

Professor Ze-Mao Gong
Science Editor,
Editorial Office, World Journal of Hepatology

April 19, 2016

Re: ESPS manuscript NO: 25063

Manuscript Type: Review

Title: **Multimodal Brain Monitoring in Fulminant Hepatic Failure**

Dear Prof. Gong

Reply to reviewers code: 00182114

Thank you for your inspiring and helpful comments and suggestions for the above referred manuscript. We have carefully revised the manuscript as suggested, and have attached our point-by-point responses to the reviewers' comments. Thanks for your consideration of this article for publication in World Journal of Hepatology.

Sincerely,

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Following the second review, we would like to address the comments made by each reviewer, and explain additional improvements to the manuscript.

Reviewers code: 00182114

1. "ICP monitoring may be considered in reversible/treatable pathologic processes that result in cerebral edema, such as meningitis/encephalitis, hypoxic ischemic injury, ischemic stroke, and hepatic encephalopathy. Please tell me the indication of ICP monitor in FHF. Please comment the Pathophysiology between the progression from hepatic encephalopathy to intracranial hypertension. Please comment the pathophysiology to intracranial hypertension oressure in FHF."

Comment: Thank you for your question, and we explain in text the pathophysiology: Cerebral edema and IH complicates approximately 75 to 80 % of patients with FHF and grade III or IV encephalopathy, in whom it remains a leading cause of death. Currently, the mechanisms that produce cerebral edema and IH in the setting of FHF is multi-factorial in etiology and only partially understood.^{20,15} Possible contributing mechanisms include cytotoxicity as a result of osmotic effects of ammonia, glutamine, other amino acids, and proinflammatory cytokines. Cerebral hyperemia and vasogenic edema occur because of disruption of the blood-brain barrier (BBB) with rapid accumulation of low molecular substances. Dysfunction of sodium-potassium adenosine triphosphatase (ATPase) pump with loss of autoregulation of cerebral blood flow (CBF) has been implicated as a cause of hyperemia.¹⁰⁻¹¹

The respective role of all of these phenomena in the development of IH in FHF remains to be determined. It can be hypothesized that brain edema (increase in brain volume) secondary to osmotic effect of glutamine in astrocytes, and cerebral hyperemia (in blood volume) secondary to vasodilation (cytokines, products of the necrotic liver, glutamine, others...) may contribute to IH leading to brain stem herniation and brain stem death in FHF. During all these FHF phenomena, the brain may respond by altering the expression of genes coding for various proteins whose role may be critical to some CNS functions, including the maintenance of cell volume neurotransmission.^{83-84,88}

2. "The major concern regarding placement of an ICP monitor is intracranial hemorrhage, which is especially problematic in patients with AFA. Initial data indicated a hemorrhage rate as high as 20% with ICP monitor placement in this population, but more recent reviews have shown a lower rate of bleeding in the range of 2.5%-10%

According to your paper, the use of VII, before ICP catheter appears to reduce the risk of intracranial bleeding. Recombinant Factor VIIa, given prior to catheter placement, can minimize bleeding complications as secondary hemostasis is restored, although recombinant factor VIIa is ineffectual in the setting of acidosis,

How about the opinion of "factor VIIa is ineffectual?"

Comment: Thank you for your question and we agree with the reviewer, and we know that Factor VIIa is not effective in clinical situations of acidosis. Hemorrhagic shock and trauma are associated with acidosis and altered coagulation. The fall in pH Has Been Reported to attenuate the activity of recombinant activated Factor VII (rFVIIa) in vitro. However, it is not known if acidosis induced by hemorrhagic shock or infusion of attenuates FVIIa activity in vivo. However current recommendations advise correcting acidosis before administering recombinant factor VII (rFVIIa). For this reason we add in the text that the use can be an alternative, but with low effectiveness in clinical situations of acidosis, requiring the correction of acidosis before the use of factor VIIa for its can be effectiveness in FHF.

2. Transcranial Doppler Ultrasonography is noninvasive ICP monitoring. Are there relationship between TCD changes and the ICP monitoring?

