Author's response to reviews

Title: Treatment of hepatic encephalopathy by on-line hemodiafiltration: A case series study

Authors:

Shinju Arata (s_arata@yokohama-cu.ac.jp)
Katsuaki Tanaka (k_tanaka@urahp.yokohama-cu.ac.jp)
Kazuhisa Takayama (k-takayama@star.ocn.ne.jp)
Yoshihiro Moriwaki (qgc3@urahp.yokohama-cu.ac.jp)
Noriyuki Suzuki (yqsuzuki@urahp.yokohama-cu.ac.jp)
Mitsugi Sugiyama (sugiyama@urahp.yokohama-cu.ac.jp)
Kazuo Aoyagi (urame@urahp.yokohama-cu.ac.jp)

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Author's response to reviews: see over
February 12, 2010  
Dear Editor of BMC Emergency Medicine:  
Object: MS: 1214835103063241  
Treatment of hepatic encephalopathy by on-line hemodiafiltration: A case series study  
Thank you for considering our paper. We have reviewed the above manuscript according to your reviewer’s comments.  

Reviewer's report  
Title: Artificial liver support for acute liver failure: improvement of hepatic encephalopathy treated by on-line hemodiafiltration: a case series study  
Version: 1 Date: 2 December 2009  
Reviewer: Vanessa Stadlbauer  

Reviewer’s report:  
This paper is well written and shows interesting data on the use of on-line HDF in acute liver failure. However, in my opinion, some questions need to be addressed before this article can be published.  
Major Compulsory Revisions  
1) Title: Calling on-line HDF artificial liver support is in my view a little bit far fetched. I would suggest calling the paper: Treatment of hepatic encephalopathy by on-line hemodiafiltration: A case series study  
   The title of the article has been changed as the reviewer indicates, “Treatment of hepatic encephalopathy by on-line hemodiafiltration: A case series study”.  
2) Methods: The criteria for choosing patients for this study are not completely clear. You describe that 8 patients were excluded from analysis. Why did you exclude these patients? I would suggest to also describe these patients in the study.  
   We described in detail about 8 patients who were excluded in the methods section of the text. The sentence in manuscript now appears as:  
   Three patients presented deep coma, and severe cerebral edema at the time of admission. All these 3 patients also presented multiple organ failure, and died 1, 2, and 4 days after admission, respectively. In a patient who presented hypovolemic shock due to dehydration, we could not obtain the consent because he did not have relatives, and standard medical therapy improved his
consciousness rapidly. In the remaining 4 patients who presented acute liver failure due to congestion, the treatment for congestive heart failure improved their condition with no need of ALS.

But we could not compare their data with those of study patients, because of too small sample. We show the data of 8 patients who were excluded below for your information.

**Changes of NH3 in 5 patients with congestive heart failure**

**Changes of total- bilirubin in 5 patients with congestive heart failure**
Changes of NH3 in 3 patients who died due to MOF

Changes of total-bilirubin in 3 patients who died due to MOF

3) It is unclear what happened to case 6 – how could the patient withdraw consent when he developed progressive brain edema? Please describe in more detail.

We describe what happened to case 6 in detail in the results section of the text. The sentence in manuscript now appears as:
During ALS with on-line HDF, 1 patient (Case 6) withdrew from the further investigation. He suffered from brain herniation with rapid progression of cerebral edema on the first day of admission and fell into deep coma. A flat wave was confirmed by electroencephalography performed on the second day. The prolongation of the treatment was thought to be not worthwhile. ALS was discontinued after we obtained his family’s consent. He died on the 5th day of hospitalization.

4) It would be interesting to see more data on the changes in biochemical measurements such as bilirubin and ammonia.

   We tried an analysis of changes in biochemical measurements, but we found the data was influenced by treatment, especially plasma exchange. We found that biochemical data did not show the effects of on-line HDF directory, especially in coagulation function. We added presentation of the changes in ammonia and bilirubin during the treatment according to your advice (Fig. 2).

