Author's response to reviews

Title: In-hospital cerebrovascular complications following orthotopic liver transplantation: A retrospective study

Authors:

Ling Li (linglirabbit@163.com)
He Xiaoshun (gdtrc@163.com)
Zeng Jinsheng (zengis@pub.guangzhou.gd.cn)
Liang Zhijian (lzj2004152000@yahoo.com.cn)

Version: 3 Date: 18 September 2008

Author's response to reviews: see over
Dear Dr. Sabina Alam,

Thank you very much for providing us with a chance to revise our manuscript entitled "In-hospital cerebrovascular complications following orthotopic liver transplantation: A retrospective study" (Manuscript ID 5770425052138950). We have now revised the manuscript following the reviewers’ kind and constructive suggestions and the changes are listed below at a point-by-point style.

We believe that the revised version of the manuscript should be in much better shape and look forward to your favorable consideration.

With best regards,

Sincerely yours,

Jinsheng Zeng, MD, PhD,
Department of Neurology and Stroke Centre,
The First Affiliated Hospital, Sun Yat-Sen University,
No. 58 Zhongshan Road 2, Guangzhou, 510080, P.R. China.

Response to the reviewers:

Reviewer: J Bradley White
Reviewer's report:
The authors report the rate of cerebral complications in post-operative OLT patients. They acknowledge that this work has been reviewed and reported in other countries. They are reporting their findings from their country.
In general, I think that the report is interesting and adds a new demographic component to this phenomenon. I have the following recommendations.

1. I would remove figure 1. It doesn’t add much to the paper and most practitioners know what an intraparenchymal hemorrhage looks like.
   Response: We quite agree with reviewer. In the revised manuscript, we removed figure 1 according to the suggestion.

2. Add a table. The table should include demographic information for patients. It should also show the statistical predictors of hemorrhage (ie – age, infection).
   Response: We appreciate reviewer for the good advice. In the revised manuscript, table 3 was added to compare the statistical predictors of intracranial hemorrhage between the patients with and without intracranial hemorrhage after orthotopic liver transplantation.

3. The authors should further clarify the numbers of the significant factors of age and infection. These numbers are unclear as written in the text currently.
   Response: We thank reviewer for the constructive suggestion. In the revised manuscript, we supplied more detail information of the significant factors of age and infection in the 4th paragraph of the Result (Page 5, Line 13-22 and Page 6, Line 1-2), as well as in the added table 2, and added some related comments in the 3rd paragraph of Discussion (Page 7, Line 20-23, Page 8, Line 1-17).

4. There are numerous grammatical and spelling errors that should be refined for the next version.
   Response: Thank you very much for your kind advice. We revised the grammatical and spelling errors in the resubmitted manuscript.
Reviewer: Bryan Young

Reviewer's report:

The paper is a retrospective review of patients with orthotopic liver transplants (OLT), examining cerebrovascular complications during the same hospital admission as for the transplants. The authors found 10 patients of 358 had cerebrovascular complications, 8 of which were hemorrhages, 6 of whom died. The hemorrhages were lobar or deep and correlated with advanced age and systemic infections, but not with coagulopathies.

The paper has merit and is of interest. There are some major issues that should, however, be addressed:

1. The association of infections with hemorrhages is striking. We need more detail about specific organisms. Did any patients have vascular imaging or post-mortem exams to reveal vasculitis or mycotic aneurysms?

Response: In our study, among 337 patients following OLT, the patients with systemic infections had a more frequency of intracranial hemorrhage than those without infections (7/155 vs 1/182, \( p = 0.026 \)). In other word, seven of 8 patients with intracranial hemorrhage had infections, including 4 patients experienced bacterial pneumonia, one had a mold fungal pneumonia, a mold fungal combined Candida tropicalis pneumonia and a bacterial pneumonia combined urinary tract infection respectively. It was a pity that none of patients with intracranial hemorrhage had vascular imaging or post-mortem exams to reveal whether they had vasculitis or mycotic aneurysms, due to the severe conditions at that time or not obtaining the informed consent from the patients or their families. Above information were added in the 4th paragraph of Result (Page 5, Line 8-19) and in Table 3, and some related comments were supplled in the 3rd paragraph of Discussion (Page 7, Line 23 and Page 8, Line 1-17).

