Original Papers

Factors predicting successful discontinuation of continuous renal replacement therapy

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Summary

This multicentre, retrospective observational study was conducted from January 2010 to December 2010 to determine the optimal time for discontinuing continuous renal replacement therapy (CRRT) by evaluating factors predictive of successful discontinuation in patients with acute kidney injury. Analysis was performed for patients after CRRT was discontinued because of renal function recovery. Patients were divided into two groups according to the success or failure of CRRT discontinuation. In multivariate logistic regression analysis, urine output at discontinuation, creatinine level and CRRT duration were found to be significant variables (area under the receiver operating characteristic curve for urine output, 0.814). In conclusion, we found that higher urine output, lower creatinine and shorter CRRT duration were significant factors to predict successful discontinuation of CRRT.

Key Words: acute kidney injury, continuous renal replacement therapy, creatinine level, urine output

Acute kidney injury is a common complication in critically ill patients, and mortality is related to its severity[1-3]. According to previous reports, approximately 6% of patients in intensive care units (ICUs) develop severe acute kidney injury (AKI), 4% of whom are treated with renal replacement therapy (RRT)[4,5]. Continuous RRT (CRRT) is preferred over intermittent RRT because the former provides patients with circulatory stability.

Although CRRT is commonly used to treat critically ill patients with acute kidney injury in ICUs, very few studies have examined the conditions under which CRRT may be discontinued in these patients[6-8]. This situation is considerably different from that of weaning from mechanical ventilation, another form of mechanical support commonly provided in ICUs[9-11]. Based on limited available evidence, the relevant guidelines simply recommend that practitioners should "discontinue RRT when it is no longer required, either because intrinsic kidney function has recovered to a point where it is adequate to meet patient needs or because RRT is no longer consistent with the goals of care". However, no specific recommendations are provided in regard to the degree of recovery of kidney function[12].

This lack of evidence and guidelines is an important issue considering the frequency with which CRRT is utilised in daily ICU practice and the necessity of discontinuing CRRT prior to patient transfer to the general ward. Therefore, in this multicentre, retrospective observational study we attempted to identify predictive factors for successful CRRT discontinuation.

Materials and methods

This multicentre, retrospective observational study was conducted at 14 ICUs in 12 Japanese hospitals. The study protocol was reviewed by the Ethics Committee or Investigational Review Board of each participating centre (ethics approval number in the first author's institution: 2011111502). Patients who were admitted to one of the participating ICUs between January 2010 and December 2010 were screened and included in this study if they were 18 years of age or older, had AKI and were receiving CRRT. Patients aged less than 18 years old, those receiving dialysis

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treatment before admission to the ICU and those with end-stage renal failure who were on chronic dialysis were excluded.

Information on the following was collected for the patients included in this study: age, sex, body weight, premorbid creatinine level, reason for ICU admission, cause of AKI (sepsis, major surgery, cardiogenic shock, hypovolaemia, nephrotoxic drugs, post-renal acute kidney injury, or hepatic failure), Simplified Acute Physiology Score II[13] and baseline creatinine level. On initiation of CRRT, information on the following was obtained: the Sequential Organ Failure Assessment score[14] without renal system parameter (Non-renal SOFA), type of CRRT, use of vasopressors, mean arterial pressure, PaO_2:FiO_2 ratio, $PaCO_2$, HCO_3^-, lactate, creatinine, albumin, total bilirubin and urea levels, platelet count, International Normalized Ratio, use of mechanical ventilation, urine output and use of diuretics. At the time of CRRT discontinuation, information on the following was collected: Non-renal SOFA score, use of vasopressors, mean arterial pressure, use of mechanical ventilation, PaO_2:FiO_2 ratio, HCO_3, lactate, creatinine and urea levels, urine output and whether diuretics were used within the 24 hour period prior to cessation of CRRT. The date and time of CRRT initiation and discontinuation were recorded and duration of CRRT was calculated. Reasons for CRRT discontinuation were identified for each patient (death during CRRT, withdrawal of treatment, haemodynamic instability, switching to intermittent RRT or recovery of renal function). ICU and hospital outcomes were recorded. In this study, there were no predefined criteria to convert from CRRT to intermittent haemodialysis (IHD). There was also no standardised protocol for CRRT dosing in any institutions. Chronic kidney disease was defined as an estimated glomerular filtration rate of <60 ml/minute/1.73 m^2 [15].

All data were collected using an electronically prepared Excel-based collection tool, sent to the central office by email and screened in detail by a dedicated intensive care specialist for any missing information, logical errors or insufficient detail. Queries were sent back to investigators if necessary.

