Author’s response to reviews

Title: The role of the specialized team in the operation of continuous renal replacement therapy: a single center experience

Authors:

Harin Rhee (island-real@daum.net)
Ihm Soo Kwak (lkhkmd@gmail.com)
Gum-Sook Jang (medi-er@hanmail.net)
Miyeun Han (myeun81@hanmail.net)
Inseong Park (polhio@naver.com)
Il-Young Kim (iykim@pusan.ac.kr)
Eun-Young Seong (sey-0220@hanmail.net)
Sang Heon Song (shsong0209@gmail.com)
Dong-Won Lee (dongwonlee@pusan.ac.kr)
Soo-Bong Lee (sbleemd@pusan.ac.kr)

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Author’s response to reviews:

To Giorgos Sakkas, PhD.
Editor-in-Chief, BMC Nephrology

Re: BNEP-D-17-00204

“The role of the specialized team in the operation of continuous renal replacement therapy: a single center experience”
Dear Editor

This letter is intended for the revision of the manuscript according to your request. First of all, we would like to appreciate editorial suggestions and reviewers' comments. We tried to correct the manuscript according to your suggestions and reviewers’ comments.

We included a cover letter responding individually to the editorial suggestions and to each reviewer and detailing all changes and corrections we’ve done.

Again, we would like to appreciate your suggestions and reviewers’ comments. We believe that this revised manuscript is highly likely to achieve the priority for publication in BMC Nephrology. We are looking forward to your favorable response.

Sincerely,

Ihm Soo Kwak, M.D., Ph. D.

Division of Nephrology, Department of Internal Medicine, Pusan National University Hospital, Gudeok-ro 179, Seo-Gu, Busan, 602-739, Republic of Korea

TEL) 82-51-240-7875  FAX) 82-51-254-3127  E-mail) lkhkmd@gmail.com

Reviewer(s)’ Comments to Author:

Reviewer 1:

The present study is a relatively large retrospective study to evaluate the role of specialized CRRT team among AKI patients.
Several issues deserve comment:

Major:

1) The manuscript does not clearly describe the background/introduction of the study. Are there any previous studies examining the role of specialized CRRT team?

A) Thank you for your kind suggestions

We found two previous studies examining the role of specialized CRRT team and added their results at the last paragraph of the introduction.

2) Please give more details regarding the baseline demographic data for the difference proportion of patients in surgical vs medical ICU and proportion of patients with elective case in ICU.

A) Thank you for your kind suggestions

As you mentioned, we added information about the proportion of the patients in medical or surgical ICU at Table 2. The proportion of elective case of CRRT after open heart surgery was about 5.1%. In the previous version, we did not discriminate these elective cases and regarded them as an indicative case of acute pulmonary edema. In this revised version, we corrected them and revised table 1 as attached. The proportions of the elective cases were not statistically different according to the period before and after the implementation of specialized CRRT team (before 4.3%, after 5.8%, p=0.274).

3) Could you please compare the additional results regarding the CRRT-related technique improvement after having specialized team such as duration of circuit life and major types of anticoagulant used between 2 groups?

A) Thank you for your kind suggestions.

As you suggested, we added filter life span (it is equal to the circuit life span) at table 3. Contrary to expectations, the filter life span was shorter after the implementation of CRRT team. This is because that, we routinely changed filter (circuit) every 24 hours in case of sepsis after the implementation of CRRT team. Instead we compared frequency of premature filter cl"
between two periods and summarized it at table 3. It was not changed (28.3% VS 27.0%, p=0.628).

We routinely changed filter to septic patients because filter membrane in itself can remove mid to large molecular solutes by adsorption which is limited by saturation of the membrane binding sites that can occur with a few hours. We believe that by changing filter, we could increase mid to large molecular clearance including TNF-a, IL-6. Also, we believe this might had a role in the survival advantages after the implementation of CRRT team especially to the patients with sepsis or systemic inflammatory response syndrome.

For this reason, comparing circuit lifespan became a totally different problem from the technical improvement you have meant. We thought it is an interesting finding of our study, and we issued and discussed about it in the discussion section (The third paragraph of the Discussion section).

As for the anticoagulant, as described in the previous manuscript, we mainly used unfractionated heparin or nafamostate. Because we used these anticoagulants interchangeably according to the patients’ condition (bleeding tendency) even in the same patients, it was very difficult to rate and compare how to use main anticoagulants of each patients.

4) Please discuss on issue that the delivered (actual) dose in patients receiving specialized team was significantly lower than the other group.

A) Thank you for your kind suggestions.

In the previous manuscript, we issued this point at the discussion section (Page 8, 30th line –page 9, 35th line). Actually delivered doses were decreased after the implementation of CRRT team, because of the changes in the management strategies of CRRT in our clinic after the implementation of CRRT team; fixed dose 2000 mL/hr (in case of sepsis, fixed dose 3000 mL/hr) -> 40 mL/kg. To avoid confusion, we explained about it in the result session of the revised manuscript.

As described in that part, even though the delivered dose was significantly lower in the post CRRT team era than the pre CRRT team era (33.99 VS 35.31 mL/kg/hr, p=0.011), delivered dose was sufficient enough to cover the recommended dose (20-25 mL/kg/hr) in the post CRRT team era. From the ATN and RENAL trial, it is clear that doses larger that the recommended
doses cannot guarantee better survival benefit, we believe that this change was not harmful to the patients. Rather, we thought that we could improve cost effectiveness; we could reduce the unnecessary consumption of dialysate and replacement solution by adjusting CRRT dose prescription according to the body weight, after the implementation of CRRT team.