5) It would be interesting to know whether there were any differences between patients who died and those who survived concerning biochemical measurements. You could also look at the changes in e.g. bilirubin or ammonia in these two groups. If you could also take the 8 patients that were excluded from the study and compare these data, it would give more weight to your hypothesis that on-line HDF improves HE.

   We added presentation of the changes in ammonia and bilirubin as mentioned above. But, we could not compare the data between survivors and non-survivors. Because, the treatment was continued in non-survivors until give up, as a result, the data of non-survivors were influenced by the treatment strongly.

6) I do not understand why you describe 2 patients in more detail. I don’t think that these case reports are necessary. Providing more data on the whole patient group would be more interesting (see above)

   A purpose of this study is to inspect utility of the liver compensation treatment for a patient in whom the liver function was abolished. The study was not designed to examine the impact of our ALS on survival. For this purpose, it is most useful to report clinical course in patients in whom liver function was completely abolished. In patients #14, #16, final liver volume and pathological findings could be presented. Their liver function was obviously completely abolished
proven by clinically and pathologically, whereas liver function of patients with spontaneous survival was estimated by only biochemical measurements and CT examination. We thought that their liver function may be not completely abolished even in the early phase of illness. So the improvement of their consciousness may not show the impact of our ALS only. Furthermore, as a mentioned above, it is difficult to compare the biochemical measurements between those of spontaneous survivor whose treatment reduced day by day and those of non-survivor or the patients who receive transplantation whose treatment was continued at full strength until give up or transplantation.


8) Please speak to a statistician if the student-t test is the correct test to use (do
your data pass normality testing?) And the spearman rank correlation coefficient is used to quantify the relationship between two independent variables (correlation) and not to compare paired sets of data.

We revised statistical processing thoroughly in consultation with the statistician. As for the revised statistics processing and results, it was confirmed that these were correct by the statistician. We revised figure 3 and the sentence in the methods section of the text has been changed as follows:

We performed simple linear regression analysis to determine whether the degree of encephalopathy (stage of hepatic encephalopathy and Glasgow Coma Scale), patient’s age, aspartate aminotransferase, total bilirubin, PT, and ammonia at the start of on-line HDF was associated with the number of sessions of on-line HDF from the start of the treatment to recovery of consciousness. We used Mann-Whitney U test to compare between continuous data of patients who survived hepatic failure without transplantation and those of patients who died of hepatic failure.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I declare that I have no competing interests

Reviewer’s report
Title: Artificial liver support for acute liver failure: improvement of hepatic encephalopathy treated by on-line hemodiafiltration: a case series study
Version: 1 Date: 27 December 2009
Reviewer: Nathan Davies

Reviewer’s report:
Major Compulsory Revisions
Figure 2, I’m not sure if this is significant as stated, though the line deviates significantly from zero, the regression coefficients are weak. A more cautious interpretation throughout the manuscript is warranted.

We revised statistical processing thoroughly in consultation with the statistician. As for the revised statistics processing and results, it was
confirmed that these were correct by the statistician. We revised figure 3 and the sentence in the methods section of the text has been changed as follows:
We performed simple linear regression analysis to determine whether the degree of encephalopathy (stage of hepatic encephalopathy and Glasgow Coma Scale), patient’s age, asparate aminotransferase, total bilirubin, PT, and ammonia at the start of on-line HDF was associated with the number of sessions of on-line HDF from the start of the treatment to recovery of consciousness. We used Mann-Whitney U test to compare between continuous data of patients who survived hepatic failure without transplantation and those of patients who died of hepatic failure.

Minor Essential Revisions
In the abstract, the numbers used should be qualified as mean +/- std dev on first usage.

We added “(mean ± SD)” on first usage in abstract.

CT should be listed as computerized tomography

We revised computed tomography to computerized tomography according to the advice.

