Title:

Handling Continuous Renal Replacement Therapy-Related Adverse Effects in Intensive Care Unit Patients: The Dialytrauma Concept

Authors:

J. Maynar Moliner[a], P.M. Honore[d], J.A. Sánchez-Izquierdo Riera[b], M.E. Herrera Gutiérrez[c], H.D. Spapen[d]

a Department of Intensive Care Medicine, Santiago University Hospital, Vitoria.

b Department of Intensive Care Medicine, Doce de Octubre University Hospital, Madrid.

c Department of Intensive Care Medicine, Carlos Haya University Hospital, Málaga, Spain.

d University Hospital, Vrije Universiteit Brussel (VUB), Brussels, Belgium.

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Abstract

Continuous renal replacement therapy (CRRT) is increasingly used for the management of critically ill patients. As a con- sequence, the incidence of complications that accompany CRRT is also rising. However, a standardized approach for preventing or minimizing these adverse events is lacking. Dialytrauma is a newly proposed concept that encompasses all harmful adverse events related to CRRT while providing a framework for prevention or, at the least, early recognition of these events in order to attenuate the consequences. A mainstay of this approach is the utilization of a dedicated checklist for improving CRRT quality and patient safety. In this context, we discuss the most important adverse effects of CRRT and review current strategies to minimize them.

Introduction

Up to 6% of critically ill patients develop acute kidney injury (AKI) during their stay in the intensive care unit (ICU) [1, 2]. In the presence of sepsis, AKI may even reach an incidence as

high as 50% [3, 4]. In patients who require extracorporeal blood purification treatment, physicians may choose between continuous (CRRT) and intermit- tent renal replacement therapies (IRRT). IRRT can be performed in standard mode or in the so called sustained low-efficiency dialysis mode [5]. Numerous studies com- paring IRRT and CRRT have failed to show superiority of one of these techniques in terms of morbidity and mortality. Therefore, the choice is determined by the hemodynamic status of the patient and logistic limitations. However, the aggregated results of the ATN [6] and the RENAL study [7], including more than 3,000 patients, clearly demonstrate that the continuous mode is preferable in hemodynamically unstable patients as it may decrease the number of patients ending with chronic dialysis by 50% [8]. Another much debated topic is the best RRT dose for treatment of AKI. A wide range of doses has been proposed varying from alternate-day dialysis to pulse high-volume hemofiltration. Different types of techniques and doses have been extensively studied, but controversy still reigns [6–12]. Interestingly, even the more stable and classic chronic renal disease syndrome is subject of ongoing debate regarding the best dose and technique [12].

Essentially, all treatments aim to achieve adequate replacement of renal function while gaining time for spontaneous restoration of organ function and, more importantly, they intend to save lives. However, the outcome may not depend only on the efficacy of the ‘artificial support’ but also on morbidity related to this support. This is in analogy with mechanical ventilation in patients with the acute respiratory distress syndrome where ‘standard’ tidal volume ventilation did improve blood gas values but resulted in worse outcome [13]. Regarding the incidence of adverse events, the recent large multicenter studies [6, 7] found significant differences between high and low RRT intensity and doses. However, the net influence of adverse events related to renal support on outcome of AKI remains ill-defined. Yet, in keeping with the philosophy of ‘first do not harm’, the initial step for improving clinical practice and outcome should be to avoid complications.

This paper reviews the most important adverse effects of CRRT and introduces the concept of ‘dialytrauma’ [9] that was developed to identify harmful adverse events related to CRRT early and to propose strategies to minimize them [14–16].

