Continuous Venovenous Hemofiltration is Associated with Improved Survival in Burn Patients with Shock: A Subset Analysis of a Multicenter Observational Study

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Keywords

Burns · Acute kidney injury · Renal replacement therapy · Hemofiltration · Multicenter

Abstract

Introduction: Acute kidney injury (AKI) is associated with high mortality in burn patients. Previously, we reported that timely initiation of renal replacement therapy (RRT) with an individualized preference toward continuous modes at relatively higher than recommended doses has become standard practice in critically ill burn patients with AKI and is associated with a historically low mortality. The purpose of this cohort analysis was to determine if modality choice impacted survival in burn patients. **Methods:** After Institutional Review Board approval, a subset analysis was performed on de-identified data collected during a multicenter, observational study. All patients ($n = 170$) were 18 years or older, admitted with severe burn injuries and started on RRT. Comparisons were made utilizing χ^2 or Fisher's exact test. Kaplan-Meier plots were utilized to assess survival. Sample size determinations to aid future research were calculated utilizing χ^2 test with a Yates Correction Factor. **Results:** Demographics and revised Baux were similar between groups. When continu-

ous venovenous hemofiltration (CVVH) was compared to all other modalities, there was no statistically significant difference in survival (56 vs. 43%, $p = 0.124$). However, survival was significantly improved (54 vs. 37%, $p = 0.032$) in the subset of patients requiring vasopressors ($n = 77$). There was no statistically significant survival difference in patients with inhalation injury (38 vs. 29%, $p = 0.638$) or acute lung injury/acute respiratory distress syndrome (51 vs. 33%, $p = 0.11$). **Discussion/Conclusion:** Survival may be improved if CVVH is chosen as the preferred modality in burn patients with shock and requiring RRT. Differences in other subsets were promising, but analysis was underpowered. Further research should determine if modality choice provides survival benefit in any other subset of burn injury.

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Background

Acute kidney injury (AKI) significantly complicates the hospital course of critically ill patients. Increased utilization of renal replacement therapies (RRTs) and advancements in the technology has reduced mortality [1, 2]. Despite improved outcomes, there is a lack of consen-

sus regarding many aspects of RRT to include modality, timing of initiation, and dose [3–9]. Varying trial designs and target populations make direct comparison of studies difficult [10, 11]. Ultimately, the choice of modality often comes down to prescriber preference and availability.

In patients with severe burn injuries, development of AKI is associated with longer length of stay and higher mortality [12–14]. Early choice of continuous venovenous hemofiltration (CVVH) over traditional dialysis was identified to improve survival and reduce vasopressor requirements in severe burn patients with AKI [2]. During the RESCUE trial, use of high-volume hemofiltration (HVHF), 70 mL/kg/h, in burn patients with shock reduced 48-h vasopressor requirements and 14-day Multiple Organ Dysfunction Score, as compared to standard doses (20–35 mL/kg/h) [5]. Concurrently, a multicenter observational study was performed to evaluate RRT practices and outcomes among severely injured burn patients [3]. We found centers initiated therapy early, preferred CVVH, and demonstrated reduced mortality and similarly better full renal recovery rates, as compared to other studies [15–21]. The purpose of this subset analysis of the study cohort was to determine if modality characteristics of RRT impacted survival.

Methods

Multilevel, Institutional Review Board approval was obtained to conduct this multicenter, observational study. Ten burn centers participated from February 2012 to February 2016. All patients or their legal authorized representative gave consent prior to enrolling in the study.

Patients

The observational study enrolled patients placed on RRT for any indication, but not enrolled in the concurrent RESCUE trial (NCT01213914). All adult patients 18 years or older, admitted with severe burns, and placed on continuous RRT for acute indications were included. Patients were excluded if they were on dialysis for ESRD on admission, prisoners, already enrolled in the RESCUE trial, or had non-thermal injuries.

Data Collected

After informed consent was obtained, data were collected prospectively. For patients already started on RRT prior to approval of this concurrent enrolling study, data were collected retrospectively. Patient demographics, injury characteristics, laboratory data at time of RRT initiation, RRT treatment data, and outcome data were collected. Data were entered into a web-based electronic data management portal (Velos, Inc., Fremont, CA, USA). Data related to RRT treatment included mode of therapy, ordered and delivered therapy dose, AKI stage at initiation (KDIGO criteria), prescribing provider specialty, and method of regional anticoagulation. Outcome data included in-hospital mortality and need for

RRT at discharge. A 6-month follow-up audit was performed to determine which survivors remained on RRT.