This cohort did not include patients for whom CRRT was terminated because of death, withdrawal of treatment or haemodynamic instability. Patients were then divided into either one of the following two groups: success group (free from RRT for 7 days after CRRT discontinuation) or failure group. Variables at study inclusion and CRRT initiation and discontinuation were compared between the two groups using the Fisher's exact test and Mann–Whitney U test. To determine factors relevant to successful CRRT discontinuation, multivariate logistic regression analysis was conducted with successful CRRT discontinuation as the dependent variable. All variables presented in Tables 1, 2, and 3 with a significance level of P <0.2 were included as independent variables in the multivariate logistic regression analysis. A backward stepwise elimination process was used to remove insignificant variables (P >0.05). The ability of urine output to discriminate successful CRRT discontinuation was assessed using the area under the receiver operating characteristic curve[16].

All analyses were performed using JMP 9 (SAS Institute Inc, Cary, NC, USA). Data are presented as medians and interquartile ranges (25th–75th percentiles) or percentages. A P value of <0.05 was used to define statistical significance.

Results

In total, 343 patients received CRRT during the study period. Among these, 89 died during CRRT, 34 had treatment withdrawn and seven became haemodynamically unstable. The remaining 213 patients were divided into the success (n = 116) and failure groups (n = 97) (Figure 1).

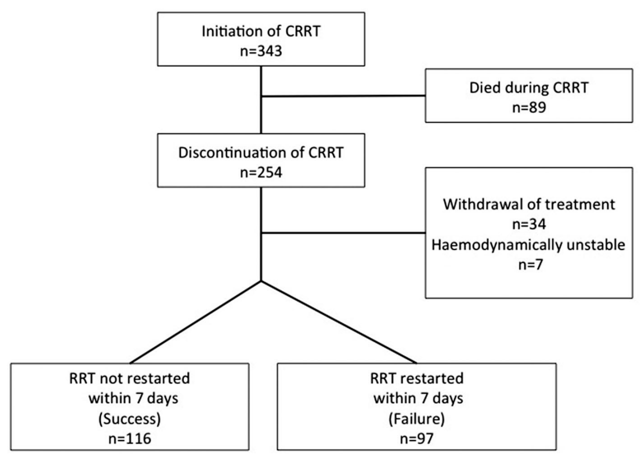

Figure 1: Patient flow chart. IRRT, intermittent renal replacement therapy; CRRT, continuous renal replacement therapy; RRT, renal replacement therapy.

Table 1 shows the characteristics of the patients included in this study. A tendency toward lower creatinine levels was observed in patients in the success group (91 µmol/l versus 105 µmol/l, P=0.11), and the number of patients with cardiovascular diseases was significantly higher in the success group than in the failure group (44.0% versus 29.9%, P=0.035).

Table 2 shows variables at the time of CRRT initiation. The mean arterial pressure was significantly lower (73 mmHg versus 78 mmHg, P=0.001), PaO_2:FiO_2 ratio was significantly higher (251 mmHg versus 198 mmHg, P=0.013) and urine output was significantly greater (30 ml/hour versus 19 ml/hour, P=0.005) for patients in the success group than for those in the failure group. Table 3 shows variables at the time of CRRT discontinuation and outcomes. Patients in the success group exhibited significantly more frequent use of vasopressors and mechanical ventilation, higher urine output, lower creatinine and urea levels, and shorter CRRT duration compared with patients in the failure group. ICU mortality was 15.5% and 19.6% in the success and failure groups, respectively (P=0.43). Hospital mortality significantly

Table 1
Patient characteristics at baseline

	Success (n = 116)	Failure (n = 97)	*P* value
Age, years	69 (58–77)	70 (58–77)	0.90
Male	66.4%	61.9%	0.49
Body weight, kg	58.0 (50.0–67.0)	59.4 (50.0–69.5)	0.36
Premorbid renal function			0.37
Normal	28.4%	21.6%	
Chronic kidney disease	47.4%	56.7%	
Unknown	24.1%	21.6%	
Premorbid creatinine, µmol/l	91 (66–166)	105 (76–183)	0.11
SAPS II	50 (38–61)	51 (39–61)	0.82
Postoperative ICU admission	36.2%	32.0%	0.51
Diagnostic grouping			0.079
Cardiovascular	44.0%	29.9%	
Respiratory	13.8%	19.6%	
Gastrointestinal	17.2%	25.8%	
Neurological	0.9%	1.0%	
Sepsis	12.9%	13.4%	
Trauma	0.0%	3.1%	
Haematologic	4.3%	1.0%	
Others	6.9%	6.2%	
Contributing factors to AKI			
Sepsis	46.5%	43.3%	0.63
Major surgery	28.4%	26.8%	0.79
Cardiogenic shock	26.7%	21.6%	0.39
Hypovolaemia	24.1%	20.6%	0.54
Nephrotoxic drugs	4.3%	8.2%	0.23
Post-renal AKI	0.9%	0.0%	0.36
Hepatic failure	0.0%	3.1%	0.056

AKI = acute kidney injury; SAPS II = Simplified Acute Physiology Score II; data presented as median (IQR) or percentage.

