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ORIGINAL ARTICLE

Continuous renal replacement therapy (CRRT) after stem cell transplantation. A report from the prospective pediatric CRRT Registry Group

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Abstract Pediatric stem cell transplant (SCT) recipients commonly develop acute renal failure (ARF). We report the demographic and survival data of pediatric SCT patients enrolled in the Prospective Pediatric Continuous Renal Replacement Therapy (ppCRRT) Registry. Since 1 January 2001, 51/370 (13.8%) patients entered in the ppCRRT Registry had received a SCT. Median age was 13.63 (0.53–23.52) years. The primary reasons for the initiation of continuous renal replacement therapy (CRRT) were treatment of fluid overload (FO) and electrolyte imbalance (49%), FO only (39%), electrolyte imbalance only (8%) and other reasons (4%). The CRRT modalities included continuous veno-veno hemodialysis (CVVHD), 43%, continuous veno-veno hemofiltration (CVVH), 37% and

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continuous veno-veno hemodiafiltration (CVVHDF), 20%. Seventy-six percent had multi-organ dysfunction syndrome (MODS), 72% received ventilatory support and the mean FO was 12.41±3.70%. Forty-five percent of patients survived. Patients receiving convective therapies had better survival rates (59% vs 27%, $P<0.05$). Patients requiring ventilatory support had worse survival (35% vs 71%, $P<0.05$). Mean airway pressure (Paw) at the end of CRRT was lower in survivors (8.7±2.94 vs 25.76±2.03 mmH_2O, $P<0.05$). Development of high mean airway pressure in non-survivors is likely related to non-fluid injury, as it was not prevented by early and aggressive fluid management by CRRT therapy.

Keywords Hemofiltration · Pediatric · Acute renal failure · Continuous renal replacement therapy · Bone marrow transplant

Introduction

Stem cell transplant (SCT) recipients commonly develop acute renal failure (ARF) [1]. Early in the post-SCT course, the most common factors associated with ARF include acute tubular necrosis, veno-occlusive disease and septic shock, while conditioning with total body irradiation and nephrotoxic agents used to treat SCT patients' co-morbid conditions contribute to ARF development more than 60 days after transplantation.

Single-center studies have reported survival rates between 19% and 42% for pediatric SCT recipients who developed ARF [2–6]. Classic poor prognostic features include the need for vasoactive pressor medications, hyperbilirubinemia, and the percentage of the patient's total body fluid overload (%FO) at the initiation of renal replacement therapy [7]. Recently, more attention has been focused on maintaining euvolemia with diuretics and early initiation of continuous renal replacement therapy (CRRT) in SCT patients who develop ARF. Michael and colleagues evaluated such a fluid management protocol in SCT recipients who had 5% fluid overload and either a doubling of serum creatinine or a 50% decrease in urine output [5]. Forty-two percent of this cohort survived, all of whom maintained less than 12% FO, suggesting that prevention of severe FO was necessary, but not sufficient, for survival of pediatric SCT recipients who developed ARF.

Maintenance of euvolemia might not be the only critical factor that would increase the survival in SCT patients. DiCarlo and colleagues reported ten pediatric patients with cancer or SCT who developed acute respiratory distress syndrome (ARDS) and received aggressive hemodiafiltration from the time ventilatory support was initiated [8]. Nine of ten patients were extubated, and eight of ten patients survived, suggesting that early initiation of CRRT in this patient population might prevent progressive inflammatory lung injury and/or worsening of fluid overload.

Our study reports the demographic and survival data of pediatric SCT patients enrolled in the multi-center Prospective Pediatric Continuous Renal Replacement Therapy (ppCRRT) Registry [9]. The aims of this study were to assess the potential association between different clinical variables and survival in this patient population.

Methods

The ppCRRT Registry Group is a multi-center collaborative formed to evaluate various clinical and therapeutic aspects of pediatric CRRT. The ppCRRT Registry is currently designed in a prospective observational format. All centers practice according to local standards of care and have agreed to collect the same data. The ppCRRT Registry does not direct care at any institution, and decisions regarding CRRT initiation, termination and modality are made in accordance with each center's practice. The current analysis comprises data collected between 1 January 2001 and 31 August 2005 from 13 US pediatric centers: Texas Children's Hospital/Baylor College of Medicine (Houston, TX), The Children's Hospital (Boston, MA), Children's Regional Medical Center (Seattle, WA), C.S. Mott Children's Hospital (Ann Arbor, MI), University of Alabama Children's Hospital (Birmingham, AL), Mercy Children's Hospital (Kansas City, MO), Children's Healthcare of Atlanta at Egleston (Atlanta, GA), Lucille Packard Children's Hospital/Stanford University (Palo Alto, CA), All Children's Hospital (St. Petersburg, FL), Columbus Children's Hospital (Columbus, OH), Cleveland

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Clinic, Children's National Medical Center (Washington, D.C.) and DeVos Children's Hospital (Grand Rapids, MI). The Institutional Review Board for each center approved the study prior to the patients' enrollment.

