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CLINICAL STUDY

The dose of continuous renal replacement therapy for acute renal failure: a systematic review and meta-analysis

Edward T. Casey[1,2], Bhanu P. Gupta[2], Patricia J. Erwin[2], Victor M. Montori[2,3] and M. Hassan Murad[2,4]

[1] *Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA*
[2] *The Knowledge and Encounter Research Unit, Mayo Clinic, Rochester, MN, USA*
[3] *Division of Endocrinology, Mayo Clinic, Rochester, MN, USA*
[4] *Division of Preventive Medicine, Mayo Clinic, Rochester, MN, USA*

ABSTRACT

Objectives: To conduct a systematic review of the literature to summarize the best available evidence regarding the mortality and morbidity associated with differing dosing regimens of continuous renal replacement therapy (CRRT) for patients with acute renal failure (ARF) in an intensive care unit setting. *Patients and Methods*: We searched for randomized controlled trials in electronic databases from January 1990 through November 2009. Eligible trials compared two or more dosing regimens of CRRT in patients with ARF. Two reviewers working independently determined trial eligibility and extracted descriptive, methodological, and outcome data. Random-effects meta-analysis was used to assess relative risks (RR) and weighted mean difference. The I^2-statistic was used to assess heterogeneity of treatment effect across trials. *Results*: Seven trials were eligible for meta-analysis. We found no reduction in mortality in patients who received higher doses of CRRT (RR 0.88, 95% CI 0.75–1.03, I^2 = 74%). There was no difference in the requirement of renal replacement therapy at the conclusion of the study period (RR 1.12, 95% CI 0.86–1.46, I^2 = 3%). The overall quality of evidence was downgraded because of imprecision and heterogeneity. *Conclusion*: Increased dosing of CRRT is not associated with a decrease in mortality of patients with ARF in an intensive care unit setting.

Keywords: continuous renal replacement therapy; acute renal failure; critical care; meta-analysis; hemofiltration; hemodiafiltration

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Correspondence: Edward T. Casey, 200 First Street SW, Rochester, MN 55905, USA; tel: +1 507 255 8716; fax: +1 507 255 1027; E-mail: casey.edward@mayo.edu

INTRODUCTION

Acute renal failure (ARF) affects up to 5% of patients with critical illness admitted to the intensive care unit (ICU).[1] When factored independent from comorbidities, ARF increases the risk of death by fourfold.[2] Over two decades ago, continuous renal replacement therapy (CRRT) was introduced and expanded the dialysis options for critically ill patients from traditional, intermittent hemodialysis (IHD) techniques. Despite new renal replacement techniques, the mortality associated with ARF has not changed over the past four decades.[3] There are wide practice variations in CRRT that is delivered to the critically ill patient with no consensus on the modality, timing of initiation, frequency, dosing, or duration.[4] Additionally, other factors such as fluid resuscitation, training of caregivers, and the performance standards of CRRT apparatus vary considerably.[1,5,6]

Clinicians who initiate CRRT for ARF are often confronted with a dilemma regarding the optimal prescribed CRRT dosage. Early studies suggested a significant reduction in mortality with escalated dose of CRRT,[7,8] whereas other studies did not reach the same conclusion.[9–12] Further confounding the decision-making process is a trial demonstrating no difference in mortality with increased intensity of renal replacement therapy (RRT) using multiple RRT modalities.[11] We conducted a systematic review of the literature to summarize the best available evidence regarding possible mortality and morbidity associated with differing prescribed dosing regimens of CRRT.

Drs. Murad and Casey contributed equally to this manuscript.

MATERIALS AND METHODS

The report of this protocol-driven systematic review is in adherence with the Quality of Reporting of Meta-analyses standards (QUOROM) for reporting meta-analyses of randomized controlled trials (RCT).[13] Whenever possible, we used the nomenclature and definitions published by the Acute Dialysis Quality Initiative.