Adverse Events Related to RRT

Loss of Valuable or Vital Substances

Nonselective transport of molecules through RRT membranes implies that not only toxins are eliminated from the plasma but also some important physiologic blood constituents. These include a variety of substances that cross the membrane and are removed by dialysis at varying rates depending on the operational characteristics. Recent RRT studies in ICU patients emphasize the positive correlation between hemofiltration dose and the frequency and magnitude of these losses that may be- come harmful if not recognized and corrected. A key is- sue in preventing these losses is recognizing the influence of the operational characteristics and duration of therapy. In general, intermittent hemodialysis management of excess solute levels requires the use of fluids containing a zero concentration of the particular component (with the exception of potassium) and the short duration of therapy limits the overall removal. The frequency and duration of intermittent dialysis can thus be tailored to achieve balance. In contrast, CRRT necessitates selection of a maximum dose and adjustments in the composition and amount of substitution fluid on an ongoing basis to maintain balance. CRRT also more effectively prevents eventual rebound effects that may compromise cerebral function in patients with or at risk for encephalopathy [17].

Electrolyte and Divalent Ion Losses

Hypokalemia is found in 5–25% of patients treated with RRT [6, 7]. It results from inadequate potassium supplementation during the dialysis procedure. Paradoxically, potassium loss can easily be avoided either by using potassium-containing fluids for replacement in hemofiltration or altering the potassium concentration in the dialysate or by administration of potassium supplements. Clinicians typically tend to avoid hyperkalemia in most patients on RRT. However, if hypervolemia is the main indication to start RRT, hyperkalemia usually is not a problem and potassium substitution within the normal blood concentration range must be encouraged [18]. Low potassium-containing fluids are only mandatory in marked hyperkalemia. It must be stressed that serum potassium levels below 3 mEq/l should absolutely be avoided as rapid correction below these levels is associated with increased mortality [19].

The incidence of hypophosphatemia during RRT varies within a range between 10.9 and 65% [6, 7]. Its clinical effect remains poorly defined, yet phosphorus is involved in many vital functions such as tissue support, enzymatic processes, oxygen transport and energy transfer. A prospective study in medical ICU patients revealed an association between hypophosphatemia and failure to wean from mechanical ventilation [20]. Troyanov et al [21] reported that adding phosphorus to the substitution fluids was safe and resulted in adequate compensation of undesired losses. Fluids

containing physiologic levels of phosphate are commercially available. Their use permits to avoid eventual errors when using homemade solutions and also diminishes the risk of contamination. If needed, phosphorus loss may be adequately balanced by intravenous bolus or enteral supplementation. Hyperphosphatemia rarely occurs during RRT and, if present, requires increased clearance and the use of phosphate-free dialysis fluids. Hypomagnesemia is seldom (3%) reported [6, 7] and easily corrected with either commercially available fluids or daily administration of 2–4 g of intravenous magnesium salt boluses.

Acid/Base Disorders

All RRT techniques are effective for improving acidosis in patients with AKI, not only by adding buffer but also by directly removing acids. The most important buffers are citrate, bicarbonate and lactate. The high concentration of these buffers in most CRRT fluids may be- come problematic during depuration by creating an excessive metabolic alkalosis. Lactate has an additional in- convenience since high replacement doses or impaired liver function may cause hyperlactatemia. The latter is not harmful in the absence of metabolic acidosis but may necessitate a switch to bicarbonate because failure to correct acidosis has been demonstrated in up to 13% of patients [22]. Studies of hepatic clearance using indocyanine green showed that hyperlactatemia related to lactate replacement fluid can unmask liver dysfunction. In patients with multiple organ failure, lactate buffering (com- pared with bicarbonate buffering) was found to increase glucose intolerance. Thus, lactate buffering may have adverse metabolic effects [23] and should be avoided in unstable and/or acidemic patients and/or when a high hemofiltration dose is used. In CRRT, it is thus essential to provide an adequate amount of buffers to compensate for the underlying process and the removal across the filter. In most intermittent techniques the dialysate provides bicarbonate base; however, the short duration and limited frequency result in a high level of serum bicarbonate immediately following the procedure with a progressive reduction in the interdialytic interval.

