April 11, 2020

Ke-Qin Hu, Koo Jeong Kang, Nikolaos Pyrsopoulos
Editors-in-Chief, World Journal of Hepatology

Re: Manuscript NO: 65396

Dear Editorial Board and Reviewers,

Thank you for your insightful review of our manuscript, titled "Therapeutic Plasma Exchange in Liver Failure".

We have responded below to each of your feedback comments and edited the manuscript accordingly. Changes to the manuscript are highlighted in red.

Sincerely,

Abimbola Chris-Olaiya

Reviewer 1 comments:

Comment #1: The manuscript is a narrative review of the current state of the art in therapeutic plasma exchange in patients with acute and acute-on-chronic liver failure.

Comment #2: The manuscript mainly evaluates the efficacy of TPE in these clinical scenarios, however, this type of review (narrative) is not adequate for the purpose. A formal systematic review according to PRISMA checklist would be more appropriate - see World J Gastroenterol. 2020 Jan 14; 26(2): 219–245. Published online 2020 Jan 14. doi: 10.3748/wjg.v26.i2.219

Reply #2: Thank you for your comment and suggestion. We believe that a formal systematic review is outside of the scope of this invited mini-review. We hope to provide a narrative review of plasmapheresis in both acute and acute-on-chronic liver failure.

Comment #3: In the introduction there is an attempt to compare TPE with ECAD - this is very interesting topic, but the main point of the paragraph is wrong. Citing: "The theoretical advantage of TPE over ECAD hinges on the exchange of plasma, which replaces plasma factors that are lacking as a result of impaired hepatic synthetic function in both ALF and ACLF". However, the main advantage of TPE is the removal of large proteins - cytokines and immunoglobulins (60-70% reduction) where MARS has a technical limit of 50-60 kDa based on the membrane). It would be useful to more thoroughly compare the two methods.

Reply #3: Thank you for elaborating on the difference between TPE and ECAD and for your suggestions. We have expanded our discussion as highlighted below

"When considering the therapeutic differences between TPE and ECAD, MARS in particular has been recognized to be more costly than TPE and can entail a more logistically complex initiation. Furthermore, the MARS filter-membrane dictates a size selection threshold of approximately 50 KDa[28], whereas TPE is capable of removing larger molecular proteins, including antibodies, immune complexes, and lipoproteins[29]. To date, no head-to-head adult clinical trial has directly compared TPE with MARS or any of the ECAD systems. However, in a retrospective single center pediatric study comparing MARS with the combination of TPE and hemodialysis (TPE/HD), TPE/HD effected a greater reduction in bilirubin, ammonia, and INR[30]. Another theoretical advantage of TPE over ECAD hinges on the exchange of plasma, which replaces plasma proteins, including clotting factors, that may be decreased as a result of impaired hepatic synthetic function in both ALF and ACLF."

Comment #4: 1st line on page 9 is unclear - what is one plasma volume?

Reply #4: One plasma volume has been clearly defined in the manuscript as shown below

"For reference, a plasma volume is an estimate of the total volume of plasma in an individual and is a common unit of measurement in therapeutic apheresis procedures. Plasma volume can be calculated from estimated total blood volume using common physiological variables, including an individual's sex, height, weight, body muscle composition, and hematocrit[55]."

Comment #5: organization of the manuscript is confounding. Outcomes and results of the same study are reported in different sections (outcomes and technical aspects) Technical aspects section should contain only options how to perform TPE with the reference to the outcomes section

Reply #5: Thank you for your thoughtful comment. The technical aspect section has been re-formatted as below to only include options on how to perform TPE. Text deleted are highlighted below

"and reported improvement in biochemical parameters and survival"

"They reported similar improvement in vasopressor requirements and MAP to those reported by Larsen et. al.[19]. However, there was no significant difference in 30-day in-hospital survival in the LV-TPE group versus the SMT group (65% vs. 50%, P = 0.369),

and no significant difference in survival rates in those who underwent LT versus those who did not (54% vs. 33%, P = 0.398)"

Comment #6: No mention about TPE in acute alcoholic hepatitis is present. These are the majority of patients with ACLF where TPE is considered.

Reply #6: We have added this last paragraph to the section on effect on biochemical parameters and clinical outcomes

"Severe acute alcohol-associated hepatitis (SAH) is recognized to be a common precipitant of ACLF[5]; however, TPE has not been specifically studied in this important patient population. Moreover, sub-group analysis of the limited number of patients with alcohol-associated liver disease included in the available trials has not been described. Case reports suggest that TPE with standard medical therapy may lead to clinical improvement in patients with SAH[51,52]. Randomized, controlled trials in patients with SAH are needed to better define the therapeutic effect of TPE for this indication."