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Review

Outcome comparisons of intermittent and continuous therapies in acute kidney injury: What do they mean?

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ABSTRACT: Despite the fact that no new clinical outcome studies comparing intermittent hemodialysis (IHD) and continuous renal replacement therapy (CRRT) for acute kidney injury (AKI) have been published in the past year, two meta-analyses addressing the topic (Bagshaw et al, Crit Care Med 2008; 36: 610-7, and Pannu et al, JAMA 2008; 299: 793-805) have been published recently. With respect to randomized controlled trials (RCTs), there was a substantial overlap between the studies considered in the analysis by Bagshaw et al and those considered in the analysis by Pannu et al. Although neither meta-analysis showed a benefit for either modality with respect to mortality or renal recovery, the two publications offered vastly different conclusions. Bagshaw et al concluded it is impossible to make any definitive recommendations about dialysis modality choice in AKI because previous studies were not adequately powered and failed to standardize for treatment dose. On the other hand, because the meta-analysis of Pannu et al demonstrated equivalent patient outcomes, and in light of the lower costs of IHD, they suggested that alternate-day hemodialysis should become the preferred therapy in many critically ill patients. As the clinical practice recommendations made by Pannu and colleagues have very important implications, we believe their analysis should be critically assessed. In this review, the weaknesses of the RCTs considered in the meta-analysis by Pannu et al are presented. Furthermore, the assumption by Pannu et al that IHD is associated with lower costs than CRRT is challenged, as they did not consider adequately both the short-term and long-term costs associated with the dialytic management of AKI patients. Based on our critical analysis, we believe the AKI dialytic treatment approach recommended by the JAMA investigators (Pannu et al) is not supported by the aggregate of the available clinical outcome data and, therefore, remains highly controversial.
We would like to join with others in the AKI field by strongly recommending that investigators and other clinicians stop trying to make conclusive determinations about dialysis modalities when robust supportive data simply are not available. Instead of additional intermodality comparisons, the focus of future clinical research should be toward generating high-quality data on intramodality interventions, such as treatment dose and timing of treatment initiation. In this regard, at least for CRRT, we anxiously await the results of the ongoing RCTs evaluating the effect of CRRT dose on patient outcome.(Int J Artif Organs 2008; 31: 213-20)

KEY WORDS: Acute kidney injury, Continuous renal replacement therapy, Hemodialysis, Outcome

INTRODUCTION

Approximately one year ago, one of us (C.R.) wrote a review addressing the issue of dialysis modality selection in acute kidney injury (AKI) for this journal (1). In the review, the major RCTs and observational studies that have assessed this issue were evaluated and critiqued. The conclusion was that not a single study in which intermittent and continuous therapies had been compared was relevant for contemporary management of critically ill AKI patients. This conclusion was predicated largely on the fact that no study had appropriately incorporated prescribed CRRT dose into the

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study design. Based on the results of two RCTs (2, 3), a recent meta-analysis (4) has suggested that the standard of care for CRRT now is prescription of at least 35 ml/kg per hour. It is fair to say that of all dialysis practices utilized in the intensive care unit (ICU), this prescription standard has the strongest evidentiary basis, as even data supporting the use of biocompatible membranes are not as robust (5-8). Unfortunately, no comparison of intermittent and continuous therapies has incorporated the 35 ml/kg per hour CRRT dosage standard into the study design.

Clinical comparisons of intermittent and continuous therapies: recent meta-analyses assessing mortality

Despite the absence of any new clinical outcome studies comparing the two modalities published over the past year, two meta-analyses addressing the topic have been published recently (9, 10). Significantly different criteria were used to decide whether or not a particular study was included in each of the analyses. The meta-analysis published by Bagshaw and colleagues (9) identified nine unique RCTs (11-19) involving 1,403 patients and published over a period from 1993 to 2006. Although their analysis showed AKI mortality is not influenced by dialysis modality, they cautioned that the results could not be applied generally in clinical practice due to deficiencies in the design, conduct, and quality of the included studies. The investigators indicated specifically that a study capable of answering the question of optimal dialysis modality in AKI would have to be adequately powered, standardize for dose delivery, and stratify by important patient characteristics. No study to date has come close to meeting these requirements.