Table 2
Variables at CRRT initiation

	Success (n = 116)	Failure (n = 97)	*P* value
Non-renal SOFA score	8 (5–9)	8 (5–10)	0.53
CRRT			
CVVHD	22.4%	26.8%	0.48
CVVH	5.2%	6.2%	0.76
CVVHDF	72.4%	67.0%	0.41
Intensity, ml/kg/h	14.8 (11.5–17.2)	13.5 (10.8–16.1)	0.37
Vasopressor use	69.0%	63.9%	0.44
Mean arterial pressure, mmHg	73 (63–80)	78 (67–86)	0.001
Mechanical ventilation	77.6%	78.3%	0.89
PaO_2:FiO_2 ratio, mmHg	251 (165–351)	198 (128–300)	0.013
$PaCO_2$, mmHg	37 (31–43)	38 (33–45)	0.33
HCO_3^-, mmol/l	21 (17–26)	20 (18–24)	0.42
Lactate, mmol/l	2.2 (1.3–4.0)	2.1 (1.3–4.3)	0.78
Diuretic use	37.1%	25.8%	0.078
Urine output, ml/h	30 (10–61)	19 (8–37)	0.005
Creatinine, µmol/l	221 (149–353)	270 (209–365)	0.14
Urea, mmol/l	17.0 (10.7–23.2)	18.6 (13.6–28.9)	0.22
Platelet count, 10^9/l	100 (62–160)	94 (57–162)	0.59
INR	1.34 (1.15–1.60)	1.27 (1.16–1.64)	0.85
Total bilirubin, µmol/l	18.8 (10.3–44.5)	17.1 (8.5–34.2)	0.72
Albumin, g/l	22 (22–31)	26 (21–31)	0.48

CRRT = continuous renal replacement therapy; CVVH = continuous venovenous haemofiltration; CVVHD = continuous venovenous haemodialysis; CVVHDF = continuous venovenous haemodiafiltration; INR = International Normalized Ratio; SOFA = sequential organ failure assessment; data presented as median (IQR) or percentage; Intensity = flow rate during CRRT.

differed between the groups (26.7% versus 42.3%, *P*=0.017). At hospital discharge, patients in the failure group exhibited a more frequent requirement for RRT compared with those in the success group (1.8% versus 13.4%, *P* <0.0001).

Multivariate analysis revealed that urine output (odds ratio [OR] 1.09/100 ml/day, *P* <0.0001), creatinine level (OR 0.99/µmol/l, *P* <0.0001) and CRRT duration (OR 0.85/day, *P*=0.0005) were significant predictors of successful CRRT discontinuation (Table 4). The area under the receiver operating characteristic curve (AUROC) values for urine output, creatinine level at discontinuation and CRRT duration as a predictive factor were 0.814 (95% confidence interval [CI] 0.748–0.865), 0.727 (95% CI 0.654–0.790) and 0.695 (95% CI 0.618–0.762), respectively.

Discussion

In this study, among patients whose CRRT was discontinued (not terminated because of death, withdrawal of treatment or haemodynamic instability), urine output, creatinine level and CRRT duration were identified as significant predictors of successful CRRT discontinuation.

To the best of our knowledge, only three studies have previously evaluated factors related to CRRT

