Choice of therapy and renal recovery

Shigehiko Uchino, MD

Objectives: **To describe the impact of choice of therapy on renal recovery.**

Design: **Literature review.**

Main Results: **Randomized controlled trials conducted have not shown a benefit of continuous renal replacement therapy in mortality over intermittent renal replacement therapy. However, renal recovery is another important outcome for patients with acute kidney injury and may be affected differently by intermittent renal replacement therapy and continuous renal replacement therapy. Because of its rapid changes in fluid status and plasma osmolality, intermittent renal replacement therapy induces a decrease in venous return and can induce intradialytic hypotension. Because of this effect, intermittent renal replacement therapy may cause renal ischemia and delay renal recovery. Observational studies, including two large epidemiologic studies, suggest that continuous renal replacement therapy may be able to reduce chronic dialysis dependence. On the other hand, randomized controlled trials conducted so far do not support an effect of continuous renal replacement therapy over intermittent renal replacement therapy in relation to renal recovery. However, all of these randomized studies have significant limitations including sample size, study design, and randomization.**

Conclusions: **Although there is much suggestive evidence that continuous renal replacement therapy may increase the rate of renal recovery, such evidence is insufficient to fully elucidate the impact of choice of therapy on this outcome. Appropriately planned trials will be required to address this issue. (Crit Care Med 2008; 36[Suppl.]:S238–S242)**

KEY WORDS: acute renal failure; epidemiology; continuous renal replacement therapy; intermittent renal replacement therapy; critical illness; hemodialysis; hemofiltration; end-stage kidney disease; renal function; intensive care unit

Acute kidney injury (AKI) is a common condition in the intensive care unit (ICU) and approximately 4% of such patients require renal replacement therapy (RRT) (1). Continuous renal replacement therapy (CRRT) is often the preferred choice over intermittent renal replacement therapy (IRRT) in the ICU, usually because of improved hemodynamic stability and better solute control (2–4). Despite its physiologic benefits, randomized controlled trials have not shown a mortality benefit of CRRT over IRRT (5–8).

However, lack of survival benefit does not imply that IRRT and CRRT are equal. Renal recovery is another important outcome for patients with AKI and may be affected differently by IRRT and CRRT. Some patients with AKI who require RRT in the ICU become dialysis dependent even after recovery from their sickness and hospital discharge. End-stage kidney disease requiring long-term hemodialysis is known to cause significant limitations in health-related quality of life. Furthermore, long-term dialysis is costly. Dr. Manns and colleagues (9) retrospectively analyzed the cost related to performing CRRT and IRRT and estimated that if the rate of renal recovery was 5% to 10% higher for patients treated with CRRT compared with IRRT, the immediate increase in costs due to the use of CRRT rather than IRRT could be offset by downstream savings.

In this review, the physiologic rationale and observational and randomized studies related to choice of therapy and renal recovery will be discussed.

Physiologic Rationale and Blood Pressure Reduction

In theory, because of its rapid changes in fluid status and plasma osmolality, IRRT induces a decrease in venous return and cardiac index. Because of this effect, IRRT may cause renal ischemia and delay renal recovery after AKI. This concern initially came from experiences in combat casualties in Vietnam (10). Tissues from biopsies and postmortem studies in patients who had prolonged AKI requiring dialysis showed the presence of focal areas of fresh tubular necrosis estimated to be 48 or 72 hrs old. The only hemodynamic instability these patients experienced was transient hypotension during hemodialysis treatments. Several animal studies were then conducted to examine the possible mechanisms for this phenomenon (11–13). These studies found a loss of renal blood flow autoregulation in acute kidney injury. Therefore, if IRRT causes intradialytic hypotension more frequently than CRRT, it is likely that IRRT can prolong renal recovery.

A few small observational studies compared hemodynamics in IRRT and CRRT (14–16), all of which showed that CRRT had better hemodynamic stability. For example, Dr. van Bommel and colleagues (14) reviewed medical records of patients with AKI admitted to a surgical ICU. Of 94 patients who received dialytic support for severe AKI, 34 patients were treated with intermittent hemodialysis (IHD) and 60 with continuous arteriovenous hemodiafiltration. Demographics of patients were comparable in terms of age and gender, but patients treated with continuous arteriovenous hemodiafiltration had lower blood pressure, higher Acute Physiology and Chronic Health Evaluation (APACHE) II score, and more organ failures at the start of RRT. Despite less severity of the patient condition, clinically relevant hypotension

From the Intensive Care Unit, Department of Anesthesiology, Jikei University School of Medicine, Tokyo, Japan.