In the second recent meta-analysis (10), Pannu and colleagues also concluded that dialysis modality is not a significant predictor of patient outcome. However, these investigators employed a very different set of criteria for study inclusion, as both seven RCTs (11-16, 20) and four observational trials (21-24) were included for the end point of mortality. Six of the RCTs in their meta-analysis (11-16) were the same as those included in the meta-analysis by Bagshaw et al. (The seventh RCT included in the meta-analysis by Pannu et al (20) was actually a comparison of CRRT and sustained low-efficiency dialysis [SLED], and was not included in the analysis by Bagshaw et al.) Pannu et al recommended that, in light of this lack of difference in outcomes and "the significantly higher cost of CRRT, intermittent hemodialysis may be preferable" for critically ill AKI patients. Notably, these investigators suggested further that the standard of care should be alternate-day IHD treatments (see below).

"The devil is in the details"

The validity of a meta-analysis is based on the quality of the studies it analyzes. As such, it is imperative to have a thorough understanding of the limitations of the studies that were considered in these meta-analyses. To assess these limitations, the seven RCTs included in the meta-analysis by Pannu et al are analyzed below. (As indicated above, all but one of these studies were also included in the meta-analysis by Bagshaw et al).

Vinsonneau et al, 2006

Although this study (18) is frequently cited as "proof" that all critically ill patients with AKI can be treated with either IHD or CRRT, there are numerous, well-recognized problems in it. First, given the *mean* HD treatment duration of 5.2 hours, the applicability of the HD results to the "real world", where HD treatment times are significantly shorter than this on a routine basis, is questionable. Second, the mean blood urea nitrogen achieved in the CRRT group was approximately 40 mg/dL – this is considered marginal CRRT metabolic control in the current era of higher dose therapy. This may explain the three-fold higher crossover rate from CRRT to HD versus the rate in the opposite direction. This is distinctly unusual, and the fact that inadequate metabolic control was one of the main reasons for patients to transfer from CRRT to HD is clearly at odds with general clinical practice. Indeed, due to the superior dose delivery capabilities of CRRT, it is exceedingly rare for this modality to be abandoned due to inadequate metabolic control. Finally, and most importantly, the average prescribed CRRT dosage was only 29 ml/kg per hour in the study by Vinsonneau et al. By comparison, in the dose trial by Saudan et al (3), the average dosage of predilution continuous venovenous hemodiafiltration (CVVHDF; the same CRRT modality used in the Vinsonneau trial) was 42 ml/kg per hour. Furthermore, based on the flow rates prescribed in the Vinsonneau trial, the pre-filter administration of replacement fluid resulted in an "adjusted" dosage of approximately 25 ml/kg per hour (25). Although predilution resulted in a similar decrease in effective dosage in the trial by Saudan et al, nevertheless, the prescribed dosage in this trial was approxi-

mately 45% higher than that in the Vinsonneau study. This may very well explain the inability of the latter study to demonstrate a survival advantage for CRRT over IHD.

Uehlinger et al, 2005

Several problems also plagued this study (17). First, the study had to be terminated early presumably because physicians enrolling patients became concerned about randomizing patients with severe hemodynamic instability to HD. As such, the study was underpowered. Second, the institution at which the trial was performed had limited availability of CRRT machines (two CRRT machines) and unlimited availability of HD machines. This limitation mandated an unusual randomization scheme which was dependent on the number of CRRT machines in current use. When both CRRT machines were available, the odds of randomization for a given patient were 2:1 in favor of CRRT, while the inverse ratio applied when only one CRRT machine was available. In this situation, allocation clearly was not concealed. Third, the fluid balance data are very difficult to reconcile with results of previous trials and standard clinical practice. Distinctly unusual findings from this study included a daily net fluid removal that was greater for HD than CRRT and a *positive* daily net fluid balance on average for both groups. Moreover, the mean net ultrafiltrate volume (patient weight loss) in the CRRT group (approximately 1.1 l/day) was far lower than the reported values in the literature and than what is routinely achievable in clinical practice. Finally, the average prescribed dosage of predilution CVVHDF (the CRRT modality used in the study) was only 27 ml/kg per hour, nearly 40% lower than the mean prescribed dosage of CVVHDF in the dose trial by Saudan et al.