Table 3

Variables at CRRT discontinuation and outcomes

	Success (n = 116)	Failure (n = 97)	*P* value
Non-renal SOFA score	6 (4–9)	5.5 (4–8)	0.40
Vasopressor use	44.0%	24.7%	0.003
Mean arterial pressure, mmHg	80 (73–90)	81 (72–92)	0.46
Mechanical ventilation	68.1%	53.6%	0.030
PaO_2:FiO_2 ratio, mmHg	298 (212–352)	286 (232–389)	0.89
HCO_3^-, mmol/l	25 (23–27)	24 (22–26)	0.12
Lactate, mmol/l	1.2 (0.9–1.7)	1.4 (1.1–1.9)	0.29
Diuretic use	37.1%	25.8%	0.078
Urine output, ml/24h	1392 (750–2389)	190 (58–906)	<0.0001
With diuretics	1835 (1020–3550)	900 (196–1650)	0.009
Without diuretics	1202 (682–1872)	150 (45–428)	<0.0001
Creatinine, µmol/l	133 (89–221)	228 (148–334)	<0.0001
Urea, mmol/l	47.7 (31.8–47.7)	81.4 (52.9–119.3)	<0.0001
CRRT duration, days	2 (1–3)	5 (2–7)	<0.0001
Switching to intermittent RRT, n (%)	5 (4.3%)	77 (79.4%)	<0.0001
Recovery of renal function, n (%)	111 (95.7%)	20 (20.6%)	<0.0001
ICU stay, days	8 (5–21)	16 (6–25)	0.88
ICU mortality	15.5%	19.6%	0.43
Hospital mortality	26.7%	42.3%	0.017
RRT at hospital discharge	1.8%	13.4%	<0.0001
Creatinine levels at discharge, µmol/l	84.9 (64.5–164)	95 (62–169)	0.54

CRRT = continuous renal replacement therapy; RRT = renal replacement therapy; SOFA = Sequential Organ Failure Assessment; data presented as median (IQR) or percentage.

discontinuation[6-8]. The first retrospective observational study was conducted in a surgical ICU in Taiwan. CRRT was used for treating 334 patients with postoperative AKI; 94 patients were free from RRT for five days, while 64 patients were free for 30 days. Multivariate logistic regression analysis identified the following independent predictors for RRT within 30 days: longer duration of RRT (OR 1.06/day), higher SOFA score (OR 1.44/score), oliguria on the day of discontinuation (OR 4.17; urine output, <100 ml/8 hours) and age >65 years (OR 6.35)[6]. The second study was a post hoc analysis of the Beginning and Ending Supportive Therapy for the kidney study (the BEST kidney study)[5] for identifying variables associated with successful CRRT[7]. Among 529 patients in whom CRRT was discontinued, 313 were free from RRT for seven days

Table 4

Multivariate logistic regression analysis for determining predictors of successful discontinuation of continuous renal replacement therapy in all patients

	Odds ratio (95% CI)	*P* value
Urine output at discontinuation, 100 ml/day	1.09 (1.05–1.14)	<0.0001
Creatinine levels at discontinuation, µmol/l	0.99 (0.990–0.996)	<0.0001
CRRT duration, days	0.85 (0.76–0.94)	0.0005

CI = confidence interval; CRRT = continuous renal replacement therapy. The area under the receiver operating characteristic curve of the final model was 0.848.

after CRRT discontinuation. Multivariate logistic regression analysis for successful CRRT identified urine output (OR 1.078/100 ml/day) and creatinine level (OR 0.996/µmol/l) as significant predictors of successful CRRT. In the third study, a single-centre retrospective cohort study, 222 patients were evaluated to determine independent factors influencing restoration of kidney function during CRRT-free intervals. Multivariate logistic regression analysis showed that the following three variables were useful to predict restoration of kidney function: number of previous CRRT cycles (OR 0.449/cycle), SOFA score (OR 0.449/score) and urine output during the first 8 hours after CRRT discontinuation (OR 1.026/ml/hour)[8]. In these three studies, urine output was consistently found to be a useful predictor of successful CRRT discontinuation. In the present study, we confirmed that urine output was related to successful CRRT discontinuation with prediction accuracy (AUROC 0.814) similar to that in the BEST kidney study (AUROC 0.845).

We also found that the serum creatinine level was a significant and an independent predictive factor. However, although creatinine levels at CRRT discontinuation significantly differed between patients in the success and failure groups (133 versus 228 µmol/l, *P* <0.0001), this difference was small and its usefulness in the clinical setting is questionable (AUROC 0.727). Previous studies also identified the creatinine level as a predictive factor of successful CRRT discontinuation, but the accuracy of this factor was poor[6, 8]. This result is justifiable, considering that serum creatinine levels are affected by many factors (e.g., the timing of CRRT discontinuation, muscle mass).

Predictive factors for discontinuation of mechanical ventilation, another form of mechanical support commonly used in ICUs, has been extensively studied[9-11, 19-22]. Because of the frequency with which CRRT is used in ICUs, further studies are required to identify useful parameters for predicting successful CRRT discontinuation. For example, two-hour creatinine clearance prior to CRRT discontinuation has been suggested as a useful predictor (AUROC 0.82)[17]. However, this finding must be confirmed in patients with anticipated recovery of renal function following discontinuation.