Subject population and data collected

The design of the ppCRRT Registry has been previously reported [9]. The ppCRRT Registry data are divided into three components: pre-CRRT initiation data, pediatric intensive care unit (PICU) data and filter data. For our analysis, data were abstracted from components of the pre-CRRT and PICU data. All subjects' records are encoded with a unique identifier that corresponds to the center and respective patient's number; each respective center's investigator knows only its own patients' identities. Data are transmitted using each center's password-protected database and incorporated into the main database at Baylor College of Medicine/Texas Children's Hospital, Houston.

For this study, data were analyzed from all subjects from the ppCRRT Registry who had received a SCT. Patients' data were collected after informed consent had been obtained from the subjects' parents or legal guardians.

The pre-CRRT initiation data collected were composed of the following: gender, age (years), primary disease leading to CRRT initiation, relevant co-morbid illnesses, reason for CRRT initiation (development or prevention of fluid overload, electrolyte imbalance, or both), days in PICU until CRRT initiation, height (in centimeters), weight (in kilograms) when admitted to the Intensive Care Unit (ICU), vascular access used (size, lumen number, anatomical site), urine output in 24 h prior to CRRT initiation (in milliliters per kilogram per hour), fluid intake from PICU admission to CRRT initiation (Fluid In; in liters), fluid out from PICU admission to CRRT initiation (Fluid Out; liters), serum creatinine at PICU admission and CRRT initiation (in milligrams per deciliter), and blood urea nitrogen at CRRT initiation (BUN; in milligrams per deciliter).

Each center's investigator initially characterized the primary illness leading to CRRT for each of its own subjects. At the time of data analysis, the ppCRRT Group's principal investigator (S.L.G.) reviewed all subjects' primary illness designations and, from these, created a standard definition set of primary illnesses. Each patient was assigned to one primary illness category, based on the standard definition set. The standard definition set and each patient's assignment were reviewed by each center's principal investigator (PI) and either they were approved or an amendment was made, based on the recommendation of the center's PI. In 17 patients the conditions were reported as the same primary diagnosis or the initial disease that led to SCT. Therefore, they could not be classified, and they were reported in the manuscript as: no single identifiable cause.

The degree of fluid overload developed from PICU admission to CRRT initiation (%FO) was calculated by the following formula:

$$\%\mathrm{FO} = (\text{Fluid In} - \text{Fluid Out})/(\text{ICU admission weight}) * 100(\%)[10].$$

The rationale for using fluid overload from ICU admission to CRRT initiation was based on many previous pediatric studies [10, 11], including one from the ppCRRT in patients with multi-organ dysfunction syndrome (MODS) [12], which demonstrated that the fluid overload status from ICU admission to CRRT initiation is independently associated with patient survival. Patients' glomerular filtration rates (GFRs) at CRRT initiation was estimated from the Schwartz formula [11].

The ICU data were composed of the following: pediatric risk of mortality (PRISM 2) score at ICU admission and CRRT initiation [13], central venous pressure (CVP, in millimeters of mercury) at CRRT initiation, inotropic agent number at CRRT initiation, inotropic medications used, with initial and maximum doses, inotropic medications weaned off (yes/no), diuretic use (yes/no), and mechanical ventilator mean airway pressure (Paw) at CRRT initiation and termination.

The primary outcome measure was subject survival to PICU discharge.

Statistical analysis

Potential associations between various clinical continuous variables and patient survival were assessed in a univariate manner by independent *t*-test. Multiple regression analysis, using the PRISM 2 score to control for severity of illness on subject survival, was performed for those variables demonstrating an association with survival by *t*-test. Potential associations between ordinal clinical variables and outcomes were assessed by chi-square analysis. A P value <0.05 was considered significant.

Results

Demographic data

Since 2001, 370 patients have been entered into the ppCRRT Registry. Fifty-one (13.8%) of the ppCRRT Registry cohort had received a SCT, 28 of whom were male.