Augustine et al, 2004

In this study (16), the period during which IHD or CVVHD was applied lasted only three days. As such, it is difficult to comprehend how such a short treatment period could influence hospital survival. The basis of the study was to control for dose by aiming for the same dose in each group. The actual dose target was based on urea clearance and was a cumulative weekly urea Kt/V of 3.6, the target used for chronic HD patients. The study design did not incorporate one of CRRT's widely accepted advantages over HD, which is greater solute clearance capabilities over an extended molecular weight spectrum. (For comparison, the delivered weekly urea Kt/V in the dose trial by Ronco et al (2) was 5.0 or more on a mean basis). In the paper reporting this study, it was acknowledged that the average dialysate flow in CVVHD was less than 1 l/hour. Based on a patient body weight of 85 kg (average body weight for ICU patients in the United States), a mean dosage of less than 12 ml/kg per hour was delivered. Finally, a low-flux dialyzer was used for both arms. Although use of such of a filter is not unusual in HD, it is extremely rare in CRRT, and the use of a low-flux filter for CRRT eliminated any possibility of achieving larger molecular clearances with this modality, especially given that the CRRT modality was CVVHD.

Kumar et al, 2004

Firstly, the "Introduction" of the paper states clearly: "The focus of this manuscript is not mortality…" (20). Second, this study was not even a comparison of CRRT and IHD, as the intermittent modality was SLED. Moreover, CRRT was not prescribed in a manner consistent with clinical practice. *The most glaring example of this is the use of a conventional HD machine for CRRT*. As such, a major potential advantage of CRRT, which is based on more precise gravimetric fluid balance technology than the volumetric technology found in conventional HD machines, could not be realized. Clearly, this negatively biased the CRRT arm from a hemodynamic perspective and calls into question the hemodynamic data reported. Moreover, the prescribed CRRT dialysate flow rate was 6-12 l/hour, far exceeding the traditional dialysate flow rate in CRRT (1-3 l/hour) and creating potential risks that do not occur with conventional CRRT. No mention of prescribed CRRT dosage was made.

Gasparovic et al, 2003

No technical details are given about the CRRT procedure studied, such as type of machine, replacement fluids, and anticoagulation (15). Moreover, because effluent rates are not given, it is impossible to estimate prescribed CRRT dosage. The authors state the prescribed dosage for the first 33 patients was 18 ml/kg per hour and 35 ml/kg per hour for the remaining 71 patients. However, no flow rate data are provided to substantiate this claim.

Mehta et al, 2001

In this study (14), the randomization process was flawed, resulting in an imbalance in the two groups that negatively biased the CRRT group due to a higher illness severity.

Therefore, it is difficult to understand how this study could have been included in the meta-analysis as a RCT. Furthermore, even if the results of the trial had been valid, they would have been difficult to apply to general clinical practice because hemodynamically unstable patients were excluded.

John et al, 2001

Of the 33 patients enrolled in the study (13), more than half had already received renal replacement therapy. This violates a standard exclusion criterion used in nearly all studies of this type and calls into question the validity of the entire study. Second, the primary end point was related to hemodynamics – no mention of assessing mortality as an end point is to be found in the paper. Third, the study duration was specified as only 24 hours. Although a 70% ICU mortality was reported for both groups, the relevance of reporting this outcome for a study in which the intervention lasted only 24 hours is very questionable, as is the case for the Augustine et al study. No mention was made of prescribed CRRT dosage.

Finally, a major general problem is that in only two of the above studies were CRRT machines used with integrated scale-based fluid balance control systems, which represent the standard of care now. A reasonable conclusion from the above is that these seven RCTs, which serve as the foundation for the mortality comparison in the meta-analysis by Pannu et al, have so many major flaws that the relevance of comparing their mortality rates is highly questionable and cannot be applied to contemporary CRRT practice. As suggested above, probably the most significant limitation is that not a single study even came close to prescribing CRRT dosages that have been shown in recent RCTs to improve patient survival.

