Continuous Renal Replacement Therapy in Sepsis and Multisystem Organ Failure

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ABSTRACT

This study reviews the role of continuous renal replacement therapy (CRRT) in sepsis with acute kidney injury (AKI) and septic shock with multiple organ failure. In addition to the conventional aim of replacing renal function in AKI, CRRT is often used with the concept of modulating immune response in sepsis. With the intention of influencing circulating levels of inflammatory mediators like cytokines and chemokines, the complement system, as well as factors of the coagulation system, several modifications of CRRT have been developed over the last years. These include high volume hemofiltration, high adsorption hemofiltration, use of high cut-off membranes, and hybrid systems like coupled plasma filtration absorbance. One of the most promising concepts may be the development of renal assist devices using renal tubular cells for implementing renal tubular function into CRRT.

Sepsis is characterized by a systemic inflammatory reaction which involves complex interactions between endothelial cells, platelets, leukocytes, coagulation system, and multiple inflammatory mediators. Worldwide, the annual incidence of severe sepsis is considered to be in the range of 3/1000 inhabitants (1). In the United States, it is considered the most common cause of death in critically ill patients and is associated with a mortality rate of around 11% (2). Sepsis may proceed to severe sepsis, septic shock and, finally, to multiple organ failure (MOF) (3). The progression to severe sepsis and septic shock has been associated with mortality rates of 50% and 68%, respectively (4). Over the years 1979–2000, the number of septic patients exhibiting MOF constantly increased (2).

Severe sepsis and septic shock are associated with AKI in 5–50% of the patients and the risk increases with positive blood cultures and worsening clinical signs of sepsis (5). On the other hand, roughly 50% of the cases of newly onset AKI in the intensive care unit (ICU) do occur as a consequence of sepsis. It remains unclear whether AKI plays a significant role in the subsequent development of MOF by its effect on metabolic homeostasis as well as on mediators of inflammation. A multicenter trial performed in 40 ICUs in 16 countries with 1411 patients using Sequential Organ Failure Assessment scores demonstrated that about 70% of patients with AKI developed MOF, whereas this was only the case in 10% of the patients without AKI (6). ICU mortality of critically ill patients with AKI is reported as roughly 60% (7,8). Mortality from septic shock in combination with AKI is even higher at roughly 75% (9,10). The role of continuous renal replacement therapy (CRRT) in sepsis and MOF can be seen from two major aspects, first from the point of renal replacement therapy (RRT) per se and second as an immunomodulatory tool helping to influence the systemic consequences of severe sepsis and septic shock.

CRRT for Organ Support in Sepsis-Associated AKI

Indications

From a general point of view, indications for CRRT in sepsis-associated AKI are not really different from other forms of AKI in the ICU. They predominantly consist of progressive azotemia, volume overload, metabolic acidosis, and severe electrolyte derangements (11). However, septic patients in the ICU often do not show very prominent azotemia when developing AKI. Because of this, some authors suggest starting CRRT earlier in order to provide some immunomodulation in addition to replacement of renal function (see below). Consequently, other criteria such as prolonged oliguria or severe metabolic acidosis have been suggested as sufficient indication to start RRT (12). This hypothesis, however, is currently only supported by retrospective cohort studies (13).

The use of CRRT is considered the favored RRT modality in patients with septic shock because of better hemodynamic tolerability than intermittent

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Seminars in Dialysis—Vol 22, No 2 (March–April) 2009 pp. 160–164
DOI: 10.1111/j.1525-139X.2008.00552.x

hemodialysis (IHD) (14) – as shown in a small prospective randomized trial of 30 patients with septic shock (15). But even in stable patients with sepsis, CRRT appears to provide some advantages over intermittent techniques, including constant control of temperature and acid-base status, and constant fluid homeostasis, thereby avoiding fluid shifts and organ edema. In direct comparisons of CRRT versus IHD, avoidance of intracerebral fluid shifts could only be achieved by CRRT (16,17). Restrictive fluid management has shown to improve oxygenation in Acute Respiratory Distress Syndrome (ARDS) patients (18). CRRT could also improve heart failure (19), which is often found complicating severe sepsis as septic cardiomyopathy. However, new hybrid techniques like sustained low-efficiency dialysis have shown to provide excellent clearance of low molecular weight solutes and good hemodynamic tolerability in critically ill (20,21). Their role as RRT in severe sepsis and septic shock is a matter for further investigation.

Timing

Although there are some retrospective trials supporting early initiation of continuous venovenous hemofiltration (CVVH) (13,22–24), the question of the benefit of early initiation has only been investigated systematically in one trial so far (25). In this randomized control trial (RCT), which included mainly surgical patients with a very low incidence of sepsis, early initiation of CRRT did not improve survival.

