

Dear Editor,

We sincerely thank you and the reviewer for taking the time to consider our manuscript 60410 “**Effect of Remote Ischemic Preconditioning among Donors and Recipients Following Pediatric Liver Transplantation: A Randomized Clinical Trial**”. The reviewer’s comments are insightful and helpful as they identified areas in need of additional clarification. As shown below, the reviewer and the editorial comments are laid out in italicized font and our response is given in normal font. Changes/additions to the manuscript are highlighted in red.

Thank you very much for your help.

### **Response to Reviewer 2:**

***Comment 1:** The article is well written and didactical and brings important data on the liver transplanattion field. I suggest the authors discuss more deeeply the previous studies that evaluated Remote Ischemic Preconditioning in liver transplantaion. I found no other problem in the manuscript.*

**Reply 1:** We added more details and discussed more deeply the previous studies that evaluated Remote Ischemic Preconditioning in liver transplantation in Discussion part. However, papers regarding RIPC and LT were too few.

### **Response to Reviewer 3:**

***Comment 1:** Are the authors planning to conduct further trials involving more centres to increase the number of patients?*

**Reply 1:** Yes. In the next step, we are planning to involve more centers to increase the number of patients and the reliability of study. We have connected with Shanghai Huashan hospital and The First Affiliated Hospital of Zhejiang University School of Medicine for the further study. The study plan is drawing up.

***Comment 2:** Is there any evidence that the washout can affect the success of the RIPC?*

**Reply 2:** Studies have postulated that the protective effects of RIPC can be summarized into triggers, signal transduction, and end-effectors. Triggers such as adenosine, cytokines, and endogenous opioids could be released locally or into blood [Kristin et al., *Pediatr Nephrol.* 2015, 30(10):1749-59; Derek et al., *Physiol Rev.* 2003, 83(4):1113-51; Peralta et al., *Transplant Proc.* 2003, 35(5):1800-2.]. Then, triggers could activate relevant signaling pathways. Studies have suggested that protective effects can be transferred by serum transfusion from a rabbit that has undergone ischemic preconditioning (IPC) to one that has not [Dickson et al., *J Thromb Thrombolysis* 1999, 8(2): 123-129]. Therefore, based on published studies, we hypothesized that the potential protective “triggers” for alleviating IRI in grafts may be flushed away before storage and introduction into the recipients. Though studies focused on the washout of grafts and the protective effects of RIPC were rare, it was understandable that some protective triggers contained in the grafts would be flushed

away. In the next clinical study, we'd like pay attention to this factor and explore if the washout of grafts will influence the protective effects of RIPC.

**Comment 3:** *Did you try to prolong the time of RIPC cycles in a small number of pediatric patients?*

**Reply 3:** Generally, the RIPC protocol is 3 cycles and 5min/cycle. It is a good idea to prolong the time of RIPC to explore if the protective effects could be enhanced. In the next study, we'd like add a group that set the time of RIPC as 10min/cycle.

**Comment 4:** *At the end of the key word section a full stop is missing, please add it; - the results and discussion sections are left-aligned, please justify them; - in the discussion section, the word "malondialdehyde" is incorrect, please check it; - in reference 24 there are two full stops at the end, please eliminate them; - in figure 1, in the first text box, there is an extra space between the words "July" and "2017" and space is missing between "2017" and "screened", please correct these errors; - the legend of Table 4 is double spaced, please uniform it to the others and justify it; - In supplementary Table 1, the p-value of "0164" needs a point.*

**Reply 4:** Thank you very much and we have corrected all points mentioned above. The word "malondialdehyde" was not found in our manuscript, the word should be "malonaldehyde" and written in paragraph 6 of Discussion part.

#### LANGUAGE QUALITY

*Please resolve all language issues in the manuscript based on the peer review report. Please be sure to have a native-English speaker edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript's language will meet our direct publishing needs.*

**Reply:** Our manuscript has been reviewed by a professional language company (Enago). Also, a native-English speaker helped us review this manuscript again. We believe that the manuscript's language meets the direct publishing needs.

#### EDITORIAL OFFICE'S COMMENTS

**Comment 1:** *I found the title was more than 18 words. The title should be no more than 18 words.*

**Reply 1:** We have modified the title as "Effect of Remote Ischemic Preconditioning among Donors and Recipients Following Pediatric Liver Transplantation: A Randomized Clinical Trial".

**Comment 2:** *I found there are two corresponding authors, which however is not permitted in all BPG journals. Please revise it accordingly.*

**Reply 2:** We have corrected this issue and only one corresponding author is labeled in the manuscript.

**Comment 3:** *I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s).*

**Reply 3:** We will upload related documents.

**Comment 4:** *I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.*

**Reply 4:** We will supply the Powerpoint and provide the original figures.

**Comment 5:** *I found the authors did not write the “article highlight” section. Please write the “article highlights” section at the end of the main text.*

**Reply 5:** We have added the “article highlights” section at the end of the main text.

**Comment 6:** *the in-text citation numbers need to be positioned before the punctuation or after the cited author’s name, with no spaces.*

**Reply 6:** We have modified them.

**Comment 7:** *please don’t include any \*, #, †, §, ‡, ¥, @....in your manuscript; Please use superscript numbers for illustration; and for statistical significance, please use superscript letters. Statistical significance is expressed as  $aP < 0.05$ ,  $bP < 0.01$  ( $P > 0.05$  usually does not need to be denoted). If there are other series of  $P$  values,  $cP < 0.05$  and  $dP < 0.01$  are used, and a third series of  $P$  values is expressed as  $eP < 0.05$  and  $fP < 0.01$ .*

**Reply 7:** We have modified these issues.

**Comment 8:** *Please write the “Conclusion” section at the end of the main text.*

**Reply 8:** We have added it.

**Comment 9:** *please provide the audio core tip file where the core tip content is recorded.*

**Reply 9:** We have added the audio core tip.

**Comment 10:** *please provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement.*

**Reply 10:** We have added these files.