2. In our experience and in the literature aspergillis is a common cause of such hemorrhages. Did any cases involve this organism?
Response: We agree with the reviewer. In accordance with your experience, some previous literatures reported that aspergillus is a common cause of intracranial hemorrhage following orthotopic liver transplantation (OLT). Cox and colleagues\cite{1} reported that an 11-year-old boy who had cystic fibrosis died of an intraventricular and intracerebral hemorrhage after OLT caused by an aspergillus brain abscess on the 48th day after surgery. Wijdicks and colleagues\cite{2} reported that in the group of 8 patients with intracranial hemorrhage after OLT, one had a Candida-associated mycotic aneurysm demonstrated by autopsy and another had disseminated aspergillosis. Generally, it is presumed that under the condition of systemic infections related to immunosuppresion following OLT, Aspergillus, Toxoplasma and any virulent bacterial organism may lead to inflammation of the arterial wall and formation of an aneurysm. In our study, we found that 7 of 8 patients with intracranial hemorrhage had systemic bacterial or fungal infection, and all of them had pneumonia, including a mold fungal pneumonia and a mold fungal combinded Candida tropicalis pneumonia. But it was very pitiful that no evidence to support that aspergillus was the direct cause of intracranial hemorrhage due to no vascular imaging or post-mortem exams in our study. We added some related comments in the 3rd paragraph of Discussion (Page 7, Line 23 and Page 8, Line 1-17).

3. The timing is important with respect to post-transplant complications. Suggest you use a table with details, including age, sex, timing of complication relative to transplant, underlying organism, type or site of hemorrhage (e.g., lobar, basal ganglionic, etc.) and medications, especially immunosuppressive drugs. There is mention of a table, but it was not included.

Response: We appreciate reviewer for the constructive suggestion. In the revised manuscript, we put more information with details in the revised Table 2, including sex, age, diagnoseof liver disease, OLT to oneset, operative persistent time, previous abdominal surgery, retransplantation, introperative blood loss volume, introperative blood transfusion, the counts of platelet, PT, APPT, introperative hypotension, pre- and postoperative hypertension, type or site of hemorrhage or infarction reaveled by
brain CT, immunosuppressive drugs, decompressive craniectomy and outcome, etc.

4. The organization/structure of the paper needs improvement. It lacks a Discussion section. This could be added, perhaps with some information removed from the results and background sections. In the Discussion the authors might compare their findings with those of other publications on the topic and offer some explanations as to how they occur. They might also suggest how further studies might be done, e.g., prospectively to identify those of greater risk, how such serious complications might be avoided, e.g., better bacteriologic surveillance, infection control measures, more prompt systemic antibiotic/antifungal therapy.

Response: Thank you for the good suggestion. In the revised Discussion, we added more detail information to compare our findings with those of previous literatures, analysis the possible risk factors such as systemic infections, and prospectively proposed some effective preventive and therapeutic regimen of intracranial hemorrhage following OLT (Page 6, Line 8-19 and Line 22-23; Page 7, Line 1-2 and 20-23; Page 8, Line 1-7 and Page 9, Line 5-11).

5. It might be useful, for more general information for the neurologist or neuro-intensivist to review the incidence of ischemic and hemorrhagic strokes in other transplant patients, e.g., these complications are more common in patients with bone marrow and cardiac transplants.

Response: We appreciate reviewer for the good suggestion. In our study, we only reported the incidence of cerebralvascular complications after OLT and did not observe the incidence of ischemic and hemorrhagic stroke in other transplant patients. But we noticed previous literatures reported that cerebralvascular complications account for 6.8% in patients after kidney transplantation\textsuperscript{[3]}, 2.9% in patients after bone marrow transplantation\textsuperscript{[4]}, 0.9% after reduced-intensity stem cell transplantation\textsuperscript{[5]} and
2% in pediatric patients after cardiac transplantation[6]. A recent brain postmortem study in pediatric patients following cardiac transplantatio reported that the incidence of cerebral infarct was 29%-41% in different primary cardiac diseases and intracranial extraparenchymal hemorrhage was 31% in obstructive lesions[7]. These data indicate cerebrovascular events, especially intracranial hemorrhage, are severe posttransplant complications which deserve more attention for the neurologists, neuro-intensivists and surgeons for organ transplantation, and more endeavours should be done prospectively to identify or avoid such complications in clinical practice. (We added some related comments in the 1st paragraph of Discussion (Page 6, Line 9-19).

Minor point: Grammatical improvements are needed. Phrasing is often awkward. Response: Thank you very much for your kind advice. We revised the grammatical and spelling errors in the resubmitted manuscript.

References