Comment: thanks for your question. ICP may be influenced by compressing the internal jugular vein, resulting in cerebrovascular changes. Under normal conditions, this leads to small changes in cerebral blood volume. However, in patients with severely impaired cerebrovascular autoregulation, cerebral blood volume Increased the in flow and obtained by compressing the internal jugular vein can lead to hemodynamic changes and secondarily cause compliance decreased and intracranial hypertension.^{3, 4} TCD can be useful in the control of the ideal arterial blood pressure by the detection of IH by ICP catheter. We include in the text the following paragraph: The use of transcranial Doppler together with the selective jugular vein compression by color Duplex sonography may suggest in determining decreased compliance and IH. ICP may be influenced by compressing the internal jugular vein, resulting in cerebrovascular changes. Under normal conditions, this leads to small changes in cerebral blood volume. However, in patients with severely impaired cerebrovascular autoregulation, cerebral blood volume Increased the in flow and obtained by compressing the internal jugular vein can lead to hemodynamic changes and secondarily cause compliance decreased and intracranial hypertension.^{3, 4} TCD can be useful in the control of the ideal arterial blood pressure by the detection of IH by ICP catheter.

Step 1. Please revise your manuscript according to the reviewers' comments.

1. Please provide language certificate letter by professional English language editing companies (Classification of manuscript language quality evaluation is B).

Comment: Thank you for your comment. We add the language certificate letter by professional English language editing companies

2. Running title, Author contributions, abstract, Key words, Conflict-of-interest statement, abbreviations / acronyms and core tip (check format for Manuscript Revision).

Comment: Thank you very much for the positive comments and suggestions made after the first review. We format for manuscript revision: review.

3. Please check that there are no repeated references! Please add PubMed citation numbers and DOI citation to the reference list and **list all authors**. Please revise throughout. The author should provide the first page of the paper without PMID and DOI.

Comment: Thank you for your comment. We checked all the references and add PMID and DOI at the end of each reference.

Editorial comments: - We appreciate the editor's suggestions and revised the manuscript according to his remarks. As requested, all changes were highlighted in the updated version of the manuscript. Please find changes in detail below:

Comment 1) Key words. Key words should not appear abbreviation, please correct it. - All abbreviations were deleted from the 'key words'-section.

Comment 2) Core tip. Please write a summary of less than 100 words to outline the most innovative and important arguments and core contents in your paper to attract readers. - We wrote a core tip with important arguments and core contents to attract the readers interest.

Comment 3) Audio core tip. In order to attract readers to read your full-text article, we request that the author make an audio file describing your final core tip, it is necessary for final acceptance. Please refer to Instruction to authors on our website or attached Format for detailed information. - We uploaded an audio core tip (.mp3 format) with the revision of this manuscript.

Comment 4) Please provide all authors abbreviation names and manuscript title here. - Abbreviation names and manuscript title were introduced. **Comment 5)** Don't forget to submit some files [Conflict-of-

Interest Statement (COI), Copyright (need signature of all authors) and Language Certificate (.pdf)] and Audio core tip (.mp3)

- All files are submitted within the revision process.

Comment 5) Abbreviations and acronyms are often defined the first time they are used within the main text and then used throughout the remainder of the manuscript. Please consider adhering to this convention. Search all abbreviations in your manuscript and do like this when they were used firstly.

- All used abbreviations and acronyms in the manuscript were double-checked.

Comment 6) Please add PubMed citation numbers and DOI citation to the reference list and list all authors. Please revise throughout. The author should provide the first page of the paper without PMID and DOI.

- The reference list was revised throughout.

Step 2. Please update the manuscript according to the Guidelines and Requirements for Manuscript Revision-Review.

- We updated the manuscript according to the above-mentioned guidelines and requirements for Manuscript Revision-Topic Highlight.

Step 3. Please provide an Audio Core Tip.

- An audio version (.mp3) of the core tip was recorded and uploaded via the EPSP system.

Step 4. Please subject the manuscript to CrossCheck analysis and the final title to Google Scholar search, and store screenshot images of the results.

- The manuscript underwent a CrossCheck analysis and a Google Scholar search. The corresponding screenshots are uploaded via EPSP system.

Step 5. Please provide the files related to academic rules and norms.

- All necessary forms including the conflict of interest statements were completed and are provided as attachment.

Step 6. Please revise the language of your manuscript.

- A language certificate is provided as attachment.

Step 7. Please sign the Copyright Assignment form.

- The copyright assignment form was completed and uploaded via the EPSP system.