Author's response to reviews

Title: Effects of crystalloid fluids resuscitation on cardiac function in patients with severe sepsis

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Version: 2 Date: 20 December 2007

Author's response to reviews: see over
Dear Dr. Hans Zauner,

We thank the two reviewers for their valuable comments. We have responded to their comment item by item in the original order. We have revised the manuscript as required. Now, we are submitting the revision and responses to you. As for the English language of our paper, we have tried our best to correct and improve. If your Journal accepts our paper and if you think it necessary, we will ask Manuscript Presentation Service or English Manager Science Editing to help us edit the paper before publishing in your Journal. Would recommend one of the services for, please? We will pay them through Bank of China.

By the way, although your journal provide only electronic copy of published papers, we still wonder if we can obtain 100 off-prints of our paper printed by your journal. We are willing to pay for them too.

Yours sincerely;
Dr. Guo Qing Yin
Reviewer's report
Title: Effects of crystalloid fluids resuscitation on cardiac function in patients with severe sepsis
Version: 1 Date: 8 October 2007
Reviewer: Sean Bagshaw
Reviewer's report:
General
Thank you for the opportunity to review this manuscript. The authors have conducted and report a small randomized trial of 3 fluid types for initial resuscitation in sepsis. This is an important and active area of investigation. This is a difficult topic for study and I applaud the authors efforts. I do have a few concerns that I think the authors could address prior to publication that I will highlight below.

Major Compulsory Revisions
1. Several grammatical errors/spelling issues
   A: Thank you for your help, the errors have been corrected in the present revision, and are showed in red.

2. Manuscript - in particular the introduction/discussion is too long - I think the authors could reduce the word count considerably without compromising their central thesis.
   A: The initial manuscript was in about 4000 words only. We used more words in the manuscript of ID 9688467131517512 because we had to answer questions on hypothesis and purpose of study, diagnostic criteria of sepsis and septic shock, criteria of inclusion and rejection, design of experiment and ethically justifiable treatment design. Those questions were raised by many experts in our universities, such as pathophysiologists, physicians of critical care and statisticians who had reviewed our manuscript. We tried to shorten the text of the present revision but found it difficult to do it satisfactorily.

3. Inclusion criteria - why include acidosis in inclusion criteria if it was not necessary - there really is no logic - further - the authors have included children (aged 2, 5, 7 yrs) and I think this population is not comparable with adults (aged 80 yrs) - this may compromise the generalizability given the authors are not reporting co-morbid illness - a major factor in predicting outcome in critically ill patients - while one may argue this was an RCT and perhaps they would balance out - they do not report their method of randomization and this study was small - thus greatly increasing the probability of a type 1 error (notably already evident for age).
   A: Ok, the third inclusion criteria in the present revision has been deleted.
   in the clinical pharmic trial of chronic illness, paired grouping of randomization was preferred in order to balance the population between treated groups. However, it is rather difficult to absolutely balance population between different groups in critical care patients. In the previous studies, the severity of patients in ICU was judged by three scores on
physiological states and by the expected mortality rates of those scores at admission. The balance of population between the treated groups in critical care was estimated by the comparison of those variables of the three scores. In the present study, the severity of patients in three groups showed no significant difference by those scores (see table 1). Therefore, there was balance of population between the three groups in general, and the grouping in the present study was consistent with statistic principles. Of course, the imbalance of age in all three groups might induce a probability of a type 1 error.

4. Reporting of trial design/randomization/concealment/analysis with intention to treat - essentially all RCTs should abide by these standards (CONSORT) and I encourage the authors to revise their methods to include this information.

A: Ok. The sentences “532 patients with severe sepsis in five hospitals were diagnosed from Jun 01, 2001 to Oct 31, 2005, and 94 of 532 subjects were enrolled in the study” were added to the end of the first paragraph in ‘Material and Methods’; and the sentences “The intervention of all the 94 patients was completed in 120 min, and the observation of them was completed in 8 hours. 5 patients in the Ns group died on the 6th, 10th, 18th, 20th and 25th days following intervention; 5 subjects in the Hs group died on the 7th, 9th, 15th, 20th and 25th days; and 5 patients in the Sb group died the 6th, 10th, 15th, 19th and 25th days” were added to the first paragraph in ‘Results’. In “the CONSORT statement”, there was a description that inclusion of the participant flow diagram in the report is strongly recommended but may be unnecessary for simple trials, such as those without any participant withdrawals or dropouts. All the 94 patients in the present study completed the intervention in 120 min and observation in 8 hours, and 15 patients died from the 6th day following intervention. During the 8 hours observation, no patients were withdrawn, and the cause of those deaths was irrelevant to the initial intervention. Therefore, the inclusion of participant flow diagram was not applied to the present manuscript.