Results 1st paragraph, figure 2 shows the consciousness level of the patients, not their clinical course.

We revised a title of table 2 according to the advice.

Figure 3 could have an improved legend as it the figure is not currently clear to interpret on first examination.

We revised legend of figure 3 according to the advice.

In results it is misrepresentative to suggest transplant listed pts are not non-survivors, it would be better to list all transplant patients with non-survivors and then state how many recieved organs.

To avoid misreading, in table 2, “prognosis” have been changed to “outcome”, and the sentence in the results section of the text has been changed as follows:

Of the 16 patients who recovered consciousness, 7 recovered without transplantation (spontaneous survival) and 3 died of congestive heart failure, sepsis, or respiratory failure. Two underwent living-related liver transplantation. The remaining 4 patients were candidates for liver transplantation, but these 4 patients died without transplantation because of the lack of a living donor candidate.
Discretionary Revisions
Authors should be aware of the paper by Hassanein et al (HEPATOLOGY 2007;46:1853-1862.), in this study a multicentred clinical trial was conducted to remove toxins up to 50KDa by dialysis therapy in liver disease patients. In this study there was an improvement in HE grade, but no statistical benefit in survival. There are also a number of publications in the literature that describe the role of inflammation as a component factor in the grade of HE. The authors should consider this issue in light of their study.


Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
University College London has applied for patent protection for the development of a liver support system that could be applied to patients with similar conditions to those described in this manuscript.

Reviewer's report
The article by Arata et al. describes their experience with HDF in 17 patients with acute liver failure.

1. The question is sound: Liver support for acute liver failure is urgently needed, and has been addressed in numerous publications over the past 5 decades. In this case series, the authors relate their results over a period of 7 years. Their accrual is slow, in keeping with the rarity of the disease.

There are many studies about ALS, however reliable liver support for acute liver failure was not established yet. We believe that it is useful very much to report our experience.

2. Are the methods appropriate and well described?
   a. The authors define acute liver failure as a disease lasting <24 weeks. Looking at Table 1, I suspect that some of their patients had chronic liver disease. For example, the AST in patient #3 (HBV infection) was only 29 IU/mL. He improved, and then deteriorated and died when he could not get transplanted. In our experience, acute liver failure is associated with high transaminases, and resolves completely if the patient gets over the initial crisis. I also think patient #11 had a diagnosis other than alcohol – acute alcoholic hepatitis is generally associated with low enzyme levels, and occurs on a background of cirrhosis. I suspect acetaminophen since the patient had very high enzymes and recovered spontaneously. I would like more assurance that this group really has acute liver failure.

In patients #3, acute hepatitis B infection was proven by virus marker (IgM-HBc positive). He had a suspicious sexual episode, and normal liver function had been confirmed by examination of health check every year before admission. And AST at the time of the admission was 6,430, and it decreased rapidly. On-line HDF was started 5 days after admission. Our ALS improved his consciousness, but his own liver function was abolished rapidly, so he died after discontinuation of our ALS. Final his liver volume estimated by CT was 467 mL. A patient #11 had history of alcohol abuse two days before onset. Virus markers, autoimmunity abnormality, sexual episode were not found. Of course,
there was not episode of the acetaminophen overdose or suicide attempt. His normal liver function was also confirmed health check before admission. Although the evidence that it caused by alcohol abuse was not provided, a diagnosis of the acute liver failure is clearly correct.

As for case 4,15,16 in whom AST at the time of start of ALS was low, the maximum of recorded AST of case 4,15,16 was 11800, 227, 84 each. They admitted our hospital 17, 60, 9 days after onset respectively.

We promise that we have proper clinical data to judge to be acute liver failure as mentioned above. We think that it is not so important describing an individual medical history in detail. The sentence in the methods section of the text now appears as:

Acute liver failure was also confirmed by the medical history, clinical findings, biochemical test, viral serologies, and imaging methods.

b. I would also like to voice concern about personal experience. Various techniques of filtration have proven ineffective over a very long period of time. One is reminded of a situation at King’s College in which charcoal hemoperfusion was considered so effective that a clinical trial was deemed unethical. When the trial was finally conducted, hemoperfusion was found to be no more effective than standard of care. In the final analysis, I don’t think another anecdotal account advances this field.