Dosing

Based on the prospective RCT by Ronco et al. (26), it was assumed that higher treatment doses in sepsis may improve survival. The study compared prescribed CVVH doses of 20, 35, and 45 ml/kg/hour and found improved survival in the 35 and 45 ml/kg/hour group as compared with 20 ml/kg/hour group. In the subgroup of patients with sepsis, which accounted for 11–14% per randomization group, there was a trend toward an even further improved survival between the two higher treatment arms. In a consecutive study comprising more than 200 patients, about 60% of them with sepsis, an added dialysis dose of 18 ml/kg/hour (summing up to an total effluent rate of 42 ml/kg/hour) with continuous venovenous hemodiafiltration (CVVHDF) showed improved survival as compared with standard CVVH.

In contrast to these findings, two trials published in 2008 seem not to support this hypothesis. Both trials included at least 60% patients with sepsis. The first one by Tolwani and co-workers (27) included 200 patients treated with CVVHDF at two different dosages, 20 and 35 ml/kg/hour. Neither survival nor renal outcome was significantly different between those two groups. The second trial by the VA/NIH Acute Renal Failure Trial Network included 1124 patients comparing intensified treatment versus standard treatment. About 615 patients were treated with CVVHDF at a dose of 20 (with a finally applied dose of 22 ml/kg/hour) or 35 ml/kg/hour (28). The results of this large trial do not suggest any influence of dose on outcome. One interesting aspect of the two latter studies, however, is that the average time to start RRT was 6 and 8 days after ICU admission, respectively. This is considerably later than the 1.4 days reported by a recent world wide practice survey [the beginning and ending supportive therapy for the (B.E.S.T.) kidney] (11). Thus, based on the current evidence, it remains unclear whether any dose above 22 ml/kg/hour does provide additional benefit in patients with sepsis, at least for those who survived the first 6–8 days of sepsis without requiring RRT.

CRRT—As Treatment Modality Conferring Immunomodulation in Sepsis

Standard Dose CRRT

Because of the introduction of continuous hemofiltration into the ICU, the idea of clearing inflammatory mediators from patients with sepsis has become a paradigm in intensive care medicine. But despite the fact that modern high flux membranes with an average cut-off around 30–40 kD should be capable of eliminating significant amounts of inflammatory mediators including chemokines and cytokines by convection, theoretical considerations have questioned whether the amount of removal is of clinical significance considering the high turnover rates of the respective mediators (29). Consequently, an elegant clinical study using CVVH at filtration rates of up to 2.6 l/hour demonstrated a lack of effect of convection on serum levels of several cytokines, including interleukin (IL)-1ß, IL-1ra, IL-6, IL-8, IL-10, and tumor necrosis factor (TNF). However, the authors could demonstrate a significant influence on serum cytokine levels resulting from adsorption occurring within the first hour after a placement of a new membrane into the circuit (30). These findings were supported by a prospective RCT in severe sepsis without renal failure, which was unable to demonstrate changes in serum levels of cytokines or complement in patients treated with isovolemic CVVH at a filtration rate of 2 l/hour (31). Furthermore, this study was unable to demonstrate any clinical benefit by this approach. Thus, on basis of the current evidence, use of standard CRRT in the absence of AKI cannot be recommended routinely.

High Adsorption Hemofiltration

To utilize the adsorptive capacities of filter membranes, some authors suggest frequent filter exchanges during CVVH. In their dose finding study, Ronco et al. used daily filter exchanges (26). In a small pilot trial, 12 patients with sepsis were investigated over a 9-hour treatment period comparing every 3 hours changes of AN69 filters to standard CVVH. A significant reduction of IL-8 and IL-10 levels over the study period, as well as faster reduction in vasopressor requirements, was found by this approach (32).

High Volume Hemofiltration (HVH)

Over the last years, the paradigm has changed from simple elimination to immunomodulation by reducing

the elevated and imbalanced levels of pro-inflammatory as well as anti-inflammatory mediators by hemofiltration, the so called peak-concentration hypothesis (33).

This hypothesis has been complemented by the idea that HVH may have additional pleiotropic effects by interfering with cardiovascular compounds (e.g., myocardial depressant factor, endocannabinoids, and endothelin) (34) and with the coagulation system (e.g., by reducing PAI-1) (35). A recent study in porcine septic shock even suggests improvement in myocardial mitochondrial function (36). To increase convective transport as well as adsorption, the application of HVH with filtration volumes ranging from 45 to 215 ml/kg/hour was proposed (37). This suggestion was based on a substantial number of animal experiments showing improved hemodynamic stability as well as better survival (34,38,39). However, at present, only a few, mostly observational studies in humans support this concept of providing intermittent HVH (pulse HVHVF) using volumes of 5–9 l/hour for 4–12 hours (40–44). One of the largest studies with 306 patients (roughly 30% with sepsis), started with a volume of 5 l/hour (an average volume of 63 ml/hour) and showed a significantly lower mortality than expected by severity of illness scores (43).