5. Data presentation - table 3 is too large - all this data should be collated – I really don't think there is a role for presenting individual patient data and it is totally redundant with table 1.

A: Ok, table 3 in the revision has been deleted.

6. Echo figures add very little and should be excluded. Similarly, figures for resprate and heart rate add very little and should likely be excluded.

A: Ok. Echo figures have been excluded in the present revision. CO, MAP, respiratory rate and heart rate are influenced by blood volume, and are main indexes of physiology during fluid resuscitation. In the design, the four indexes were simultaneously measured and registered during the 8 hours observation. In our initial manuscript, the four indexes were listed in one table. Some experts suggested us transforming the table into four figures, because figures are more understandable for readers. Therefore, we think it better to keep the CO, MAP, respiratory rate and heart rate
7. Limitations - this is a small trial - prone to both type I and type II error, it has limited power, the event rate was low (mortality rather low for septic shock), the groups were not similar at baseline and the authors did not attempt to adjust for this, the entire population has hematologic malignancy thus limits the generalizability. These factors should be discussed. Further, the authors perhaps need to ethically justify a little more clearly why they would limit therapy in these patients with septic shock for 120 min to the randomized fluid in the context of septic shock - where the worldwide standard would likely entail some form of early-goal directed therapy (i.e. no pressors or other fluids allowed). Moreover, when one estimates the amount of fluid these patients received as a bolus as perprotocol - there would be concern they may be woefully under-resuscitated. This needs to be defended and/or justified.

A:
Yes. The present investigation is with limitations, including a small trial, low observed mortality at 28 day, patients with hematologic malignancy and imbalance of age in the three groups. The balance of population between the treated groups in critical care was estimated by the comparison of those variables of the three scores. In the present study, the severity of patients in three groups showed no significant difference by those scores (see table 1). Therefore, there was balance of population between the three groups in general, and the grouping in the present study was consistent with statistic principles. Clinical trials emphasize ethical principles. To ensure a favorable risk-benefit profile, all treatment regiments must provide efficacy and limited risk, with minimal or no emergence of organ injury. Therefore, a regiment in the present study was utilized, including a bolus of 5ml/kg of various solutions at T_{0min}, no vasoactive agents or colloid before T_{120min}, a permitted use of vasoactive agents or colloid for hemodynamic stability after T_{120min}. At admission, patients with severe sepsis or early-phase septic shock were included, and subjects with last-phase septic shock characterized by coma, seizure, diffusing intravascular coagulation (DIC), pulmonary edema and anuria on admission were excluded. The patients included in trial were tolerant to crystalloid fluids resuscitation without other medicine within 120 min. All the 94 patients completed intervention in 120 min and observation in 8 hours. 15 patients in three groups died from the 6th day following intervention. The present regiment was well tolerated by the patients with severe sepsis, and was accorded with ethics.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

A:
According to Instruction for Authors BMC Infect Dis we have checked and labeled all the figures. By publishing request in BMC Infect Dis, we uploaded all the figures separately to the Journal. We named all the figures in the uploaded files and figure legends. If BMC Infect Dis accepts our paper, we will ask Manuscript Presentation Service or English Manager Science Editing to edit our paper before publishing it.
Discretionary Revisions (which the author can choose to ignore)

1. Key words - the authors mention hypotonic saline - which I don't believe they used and this should be corrected.
   A: Ok, the words, hypertonic sodium chloride, were detected in the revision.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions
Level of interest: An article of importance in its field
Quality of written English: Not suitable for publication unless extensively edited
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests.
Reviewer's report
Title: Effects of crystalloid fluids resuscitation on cardiac function in patients with severe sepsis
Version: 1 Date: 5 November 2007
Reviewer: Charles Wade
Reviewer's report:
General
The authors have conducted a study of three crystalloid solutions on outcomes of patients with sepsis. They have used well defined clinical criteria for enrollment and have conduct one of the most definitive studies to date.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