Carbohydrate

Carbohydrate loss during RRT is a less well documented, yet unquestionably relevant issue particularly for continuous therapies. Glucose losses can be computed by multiplying the effluent levels measured in an aliquot with the total volume of daily effluent. Frankenfield et al [24] prospectively studied glucose balance in polytrauma patients treated by dextrose-free

continuous hemodiafiltration with or without addition of dextrose-containing fluids. Glucose loss reached 82 8 61 g/day with glucose containing solutions and 57 8 22 g/day with glucose-free fluids ($p < 0.05$). A net, though somewhat lower in the dextrose-free cohort, positive uptake was detected in both groups [24]. Still, several problems regarding the addition of glucose to dialysis solutions have been recognized [25] and the dynamics of the dialyzer mass transfer for glucose have not been definitely clarified [26]. Supplementing glucose to the replacement fluid may produce a net glucose uptake of up to 300 g/day in patients under arteriovenous hemofiltration [27]. However, since the publication of the above results considerable changes in the application of CRRT have occurred such as a shift to venovenous modalities and a substantial increase in the hemofiltration dose. Nonetheless, we can assume that the use of glucose free solutions leads to a small and predictable glucose loss and that glucose containing solutions will cause a positive glucose intake, making losses in the circuit less predictable. Addition of glucose to dialysis fluid also revealed that a progressive increase in glucose concentration produced linear increments in the net glucose transfer to the patient [28]. Another poorly studied aspect of using solutions supplemented with glucose is the eventual effect on ultrafiltration capacity and dialysis dose delivery during high-flux hemodiafiltration with polysulfone membranes [29]. Finally, higher plasma glucose levels and a higher glucose turnover have been described when lactate based solutions are employed [30]. It remains unclear whether or not glucose losses should be compensated, but current evidence suggests that keeping glycemia within normal range is beneficial [31].

Nitrogen

CRRT produces a significant nitrogen loss which, if not properly supplemented, may result in a nitrogen ‘deficit’. Amino acids have different rates of elimination during extended or continuous RRT and losses need to be counterbalanced by increasing the amino acid supply by approximately 0.2 g/kg/day [32]. Since nutritional support is not limited by volume during RRT, adequate amounts of protein can be provided to compensate for these losses. Addition of glutamine during CRRT has been advised (0.3–0.6 g/kg/day alanyl glutamine dipeptide) by the ESPEN [33].

Water-Soluble Vitamins and Trace Elements

Patients with AKI are at risk of trace element depletion [34–36]. Reasons are multifactorial, including variable protein binding, redistribution between plasma and tissues, acute losses of biological fluids, dilution, varying concentrations of trace elements in dialysis/hemofiltration

fluids, nutrient intake, and removal from plasma by CRRT. Water-soluble vitamin and trace element losses and requirements during RRT remain subject of debate and research. Whole-blood concentrations of these sub- stances are not directly associated with removal. Also, the clinical significance of these losses remains unclear. However, water-soluble vitamins are highly removed by RRT (e.g. 68 mg vitamin C and 290 μg folic acid per day). Recommendations [37] for daily supplementation of water soluble vitamins have been proposed (i.e. 2 mg vita- min B1, 2 mg vitamin B2, 20 mg vitamin B3, 10 mg vita- min B5, 200 mg biotin, 1 mg folic acid, and 4 mg vitamin B12). Vitamin C intake in patients with AKI should not exceed 250 mg/day because of the potential risk of nephrotoxic secondary oxalosis [35]. Thiamine loss may exceed more than 1.5 times the daily provision of this vita min by standard total parenteral nutrition. The fat soluble vitamins E and K should also be supplemented (10 IU/ day and 4 mg/week, respectively), whereas the dose of vitamin A must be reduced to compensate for deficient retinol degradation [35].

Daily parenteral supplementation with standard doses of trace elements is supposed to overcome the amount removed by CRRT [38]. However, data regarding the optimal dose of trace element preparations in patients on CRRT are currently not available. Actually, the most convenient option to compensate for trace element losses is to provide a double dose of currently used intravenous trace element solutions, even when patients are fed enterally. Among the micronutrients, selenium and thiamine are at highest risk of depletion. An additional 100 μg (at least 20–60 μg) of selenium and 100 mg of thiamine should be intravenously delivered daily during CRRT [39]. To date, supplementation of vitamins and trace elements during RRT has shown no proven benefit on survival rate.

