Author's response to reviews

Title: Early utilization of hypertonic peritoneal dialysate and subsequent risks of non-traumatic amputation among peritoneal dialysis patients: A nationwide retrospective longitudinal study

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

Thank you very much for your letter and Reviewers' comments of above referred manuscript.

We have responded the comments and revised our manuscript further according to the comments. Both the revision of the manuscript and our response to Reviewers' comments point-by-point are submitted for your review.

Thank you very much for your consideration of publication of our article.

Sincerely yours,
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Reviewer: stephen riley
Reviewer's report:
Major Compulsory Revisions
I am concerned about how the 2 groups have been compared. The control group is indexed at start of peritoneal dialysis whereas the hypertonic group is indexed at the start of the hypertonic solution. My feeling is that both groups should be treated the same and indexed at the start of PD treatment. This will eliminate problems with lead time bias.

Response:
Thanks for this valuable comment. To eliminate the possible effects of lead time bias, we have re-defined the index date as the date of initiating PD in the control and in the study cohort and carried out the statistics again. New results were similar as previous results. We have replaced the tables, and figure and all associated descriptions in the manuscript.

In addition I would like to see information about how the control group was chosen from the database. There does not seem to be any attempt to age match or diabetes match the 2 cohorts - was this considered?

Response:
We choose all new PD patients during 1998-2009 without receiving hypertonic solution within the first 6 months as control group. We were unable to match age or diabetes in cohorts selection because we were afraid of establishing study cohorts with small sample sizes by doing so. We might not be able to identify the amputation at risk if we have small sample sizes. Controlling for age and diabetes in the data analysis is an alternative to prevent the disadvantage of small sample sizes.

Minor revisions
line 81 remove the word has
We have removed“ has“ accordingly.
line 82 insert "is" after and and before contracted.
We have re-written the sentence as “ is contracted with 97% of clinics and hospitals throughout the nation.”
Reviewer: Frances Game
Reviewer's report:
This is a well designed, well executed study of the association of the use of hypertonic peritoneal dialysate and subsequent limb amputation.
I have only one question and one comment. The question relates to the definition of amputation. I assume that the data relate to major, that is above ankle amputations. Minor amputations are limb sparing whereas a major amputation is done when the limb cannot be spared. I assume that the data relate to major amputations as the references are to studies that looked at major amputations, but it was not made clear.

Response:
We followed the cohorts until diagnosis and surgery for the first amputation (ICD-9-CM 785.4 and 440.24; ICD-9-CM 84.10-84.17) been made.
The ICD-9 CM 84.10 lower limb amputation, not otherwise specified
   84.11 amputation of toe
   84.12 amputation through foot
   84.14 amputation of ankle through malleoli of tibia and fibula
   84.15 other amputation below knee
   84.17 amputation above knee
Therefore, our data is related to either major or minor amputation. To make the statement clear, we have re-written the statement as” We followed the cohorts until diagnosis and surgery for the first amputation, either major or minor, (ICD-9-CM 785.4 and 440.24; ICD-9-CM 84.10-84.17) been made, withdrawal from insurance, loss to follow-up, or December 31, 2009, whichever was the latest.”

My only other point is that the authors have demonstrated an association, not causation. Perhaps the conclusion of the abstract is overstating the case a little.
Response:
Thanks. We have re-written the conclusion in the abstract as “Early utilization of HPD in PD patients is associated with increasing risk of amputation”.