Cost comparisons of dialysis modalities in the ICU

The above weaknesses in the studies included in the meta-analysis by Pannu et al notwithstanding, these investigators suggested IHD should be the preferred initial dialysis modality due to its lower costs relative to CRRT. However, this recommendation also requires closer scrutiny and needs to be put in the appropriate context of a critically ill AKI patient.

The largest investigation of the overall hospitalization costs for a critically ill, dialysis-dependent AKI patient was the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment (SUPPORT) trial (26). The analyses indicated that the average mean cost for the entire index hospitalization of a patient receiving renal support for AKI in an ICU is approximately US $108,000 (when converted from 1994 US dollars to the equivalent in 2005 US dollars, based on a 5% inflation rate). Moreover, the analysis showed that approximately 50% of the overall hospitalization costs are incurred prior to the initiation of renal support.

This distribution of costs can be applied to recent cost data provided by Manns and colleagues from two ICUs in the area of Calgary, Canada (27). (It is worthwhile to note here that some of the authors of this report also contributed to the paper in JAMA by Pannu et al). For HD, a dialysis frequency essentially of one treatment per two days was assumed. Of note is the fact that this frequency has been shown to be associated with patient survival that is significantly less than that achieved with daily HD (28). The most useful piece of information provided by the study by Manns et al may be the estimate for the hospitalization cost after the initiation of renal replacement therapy, which was also provided by the SUPPORT trial analysis above. In the Manns et al study, this mean cost was estimated to be approximately Can $50,000 (in 2005 Canadian dollars; 5% inflation rate). Based on this value and the finding from the SUPPORT trial that approximately 50% of the total hospitalization costs are incurred prior to this time, an estimate of approximately Can $100,000 (in 2005 Canadian dollars) can be derived for the total mean hospitalization cost in the trial by Manns et al.

Although dialysis therapy in the ICU clearly is an expensive procedure, so are most life-saving interventions in the critical care environment. Therefore, although direct cost comparisons of different dialysis modalities provide some useful information, the more relevant consideration is the cost of renal support as a percentage of the total cost of caring for a critically ill ARF patient. From this perspective, the cost of renal support is relatively modest, comprising only 3.2% (daily HD) to 5.0% (CRRT with heparin) of the total hospitalization costs. Furthermore, the difference between HD and CRRT represents only 1.7% of the total hospitalization costs. (This comparison does not account for the potential health care cost savings potentially attributable to greater recovery of renal function provided by CRRT, as discussed below.)

The breakdown of hospitalization costs before and after

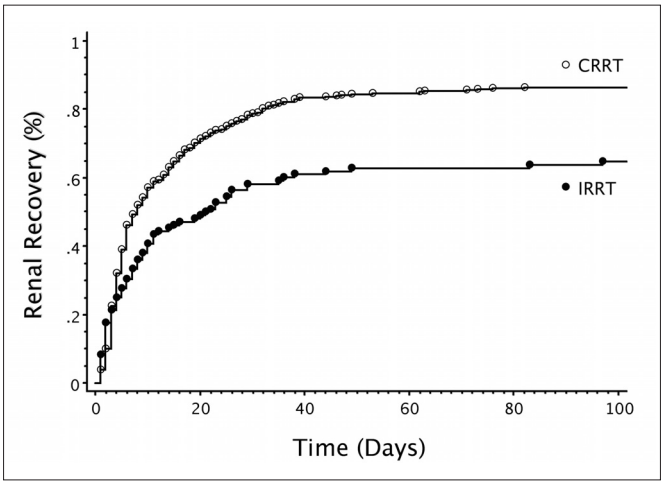

Fig. 1 - *Renal recovery at hospital discharge as a function of initial dialysis modality in the BEST Kidney study (22). CRRT: continuous renal replacement therapy; IRRT: intermittent renal replacement therapy.*