Statistical Analysis

Analysis was performed on de-identified data. χ^2 test was utilized for categorical comparisons. Continuous variables were compared using one-way ANOVA. Demographics were expressed as means with standard deviations or medians with minimum and maximum ranges, depending on normality determined via Shapiro-Wilk test. Sample size determinations were calculated utilizing χ^2 test with a Yates Correction Factor to attain at least an 80% power with an alpha of 0.05. Kaplan-Meier plots were utilized to assess survival impact over time. SPSS 22.0 was utilized for statistical analysis.

Results

During the study, data from 171 enrolled patients were collected for analysis. One patient was excluded from the analysis for incomplete data. Patients in the cohort had a mean age of 51 ± 17.4 years, and 80% were male. The mean total body surface area burned was 38% with 24% being full thickness. Thirty-four percent sustained inhalation injuries. The mean Acute Physiology and Chronic Health Evaluation II score was 26. Ninety-one patients (54%) were treated with CVVH, 53 (31%) with continuous venovenous hemodiafiltration, and 26 (15%) with some form of dialysis. Twenty-three patients were started on continuous venovenous hemodialysis, 2 on intermittent hemodialysis, and 1 on sustained low-efficiency dialysis. Demographics and treatment characteristics were not significantly different between groupings, based on modality (Table 1). Comparisons between survivors and non-survivors can be seen in Table 2. Non-survivors were significantly older with large burns and more likely to sustain an inhalation injury. Survivors were significantly less likely to require vasopressors. Likely related to longer lengths of stay, survivors were also more likely to acquire a ventilator-associated pneumonia.

When comparing patients treated with CVVH versus all other modalities, there was no statistically significant difference in survival; however, the analysis was underpowered (56 vs. 43%; $p = 0.124$; power = 0.319) (Fig. 1). To adequately detect the presence of the 13% difference in mortality with an 80% power, 546 patients would be required. Survival was improved in the subset of patients receiving vasopressors ($n = 77$) at the time of RRT initiation (54 vs. 37%; $p = 0.032$) (Fig. 2). For patients sustaining inhalation injury, there was no difference in survival (53 vs. 47%; $p = 0.638$; power = 0.071). There was no statistical survival difference in patients developing acute

Table 1. Demographics and treatment characteristics

Variable	Hemofiltration (<i>n</i> = 91)	Hemodiafiltration (<i>n</i> = 53)	Dialysis (<i>n</i> = 26) ^a	<i>p</i> value
Age, years ^b	48 (36, 65)	54 (43, 65.5)	53.5 (36, 64.5)	0.550
Male ^c	71 (78)	44 (83)	21 (81)	0.766
TBSA, % ^b	30 (15, 54.8)	35 (16.8, 66)	36 (28.5, 57.8)	0.295
Inhalation injury ^c	26 (29)	19 (36)	12 (41)	0.382
Revised Baux score ^d	90.9±28.2	100.1±28.4	97.1±33.3	0.169
Days from injury to initiation ^b	7 (1, 15)	3 (1, 13)	7.5 (1.3, 22.8)	0.459
Prescribed therapy rate, mg/kg/h ^b	37.4 (28.3, 53.9)	39.8 (31.1, 49.6)	39.0 (30.3, 59.6)	0.816
Delivered therapy rate, mg/kg/h ^b	34.1 (26.1, 51.9)	36.9 (20.2, 51.9)	36.5 (18.6, 58.1)	0.935
KDIGO 1 at initiation ^c	22 (26.8)	9 (17)	6 (24)	0.413
Vasopressors at initiation ^c	37 (41)	23 (44)	17 (65)	0.078

CVVHD, continuous venovenous hemodiafiltration; IHD, intermittent hemodialysis; KDIGO 1, Kidney Disease: Improving Global Outcomes Stage 1; SLED, sustained low-efficiency dialysis; TBSA, total body surface area burned. ^a CVVHD (*n* = 23), IHD (*n* = 2), SLED (*n* = 1). ^b Median (interquartile range). ^c *n* (%). ^d Mean ± SD.

Table 2. Outcome according to patient characteristics and complications

Variable	Survivors (<i>n</i> = 85)	Non-survivors (<i>n</i> = 85)	<i>p</i> value
Age, years ^a	47 (38, 60)	56 (36, 68)	0.028
Male ^b	65 (76.5)	71 (83.5)	0.338
TBSA, % ^a	26 (14.8, 44.5)	44 (24.5, 68.5)	<0.001
Inhalation injury ^b	19 (22.4)	38 (44.7)	0.003
Revised Baux score ^c	82.8±25.8	106.6±27.8	<0.001
KDIGO 1 at initiation ^b			
No AKI	4 (4.7)	6 (7.1)	0.309
Stage 1	14 (16.5)	23 (27.1)	
Stage 2	16 (18.8)	14 (16.5)	
Stage 3	51 (60)	42 (49.4)	
Vasopressors at initiation ^b	31 (36.5)	46 (54.8) ^d	0.036
Central line-associated infection ^b	14 (16.5)	16 (18.8)	0.841
Venous thromboembolism ^b	15 (17.7)	12 (14.1)	0.675
Ventilator-associated pneumonia ^b	37 (43.5)	22 (25.9)	0.024

KDIGO 1, Kidney Disease: Improving Global Outcomes Stage 1; TBSA, total body surface area burned. AKI, acute kidney injury; TBSA, total body surface area burned. ^a Median (interquartile range). ^b *n* (%). ^c Mean ± SD. ^d *n* = 84.

lung injury or acute respiratory distress syndrome (ARDS) (Fig. 3).