Drug, and Specifically Antibiotic, Losses

Despite the well-recognized impact of particular drugs (e.g. antimicrobials) on the outcome of critically ill patients, drug elimination during RRT remains largely unexplored. Many reports describe a significant loss of various drugs during RRT. However, results are difficult to generalize due to variation in RRT settings, heterogeneity of studied patient populations, and different interactions between drug and filtration membranes [40, 41]. Nonetheless, losses resulting from extracorporeal plasma clearance may replace the (inactive) renal clearance. The profile of antimicrobials at risk of RRT elimination encompasses low protein binding, low volume of distribution and a preponderant renal clearance. Therefore, it must be registered which drugs

are potentially and/or significantly removed by RRT in order to avoid or, at least, reduce the risk of insufficient dosing. Risk of overdose is well anticipated in AKI, but applying the same dose recommendations during continuous plasma clearing may expose patients to underdosing. Guidelines for appropriate antimicrobial dosing are now available [42–46] and the general principles are summarized in table 1.

Heat Loss

CRRT provokes greater heat loss than intermittent hemodialysis. Studies comparing both types of RRT [47] may therefore be potentially biased. A higher dialysis dose is also associated with a higher incidence of hypothermia [48]. The time during which blood circulates outside the body as well as the contact with cold dialysate and/or replacement fluids explain why CRRT offers superior body cooling from the central compartment. Though useful in certain clinical situations [48], long term body cooling may have unwarranted or potentially negative effects [49] including energy loss, increased oxygen demand due to shivering, vasoconstriction, impairment of leukocyte function and coagulation disorders. As a consequence, monitoring of body temperature is imperative. If the incorporated RRT heating system fails to maintain the desired patient temperature, external heating must be utilized aiming at a temperature above 37°C.

Circuit Issues

Complications Related to Vascular Access

A correct vascular access is a major determinant of circuit survival during RRT. Thrombosis present before or occurring after catheter placement, arterial puncture, pneumothorax and catheter sepsis are amongst the most common complications. Reducing complications to an absolute minimum requires strict adherence to a bedside protocol, including rigorous antiseptic precautions and use of ultrasonography to guide venous puncture [50, 51]. The most suitable catheter insertion site remains a controversial topic. Since complications often occur with long term use of the jugular or subclavian vein (e.g. stenosis, thrombophlebitis) and repeated catheter placements are often needed [52], the femoral approach is commonly preferred. Of note, recent data regarding filter life span suggest the superiority of the right internal jugular vein access (with the soft tip inside the right atrium) [53, 54].

Clotting and Bleeding Problems

Filter overclotting causes blood loss, which may enhance platelet and red blood cell transfusion. Anticoagulant therapy is applied to overcome this problem during CRRT, but at the cost of an increased bleeding risk and higher treatment expenses. Heparin based anticoagulation is most commonly applied. However, the high bleeding risk and eventual platelet activation and antibody formation with resulting thrombosis or thrombocytopenia associated with heparin use have incited a search for other anticoagulation strategies. A basic strategy for increasing circuit patency consists of careful priming, proper vascular access, blood flow 6200 ml/ min and administration of substitution fluids before the membrane (i.e. predilution mode). Nevertheless, some authors advocate a more dynamic approach to assure circuit patency [55], based on decreasing filtration fraction by adding diffusion as part of the dose, epoprostenol administration, assessment of antithrombin III activity
[56] and regional anticoagulation with citrate. Interestingly, citrate anticoagulation has been linked to optimal circuit patency and a better outcome [57]. However, this apparent benefit is somewhat offset by the complexity of this treatment requiring strict calcium, buffer and sodium control and the use of standardized protocols. In general, we are in favor of the dynamic approach to assure circuit patency since it best reconciles the risks of overclotting and bleeding. When bleeding is a major issue, RRT without anticoagulation is feasible and safe. Circuit life time did not differ significantly when heparin (20.9 h), no anticoagulation (19.3 h) or protamine (21.2 h; $p = 0.38$) were compared and was similar to previously reported values for regional and nonregional anticoagulation [58].