The amount of substitution fluid of our method is much different in comparison with the those of the previous method. We described the setting of blood purification in detail in the methods section of the text, and we revised to emphasize a difference with the conventional treatment at the point of the amount of substitution fluid in the text. The sentence in the discussion section of the text now appears as:

Previous studies which described efficacy of hemodiabsorption or hemofiltration also reported some beneficial effects on hepatic encephalopachy, but failed to demonstrate sufficient improvement of hepatic encephalopathy [19, 28, 29]. Our ALS is much different from these studies at the point of amount of substitution fluid.

In conclusion, we specified that this effect had been confirmed only in our 16 patients, and we revised the predicable expression. I hope an opportunity to publicize that a large amount of filtration is useful is given. The sentence in the conclusion section of the text has been changed as follows:
ALS with on-line HDF was effective in patients with acute liver failure; in our experience of 16 patients, the patient's consciousness could be maintained as long as the duration of ALS even in conditions in which hepatic function was considered to be completely abolished. Although further investigation is necessary to clarify whether the new ALS system improves the rate of spontaneous survival, this system may provide sufficient time to prepare for transplantation in patients with acute liver failure.

3. Are the data sound? Although I believe the outcomes as reported, I do not feel these can be generalized to other centers. For this reason, I do not believe the data are sound. I would like the authors to distinguish between patients with underlying chronic liver disease and those with true, acute liver failure. I would also like them to explain the difference between HBV and HBV carrier (Table 1).

   We have already given diagnostic criteria of the acute liver failure definitely in the methods section of the text. All of the study patients met the criteria.

   We revised to explain the difference between HBV and HBV carrier in the text according to the advice. We also revised “HBV” in table 1 to “HBV acute infection”. The sentence in methods section of the text now appears as:

   In eight patients of 10 patients who suffered from hepatitis B virus infection, the hepatitis B surface antigen and an IgM antibody to the hepatitis B core antigen were positive (acute infection). In the remaining 2 patients, the medical history that they had been healthy carriers of hepatitis B virus was proven by their medical records, and viral serologies on admission revealed acute exacerbation of hepatitis B infection. Acute liver failure developed in a patient of these 2 patients after the interruption of administration of steroids for multiple myeloma.

4. The manuscript adheres to relevant standards of reporting although many of the references are quite old. Some of these should be updated.

Liu J, Als-Nielsen B, Gluud C: Artificial and bioartificial support systems for acute and acute-on-chronic liver failure: a systematic review. *JAMA.* 2003 Jan 8;289(2):217-22., we added one of these to the reference (Ref. #34).

5. Balance: The discussion should address why many others have failed to achieve these dramatic results, and admit that this is an uncontrolled trial

We revised to emphasize a difference with the conventional treatment at the point of the amount of substitution fluid in the discussion section of the text. In conclusion, we specified that this effect had been confirmed only in our 16 patients, and we revised the predicable expression.

6. The writing is good – I congratulate the authors on their clarity.

**Level of interest:** An article of insufficient interest to warrant publication in a scientific/medical journal

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**
I do not have competing interests.
1. I was the founder of a Hepatix Inc., a bioartificial liver company - I no longer hold an interest.
2. I am a Board member of Stem Cell Innovations - no artificial liver anticipated in the near future
3. I am a Board member of HepaHope, a bioartificial liver company. HepaHope is in pre-clinical testing. I do not believe this sways my opinion of the manuscript under review.

We think that we could cope with your concerns point by point. We hope that you will find our revised manuscript suitable for publication in your journal and look forward to hearing from you.

Sincerely yours,
Shinju Arata