Author's response to reviews

Title: Predictors of neurological outcomes after successful extracorporeal cardiopulmonary resuscitation

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Author's response to reviews:

Dear Editor

Thank you for the opportunity to revise and resubmit our manuscript. I agree with your comments and the comments of the reviewers. We have revised the manuscript as the reviewers suggested and hope that it is now suitable for publication. Thank you for your kind comments.

Sincerely yours,

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Comments to Editor and Reviewers

Editor's comment

Comment: We recommend that you copyedit the paper to improve the style of written English. If this is not possible, you may need to use a professional language editing service. For authors who wish to have the language in their manuscript edited by a native-English speaker with scientific expertise, BioMed Central recommends Edanz.
Response: I agree with the editor’s comment. I used a professional language editing service to copyedit my manuscript to improve the English. Thank you for your kind comments on my manuscript.

Reviewer 1 Comments for the Author

Comment: MAJOR COMPULSORY REVISIONS
1. Abstract, Conclusion and Discussion, page 11, lines 17-18: association of less good neurological outcome with lower hemoglobin levels does not allow in turn to argue that a higher hemoglobin level induced by transfusion would be neuro-protective. The effects of transfusion were not studied and a retrospective study is hypothesis generating – at best. Transfusions are known to have side effects and tolerating lower transfusion triggers resulting in comparable or even better outcome as shown recently in an increasing number of studies in other settings, which is somewhat conflicting with your findings. Please discuss.

Response: I agree with the reviewer’s comment that transfusions have side effects and tolerating lower transfusion triggers can result in comparable or even better outcomes. Although high hemoglobin levels were associated with good neurological outcome after ECPR in our study, no studies have determined if a higher hemoglobin level induced by transfusion would be neuroprotective. A recent hypothesis states that regular blood transfusions might prevent silent ischemia and cognitive impairment in septic shock patients [1]. A recent controlled trial by DeBaun et al. showed that regular blood-transfusion therapy significantly reduced the incidence of recurrence of both silent and overt cerebral infarction in patients with sickle cell anemia, who require dialysis, or have #-thalassemia [2]. Recurrence of both silent and overt cerebral infarction is associated with cognitive impairment. Transfusions have side effects and tolerating lower transfusion triggers results in comparable or even better outcomes, as shown recently in studies in other settings. Thus, the association of good neurological outcomes with higher hemoglobin levels induced by transfusions requires further investigation. I agree with the reviewer and revised the manuscript accordingly (manuscript page 11, lines 11-23).

Comment: MAJOR COMPULSORY REVISIONS
2. The number of patients that received hypothermia is low, despite the fact that body temperature can be easily controlled during ECMO. Why? This limitation was mentioned but the reason not explained.

Response: I agree with the reviewer. The limited therapeutic hypothermia was not mentioned in previous manuscript. Therapeutic hypothermia was performed for a limited number of patients in our study. There were three reasons for the limited use of therapeutic hypothermia in the study. First, hypothermia can cause coagulopathy, so therapeutic hypothermia was not tried when the patient had significant bleeding after ECMO insertion. Second, a controlled-surface cooling device was not available before 2009 in our hospital. Since 2010, we have selectively used therapeutic hypothermia in ECPR patients. Third, most ECPR
patients had a low body temperature caused by extracorporeal circulation and external volume infusion. Therefore, ECMO itself might have offered some degree of neuroprotection through hypothermia. I agree with the reviewer and revised the manuscript to add the reason for the limited therapeutic hypothermia (manuscript page 12, lines 21-24 and manuscript page 13, lines 1-4).

Comment: MINOR ESSENTIAL REVISIONS
1. page 5, lines 20-21 “This study was performed retrospectively...” contains duplicate information and can be omitted.
Response: I agree with the reviewer’s comment and deleted this sentence.

Comment: MINOR ESSENTIAL REVISIONS
2. Abstract: number of non-included patients unclear: how many dies and how many were lost due to missing outcome?
Response: I agree with the reviewer and inserted these numbers into the abstract. Excluded were 22 patients who did not survive longer than 24 hours after ECPR (no successful ECPR) and 90 patients who died due to unknown causes or causes other than brain death, and patients whose neurological status could not be assessed at discharge. A total of 115 patients were included in this study and 24 died from brain death. I revised the manuscript to add numbers (manuscript page 3, lines 11-13 and lines 20).

Comment: MINOR ESSENTIAL REVISIONS
3. Page 12, line 2: “affected by” better: “associated with”, because poor neurologic outcome is not caused by lactic acid but by low cardiac output. Thus, lactic acid and neurologic outcome are not causally linked.
Response: I agree with the reviewer’s comment and changed this sentence as recommended (manuscript page 12, lines 7).

Comment: DISCRETIONARY REVISIONS
1. Abstract: Statistical method for identifying risk factors is not mentioned in the methods but in the results. Consider changing.
Response: I agree with the reviewer and revised the manuscript to include statistical methods in the Methods section and deleted the word in the Results section (manuscript page 3, lines 14-15).

Reviewer 2 Comments for the Author
Comment: This is a retrospective cohort study assessing the predictors of favorable neurological outcome in ECLS. This study has some problems. First, the findings of this study indicate not causality but mere association. The authors should refer to this point. In addition, the findings has no novelty. I think it is difficult to publish this paper as an original research article.

Response: I appreciated the reviewer’s honest criticism. Many factors are associated with neurological prognosis of patients after ECPR. However,
investigating ECPR by a prospective, randomized method would not be easy. Thus, identifying causality is difficult. We tried to find neurologically prognostic factors after ECPR and found factors associated with neurological prognosis. Although a few studies have investigated ECPR and neurological outcomes, most included all ECPR patients and failed to suggest prognostic factors for favorable neurological outcomes. Therefore I think this study investigating predictors of neurological outcome after ECPR was worthwhile and novel.

Reviewer 3 Comments for the Author

Comment: Major compulsory revisions
1. I would suggest to add into limitation section specifically the percentage of excluded patients, compare your very low percentage of cooling/TTM to other studies – these factors may have seriously affected outcome of your patients and thus interpretation of your data.

Response: I agree with the reviewer. The limited therapeutic hypothermia was not mentioned in previous manuscript. Therapeutic hypothermia was performed for a limited number of patients in our study. There were three reasons for the limited use of therapeutic hypothermia in the study. First, hypothermia can cause coagulopathy, so therapeutic hypothermia was not tried when the patient had significant bleeding after ECMO insertion. Second, a controlled-surface cooling device was not available before 2009 in our hospital. Since 2010, we have selectively used therapeutic hypothermia in ECPR patients. Third, most ECPR patients had a low body temperature caused by extracorporeal circulation and external volume infusion. Therefore, ECMO itself might have offered some degree of neuroprotection through hypothermia. I agree with the reviewer and revised the manuscript to add the reason for the limited therapeutic hypothermia (manuscript page 12, lines 21-24 and manuscript page 13, lines 1-4).

Comment: Major compulsory revisions
1. I would appreciate to add specific location of arrest in hospital: ICU, ward, cathlab…?

Response: I agree with the reviewer’s point. I revised Table 2 to add the location of ECMO insertions.

Comment: Minor issues, please correct spelling/English
9 - patients never be awaken and spontaneous awakening trial
10 - They had needed continuous sedation
12 - We excluded those patients were not possible to define neurologic status

Response: The reviewer is correct and I changed the sentences according to the recommendation (manuscript page 6, lines 6-8 and line 9-11).

References