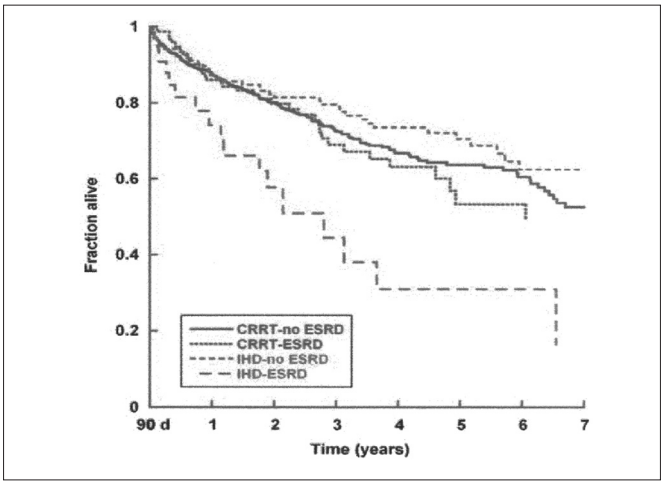

Fig. 2 - *Survival among patients who developed ESRD after acute kidney injury in the intensive care unit. Long-term survival on ESRD therapy among patients initially treated with IHD for acute kidney injury (bottom curve) was significantly lower than that among patients initially treated with CRRT (narrowly-spaced broken curve) (30).*

the initiation of renal support can also be applied to a recent cost comparison of SLED and CRRT reported by Berbece and Richardson of Toronto, Canada (29). Based on a mean duration of renal support of six days, data from these investigators suggest the total cost for SLED is Can $1,430 and for heparin CRRT is Can $2,240 (both in 2005 Canadian dollars). The estimate from the Manns et al study for total hospitalization costs in a critically ill ARF patient is approximately Can $100,000 (2005 Canadian dollars; 5% inflation rate). Based on these numbers, the percentage of the total hospitalization cost related to dialysis ranges only from 1.4% for SLED to 2.2% for heparin CRRT. Furthermore, the difference in cost between the two therapies is minimal (less than 1% of the total hospitalization cost). In total, the data from these two recent Canadian studies actually provide compelling evidence that dialysis therapy comprises a relatively small percentage of total hospitalization costs for critically ill ARF patients. Furthermore, the data show that cost differences between different dialysis modalities are very small. This finding is acknowledged by Pannu et al in their meta-analysis: "the incremental costs of providing RRT in critically ill patients are small compared with the large costs of the index hospitalization and beyond" (10).

Pannu et al also acknowledge that chronic dialysis dependence due to nonrecovery of renal function after AKI has "substantial implications given its high costs" and further state that "relatively costly interventions may be attractive if proven to improve" long-term outcomes (10). The analysis by Manns et al (27) also demonstrated that nonrecovery of renal function after AKI has important health economic implications. Hospitalization costs after the initiation of dialysis were significantly higher in patients failing to recover renal function compared with those who recovered renal function (Can $75,000 vs. Can $63,900; in 2005 dollars; $p<0.05$). This difference was associated with a significantly longer duration of hospitalization in the former group after the first dialysis treatment (47.7 vs. 38.2 days; $p<0.05$). An additional cost analysis compared annual health care costs in the subsequent year after hospital discharge in the same two groups of patients. Largely reflecting the costs of chronic dialysis therapy, a striking seven-fold difference in costs was reported (Can $98,100 vs. Can $15,000; in 2005 dollars; $p<0.05$). Thus, nonrecovery of renal function is clearly associated with an increase in both short-term and long-term costs.

With respect to renal recovery, the analysis by Pannu et al included five RCTs (total of 308 patients) and four observational trials. The authors concluded that overall the studies included did not suggest a benefit from CRRT for renal recovery. However, they acknowledged that the two largest observational trials (involving a total of approximately 1,500 patients) demonstrated an advantage for CRRT for this outcome. The larger of these two observational trials was performed by the BEST Kidney investigators (22) and consisted of 1,218 AKI patients treated with