There was no difference in survival when comparing patients treated with some form of convection to diffusion alone (53 vs. 31%; *p* = 0.055; power = 0.47). Three hundred fifty-one patients would be needed to meet 80% power. Parallel to sample attrition, power significantly decreased when analyzing patients requiring vasopressors (*n* = 77). Survival difference did not meet statis-

tical significance (47 vs. 18%; *p* = 0.061; power = 0.571) but would require 167 patients to be adequately powered. There was a difference in survival for patients sustaining inhalation injury, as there were unfortunately no survivors in the diffusion group (42 vs. 0%; *p* = 0.005) (Fig. 4).

Therapy dose was analyzed based on delivered dose, comparing ≥35 mL/kg/h (HVHF) to standard doses. There was no statistical difference in overall mortality (55 vs. 35%; *p* = 0.131; power 0.308) (Fig. 5). To give proper

Fig. 1. Kaplan-Meier analysis of entire cohort ($n = 170$) comparing survival of patients receiving CVVH to all other modalities. CVVH, continuous venovenous hemofiltration; Trt, treatment.

Fig. 2. Kaplan-Meier analysis of patients receiving vasopressors at initiation of RRT ($n = 77$) comparing survival of patients receiving CVVH to all other modalities. CVVH, continuous venovenous hemofiltration; Trt, treatment.

Fig. 3. Kaplan-Meier analysis of patients with acute lung injury/ARDS ($n = 104$) comparing survival of patients receiving CVVH to all other modalities. CVVH, continuous venovenous hemofiltration; Trt, treatment.

Fig. 4. Kaplan-Meier analysis of patients with inhalation injury ($n = 57$) comparing survival of patients receiving some form of continuous hemofiltration to all other modalities. CVVH, continuous venovenous hemofiltration; CVVHDF, continuous venovenous hemodiafiltration; Trt, treatment; IHD, intermittent hemodialysis; SLED, sustained low-efficiency dialysis.

chance to detect the observed 20% difference in mortality, 257 patients would be needed. For patients receiving vasopressors, HVHF did not provide a statistically significant survival difference (54 vs. 37%; $p = 0.241$; power = 0.201). Assuming only a 15% survival benefit, 485 patients would need to be enrolled to be adequately powered. Unfortunately, only 23 patients with inhalation in-

jury had complete data regarding delivered dose, making it difficult to compare survival. Survival failed to meet statistical significance for patients with inhalation injury receiving some form of HV convection ($n = 4$) versus all other modalities and lower doses ($n = 19$) (75 vs. 21%; $p = 0.067$; power = 0.561).

Fig. 5. Kaplan-Meier analysis of patients based on delivered therapy dose ($n = 57$) comparing survival of patients receiving greater than or less than 35 mL/kg/h. Trt, treatment

Discussion

This is the first multicenter cohort study to analyze outcomes based on RRT modality in subsets of burn patients. CVVH demonstrated improved survival in patients requiring vasopressors. Although this observational study does not elucidate the mechanism, the use of convection appears to have benefit in subsets of the burned population, especially in patients requiring vasoactive medications.

Conflicting data exist as to the impact of modality choice on outcomes in critically injured patients with AKI [10, 18, 21–26]. However, a high heterogeneity exists between studies, making generalization and conclusions difficult. This study is the first to analyze mortality in burn patients requiring RRT. While this study was underpowered for some of the subgroup comparisons, the divergence of outcomes is noteworthy. The data within should be helpful for future investigators.

Utilizing convection benefited patients with burn injuries in this study. While cytokine removal has been the theorized mechanism leading to enhanced hemodynamic stability, clinical data supporting this hypothesis remains conflicting [5, 27–31]. In the RESCUE study, patients treated with HVHF had a faster resolution of their shock, but it did not appear related to removal of interleukin (IL) 6, IL8, IL10, and IL12, interferon- γ , or tumor necrosis factor- α . Of the cytokines chosen to study, none varied over the 48-h measurement period. It is possible different cytokines could be influential or alternative mechanisms

could be responsible for the improvement (e.g., metabolic control). Recently, You et al. [32] showed significant removal of cytokines through early application of HVHF in burn patients with sepsis, especially in a subset of patients with very severe burn injuries (>80% total body surface area). The authors also found improved ratios of arterial oxygen partial pressure to fraction of inspired oxygen, improved immunologic function, decreased incidence of sepsis, and improved survival. HVHF was initiated within 3 days postburn and circuits changed routinely at 24 h regardless of clotting. It is unclear if differences existed in daily fluid balances and, if so, could have impacted the findings. It is likely the ideal marker of most benefit has yet to be identified.