For information regarding this article, E-mail: s.uchino@jikei.ac.jp

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Table 1. Observational studies of renal replacement therapy (RRT) for acute renal failure reporting renal recovery

First Author	Published Year	Reference	No. of Patients	Treated with CRRT (%)	Survived	Dialysis Dependence (%)
Barton	1993	19	250	250 (100)	132	4 (3.0)
Consentino	1994	20	363	194 (53.4)	76	26 (34.2)
Chertow[a]	1995	21	132	52 (39.4)	39	13 (33.3)
Swartz	1999	22	349	166 (47.5)	143	52 (36.4)
Cole	2000	23	116	110 (94.8)	59	11 (18.6)
Korkeila	2000	24	62	46 (74.2)	34	11 (32.4)
Silvester	2001	25	299	292 (97.7)	159	25 (15.7)
Manns	2003	9	261	178 (68.2)	98	28 (28.6)
Bell	2005	26	207	207 (100)	105	5 (4.8)
Ahlstrom	2005	27	703	207 (29.4)	294	37 (12.6)
Bagshaw[a]	2005	28	240	192 (80.0)	87	19 (21.8)
Jacka	2005	29	93	65 (69.9)	38	12 (31.6)
Maccariello	2007	30	214	178 (83.2)	52	10 (19.2)

[a]1-yr outcomes. Dialysis dependence is rate of patients who remained on dialysis at hospital discharge among survivors.

occurred in 19% of IHD procedures, which often led to premature termination of IHD and/or ineffective fluid removal. On the other hand, continuous arteriovenous hemodiafiltration hemodynamically was well tolerated and no significant changes in heart rate and blood pressure were observed during treatment.

Dr. Manns and colleagues (16) monitored blood pressure and renal functions in 27 patients with IHD and 16 patients with continuous venovenous hemodialysis. During dialytic treatment, IHD caused reduction in mean arterial pressure (MAP) by 6.9% on average compared with pretreatment baseline. Although pretreatment MAP was lower in continuous venovenous hemodialysis (84 vs. 74 mm Hg; $p < .05$), there was no significant reduction in MAP (2.3% on average) in the first 3 hrs after commencing treatment. Moreover, the reductions in creatinine clearance (23.9% vs. 9.2%; $p < .05$) and urine volume (48.9% vs. 18.4%; $p < .05$) also were less significant in continuous venovenous hemodialysis compared with IHD.

The results of randomized controlled trials are more controversial (2, 6, 7, 17). Dr. Davenport and colleagues (2) randomized 32 patients with combined acute hepatic and renal failure to receive either intermittent hemofiltration or CRRT (continuous arteriovenous hemofiltration or continuous arteriovenous hemodiafiltration). During the first hour of treatment, there was a reduction in cardiac index of 15% during intermittent hemofiltration compared with no significant change during CRRT (3%). This reduction in cardiac index during intermittent hemofiltration was associated with a reduction in MAP from 82 to 66 mm Hg ($p < .001$). Dr. Augustine and colleagues (6) also reported a significant reduction in MAP during IHD, which was not observed during continuous venovenous hemodialysis. On the other hand, Dr. Misset and colleagues (17) conducted a crossover randomized trial comparing IHD and continuous arteriovenous hemofiltration. Twenty-seven patients received both treatments. The greatest changes in blood pressure (highest − lowest MAP) were the same during the two periods (46 mm Hg for continuous arteriovenous hemofiltration vs. 48 mm Hg for IHD; $p = .73$), as were the frequencies of decreases in MAP >10 mm Hg among the total number of MAP measures (25% vs. 26%; $p = .72$). There was also no difference in variations in MAP during the 4-hr period of IHD and the first 4 hrs of continuous arteriovenous hemofiltration. Dr. Uehlinger and colleagues (7) also reported a similar frequency of hypotension (an average daily MAP of <65 mm Hg) between IHD and continuous venovenous hemodiafiltration (CVVHDF).