Eligibility criteria

Eligible studies were RCT that enrolled adult patients in a critical care setting with ARF and compared different dosing regimens of venous to venous CRRT. To be eligible, studies needed to measure the outcomes of interest: death, ICU length of stay, hospital length of stay, duration of RRT, need for RRT at the conclusion of the study period, improvements in fluid balance, or the need for vasopressor support. We excluded review articles, articles without original data, and observational studies. Because continuous renal replacement techniques using an arterial access are not comparable to techniques utilizing venous to venous access, we excluded studies of patients with arterial access for CRRT.

Study identification

An expert reference librarian (PJE) designed and conducted the electronic search strategy after input from study investigators with expertise in conducting systematic reviews. We searched electronic databases from January 1990 through November 2009 (MEDLINE, EMBASE, Cochrane CENTRAL, Web of Science, Scopus; Regional Medical databases: KoreanMed, Scielo, LILACs, Imbiomed, Eastern Mediterranean Index, IndMed, ExtraMed). The strategy utilized a combination of controlled subject headings where available and text words to describe the concepts of interest. In MEDLINE, regional MEDLINES, EMBASE, and CENTRAL, the terms included renal dialysis, renal replacement therapy, hemodiafiltration, hemofiltration, kidney failure, critical illness, critically ill, and acute/therapy in conjunction with intensive care units. EMBASE included specific terms for CRRT. Specific outcomes of interest were mortality, length of stay, treatment outcomes; we also searched for controlled trials, meta-analyses, comparative studies, or systematic reviews. Text words were employed with appropriate synonyms and abbreviations in the other keyword-based databases. We also sought references from experts, bibliographies of included trials, and the ISI Science Citation Index for publications that cited included studies.

Data collection

Two reviewers (ETC and BPG) working independently and blindly using a standardized form extracted descriptive, methodological, and outcome data from all eligible studies. Inter-reviewer agreement was measured using the kappa statistic. We attempted to contact authors of all included studies by e-mail to obtain missing data.

Meta-analyses

From each trial, we pooled the relative risks (RR) for dichotomous outcomes and the weighted mean difference (WMD) for continuous outcomes. Anticipating significant heterogeneity in CRRT methods, settings, and patients, we used the DerSimonian and Laird random-effects model.[14] We estimated the 95% confidence intervals for each outcome and calculated the I^2-statistic which represents the proportion of variability across trials that is not attributable to chance.[15] Statistical analysis was conducted using Comprehensive Meta-Analysis, Version 2 (Biostat Inc., 2005, Englewood, NJ, USA).

Sensitivity, subgroup, and publication bias analyses

We planned to repeat analysis using the fixed effect model to determine whether the choice of statistical model affects study conclusions. To explain possible heterogeneity, we planned to conduct subgroup analyses based on patients' gender, age (<65 vs. ≥65 years), the presence of diabetes, sepsis, chronic kidney disease, and type of ICU admission (medical, surgical, cardiac surgery). We tested whether the methodological quality of the study, mainly driven by allocation concealment as blinding is not feasible, would affect study conclusions. Treatment effect–subgroup interactions were assessed by the analysis of variance method (ANOVA) with two-tailed alpha set at 0.05. Meta-regression was used to test the effect of the length of study follow-up and the severity of illness score on the effect size (log RR). We visually inspected funnel plots and conducted Egger's regression test to evaluate publication bias. In this regression model, precision is used to predict the standardized effect size; the size of the treatment effect is captured by the slope of the regression line and bias is captured by the intercept.[16]

RESULTS

Study identification

Our search and selection procedure is depicted in Figure 1. We found seven eligible trials that compared different prescribed doses of venous to venous CRRT to critically ill patients with ARF (3545 participants,

