Optimizing continuous renal replacement therapy in the ICU

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Chapter 11

Summary and future perspectives

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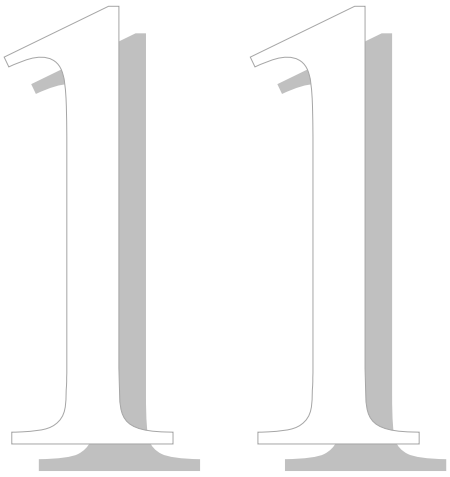

Acute kidney injury (AKI) often complicates the clinical course of critically ill patients admitted to the intensive care unit (ICU). The incidence varies across the world and depends on the case-mix and criteria used to define AKI.[1-5] More than 35 definitions of AKI currently exist in the literature.[6] Starting the past decade there is a growing awareness of this lack of consensus. That is why there have been united initiatives to come to a universal definition of AKI which is especially important when performing and comparing clinical trials.[7-10] AKI is a serious condition because nowadays we know that already a slight deterioration of renal function implies a worse overall prognosis.[9,11] Moreover, renal function loss is an independent risk factor for enhanced morbidity and high mortality in the ICU setting. Over the past decades the management of AKI on the ICU underwent tremendous changes and improvements. Much attention is placed on preventing AKI. However, once AKI has established initiation of supportive therapy is usually mandatory in order to maintain physiologic and biochemical homeostasis. When such supportive measures are insufficient, at some point renal replacement therapy (RRT) must be initiated. Several methods of RRT have been used for renal failure over the last 60 years and the treatment modalities have become increasingly sophisticated. Despite this impressive evolution, the basic principles to guide the use of RRT have changed very little. Furthermore, the practice patterns vary widely regarding issues such as timing, dosing and modality of RRT and the anticoagulation used.[12,13] Not surprisingly these issues are topics of fierce debate. In this thesis we address several of these controversial issues.

In **chapter 2** a general overview is given on RRT on the ICU. Apart from the practical considerations when applying RRT, controversial issues like dosing, timing, modality and anticoagulation are discussed as well as the non-renal indications of blood purifying techniques.

"First do no harm" *(primum non nocere)* is one of the principle precepts of medical ethics around the world. In some medical situations it is prudent not to do anything at all rather than to do something that imposes the risk of causing more harm than good. In daily clinical practice it is important to keep this precept in mind also when considering RRT, especially when starting it early or for non-renal debatable indications. In **chapter 3** a description is given of the several forms of potential harm RRT can cause to the critically ill admitted to the ICU.

One of the controversies surrounding continuous venovenous hemofiltration (CVVH) relates to the infusion site of the replacement fluid. In predilution mode clearance may be limited because blood is diluted before it enters the filter. The latter, however, results in a lower blood viscosity which may retard coagulation, prolong filter life and thereby improve RRT efficacy. Less clotting may thus render predilution preferable over postdilution when systemic anticoagulation is contraindicated. The available data concerning this issue is scarce and conflicting. In **chapter 4** the results are presented of a study in which we evaluated a relatively large number of homogenous critically ill patients and filters used for CVVH in pre- and postdilution mode. All patients were administered heparin as systemic anticoagulation. We found that the filter life was similar in both groups (median ± interquartile range: 24 ± 38 and 29 ± 46 h (P=0.58) for pre- and postdilution, respectively). Furthermore, the hemodilution-induced 19% dose reduction in predilution CVVH appeared to be too small to result in a difference in azotemic control. So, we concluded that pre- and postdilution CVVH is equivalent in heparinised patients.

Over the past decade there have been several studies addressing the issue of delivered dose in RRT.[14-19] After the landmark trial of Ronco et al. in 2000, it was widely accepted that RRT should be dosed with a minimum of 35 ml/kg per hour.[14] Indeed, in the past 5 years several large randomized trials provided no evidence for a survival benefit afforded by higher doses of RRT.[16-19] In these studies septic and non-septic AKI were lumped together and the question arises if this was justified. In post-hoc analyses of these studies and in a meta-analysis higher dose of RRT did not confer a survival benefit in sepsis.[14,19,20] The issue of dose in sepsis, however, still remains intriguing as several observational studies do suggest hemodynamic benefits of high dose CVVH.[23,24] We performed an analysis on the influence of CVVH characteristics on survival in patients with septic AKI **(chapter 5)**. The mortality rate up to 28 day after start of CVVH was 44%. The delivered dose of CVVH in patients surviving septic AKI was about 10% higher than non-survivors (median 23 vs 20 mL/kg/h, P=0.01). The results of this study suggest that CVVH dose rather than timing, mode of administration and azotemic control was an independent predictor of mortality in sepsis-induced AKI. A minimum allowable dose of 20 ml/kg per hour was identified. This study argues in favour of a prospective trial on delivered doses of CVVH in sepsis-induced AKI with 20 ml/kg per hour as the lower limit.