either CRRT or IHD. Overall, 17% of surviving patients were dialysis-dependent at the time of hospital discharge. However, among patients surviving to hospital discharge, a significantly higher percentage of patients initially treated with intermittent renal replacement therapy (IRRT) vs. CRRT were dialysis-dependent (35% vs. 11%; $p<0.0001$) (Fig. 1). Although not included in the meta-analysis by Pannu et al, a second recent observational study (the SWING Study (30)) of considerable size (approximately 1,100 patients) involved multiple centers in Sweden and had two major findings. One was the twofold higher rate of dialysis dependence at 90 days in AKI patients treated with HD vs. patients treated with CRRT. Specifically, 16.5% of the HD-treated patients did not recover renal function at 90 days, while the same figure for the CRRT group was only 8.3%. The second major finding of the study is that for those patients who did develop end-stage renal disease (ESRD), the subsequent survival rate was significantly lower in patients treated initially with HD compared with CRRT-treated patients. For example, approximately four years after initiation of chronic dialysis after AKI, only 30% of patients treated with HD were alive, while approximately 65% of the CRRT-treated patients were alive at the same time point (Fig. 2).

It should be emphasized that the combined patient number from the BEST Kidney and SWING studies (approximately 2,300) is approximately sevenfold greater than the number of total number of patients from RCTs examined in the renal recovery analysis by Pannu et al. Furthermore, we disagree with the suggestion by Pannu et al that lack of renal recovery is not an outcome of importance by itself but instead should be assessed as part of a composite end point that includes mortality. We believe the "survivorship bias" argument has little merit due to the clear health economic implications of renal recovery itself, clearly justifying its use as a stand-alone outcome parameter.

Practice recommendations from clinical trial results: a note of caution

As noted above, the dialysis management strategy for critically ill AKI patients suggested by Pannu et al is as follows: "In otherwise stable patients, alternate-day dialysis treatments…are usually sufficient in patients with or without concomitant critical illness" (10). We believe this is a very confusing and potentially dangerous recommendation that seems to be based only on their own flawed analysis itself without regard for other important clinical trial data. First, we are not clear on what Pannu et al really mean when they refer to "otherwise stable patients", as by definition nearly all critically ill AKI patients are *unstable*! Second, the authors suggest that critically ill AKI patients, such as those with AKI in the setting of multiorgan failure, can be managed in the same way as patients with relatively uncomplicated, "single-organ" AKI. (Of course, dialysis for patients falling in the latter category very rarely occurs in the contemporary ICU environment.) Most importantly, the recommendation by Pannu et al represents a total disregard for the results of an RCT (28) which clearly indicated that both survival and renal recovery are improved by daily application of IHD, in comparison with a schedule very closely resembling the schedule that they recommend. We do not believe the totality of data in the literature supports this recommendation and feel that the recommendation by Pannu et al is not in keeping with the aggregate of the available evidence.

CONCLUSIONS

Clinical outcome comparisons of CRRT and HD continue to be very problematic. As mentioned recently (1), with the availability of the recent CRRT dose vs. outcome data discussed above, the interpretation of CRRT vs. HD trial data now becomes nearly impossible because of the low-dose handicap that has existed in the CRRT arms in all of the comparative trials, including the studies analyzed in the meta-analyses of Bagshaw et al and Pannu et al (9, 10). Although Bagshaw and colleagues recognized this limitation and made appropriate conclusions in their meta-analysis, unfortunately Pannu and colleagues did not. Furthermore, the AKI dialytic treatment approach recommended by Pannu et al is not supported by the *aggregate* of the available clinical outcome data and, therefore, remains highly controversial.

We would like to join with others in the AKI field by strongly recommending that investigators and other clinicians stop trying to make conclusive determinations about dialysis modalities when robust supportive data simply are not available. Instead of additional *intermodality* comparisons, the focus of future clinical research should be generating high-quality data on *intramodality* interventions, such as treatment dose and timing of treatment initiation. In this regard, at least for CRRT, we anxiously await the results of the ongoing RCTs evaluating the effect of CRRT dose on pa-

tient outcome. Specifically, the results of the ATN Trial, which has enrolled nearly 1,200 patients in the United States, will be presented soon, while the ongoing RENAL trial will enroll 1,500 patients in Australia and New Zealand by the completion of the study (target date late 2008). These two studies will provide important additional evidence upon which clinicians can base their CRRT prescription decisions.

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