury. Chest 2005;128:3098-108.
11. Merlin C Thomas, Harris DC. Problems and advantages of continuous renal replacement therapy. Nephrology 2002;7:110-4.

12. Prowle JR, Kirwan CJ, Bellomo R. Fluid management for the prevention and attenuation of acute kidney injury. Nat Rev Nephrol 2014;10:37-47.
13. Arikan AA, Zappitelli M, Goldstein SL, Naipaul A, Jefferson LS, Loftis LL. Fluid overload is associated with impaired oxygenation and morbidity in critically ill children. Pediatr Crit Care Med 2012;13:253-8.
14. Goldstein S, Somers MJ, Baum M, Symons JM, Brophy PD, Blowey D, *et al*. Pediatric patients with multi-organ dysfunction syndrome receiving continuous renal replacement therapy. Kidney Int 2005;67:653-8.
15. Proulx F, Gauthier M, Nadeau D, Lacroix J, Farrell CA. Timing and predictors of death in pediatric patients with multiple organ system failure. Crit Care Med 1994;22:1025-31.
16. Modem V, Thompson M, Gollhofer D, Dhar AV, Quigley R. Timing of continuous renal replacement therapy and mortality in critically ill children*. Crit Care Med 2014;42:943-53.
17. Shi J, Chen Q, Yu W, Shen J, Gong J, He C, *et al*. Continuous renal replacement therapy reduces the systemic and pulmonary inflammation induced by venovenous extracorporeal membrane oxygenation in a porcine model. Artif Organs 2014;38:215-23.
18. Basu RK, Wheeler DS, Goldstein S, Doughty L. Acute renal replacement therapy in pediatrics. Int J Nephrol 2011;2011:785392.