Demographic data for SCT patients are listed in Table 1. The geographic distribution of the SCT patients by center was as follows: Seattle (n=10, 19.6%), Atlanta (n=9, 17.6%), Ann Arbor (n=9, 17.6%), Houston (n=7, 13.6%), Boston (n=6, 11.7%), St. Petersburg (n=5, 9.8%), Birmingham (n=4, 7.8%), Grand Rapids (n=1, 1.9%). The

Table 1 Demographic and clinical data of the patients on admission to PICU and initiation of CRRT

Variable	Mean ± SE	Median (range)
Age (years)	11.24±0.97	13.63 (0.53-23.52)
Weight (kg)	45.49±6.09	38.2 (4.43-116.7)
PRISM 2 score	12.71±0.92	12 (2-29)
PICU days to CRRT initiation	4.66±1.1	2 (0-39)
PRISM 2 score at CRRT initiation	15.04±0.94	14 (3-36)
GFR at CRRT initiation (ml/min per 1.73 m^2 body surface area)	51.46±4.36	45 (0-130.62)
%FO at CRRT initiation	12.41±3.70	3.28 (-9.26-158.04)
No. inotropes at CRRT initiation	0.85±0.16	0 (0-3)
CVP at CRRT initiation (mmHg)	13.33±1.28	13 (0-28)
Paw at CRRT initiation (mmH_2O)	16.65±1.47	15 (0-35)
Paw at end of CRRT (mmH_2O)	20.26±2.20	21 (0-51)
Urine output (ml/kg per hour)	1.43±0.18	1.2 (0-5)
Duration of RRT (days)	10.71±1.56	6 (1-52)

SE standard error

most common causes cited leading to ARF and the need for CRRT were: no single identifiable cause (n=17, 33%), respiratory insufficiency (n=9, 18%), sepsis (n=8, 16%), MODS (n=6, 12%), veno-occlusive disease (n=4, 8%), hepatorenal syndrome (n=4, 8%), drug toxicity (n=3, 8%).

Primary reasons for CRRT initiation were treatment of fluid overload and electrolyte imbalance (n=25, 49%), treatment of fluid overload only (n=20, 39%), treatment of electrolyte imbalance (n=4, 8%), and other reasons (n=2, 4%).

The most frequent vascular access for CRRT was a femoral vein catheter (n=45; 88%), internal jugular vein catheter (n=5, 10%) and subclavian vein catheter (n=1, 2%). Twenty-eight of 51 patients (54%) were receiving diuretics upon initiation of CRRT. Twenty-two patients (43%) received continuous veno-veno hemodialysis (CVVHD), nineteen patients (37%) received continuous veno-veno hemofiltration (CVVH) and ten patients (20%) received continuous veno-veno hemodiafiltration (CVVHDF). The mean percent fluid overload in this cohort was 12.41±3.70%. Thirty-nine patients (76%) were reported to have MODS and 37 of 51 patients (72%) were receiving ventilatory support.

Outcome data

Twenty-three of 51 (45%) SCT patients survived to discharge from the PICU. Patients requiring ventilatory support had a lower survival rate than did non-ventilated patients [13/37 (35%) vs 10/14 (71%), P<0.05]. SCT patients with MODS had a nearly 50% lower survival rate than patients without MODS [14/39 (36%) vs 8/12 (66%), P>0.05], yet the difference was not statistically significant, likely as a result of the small patient numbers. Mean %FO was 12.41±3.7%. Patients who received convective therapies (CVVH or CVVHDF) had a better survival rate that those who received diffusive therapy [17/29 (59%) vs 6/22 (27%), P<0.05].

Table 2 summarizes the data comparing clinical variables between survivors and non-survivors. Patient age, weight, days from PICU admission to CRRT initiation, CVP at CRRT initiation, Paw at CRRT initiation, %FO, GFR at CRRT initiation, urine output, duration of CRRT and filtration volume were no different between survivors and non-survivors. In contrast, Paw at the end of CRRT was significantly lower in survivors than in non-survivors (8.7± 2.94 vs 25.76±2.03, P<0.05). Non-survivors had higher, but not statistically significant, PRISM 2 score at PICU admission and CRRT initiation, and number of inotropes at CRRT initiation. We performed a multivariate analysis using PRISM 2 score at PICU admission or CRRT initiation to control for patient severity of illness to determine if Paw at CRRT termination was an independent mortality risk factor. Paw was shown to be an independent predictor of mortality in these analyses.

Discussion

The development of ARF remains a common complication following SCT in pediatric patients. Recently, more attention has been paid to the need for better fluid and electrolyte balance, and recent reports have shown an improvement in the survival rates when aggressive fluid management is initiated early in the course of acute renal failure [6].