This study has several limitations. First, this study is a retrospective observational study, which increases the potential for bias. In addition, because of the lack of standard criteria for CRRT discontinuation, clinical judgement about the optimal timing of treatment discontinuation was left to individual attending physicians. Third, we could not truly evaluate the group of patients who were not switched to IHD. Fourth, we did not distinguish the way of CRRT discontinuation such as medical decision or opportune moments. The exact timing of CRRT discontinuation (and also the variables at that time) would have been affected by opportune moments.

Despite these limitations, because the number of studies regarding the timing of CRRT discontinuation is limited, we believe our findings to be of value.

Conclusions

Higher urine output, lower creatinine and shorter CRRT duration were significant predictors among patients with successful discontinuation of CRRT in this study. More studies are required to identify useful indices for predicting successful dialysis discontinuation in patients with severe acute kidney injury.

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References

1. Liangos O, Wald R, O'Bell JW, Price L, Pereira BJ, Jaber BL. Epidemiology and outcomes of acute renal failure in hospitalized patients: a national survey. Clin J Am Soc Nephrol 2006; 1:43-51.
2. Lassnigg A, Schmidlin D, Mouhieddine M, Bachmann LM, Druml W, Bauer P, Hiesmayr M. Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study. J Am Soc Nephrol 2004; 15:1597-1605.
3. Chertow GM, Soroko SH, Paganini EP, Cho KC, Himmelfarb J, Ikizler TA, Mehta RL. Mortality after acute renal failure: models for prognostic stratification and risk adjustment. Kidney Int 2006; 70:1120-1126.
4. Hoste EAJ, Clermont G, Kersten A, Venkataraman R, Angus DC, De Bacquer D, Kellum JA. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. Crit Care 2006; 10:R73.
5. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S et al. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 2005; 294:813-818.
6. Wu V-C, Ko W-J, Chang H-W, Chen Y-W, Lin Y-F, Shiao CC et al. Risk factors of early redialysis after weaning from postoperative acute renal replacement therapy. Intensive Care Med 2008; 34:101-108.
7. Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I et al. Discontinuation of continuous renal replacement therapy: a post hoc analysis of a prospective multicenter observational study. Crit Care Med 2009; 37:2576-2582.
8. Heise D, Gries D, Moerer O, Bleckmann A, Quintel M. Predicting restoration of kidney function during CRRT-free intervals. J Cardiothorac Surg 2012; 7:6.
9. Esteban A, Frutos F, Tobin MJ, Alia I, Solsona JF, Valverdu I et al. A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. N Engl J Med 1995; 332:345-350.
10. Esteban A, Alia I, Tobin MJ, Gil A, Gordo F, Vallverdu I et al. Effect of spontaneous breathing trial duration on outcome of attempts to discontinue mechanical ventilation. Spanish Lung Failure Collaborative Group. Am J Respir Crit Care Med 1999; 159: 512-518.
11. Brochard L, Rauss A, Benito S, Conti G, Mancebo J, Rekik N et al. Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. Am J Respir Crit Care Med 1994; 150:896-903.
12. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012; 120:c179-184.
13. Le Gall J R, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 1993; 270:2957-2963.
14. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996; 22:707-710.
15. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002; 39:S1-266.
16. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982; 143:29-36.
17. Frohlich S, Donnelly A, Solymos O, Conlon N. Use of 2-hour creatinine clearance to guide cessation of continuous renal replacement therapy. J Crit Care 2012; 27:744.e1-5.
18. de Mendonca A, Vincent JL, Suter PM, Moreno R, Dearden NM, Antonelli M et al. Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. Intensive Care Med 2000; 26:915-921.
19. MacIntyre NR, Cook DJ, Ely EW Jr, Epstein SK, Fink JB, Heffner JE et al. Evidence-based guidelines for weaning and discontinuing ventilatory support: a collective task force facilitated by the American College of Chest Physicians; the American Association for Respiratory Care; and the American College of Critical Care Medicine. Chest 2001; 120:375S-395S.
20. Ely EW, Meade MO, Haponik EF, Kollef MH, Cook J, Guyatt GH, Stoller JK. Mechanical ventilator weaning protocols driven by nonphysician health-care professionals: evidence-based clinical practice guidelines. Chest 2001; 120:454S-463S.
21. Esteban A, Alia I, Gordo F, Fernandez R, Solsona JF, Vallverdu I et al. Extubation outcome after spontaneous breathing trials with T-tube or pressure support ventilation. The Spanish Lung Failure Collaborative Group. Am J Respir Crit Care Med 1997; 156: 459-465.
22. Epstein SK, Ciubotaru RL, Wong JB. Effect of failed extubation on the outcome of mechanical ventilation. Chest 1997; 112: 186-192.

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