There are a number of major questions that should be addressed in the paper. The first is the selection of the patients. The authors note that patients who required vasopressors, inotropic agents, colloids or mechanical ventilation during the first two hours were “rejected” from the study (page 5). How many patients were withdrawn from each group? These type of interventions should be a major endpoint in the evaluation of a solution as they represent inadequate resuscitation and a failure of the treatment.

A:
532 patients with severe sepsis in five hospitals were diagnosed from Jun 01, 2001 to Oct 31, 2005, and 94 of them were enrolled in the study according to the criteria of Enrollment and Exclusion. All the 94 patients completed crystalloid fluid resuscitation without other medicine in 120 min and observation in 8 hours. 5 patients in the Ns group died on the 6th, 10th, 18th, 20th and 25th days following intervention; 5 subjects in the Hs group died on the 7th, 9th, 15th, 20th and 25th days; and 5 patients in the Sb group on the 6th, 10th, 15th, 19th and 25th days.

Please provide a progressive break down of your patient population in the results. How many patients were screened for the study, how many did not meet the various entry/exclusion criteria, how many were rejected from each treatment group?

A:
All the 94 patients completed crystalloid fluid resuscitation without other medicine in 120 min and observation in 8 hours.

The authors present the percentage of patients surviving for the various solutions and show no difference. The time of death should also be included. A Kaplan-Meier plot would aid in interpretation of the data. AS the treatment period was 120 min upon initial diagnosis if patients died in the first 24 hour in contrast to 30 days later the in pact of which solution was used would be different.

A:
5 patients in the Ns group died on the 6th, 10th, 18th, 20th and 25th days following intervention; 5 subjects in the Hs group died on the 7th, 9th, 15th, 20th and 25th days; and 5 patients in the Sb group died on the 6th, 10th, 15th, 19th and 25th days. The cause of those
deaths was irrelevant to the initial intervention. During 24 hours, no patients were withdrawn from the trial.

In the analysis was there an adjustment for repeated measures. However, there appears to be no group (treatment) effects but time effects. There is a question as to significance of some of the interactions. Please state the significance at the level of the interaction prior to comparison between groups at individual times.

A:
No differences were shown in CO, MAP, respiratory rate and heart rate at the same time points in all the three groups. Those data have been showed in the ‘Results’ of the manuscript. It is indicated that all the three groups improved their CO and MAP after solution resuscitation.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

A:
According to Instruction for Authors BMC Infect Dis we have checked and labelled all the figures. By publishing request in BMC Infect Dis, we uploaded all the figures separately to the Journal. We named all the figures in the uploaded files and figure legends. The errors have been corrected in the present revision, and showed in red.

Abstract: State what the normal solution is. From the methods it is assumed to be 0.9% saline.

A:
Yes, normal solution =0.9% saline chloride.

Page 3, line 1: Please clarify the patient population as sepsis is a relative low cause of death in the overall population. …account for substantial morbidity and mortality in critically ill patients admitted to an intensive care unit.

A:
Severe sepsis is a common fatal disease and is essentially an exaggerated inflammatory response. The epidemiology of severe sepsis and septic shock has been difficult to determine because of an inconsistent approach to definitions and diagnosis. Patients with sepsis account for approximately a third of hospital and intensive care unit bed days and mortality ranges from 25% to 80% [1, 2]. Because we focused our work on crystalloid fluid resuscitation for early-phase septic shock, the patients with severe sepsis and early-phase septic shock were included, but the patients with last-phase septic shock were excluded. So, total mortality rate in the three groups was 15/94 (15.96%), and was relatively low comparing with that from other ICU.

Because the introduction of manuscript was too long, irrelevant background introduction in the text was omitted. Those questions were answered in the cover letter.


Page 3, line 32: The inference here is the data on acidosis is from a clinical study but the work sited is all from animal. The authors should make this clear.
A: Pathogenesis of acidosis was generally found by animal experiment or experiment in vitro. Then those findings were cited in clinical reviews and textbooks. The references in page 3, line 32 were cited from experiment on animals. The three words ‘on critical illness’ were detected in the revision.