When analysing patients with AKI but now *without* sepsis, CVVH characteristics did not influence outcome as it did in patient *with* sepsis. During a 28-day period after start CVVH 43%

of patients died. In these patients underlying or concurrent, acute and severe disease rather than CVVH characteristics determined mortality. The results of this study are described in **chapter 6**. The data arising from our studies on septic and non-septic AKI strongly suggest that these two conditions are separate entities, requiring different treatments.

The extracorporeal circuit in CVVH, including the hemofilter, activates the clotting system and anticoagulation is needed to keep filters open, to prevent 'down time' and thus enhance the efficiency of RRT. For this purpose heparin, either unfractionated or low molecular weight, is used most often. These agents, however, are associated with increased risk of bleeding and the development of heparin induced thrombocytopenia.[25-27] Furthermore, patients at increased risk of bleeding may not be administered systemic anticoagulation. In the latter group CVVH is generally applied in predilution mode without anticoagulation. However, in a majority of cases this will limit RRT efficiency as a result of frequent filter clotting and increased down time. Regional anticoagulation of the extracorporeal circuit using citrate-based regimens has emerged as the most suitable method to overcome these limitations. Two methods of regional citrate anticoagulation are being used effectively. The first and most frequently used method employs concentrated trisodium citrate together with the use of hypotonic alkali free replacement solution c.q. dialysate as reported by Mehta et al. and Kutsogiannis et al..[28,29] In this setting the dosing of trisodium citrate is dictated by the anticoagulant need. There is no coupling with ultrafiltration rate, which means that there can be swings both in acid-base balance and sodium balance. When the calcium containing replacement solution is delivered post filter, there is no need for a separate calcium pump. However, in this situation the venous line is not anticoagulated. The second method employs trisodium citrate-containing replacement solution that is isotonic and has an adjusted concentration of citrate set so, that the amount of bicarbonate equivalents is similar to that employed when lactate- or bicarbonate- buffered solution are used.[30] In this setting the alkali infusion is coupled to alkali filtration with predictable acid-base effects. In order to keep this method simple, the dosing of trisodium citrate and thus predilution solution is fixed and is not being adapted for ionised calcium in the extracorporeal circuit. With this method the regional anticoagulation includes the venous catheter line as well. A separate calcium infusion, however, is needed. There is very little experience with this method worldwide, partly because the limited commercially availability of citrate-containing replacement solution. Because of its simplicity and the theoretical small risk of adverse events we decided to adopt the method using citrate-buffered replacement solution. In **chapter 7** we provide a detailed description of the technique of

CVVH using a custom-made trisodium citrate-containing replacement solution as regional anticoagulant.

Approximately 35% of patients admitted to the Intensive Care Units of our hospital who were about to start RRT have an increased bleeding risk. The latter is arbitrarily defined as a platelet count of less than $40x10^9$/L, an APTT of longer than 60 seconds, a PT-INR of more than 2,0 or a recent major bleeding. These patients were historically treated by predilution CVVH without anticoagulation. After the availability of the custom-made citrate-containing replacement fluid, patients in need foor RRT with increased risk of bleeding have been routinely treated by CVVH with citrate as regional anticoagulant. We performed a prospective observational sequential cohort study comparing predilution anticoagulant-free CVVH with CVVH using citrate-containing replacement fluid as a regional anticoagulant in patients at increased risk of bleeding (**chapter 8**). Not surprisingly, the results of this study suggest that CVVH with citrate is superior regarding filter life (median ± interquartile range: 41 ± 42 and 12 ± 20 h (P=0.001) for citrate and anticoagulant-free CVVH, respectively) and azotemic control. It appeared to be a safe and simple technique with no metabolic and bleeding complications at costs comparable to CVVH with lactate- or bicarbonate-buffered solution.

Treatment with citrate as regional anticoagulant carries the potential risks of electrolyte and acid-base disorders.[31,32] When applying CVVH with citrate-containing replacement solution, these risks are by theory minimized. An often mentioned drawback of this technique, however, is that the buffer cannot be dosed separately from the substitution fluid, which can be a problem in severe acidosis. In order to address this issue we made a comparison between citrate- and bicarbonate-buffered replacement solution concerning the effects on acid-base balance and electrolytes (**chapter 9**). Treatment with citrate-containing solution corrected the metabolic acidosis as rapidly as with bicarbonate-containing replacement solution with similar electrolyte control.