5) Is it possible to add total ultrafiltrate (ml/day), total urine output (ml/day), and percentage of AKI patients with renal recovery in Table 3?

A) Thank you for your nice guidance.

As you know, in CRRT patients, total ultrafiltrate is determined by net ultrafiltrate and substitution fluid which is variable according to the patients’ condition. The effluent flow rate (actually delivered dose) which is the final results of the filtration process in the CRRT operation is already described in the previous version (Table 2).

We guess that you wanted us to reveal the association between net UF (total ultrafiltrate minus total substitution) plus UO and renal outcomes in our cohort. We agree that this is one of the most important points in the operation of CRRT. However, to analyze this association, we have to know patient’s initial volume status which we can’t get due to the retrospective manner of this study. We think it should be analyzed in a prospective setting to find out optimal net UF rate considering urine output.

Instead, in this revised version, we simply summarized renal outcome of the survivors in the table 6. We did not further analyze the factors associated with renal outcome, because some important factors were missed in our setting; such as patients’ initial volume status, net ultrafiltration rate and urine output. We declared them as a limitation of our study in the revised manuscript.

## When we performed multivariable analysis, higher serum protein, higher serum creatinine level and higher tCO2 levels were associated with renal death (dialysis dependence at the time of discharge). We thought we can’t accept these results because essential parameters were missed (such as patients’ initial volume status, net ultrafiltration rate and urine output). To avoid confusion, we did not add them in the revised manuscript.
6) Is it possible to show the number for both uni- and multivariable regression analysis in Table 4 and 5?

A) Thank you for your nice guidance. We added univariable analysis results in table 4 and 5 in the revised manuscript.

Minor:

1) Page 4 line 45, please change "dialysis and filtration" to "diffusion and convection".

A) We revised it as you suggested.

2) Page 4 line 50, please specify the criteria for "CRRT weaning".

A) We did not have clear criteria on when to stop CRRT and it was determined by the nephrologist who was responsible for the patient. As described in the previous manuscript we considered CRRT weaning when the blood pressure had recovered without the assistance of vasopressors or when the amount of urine showed a trend of increasing output. We added reference of them, in the revised manuscript.

3) Page 5 line 50, do the authors mean using a log rank test to compare mortality between two groups?

A) We used Pearson Chi-Square test to compare mortality between two groups.

4) Please spell out the word "Etc" or using other word instead.

A) We erased Etc in Table 1. We think it is confusion and redundant.
5) Figure 2b, please correct the name of y-axis.

A) We correct them as you recommended. Thank you.

6) Please fill the missing p-value for BMI in Table 2.

A) We fill that at Table 2 in the revised version.

Reviewer: 2

The manuscript entitled "The role of the specialized in the operation of continuous renal replacement therapy: a single center experience" is a retrospective study whose objective is to study the association of implementation of a specialized CRRT team on therapy performance and patient outcome.

For this study, the investigators reviewed charts from patients undergoing CRRT before and after implementation of a specialized CRRT team. The specialized CRRT team consisted of one nephrologist and two nurses. These individuals were "responsible for the operation and management of the CRRT machine and procedure. The main duty of the CRRT team was to initiate and manage the CRRT". The specialized team was deployed in March 2013. The investigators compared CRRT performance and patient outcomes pre-specialized team implementation (i.e. from the time period of 2011 to 2013) to post specialized team implementation (i.e. from 2013-2015). The authors found that with utilization of the specialized CRRT team, patients experienced reduced initiation time to CRRT, less CRRT downtime, and less CRRT down time per day. In addition, the investigators found a lower all-cause mortality rate in the time period after implementation of the CRRT team. In addition, the authors studied factors associated with all-cause mortality and CRRT mortality. Factors found to be associated with all-cause mortality in multivariate analysis included serum albumin, CRRT operation duration, CRRT initiation time, SOFA score, and INR. Factors found to be associated with CRRT mortality included total protein, CRRT initiation time, SOFA score, and INR. These associations were determined in multivariate analysis.

Overall, this study was methodologically well done and the statistical methods used were appropriate for the project.
The value of this study stems from the fact that improved CRRT performance and patient outcomes can possibly be associated with deployment of a specialized CRRT team. The strengths of this study include the fact that this was a large study done over a period of 4 years. Also, this study correctly emphasized the importance of limiting interrupted treatment time and possibly earlier initiation times in patients undergoing CRRT. Despite this, the study does have some weaknesses. Obviously, the lack of randomization and the separation of 2 study groups by a difference in time periods creates a possibility of different subject characteristics between the 2 groups. In fact, vasopressor use and ventilator use was lower in the post CRRT team implementation time period. In addition, team implementation did not directly influence patient mortality but it did so indirectly by the association between team implementation and improved CRRT initiation time.

The main suggestions I would have includes improved definition of the variables including initiation time, down time, and how variables such as CRRT initiation time was defined in mortality analysis.

A) Thank you for your comments and good guidance.

We added a definition for ‘CRRT down time’ in the method section, data collection part with a reference.

As you know, various parameters had been used to define CRRT initiation time; urine output, serum BUN, cr, SOFA score, time relative to the development of AKI, time relative to hospital or ICU admission. Among them, we defined CRRT initiation time as time from ICU admission to the CRRT initiation as described in the previous manuscript. Also, we adjusted it as a continuous variable in the mortality analysis.

In addition, given the differences in the two groups, I would suggest using multivariate linear or logistic regression in the analyses that were performed for and displayed in Table 3.

A) Thank you for your good guidance. As you suggested we did multivariable linear regression analysis and revealed the contribution of the implementation of CRRT team in reducing CRRT initiation time and down time. We added them in the supplement table 1 and 2.