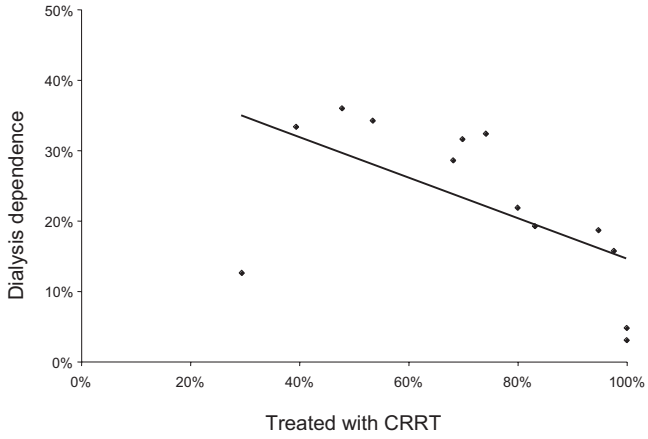

Figure 1. Relationship between the use of continuous renal replacement therapy (*CRRT*) and the prevalence of dialysis dependence among survivors.

The reasons for such controversial results in randomized trials are unclear. However, in general, randomized trials are conducted with strict protocols and observational studies may better reflect what happens in the "real world." Indeed, even after introducing practice guidelines to improve hemodynamic tolerance of IHD, Dr. Schortgen and colleagues (18) reported that hypotensive episodes or need for therapeutic interventions occurred in 61% of IHD sessions, although less frequently than in the preguideline period. Therefore, it is likely that IRRT causes intradialytic hypotension more often than CRRT.

Observational Studies for Renal Recovery

There are multiple observational studies reporting renal recovery in patients

with AKI requiring RRT. In most of such studies, both IRRT and CRRT were used by physician's choice. Table 1 is a summary of the studies, reporting CRRT usage and the prevalence of dialysis dependence at hospital discharge among survivors (9, 19–30). CRRT usage and the frequency of dialysis dependence were varied, from 30% to 100% and 3% to 40%, respectively. Figure 1 shows the relationship of CRRT usage and frequency of dialysis dependence among survivors. Interestingly, there is almost a linear relationship between the two: The more patients that are treated with CRRT, the lower the rate of dialysis dependence is.

Among the studies shown above, only a few studies have compared renal recovery in IRRT and CRRT directly (9, 22, 29). Dr. Swartz and colleagues (22) retrospectively analyzed data from all adult patients undergoing RRT for AKI in their unit. They found 349 patients who received RRT (continuous venovenous hemofiltration [CVVH] or IHD). They then excluded 122 patients who had systolic blood pressure of <90 mm Hg or total bilirubin of >15 mg/dL at initiation of RRT, or had RRT for <48 hrs, because CVVH was chosen simply by the severity of their illness in these patients or the period of RRT was too short to reflect the effect of treatment modality. CVVH was initially chosen in 90 patients and IHD in 137 patients. Although hospital mortality was higher in patients with initial CVVH (68% vs. 41%; $p < .0001$), when adjusted with covariates, the odds ratio (OR) of initial CVVH for hospital mortality was not found to be significant (OR, 1.09; $p = .72$). Furthermore, almost half of survivors after initial IHD became dialysis dependent at hospital discharge, which was 60% greater than in survivors after initial CVVH, but given the limited study size this failed to achieve significance (27.6% vs. 44.4%; $p = .13$).

Dr. Jacka and colleagues (29) reviewed the medical records of 93 patients undergoing RRT for the treatment of AKI in their ICU. Patients with CRRT were younger, had lower creatinine at ICU admission, had acute lung injury, and required vasoactive drugs more frequently compared with IRRT. The APACHE II score was similar between the two modalities. Although hospital mortality was not statistically significant (63% vs. 50%; $p = .24$), renal recovery at hospital discharge was more common in patients with CRRT than IRRT (87% vs. 36%; $p = .0003$). Therefore, observational studies consistently support the notion that IRRT may delay renal recovery.

Randomized Controlled Studies for Renal Recovery

CRRT and IRRT have been compared in several randomized controlled trials. Among them, in my knowledge, four studies reported the prevalence of renal recovery (5–8). The summary of these studies is shown in Table 2. Only two studies were conducted in a multicentered setting (5, 8). Dr. Mehta and colleagues (5) randomized 166 patients in four centers to receive CVVHDF or IHD. Despite randomization, there were significant differences in gender, hepatic failure, APACHE II and III scores, and the number of failed organ systems, in each instance biased in favor of the IHD group. Although the crude hospital mortality was higher in patients with CVVHDF (65.5% vs. 47.6%; $p < .02$), using multivariate logistic regression analysis the OR of CVVHDF for hospital mortality was not significant. Of the surviving patients, 7% in IHD and 14% in CVVHDF remained on dialysis at hospital discharge. However, patients with hemodynamic instability (MAP <70 mm Hg) were excluded from the study. Such patients are the ones in whom the advantages of CRRT should be most evident. Furthermore, CVVHDF was associated with a significantly higher rate of complete renal recovery in surviving patients who received an adequate trial of therapy with no crossover (92.3% vs. 59.4%; $p < .01$).