Hemodynamic Monitoring Disturbances

CRRT may hamper a dedicated hemodynamic strategy. Treatment at low blood flow (<150 ml/min) does not influence hemodynamic measurements obtained by transpulmonary thermodilution [59]. In contrast, flows above 200 ml/min resulted in a significant drop of measured cardiac index [60] and global end diastolic volume. It is advised to stop fluids and to slow down blood flow to 100 ml/min during transpulmonary thermodilution or lithium dilution measurements.

Complications Related to Fluid Management

Despite being an important trigger to start RRT, volume overload may paradoxically become a complication in some patients. Indeed, much attention is often devoted to daily fluid balances

while the cumulative fluid balance over a period of several days is neglected. Recent observations have shown that a negative fluid balance obtained during the initial 72-hour resuscitation period may easily become positive if the patient remains hospitalized for a week or longer, thereby increasing mortality rate [61]. Another important issue is online integration of the RRT related fluid balance into the general chart fluid balance of the patient in order to avoid relying on the 6- or 12- hour chart fluid balance. Online systems that allow 2-hourly modulation of chart fluid balance could potentially sustain a negative fluid balance while under RRT [53]. Finally, the composition of the substitution fluid may also have an impact on the fluid balance. For instance, modification of the sodium content (increase) has been shown to induce a sodium-related fluid overload [62].

Strategies for Minimizing Dialytrauma

As we have discussed earlier, there is a broad range of possible complications associated with CRRT that vary not only in their intensity but the timing during the course of therapy. We have suggested some specific solutions for each of these; however, a key issue is combining primary prevention with early recognition to minimize these complications. We have developed a summary in the form of a dialytrauma checklist (table 2). It offers a stepwise approach before starting CRRT in an individual patient and can be addressed at each morning shift when the circuit remains in place for a longer period. Implementation of the proposed checklist may allow early detection and offer solutions for potential and/or actual complications. For example, blood phosphate level is not measured and/or evaluated daily to balance CRRT losses. Hypophosphatemia is a prominent component of dialytrauma [6, 7]. Checklist use would allow timely correction of hypophosphatemia either by bolus supplementation or by changing the composition of the dialysate and/or restitution fluid. In contrast, other clinical situations such as poisoning and life threatening metabolic disorders or hyperthermia [63] do require higher doses. In analogy to other areas of medicine [15], this checklist is an incentive to improve safety and quality. We believe it is an important tool to facilitate a dynamic approach to RRT therapy that will enable timely tailoring of the dose to the patient's needs in a safe and efficient manner [9]. In summary, efforts to decrease the mortality rate of critically ill patients who develop AKI must be stimuated. CRRT has a pivotal and well-defined place in the treatment of AKI. Unfortunately, performing CRRT confronts the clinician with inherent technical difficulties and laborious efforts to find the right replacement dose. Studies using fixed dose regimens have limitations that

preclude generalization. In contrast, quality programs based on safety measures may be a better way to improve outcome. However, no single study so far has confirmed the presumed relationship between dialytrauma and superimposed mortality. Nonetheless, we strongly believe that the concept of dialytrauma (i.e. anticipation and recognition of all possible complications together with dedicated problem-solving proposals, presented as a detailed checklist) in association with a dynamic approach for managing AKI may help to accomplish this objective.

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Table 1. The 'ten commandments' to guide drug dosing during CRRT

