Editorial

Should we apply "early" initiation of renal replacement therapy to critically ill patients with acute kidney injury?

Matthieu Legrand[1,2,3]

[1]AP-HP, Department of Anesthesiology and Critical Care and Burn Unit, St-Louis hospital, Paris, France; [2]Univ Paris Diderot, F-75475, Paris, France; [3]UMR INSERM 942, INSERM, Lariboisière hospital, Paris, France

Correspondence to: Matthieu Legrand, MD, PhD. Department of Anesthesiology and Critical Care and Burn Unit, St-Louis Hospital, Assistance Publique-Hopitaux de Paris, Paris, France. Email: matthieu.legrand@aphp.fr.

Submitted Sep 04, 2016. Accepted for publication Sep 07, 2016.
doi: 10.21037/jtd.2016.10.90
View this article at: http://dx.doi.org/10.21037/jtd.2016.10.90

Renal replacement therapy (RRT) remained one of the cornerstones of treatment of severe acute kidney injury (AKI). Large randomized controlled trials had addressed the question of dosing of RRT in critically ill patients with AKI and failed to show an impact on mortality of high dosing using hemodiafiltration with standard membranes (1,2). With respect to strategy of RRT management in intensive care unit (ICU) patients the focus has now moved toward the question of timing of RRT in patients with AKI. Higher in-hospital mortality has been observed in retrospective cohort studies when RRT was applied lately in patients with AKI. Based on these findings and even though well-performed large scale randomized controlled trials were largely lacking, an early or preemptive used of RRT has been suggested to improve outcome in patients with AKI (3).

On the opposite, two randomized controlled trials have suggested an increased risk of poor outcome when RRT was applied "early" after the diagnostic of AKI. In a single center randomized controlled trial performed in India comparing early use of RRT (mostly intermittent dialysis) compared to control used, Jamale *et al.* reported longer time to renal recovery with early use of RRT (4). In another multicenter randomized trial, Payen *et al.* reported worst clinical outcome with a trend toward higher mortality when low volume hemofiltration (20 mL/kg/hour) was applied to septic shock patients. Patients randomized in the group treated with hemofiltration were longer under vasopressors than controls (5). Of note, the presence of AKI was not a criterion of inclusion in this study.

Few months ago the results of the ELAIN trial were released (6). This was a single center randomized controlled trial which aimed at comparing the impact of RRT at stage 2 AKI with blood neutrophil gelatinase associated lipocalin >150 ng/mL *vs.* stage 3 AKI (or an absolute indication). The authors observed a reduced risk of dying using early initiation with continuous veno-venous hemofiltration (CVVH).

The design and results of the study however raise some questions. First all patients received RRT in this study which was not designed to evaluate the indication of RRT and almost all patients included did receive RRT. It therefore appears that the authors had the conviction that RRT is mandatory in all patients with stage 3 AKI even though no absolute indications are met (e.g., severe hyperkalemia, fluid overload). However there are still many uncertainties regarding the indications of RRT. Recently, Gaudry *et al.* reported the results of the AKIKI study comparing a strategy of RRT initiation in stage 3 AKI compared to a strategy of RRT initiation based on consensual indication of RRT (7). The authors hypothesized that a restrictive indication of RRT would be associated with lower mortality rate. The study was found negative with no difference in mortality. However a substantial number of patients randomized in the restrictive strategy were found to have never received RRT. Regarding the indication again of RRT, the use of biomarkers of AKI appeared to have very limited impact on the selection of patients in the ELAIN study since only three patients were screened but not included because of plasma NGAL <150 ng/mL. Of note, most of patients from the ELAIN study were post-operative from cardiothoracic surgery while most from the AKIKI were septic.