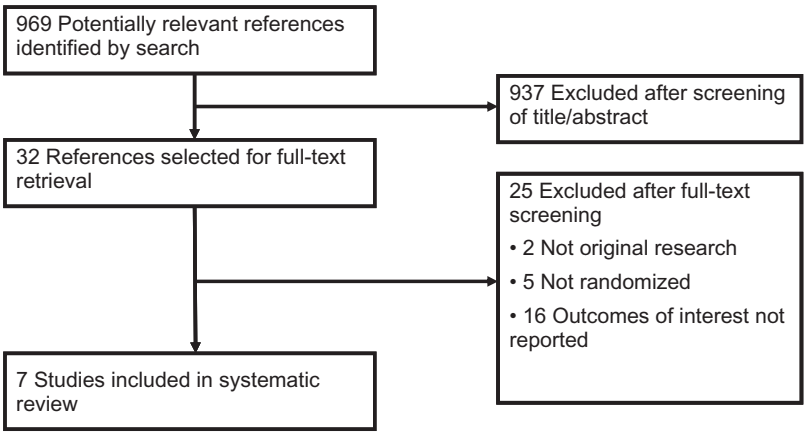

FIGURE 1. Flow chart of study selection.

TABLE 1. Baseline characteristics of patients at the time of randomization.

First author, year	Total no. of patients	Age (years; mean)	Male (%)	Weight (kg; mean)	Presence of CKD (%)	Most common cause of ARF	Illness score type	Average illness score	Presence of sepsis (%)	Serum creatinine (mg/dL)	Serum BUN (mg/dL)
Bouman,[10] 2002	106	68	59	59	NR	Cardiac surgery	Apache 2	22.9	NR	NR	46 & 105
Boussekey,[17] 2008	19	70	79	77	32	Sepsis	Apache 2	32.3	100	2.2	70
Network,[11] 2008	1124	59.7	71	84	34	Ischemia	Apache 2	26	63	NR	66
Ronco,[7] 2000	425	61	56	68	NR	Surgical	Apache 2	22.7	13	3.6	53
Saudan,[8] 2006	206	63	61	73	33	Sepsis	Apache 2	25	60	4.9	83
Tolwani,[9] 2008	200	60	58	91	42	Sepsis	Apache 2	26	54	4.3	75
Investigators RRTS,[12] 2009	1465	64	65	80	32	NR	Apache 3	102	49	3.7	66

Notes: CKD, chronic kidney disease; ARF, acute renal failure; NR, not reported or unclear.

mean sample size of 506).[7–12,17] The mean age of patients was 64 years. Table 1 describes the patient characteristics at the time of study randomization. On admission to ICU, 49% of the patients had sepsis; 33% had history of chronic kidney disease; and 31% were surgical or trauma patients. The median study period for mortality and the need for continuing RRT were 60 days and 71 days, respectively. Table 2 summarizes the characteristics of the included studies. Authors of six of these studies responded to our request for missing information.[8–11,17] We excluded one small trial as the dosage of CRRT and patient demographics were not reported.[18] Repeated attempts to contact the primary author for further data were unsuccessful.

Methodological quality

Table 3 summarizes the methodological quality of the included studies. Reviewers had adequate chance-adjusted agreement in judging study quality (k = 1.00). Overall, the studies were unblinded, and allocation of study participants was not concealed. There were no patients lost to follow-up in three of the trials.[7–9] Funding sources were nonprofit, nonprofit and industry, or not reported.

Meta-analysis

Pooling results from the seven trials that compared different doses of CRRT demonstrated no reduction in mortality in patients who received higher doses of CRRT (seven studies: RR 0.88, 95% CI 0.75–1.03, I^2 = 74%, Figure 2). There was no difference for the requirement of RRT at the conclusion of the study period (five studies: RR 1.12, 95% CI 0.86–1.46, I^2 = 3%, Figure 3), ICU length of stay (five studies: WMD –0.08 days, 95% CI –1.13 to 0.98, I^2 = 31%,), or hospital length of stay (four studies: WMD 0.65 days, 95% CI –0.81 to 2.10, I^2 = 0%). The outcome of

TABLE 2. Study characteristics.