Page 4, line 28: Please state this as a hypothesis. Was the assumption that hypertonic solutions would improve outcome?
A: Oliveira et al have reviewed the effects of hypertonic solutions for treating the patients with severe sepsis and septic shock. The benefit of hypertonic solution resuscitation for macaque with early-phase septic shock has been demonstrated in our recent paper. Therefore, we speculated that hypertonic solution is effective on initial volume loading for severe sepsis. Furthermore, osmolality of 3.5 % saline chloride is similar to that of 5% sodium bicarbonate, and this solution was used to control osmolality.

Page 7, line 11: Figures 1 and 2 are not necessary.
A: Ok, Fig 1 and Fig 2 in the revision have been detected.

Page 7, line 12: The CO was reduced from what? Please include normal values in your population if an abnormal level needs to be stated.
A: The patients with low CO at admission were included in the study, and the change of their CO was observed during 8 hours. We focused our work on comparing CO at T_0 with those at other time points in same patient.
The sentence “At T_{min}, the CO was reduced to 3.17±0.79 L/min in the Ns group, 3.37±0.99 L/min in the Hs group and 3.34±0.65 L/min in the Sb group” was corrected as “At T_{min}, the CO was 3.17±0.79 L/min in the Ns group, 3.37±0.99 L/min in the Hs group and 3.34±0.65 L/min in the Sb group”. The words ‘reduced to’ were deleted.

Page 7, line 28: The data in figures 5 and 6 are better presented in a table as there were minimal differences between treatments.
A: CO, MAP, respiratory rate and heart rate are influenced by blood volume, and were the main indexes of physiology during fluid resuscitation. In the design, five indexes were simultaneously measured and registered during 8 hours observation. In the initial manuscript, four indexes, namely CO, MAP, respiratory rate and heart rate, were listed in a table. Some experts suggested that we transform the table to four figures, because
figures are easier to read and understand. Therefore, figures are preferred here.

Page 8, line 14: …normal saline infusion…
A: Yes, normal solution = 0.9% saline chloride.

Page 9, line 2: The statement that 3.5% sodium chloride of 5 ml/kg did not alter MAP is in conflict with the presentation in the results section (Page 7, line 22) and Figure 4.
A: Thanks. The sentence ‘3.5% saline chloride of 5ml/kg did not alter MAP and CO in patients with severe sepsis during 120 min trial in the present study’ was corrected as ‘3.5% saline chloride of 5ml/kg did not alter CO in patients with severe sepsis during 120 min trial in the present study’. The words, ‘MAP and’ were detected in the revision.

Page 10, line 20: There appears to be pronounced differences in acid-base balance based on lactate concentrations and base excess in the present study. This should be developed further. For example why is the normal group so different in lactate but the BE does not change? There is a reduction in BE with sodium bicarbonate but no change in lactate? There are explanations for the data that should be presented to the reader.
A: Base excess (BE) indicates total basic material in blood, and lactate acid is an acid material. Lactate acid change is not absolutely related to BE alteration. Sodium bicarbonate is a basic material. Sodium bicarbonate perfusion increased BE in blood, but did not change the lactate acid. The changes of BE and lactic acid in Sb groups agreed with the regulation of acid-base balance. All clinicians understand the acid-base balance following sodium bicarbonate perfusion.

Page 10, line 30: 1)…no difference between the three groups… 2) A difference in observed mortality…
A: Yes. Thank you for your correction, which we have done in the revision.

Page 11, line 31: …observation, 52 months, which could not…
A: Thanks. 52 months indicated a duration of 52 months from Jun 01, 2001 to Oct 31, 2005.

Page 11, line 35: …an invasive technique…
A: ‘…an invasive technique…..’ means that a pulmonary artery catheter was inserted into the jugular vein. This was an invasive operation.

Page 12, line 11: …normal saline solution
A: Normal saline solution = 0.9% saline chloride.
Page 12, line 12: A statement should be made that all groups improved their CO and MAP after infusion of the solutions.

A: Ok, the sentence has been added to “Key messages”.

Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An exceptional article

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.