1. Loading dose does not require adaptation for extracorporeal removal but for differences in volume distribution
2. Adapt maintenance dose to the reduced renal function according to drug information
3. Increase maintenance dose in patients with AKI receiving RRT when extracorporeal clearance is clinically significant (i.e. ≥25%) [40]
3a. Select dose based on published data
3b. Select dose based on current creatinine clearance (i.e. residual and extracorporeal). This does not apply for drugs with tubular secretion or reabsorption (e.g. fluconazole dose must be increased because tubular reabsorption is absent in AKI and RRT) [43]
3c. Calculate empirical dose as normal dose multiplied by current clearance fraction [41]
3d. Calculate the dose from dose used in anuria [41]
4.- Compare different methods of rule 3 and select the maximum dose. In case of nontoxic drugs, mainly antimicrobials, a 30% dose increase is acceptable
5. Select dose or modify dosing interval depending on drug pharmacodynamic profile [time above minimal inhibitory concentration (MIC) vs. peak/MIC]. For aminoglycosides, the highest dose must be administered to reach the highest peak concentration which provides a postantibiotic effect and less toxicity [64]. For β-lactams, the interval will be maintained with the calculated dose
6. In case drug plasma levels can be monitored, recorded levels must guide the dose accordingly, i.e. dose = (target plasma concentration) * clearance * timing
7. The dose of drugs such as catecholamines, analgesics and sedatives is guided by clinical information. Of note is that the half-life of opioids and benzodiazepines and/or their active metabolites are increased during AKI and RRT, necessitating close monitoring to avoid overdosing
8. Particular drugs can be monitored by their activity, e.g. the dose of low-molecular-weight heparin is adapted based on thrombin generation time [45]
9. If possible, select drugs with doses unaffected by renal impairment
10. Bear in mind that the higher the dose, the higher the need to counterbalance drug losses

Table 2. The dialytrauma checklist

Potential problem	Action to be considered
Bleeding/clotting	
aPTT >1.5 baseline value INR >1.5 Platelets <50,000/mm^3	No systemic anticoagulation
Fibrinogen <100 mg/dl Other clinical reason to avoid systemic anticoagulation	Regional anticoagulation: citrate
Filter overclotting	Check catheter; $^{\downarrow}$ filtration fraction ($^{\uparrow}$ Qb, predilution or increase diffusion); PGI2; citrate anticoagulation
Acid/base and electrolyte disorders	
pH <7.2 and/or hemodynamic instability and/or hyperlactatemia	Fluids with bicarbonate
pH >7.4	Fluids with lactate or physiologic bicarbonate Fluids with potassium
Potassium <3.5 mEq/l	Fluids without potassium; higher RRT dose vs. IHD[a]
Potassium >5.5 mEq/l	Magnesium replacement
Magnesium <1.5 mg/dl	Fluids without magnesium; higher RRT dose vs. IHD[a]
Magnesium >2.5 mg/dl	Phosphorus replacement/P+ fluids
Phosphorus <3.5 mg/dl	Fluids without phosphorus; higher RRT dose vs. IHD[a]
Phosphorus >4.5 mg/dl	
Patient connection to EBPT	
Patients at risk of bleeding	Simple connection and/or nonanticoagulant priming
Patient at risk of hypotension (unstable patients)	Double connection
Hypotension (all patients)	Connection with Qb ≤100 ml/min
Air embolism	Check return line (‘venous’)
Temperature disorders	
<36°C (no clinical indication for hypothermia)	Heater on, if insufficient -> external heating
>37.5°C	Heater off and continue temperature monitoring
Others	
Plasma urea <90 mg/day	f RRT dose if clinically acceptable
Plasma urea >150 mg/day	d RRT dose
Dose of drugs to be modified: antimicrobials, LMWH, sedation, nutrition	Drug dose adjustment for AKI-RRT: check $^{\uparrow}$ antimicrobials and vitamins; $^{\uparrow}$ amino acids and glucose; $^{\downarrow}$ sedatives
Hemodynamic monitoring with transpulmonary dilution: calibration	Stop fluids treatment and $^{\downarrow}$ Qb ≤80 ml/min
RRT catheter close to the tip of the infusion one	Check X-ray film and remove mm if tips are too close Avoid
Angiotensin-converting enzyme inhibitor therapy	AN69 membrane

All potential problems have matched actions to be considered as potential solution. Figures of each item should be adapted to local RRT protocols.
aPTT = Activated partial thromboplastin time; INR = international normalized ratio; Qb = blood flow; IHD = intermittent hemodialysis; EBPT = extracorporeal blood purification therapies; LMWH = low-molecular-weight heparin.
[a] IHD is preferred due to efficacy.