Our ppCRRT analysis comprised the largest pediatric SCT recipient CRRT cohort ever studied. Our ppCRRT data demonstrate that, in contrast to those in previous

Table 2 Clinical variables and outcome

Variable	Survivors	Non-survivors	*P*
Age at admission (years)	12.28±1.44	10.38±1.31	NS
Weight at admission (kg)	49.82±6.1	41.93±5.53	NS
PRISM 2 score at admission to PICU	10.67±1.37	14.25±1.19	0.05
PICU days to CRRT initiation	3.45±1.69	5.56±1.45	NS
PRISM 2 score at CRRT initiation	12.95±1.39	16.61±1.21	0.05
GFR at CRRT initiation (ml/min per 1.73 m^2 body surface area)	50.17±6.55	52.53±5.94	NS
%FO at CRRT initiation	10.60±5.55	13.90±5.03	NS
No. inotropes at CRRT initiation	0.5±0.23	1.1±0.19	0.05
CVP at CRRT initiation (mmHg)	12.5±2.05	13.89±1.68	NS
Paw at CRRT initiation (mmH_2O)	15.15±2.5	17.46±1.84	NS
Paw at end of CRRT (mmH_2O)	8.7±2.94	25.76±2.03	<0.001
Urine output (ml/kg per hour)	1.55±0.3	1.36±0.23	NS
CRRT Duration (day)	7.56±2.25	13.28±2.04	NS
Filtration (ml/min per 1.73 m^2 body surface area)	2187.49±189.26	2569.28±201.76	NS

Values are means ± standard errors. *NS* not significant

studies, the majority of patients in this multi-center study were not subject to severe fluid overload. Previous CRRT analysis of all patients with multi-organ system failure showed a significant survival advantage for patients who were started on CRRT with less than 20% cumulative fluid overload [12]. In our analysis, even non-survivors had a mean percent fluid overload of only 13.9%, suggesting that ppCRRT investigators are initiating CRRT early in order to prevent severe fluid overload in their patients with SCT.

The 45% ppCRRT Registry survival rate for SCT patients with ARF is similar to rates reported in previous publications [4, 5], and it is better than that in a single-center report (3/16) on patients who received CRRT [7]. In our cohort, a better survival rate was seen in patients who received convective (rather than diffusive) therapies and in those who did not require ventilatory support, and the best survival rate was seen in those patients who achieved a lower Paw at the end of CRRT. In contrast to previous reports, the absence of MODS did not provide a significantly better survival rate in this cohort, despite a nearly 50% lower survival rate seen in SCT patients with MODS [12]. Considering these data, and the lack of severe fluid overload or increased filtration volume in this ppCRRT cohort, we suggest that an underlying pulmonary process, and not fluid overload-associated pulmonary edema, may be a primary cause of death in non-survivors. Most likely, underlying pulmonary infection and/or fibrosis from pre-SCT events, including chemotherapy and total body irradiation, account for some of these pulmonary processes, which might be refractory to CRRT and fluid removal, although we did not collect specific data to support these assumptions.

Most case series have found the requirement for mechanical ventilation in pediatric SCT patients to be a poor prognostic factor for survival [14–17] and to be correlated with increased mortality [7]. Survival rates in SCT patients requiring both mechanical ventilation and CRRT have been dismal. Rossi et al. reported only one of eight patients surviving after receiving both RRT and mechanical ventilation [16]. Keenan et al. reported no survivors in patients receiving both therapies [14]. Jacobe et al. also had no survivors among intubated SCT patients also receiving CRRT [15]. Similarly, intubation and dialysis during the ICU stay remained a poor prognostic predictor in a more recent pediatric SCT series [17]. Thus, in comparison, a survival rate of 35% in ventilated SCT patients on CRRT in our ppCRRT series is quite encouraging.

The ability to mitigate the impact of fluid overload on SCT recipient outcome may lead to practical management consequences. Even with the prevention of severe fluid overload and with aggressive fluid removal, non-survivors maintained significantly higher Paw. Thus, physicians treating SCT recipients may need to focus their attention on less traumatic modes of ventilatory support and more aggressive management of other pulmonary processes if any further improvements in outcome can be realized in SCT recipients who developed ARF. The improved survival rate seen in the SCT patients treated with convective therapies suggests that the removal of small and middle-sized molecules by convective versus diffusive modalities provides an added beneficial effect. However, this improvement could also be a reflection of the preferred CRRT modality by the centers treating the larger number of SCT patients. A current multi-center study is evaluating the effect of CRRT initiation prior to institution of mechanical ventilation on outcome in SCT recipients, based on the premise that CRRT may decrease inflammation by modulating the serum and pulmonary interstitial concentration of pro-inflammatory cytokines.

Our ppCRRT Registry study had a number of limitations that caution over interpretation of data: We did not collect data regarding the underlying diseases leading to the need for SCT, the specific SCT protocols used, or primary cause of death for each patient. The ppCRRT Registry was not designed to collect these data, and future prospective studies of SCT recipients who develop ARF should evaluate these parameters to improve understanding of the factors associated with poor outcome. Nevertheless, our ppCRRT data do lend new insight into the current state of the treatment of pediatric SCT recipients with ARF by showing that "early" CRRT initiation at low degrees of % FO is possible, and that non-surviving SCT/CRRT patients have significant non-fluid-related pulmonary disease as the major clinical parameter, which distinguishes them from survivors.

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