First author, year	Total no. of patients	Modality	CRRT replacement fluid composition	Anticoagulation used	Prescribed low dosage (mL/kg/h)	Prescribed high dosage (mL/kg/h)	Delivered low dosage (mL/kg/h)	Delivered high dosage (mL/kg/h)	Primary outcome measure
Bouman,[10] 2002	106	CVVHF	Bicarbonate	Heparin, nadroparin	NR	NR	20.1 and 19.1	48.2	Survival at day 28 and recovery of renal function
Boussekey,[17] 2008	19	CVVHF	Bicarbonate	Heparin	35	65	32	62	Decrease of vasopressor dose along with a MAP>65 mmHg
Network,[11] 2008	1124	CVVHDF	Bicarbonate	Citrate, heparin, or none	21.5	36.2	22	38.5	Duration of survival in ICU and renal recovery
		SLED		Heparin					
				Citrate					
		IHD							
Ronco,[7] 2000	425	CVVHF	Lactate	Heparin	20	35 and 45	NR	NR	Survival 15 days after discontinuation of treatment
Saudan,[8] 2006	206	CVVHF	Lactate, bicarbonate	Heparin	25	42	NR	NR	Survival at 28 and 90 days
		CVVHDF							
Tolwani,[9] 2008	200	CVVHDF	NR	Citrate	20	35	17	29	Survival to ICU discharge or 30 days
Investigators RRTS,[12] 2009	1465	CVVHDF	Bicarbonate	Heparin	25	40	22	33	Survival at 90 days

Notes: CVVHF, continuous venous to venous hemofiltration; CVVHD, continuous venous to venous hemodialysis; CVVHDF, continuous venous to venous hemodiafiltration; SLED, slow low-efficiency dialysis; IHD, intermittent hemodialysis; MAP, mean arterial pressure; NR, not reported or unclear.

TABLE 3. Study quality.

First author, year	Study design	Allocation concealment	Blinding				Funding	Lost to follow-up (%)
			Patients	Care givers	Outcome assessors	Data collectors		
Bouman,[10] 2002	Randomized	Yes	No	No	No	No	NR	NR
Boussekey,[17] 2008	Randomized	No	No	No	No	No	Nonprofit	NR
Network,[11] 2008	Randomized	Yes	NR	NR	Yes	No	Nonprofit	<1
Ronco,[7] 2000	Randomized	NR	No	No	NR	NR	NR	0
Saudan,[8] 2006	Randomized	Yes	No	No	No	No	NR	0
Tolwani,[9] 2008	Randomized	Yes	No	No	No	No	Nonprofit/industry	0
Investigators RRTS,[12] 2009	Randomized	Yes	No	No	NR	NR	Nonprofit	<1

Note: NR, not reported or unclear.