Only two small RCTs investigated the effect of HVH in septic shock. Cole et al. used a crossover design in 11 patients with septic shock and MOF (45). Eight hours of HVH at 6 l/hour resulted in some reduction of complement levels (C3a and C5a) and IL-10, as well as a more rapid decline in vasopressor requirements as compared to the standard CVVH at 1 l/hour. This advantage, however, was lost after 24 hours. The second trial enrolled 33 patients with severe sepsis/septic shock and compared 35 ml/kg/hour with 6 hours of 100 ml/kg/hour (maximum 6 l/hour) (46). The main finding was a significant reduction of IL-6 levels. Both studies were not powered to find a difference in mortality. To clarify the question of benefit of HVH, the European multicentre hIgh VOlume in intensive caRE (IVORIE) study, designed to include more than 460 patients with septic shock and AKI, was recently initiated to compare 35 ml/kg/hour with 70 ml/kg/hour (47).

High Cut-Off (HCO) Hemofiltration or Hemodialysis

With respect to immunomodulation the use of HCO membranes must be considered an alternative approach to HVH. HCO membranes show a nominal cut-off of 60–150 kD which equals 40–100 kD in human blood. In vitro experiments demonstrate increased elimination of several mediators by these membranes as compared with conventional membranes (48). Several animal models of septic shock further established increased cytokine removal and improved cardiocirculatory function by applying HCO membranes (49–51). Pilot trials in septic patients with AKI demonstrated immunomodulation by altering neutrophil phagocytosis as well as mononuclear cell function ex vivo (52,53). In an initial pilot trial applying CVVH for 12 hours over 5 consecutive days in patients with sepsis and MOF, a reduction in IL-6 serum levels could be demonstrated (54). In the following phase I trial comparing HCO membranes during CVVH and CVHD using either 1 or 2.5 l/hour ultrafiltrate/dialysate, significant IL-6 and IL-1ra clearances influencing patient serum levels were found with convection playing a bigger role than diffusion (55).

A Phase II trial has been conducted in 30 patients with septic shock using HCO in CVVH at an ultrafiltration rate of 2.5 l/hour (56). In addition to the already demonstrated significant reductions of IL-6 and IL-1ra levels, more rapid reductions of norepinephrine (NE) requirements and significant reductions in Simplified Acute Physiology II scores were seen in patients treated with HCO-CVVH as compared with conventional CVVH at the same dose. A major adverse event during HCO-CVVH was the significant albumin loss observed during higher ultrafiltration rates. Currently, a multicenter study Phase II trial is investigating the effect HCO-CVVHD used in septic shock on patient outcome.

Hybrid Techniques

This category comprises the combination of CRRT with other purification methods such as plasmapheresis or a bioartificial kidney device.

Coupled plasma filtration adsorption (CPFA)

This technique involves plasma separation followed by an adsorptive step over activated charcoal sorbent allowing nonspecific removal of mediators. After return of the cleaned plasma to the circuit, standard hemodialysis is applied. The feasibility of this concept has been investigated in animal experiments (57). A pilot trial in 10 patients with septic shock using a cross-over design demonstrated a more rapid reduction in NE requirement during 10 hours of CPFA as compared with 10 hours of standard CVVHDF without a significant effect on IL-10 or TNF levels (58).

Renal Artificial Device (RAD)

One of the most promising developments in enhancing CRRT techniques for septic shock is the renal tubule cell assist device (RAD), which uses nonautologous human renal tubule cells grown along the inner surface of hollow fibers aligned in a cartridge. RAD is incorporated in an extracorporeal perfusion circuit where the ultrafiltrate is pumped through the RAD, allowing the renal cells to reabsorb and eliminate substances from the blood circuit and thereby emulating the transport, metabolic, and endocrinologic activities of the kidney (59,60). After proof of principle in several animal experiments (61,62), RAD was safely applied for up 10 hours in 10 ICU patients in an open phase I/II clinical trial (63). Just recently a multicenter, open label, RCT phase II trial including 50 critically ill patients was published. With roughly 70% of the patients having sepsis and most of them at least three organ failures a relative reduction of both 28 and 180 days mortality of more than 50% could be achieved (64).

Conclusion

Based on current literature, the use of CRRT in patients with sepsis-associated AKI does not differ substantially from treatment of other forms of AKI in critically ill patients. Current clinical practice, however, supports broader indications, earlier initiation with a higher dose of CRRT for patients in septic shock. Preliminary data indicate the feasibility of immunomodulation by modified CRRT techniques in septic shock and MOF. Their impact on patient outcome, however, still needs proof by larger RCTs.

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