Overall mortality was 50% in the observational study and 62% in the interventional study. While still poor, the improvement is noteworthy and consistent with the outcomes trended through the years [12]. In their meta-analysis, Brusselaers et al. [12] noted a median mortality of 80% for patients with AKI requiring RRT. However, there was a significant improvement in outcomes trended from 1950 to 2010.

Although underpowered, HVHF demonstrated a 20% decrease in overall mortality in this study, which conflicts with recent literature on the use of higher doses in critically ill patients. A recent systematic review (4 studies) concluded with a low-level recommendation against the use of HVHF over standard doses but stated the inconsistencies in data and significant heterogeneity across studies resulted in low quality of evidence with more studies needed [33]. Conversely, a large meta-analysis of 21 studies reported a significant survival benefit with use of HVHF, especially in the subsets of patients with sepsis and ARDS [34]. The authors assessed for 2 levels of bias and judged none of the included studies to be at low risk of bias.

Perhaps, the “tip of the iceberg theory” should be revisited [28, 35]. Measuring mediator concentrations in the plasma may not necessarily adequately represent concentrations throughout other multiple compartments. Additionally, simply measuring concentrations of cytokines may not be enough, as substantial interpatient variability exists regarding receptor expression and mediator affinity. It may be enlightening to measure and compare mediator differences between multiple compartments within the burn patient. New theories are shifting focus toward beneficial effects attributed to damage-associated molecular pattern (DAMP) removal, but may require the use of an alternative membrane [28, 36, 37]. DAMPs are released after burn injury and have been linked with in-

flammation and monocyte activation [38]. Simmons et al. [39] demonstrated the presence of DAMPs in reportedly apheresed, leukocyte-reduced transfusion products, and their link to clinical outcomes [40]. Blood product administration is frequently a component of shock resuscitation in burn patients, but was not collected in this cohort [41].

This study was limited by its observational design. Also, data collection occurred both prospectively and retrospectively, based on approval timing of the observational, parallel randomized controlled trial. The likely presence of bias toward prescribing CVVH in the experienced participating burn centers should be noted. Center effect cannot be excluded, as centers can be biased toward treatment preference. AKI stage was collected, but specific indication was not and is a limitation. Delay in initiation was also much higher than some studies in burn patients showing benefit [8, 32]. The analysis is limited to the data chosen to be collected, and potential exists for other data to be of value. While history of ESRD requiring dialysis was excluded, presence of other stages of chronic kidney disease was not collected. Specifics regarding management of each case of shock were not collected and could have influenced the results. Similarly, this study was not designed to answer if removal of endotoxin could play a role in survival. While mean prescribed therapy dose was 42 mL/kg/h and evenly divided between HV and standard doses, delivered dose was not recorded for 73 patients. Due to incomplete data for some subsets, much of the analyses suffer from being underpowered. Baseline characteristics were not different between modality subsets (e.g., revised Baux score); however, there is a chance a difference still exists and a type II error present. The authors hope the power and sample size analysis will aid future researchers in developing studies to answer much needed questions in this population. However, for this multicenter study, the investigators predicted enrollment of 540 patients over the 4-year study period, demonstrating the difficulty and likely unfeasibility of much larger trials in this population.

Conclusions

This observational study is the largest cohort to date to perform a subset survival analysis of burn patients started on RRT. This study adds supportive survival data for use of convection-based clearance in septic burn patients, although definitive conclusions cannot be drawn from this study alone. The exact mechanism responsible for the

possible benefit remains to be elucidated. Convection may benefit patients with extreme inflammatory pathogenesis, such as burn patients with inhalation injury and acute lung injury/ARDS. More research is needed in high-risk acutely ill populations to delineate why CVVH provides a survival benefit for burn patients with AKI and shock.

Declarations

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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Statement of Ethics

IRB approval was granted, and informed consent was given by each patient.

Conflict of Interest Statement

The authors declare to have no conflicts of interests.

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Author Contributions

All authors made substantial contributions to the conception, design, and acquisition of data. D.M.H., J.K.A., and K.K.C. made substantial contributions to analysis and interpretation of data. D.M.H. drafted the manuscript. All authors were involved in revising the manuscript. All authors gave approval of the final manuscript to be published.

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