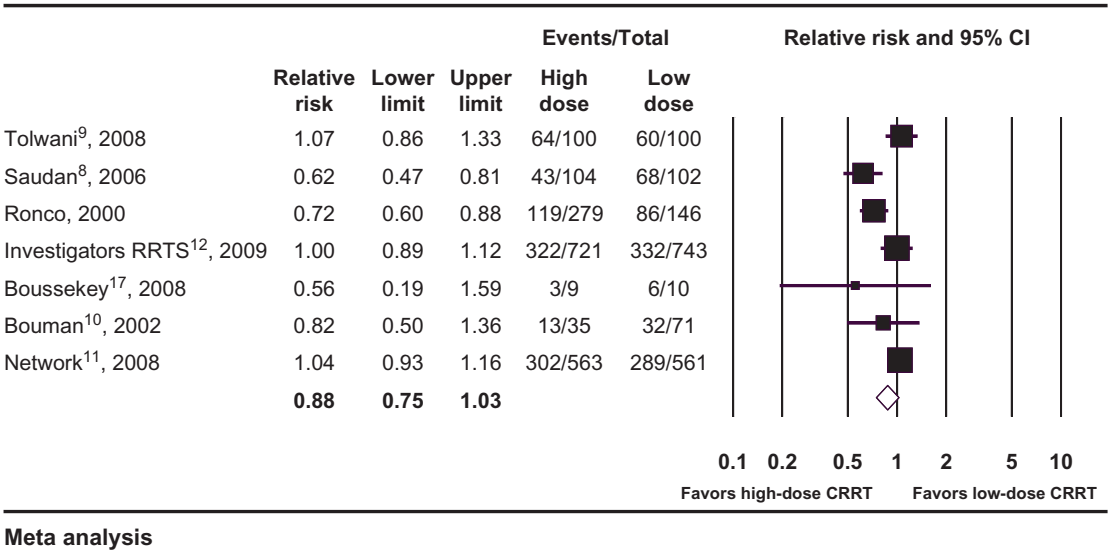

FIGURE 2. Risk of death.

vasopressor requirements was reported in only one study[17] and showed a decrease in the mean norepinephrine dosing >75% at 24 hours with higher prescribed dosage of CRRT ($p = 0.004$).

Sensitivity, subgroup, and publication bias analyses

Meta-regression did not demonstrate an association between the length of study follow-up and the severity of illness score on the effect size although this analysis was clearly underpowered. Study quality did not affect the effect size (high quality vs. low quality; p-value for the test of interaction for the outcomes of death and requirement of long-term RRT was 0.13 and 0.20, respectively). Data were insufficient to conduct several other planned subgroup analyses. There was no evidence for publication bias as demonstrated by visual inspection of funnel plots or by Egger's test (p-value for the outcomes of death and requirement of long-term RRT was 0.17 and 0.21, respectively). The use of fixed effect model did not change study conclusions. The exclusion of the RENAL study[12] (as it had the most weight in meta-analysis) or the ARF Trial Network study[11] (in which integrated HD strategies were used) or Bousskey et al.[17] (in which the population seemed older and all had septic shock) did not change study conclusions (RRs respectively: 0.84, 95% CI 0.67–1.04; 0.83, 95% CI 0.68–1.02; and

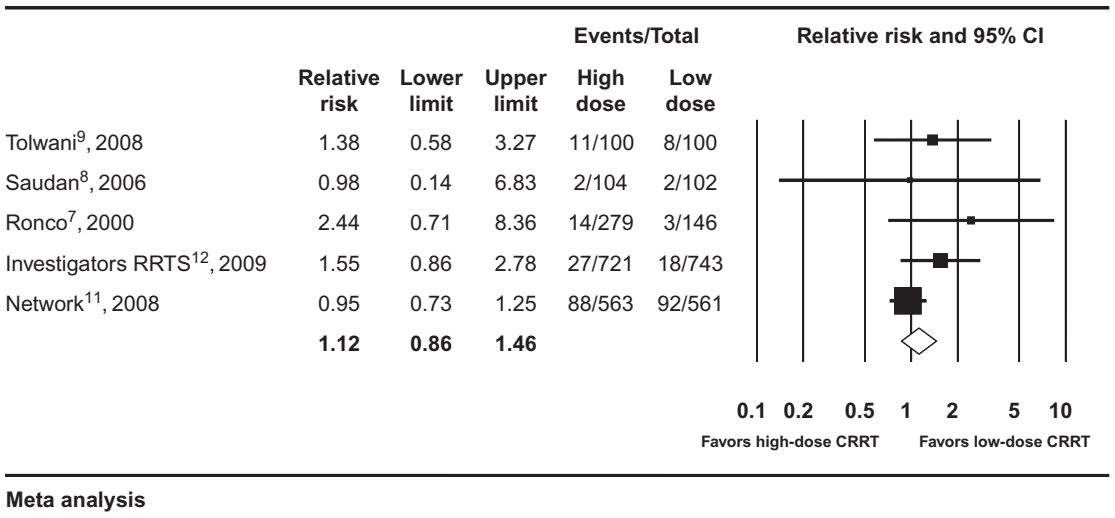

FIGURE 3. Risk of long-term requirement of renal replacement therapy.