The superiority of CVVH with citrate-containing replacement solution as compared to anticoagulant-free CVVH was demonstrated as well as its comparability with bicarbonate-containing replacement solution. The most important question to answer, however, concerns the safety and efficacy of this custom-made solution. In a prospective observational study we analysed a large cohort of patients with a contra-indication for systemic anticoagulation treated by CVVH with citrate-containing replacement solution (**chapter 10**). We evaluated the

occurrence and risk factors for citrate accumulation and the control of azotemia and acid-base balance and whether these contributed to hospital mortality. In this study outcome was dependent on patient characteristics rather than on CVVH characteristics including citrate accumulation and azotemic control. Treatment by CVVH with citrate did not contribute to mortality. Seventy-nine patients were included and the hospital mortality was 60% with a standardized mortality ratio of 1.1 (95% confidence interval 0.90-1.40). Citrate accumulation occurred in 9% and was timely identified. The combination of elevated transaminases and high CVVH dose are risk factors for accumulation that may not contribute to mortality if timely recognized and followed by discontinuation of citrate.

Conclusions

AKI on the ICU still has a high incidence and is associated with a substantial increase in morbidity and mortality. The management of AKI on the ICU underwent an impressive development over the past decades but many questions remain unanswered with respect to early identification and prevention of AKI as well as optimal timing of initiation, dosing and modality of RRT. Recently several large randomized trials have addressed the issue of intensity of RRT thoroughly but there still is a lack of consensus on many other topics. In this thesis we have addressed several of the unresolved issues of RRT such as mode of CVVH, dose and anticoagulation.

We have shown the equivalence of pre- and postdilution CVVH in heparinised patients concerning azotemic control despite a substantial difference in delivered dose. With this knowledge we adopted a technique of CVVH with regional anticoagulation using a citrate-containing replacement solution which has to be delivered in the predilution mode. This technique proved to be superior to predilution anticoagulant-free CVVH and we demonstrated its safety and efficacy. Furthermore we have shown its equivalence to bicarbonate-buffered replacement solution concerning acid-base and electrolyte control. In patients with a contraindication for systemic anticoagulation warranting CVVH, treatment with citrate as a regional anticoagulant should be considered the first choice modality for anticoagulation. Whether this holds true for all patients is a question yet to be answered.

There is emerging consensus that a delivered RRT dose in AKI of more than 25 ml/kg per hour does not improve outcome in the ICU. Our studies in septic and non-septic AKI argue for a distinction in aetiology of AKI as patients with sepsis-induced AKI may indeed benefit of a higher delivered dose unlike patients without sepsis.

Future perspectives

With respect to the topic of AKI on the ICU there are numerous issues to address in the future. Currently, much attention is focussed on identifying AKI earlier in the course by applying novel biomarkers such as cystatin C and neutrophil gelatinase-associated lipcalin. Once detected early, an attempt can be made to pharmacologically prevent renal function deterioration. The erythropoietic agents and recombinant human atrial natriuretic peptide are being analysed for that purpose and the first results of their clinical use seem promising. The administration of mesenchymal stem cells as a new tool to prevent AKI or to stimulate renal function recovery is also gaining interest.

Once RRT is necessary the optimal mode of treatment is still unclear. The renal assist device in which the tubular function of the original kidney is mimicked and added to conventional RRT is a promising novel technique which might be superior to conventional RRT alone. The available data on safety and efficacy so far are encouraging.

There is lack of consensus on the issue of timing of RRT. Studies investigating timing of RRT are predominantly observational and show conflicting results. Future randomized studies should consist of well matched early and late treatment arms using the widely accepted uniform RIFLE consensus definition of AKI. To avoid large heterogeneity between groups, a distinction should be made between sepsis and non-sepsis induced AKI.

Although there is emerging consensus that there is an upper limit of intensity of delivered RRT dose, this may not be true for sepsis-induced AKI. The IVOIRE trial, which studies the impact of high-volume CVVH in the early management of septic shock patients with acute renal failure, will give some clarity on this issue (NCT00241228). If a higher delivered dose indeed proves to be beneficial to septic patients, the question arises by which mechanism this effect occurs: is it the removal of pro-inflammatory mediators or just a cooling effect? The peak concentration hypothesis should then be tested more thoroughly. This hypothesis states that in sepsis there is an exaggerated harmful pro- and anti-inflammatory response with peak concentrations of pro- and anti-inflammatory mediators. By the non-selective removal of the excess of these mediators with RRT, a situation of immunohomeostasis can be restored.[33]

RRT with citrate as regional anticoagulant is an attractive alternative for systemic heparin. There are less bleeding complications and this treatment strategy may improve survival. One trial using hypertonic citrate showed a reduced mortality as compared to nadroparin.[34] However, another recent trial with citrate-containing replacement solution

showed no survival benefit when compared to heparin.[35] The results of the CASH-trial (Citrate Anticoagulation versus Systemic Heparinisation) comparing citrate-containing replacement solution with systemic heparinisation are awaited for; the endpoints of this trial are mortality and renal function recovery (NCT 0209378). Interesting in that respect is what the effects of heparin and citrate are on inflammation and coagulation. By chelating calcium, citrate may attenuate a potential harmful immune response, provoked by the extracorporeal circuit, leading to a lower polymorphonuclear cell degranulation. The latter are topics of currently ongoing research in our center.

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