Dr. Vinsonneau and colleagues (8) randomized 359 patients in 21 centers to receive CVVHDF or IHD. There was no difference in 60-day mortality (primary end point) between the two groups (32.6% vs. 31.5%; $p = .98$). However, there was unexpected and significant improvement in survival rates in the IHD group over time, which was not observed in the CVVHDF group. For renal recovery, there was only one patient among all included patients who was dialysis dependent at hospital discharge. Unfortunately, this study excluded patients with chronic renal impairment, who are the patients most at risk of developing dialysis dependence after RRT and should be the ones most likely to benefit from CRRT in terms of renal recovery.

Recent Evidence: Large Epidemiologic Studies

Recently, two large epidemiologic studies reporting comparisons of CRRT and IRRT in terms of renal recovery have been published (31, 32). We published a study comparing CRRT and IRRT using the Beginning and Ending Supportive Therapy kidney database (31). The kidney study is a multinational, prospective, epidemiologic study of AKI in the ICU including >1700 patients at 54 centers in 23 countries (1). From this large international cohort, we enrolled 1218 patients treated with CRRT or IRRT. We obtained demographic, biochemical, and clinical data and followed patients to either death or hospital discharge. Information was analyzed to assess the independent impact of treatment choice on survival and renal recovery. Patients treated first with CRRT (n = 1006, 82.6%) required vasopressor drugs and mechanical ventilation more frequently compared with those receiving IRRT (n = 212; 17.4%) ($p <$

Table 2. Randomized controlled trials comparing renal recovery between intermittent (IRRT) and continuous (CRRT) renal replacement therapies

Author	Published Year	Reference No.	No. of Centers	Sample No. (IRRT:CRRT)	Severity (IRRT:CRRT)	Dialysis Dependence, %, IRRT:CRRT	*p* Value
Mehta	2001	5	4	166 (82:84)	87.7:96.4[a]	7.0:13.8	.43
Augustine	2004	6	1	80 (40:40)	12.0:11.6[b]	66.7:61.5	>.99
Uehlinger	2005	7	1	125 (55:70)	55:55[c]	3.7:2.7	>.99
Vinsonneau	2006	8	21	359 (184:175)	63.7:64.7[c]	0:1[d]	?

[a]Acute Physiology and Chronic Health Evaluation III, $p < .045$; [b]Cleveland Clinic Foundation severity score; [c]Simplified Acute Physiology Score II; [d]No. of patients is shown because hospital mortality is not provided. Dialysis dependence is rate of patients who remained on dialysis at hospital discharge among survivors.

.0001). Unadjusted hospital survival was lower (35.8% vs. 51.9%; $p < .0001$). However, multivariable logistic regression showed that choice of CRRT was not an independent predictor of hospital survival. Unadjusted dialysis independence at hospital discharge was higher after CRRT (85.5% vs. 66.2%; $p < .0001$) and the choice of CRRT was a predictor of dialysis independence at hospital discharge among survivors (OR, 3.333; 95% confidence interval [CI], 1.845–6.024; $p < .0001$). Further adjustment using a propensity score did not significantly change these results.

Dr. Bell and colleagues (32) retrospectively collected data from 2202 patients treated with RRT for AKI from 32 ICUs in Sweden. CRRT was used for 1911 patients and IHD for 291. There were no differences between CRRT and IHD regarding baseline characteristics, such as age, sex, and comorbidities. Ninety-day mortality was not significantly different (45.7% vs. 50.6%) between the two groups. Among 944 survivors treated with CRRT, 8.3% never recovered their renal function and became dialysis dependent. On the other hand, the proportion was significantly higher among IHD patients, in which 26 patients out of 158 survivors (16.5%) became dialysis dependent. Multivariate analysis showed that the adjusted OR of dialysis dependence in IHD patients was 2.60 compared with CRRT.

CONCLUSIONS

A strong physiologic rationale and many observational studies, including the two large epidemiologic studies totaling >3,000 patients, suggest that IRRT may increase dialysis dependence after acute AKI compared with CRRT. On the other hand, randomized controlled trials conducted so far do not fully support the findings of observational studies. However, all randomized studies have significant limitations, including inadequate sample size, a study design excluding patients at risk of nonrecovery, and randomization problems, and were thus unable to address this issue. Appropriately planned trials are required to test whether IRRT increases dialysis dependence compared with CRRT.

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