0.89, 95% CI 0.75–1.04). Considering the date of study publication as a source of heterogeneity shows that earlier studies[7,8,10] published between 2000 and 2006 did in fact show a reduction in mortality (RR 0.70, 95% CI 0.60–0.81); however, these studies were quite small. Larger studies with markedly more events and power were contradictory and drove the pooled estimate clearly toward a no effect on mortality.

DISCUSSION

Early evidence suggested that higher dosages of CRRT may improve patient outcomes. Studies conducted on animals that were given systemic endotoxins followed by CRRT suggested improved hemodynamics and cytokine removal with high-volume hemofiltration.[19–21] A large retrospective study found that higher dosages of CRRT lead to decreased mortality in a subset of patients.[22] Another study showed improved acid–base balance and increased uremic clearance with higher dosage of CRRT.[23] Although high-efficiency blood purification may be achieved with CRRT or IHD, the optimal balance of efficiency, safety, and improved patient outcomes continues to be investigated.

We conducted a systematic review that demonstrated no statistical difference toward decreased mortality in patients receiving higher dosage of CRRT as treatment for ARF in an ICU setting. We did not find a difference in ICU or hospital length of stay, or the need for RRT at the end of study period between lower or higher dosages of CRRT. The quality of evidence generated by these randomized trials was downgraded because of imprecision (CIs that include both harm and benefit) and the significant heterogeneity of treatment effect on the outcome of mortality across trials that could not be explained by subgroup interactions or meta-regression.

Although in a typical clinical setting patients with ARF may receive both intermittent and continuous forms of RRT, we included studies of patients in an ICU setting with ARF in whom treatment with CRRT is started and a prescribed dosage is required, also a common clinical scenario. As we conducted a systematic review of the literature to summarize the best available evidence regarding the mortality and morbidity associated with differing dosing regimens of CRRT for patients with ARF in an ICU setting, we did not include studies of IHD dosing. Of the studies we included, there was insufficient reporting for analysis of the frequency, dose, or duration of IHD that patients may have received after CRRT was discontinued. Patients enrolled in the Intensity of Renal Support in Critically Ill Patients with Acute Kidney Injury[11] and the Randomized Control Trial of Normal versus Augmented Level of Renal Replacement Therapy [12] comprised about 73% of the patients in our systematic review, and the results of these studies heavily weighted our findings. However, the exclusion of these trials from analysis does not change the conclusions of this review regarding any outcome.

Strengths and limitations of this review

The strengths of this review stem from the comprehensive search strategy and the bias protection measures taken by reviewers, such as reviewing in duplicate and author contact. We conducted several a priori exploratory analyses looking for causes of heterogeneity and publication bias.

Although blinding of patients and caregivers may not be feasible in CRRT studies, allocation concealment and blinding of data collectors and outcome assessors are possible and desirable. The RCT included in this review had inconsistent allocation concealment and non-blinded outcome and data collection. Due to these methodological limitations, as well as the statistical imprecision and heterogeneity, the quality of evidence presented in this review is considered of lesser quality (i.e., at higher risk of bias). In addition, although we found no evidence of publication bias, the methods used can miss the presence of such bias when the number of included studies is small.[24] We were unable to test certain patient characteristics that would have been very useful clinically and may have explained heterogeneity. These characteristics are difficult to ascertain via subgroup analysis in a summary-data meta-analysis such as this one because of lack of power, ecological bias, and sparse data and are best evaluated in a large RCT or in a patient-level meta-analysis.

CONCLUSIONS

Evidence of moderate to low quality demonstrated no change in mortality with escalated dosing of CRRT for patients with ARF in an ICU setting. The need for continuing RRT, or patient ICU and hospital length of stay were also unaffected by the dose of CRRT.

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