In the view of the ELAIN design, RRT was seen as an adjunctive therapy and not solely as a supportive treatment for kidney insufficiency. In this line, as a secondary endpoint, the authors observed lower concentration of pro-inflammatory cytokines in the early group [interleukin (IL)-6 and -8] 24 hours after randomization. They furthermore observed an association between plasma cytokines concentration and outcome. Although the association between circulating cytokines level and outcome is not surprising, the observation of a decrease of IL-6 and IL-8 after CVVH is questionable. Low volume hemofiltration was applied in this study, with a median effluent dose of 26.6±4.7 mL/kg/hour in the early group. Molecular weight of IL-6 is 21 kDa, therefore very close form cut-offs of most standard membranes. Previous studies reported that standard hemofiltration does not allow significant removal of plasma inflammatory cytokines (5,8) unless high-cut off membranes are used (9). Although hemoadsorption might occur, it unlikely allowed significant clearance of cytokines (10). It would therefore be essential to know if high-cutoff membranes (cutoff >40 kDa) were used in the ELAIN study to better get insights into the potential impact of early used of CVVH on cytokines removal in the study. Unfortunately the characteristics of the membrane used in the ELAIN study were not reported. If a low cutoff membrane was used, the decrease of plasma cytokines level and outcome improvement is most likely rather due to a false positive result with a type 1 error rather than a direct consequence of early used of CVVH.

To conclude, the authors of the ELAIN trial first should be congratulated for performing such a study on an important and highly difficult question of timing of initiation of RRT in critically ill patients with AKI. It however appears premature to recommend the use of RRT as soon as stage 2 AKI definition is met in critically ill patients based on the above-mentioned concerns. Physicians should still take into account clinical conditions, which hamper the probability of rapid recovery (e.g., previous chronic renal failure, septic shock, multiple organ dysfunction), the response to first line therapeutics (e.g., fluid and vasopressor challenge in oliguric patients), and the occurrence of acute electrolytes disorders such as hyperkalemia to indicate the initiation of RRT. Finally, there is still an important unmet need of fluid balance evaluation and control in AKI patients (11), which is likely to play a central role in the indication of RRT in critically ill patients with AKI.

Acknowledgements

None.

Footnote

Provenance: This is an invited Editorial commissioned by the Section Editor Zhiheng Xu (State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, Department of Intensive Care, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China).
Conflicts of Interest: The author has no conflicts of interest to declare.

Comment on: Zarbock A, Kellum JA, Schmidt C, *et al.* Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury: The ELAIN Randomized Clinical Trial. JAMA 2016;315:2190-9.

References

1. RENAL Replacement Therapy Study Investigators, Bellomo R, Cass A, et al. Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med 2009;361:1627-38.
2. VA/NIH Acute Renal Failure Trial Network, Palevsky PM, Zhang JH, et al. Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med 2008;359:7-20.
3. Prowle JR, Davenport A. Does early-start renal replacement therapy improve outcomes for patients with acute kidney injury? Kidney Int 2015;88:670-3.
4. Jamale TE, Hase NK, Kulkarni M, et al. Earlier-start versus usual-start dialysis in patients with community-acquired acute kidney injury: a randomized controlled trial. Am J Kidney Dis 2013;62:1116-21.
5. Payen D, Mateo J, Cavaillon JM, et al. Impact of continuous venovenous hemofiltration on organ failure during the early phase of severe sepsis: a randomized controlled trial. Crit Care Med 2009;37:803-10.
6. Zarbock A, Kellum JA, Schmidt C, et al. Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury: The ELAIN Randomized Clinical Trial. JAMA 2016;315:2190-9.
7. Gaudry S, Hajage D, Schortgen F, et al. Initiation

Strategies for Renal-Replacement Therapy in the Intensive Care Unit. N Engl J Med 2016;375:122-33.
8. Cole L, Bellomo R, Hart G, et al. A phase II randomized, controlled trial of continuous hemofiltration in sepsis. Crit Care Med 2002;30:100-6.
9. Morgera S, Haase M, Kuss T, et al. Pilot study on the effects of high cutoff hemofiltration on the need for norepinephrine in septic patients with acute renal failure. Crit Care Med 2006;34:2099-104.
10. Rimmelé T, Kellum JA. Clinical review: blood purification for sepsis. Crit Care 2011;15:205.
11. RENAL Replacement Therapy Study Investigators, Bellomo R, Cass A, et al. An observational study fluid balance and patient outcomes in the Randomized Evaluation of Normal vs. Augmented Level of Replacement Therapy trial. Crit Care Med 2012;40:1753-60.

Cite this article as: Legrand M. Should we apply "early" initiation of renal replacement therapy to critically ill patients with acute kidney injury? J Thorac Dis 2016;8(10):E1271-E1273. doi: 10.21037/jtd.2016.10.90

