

ANSWERING REVIEWERS

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Title: Cooling Dialysate During In-Center Hemodialysis: Beneficial and Deleterious Effects

Thank you for the review of our manuscript. We appreciate the thoughtful comments from the reviewers and have incorporated revisions based on these comments. In the Response below, Reviewers' comments are in **bold** followed by our response. We have also included revised sections from the paper following our responses.

Reviewer 1:

This is a review of a subject with limited number of published studies, so one expects all the existing data to be cited and reviewed in your paper. Nonetheless some of the existing studies have not been reviewed including those by Rezki et al (PMID: 17679746) and Shahgholian et al. (PMID: 22224109). - While there is a valuable systematic review published in 2006, how much your paper adds to our knowledge. If there is significant data afterwards, an update systematic review would make more sense.

We have added the Rezki, *et al* reference that you cited (PMID: 17679746) to strengthen our section on "cooled dialysate compared to other modalities used to minimize IDH." We preferred not to include the second reference (PMID: 22224109) as the methods in this paper were not as clearly defined as in other papers we cited in our minireview. For example, there was no definition of "cold dialysate" nor did the authors define what the "sodium profile 3" and "ultrafiltration profile 3" entailed. For these reasons, we preferred to focus on the data presented by Rezki, *et al* and Dheenah and Henrich in our section on "cooled dialysate compared to other modalities used to minimize IDH."

As you have pointed out, there is an excellent systematic review by Selby, *et al*, which was published in 2006. While we referenced some of their results in our minireview, we preferred to avoid re-creating their analysis for multiple reasons, including the following: First, there have been few studies since 2006 evaluating the effects of cooled dialysis on intradialytic hypotension. Performing a systematic review including the few studies published since Selby's paper would largely re-create their analysis and results. Second, the study designs and quality of the studies since Selby's publication were highly varied which further decreased the number of studies we could include in a systematic review. Selby alludes to this problem and notes that of the 22 studies included in the review, 19 had a score of 2 (per the Jadad scoring method, which scores studies on a scale from 0 to 5, with 5 indicating the highest quality). We opted not to re-create their analysis largely because we believed we would not be contributing any new findings to the current literature.

We believe that our minireview is unique to the current literature, however. To our knowledge, there has been no prior publication detailing the pros and cons of cooled dialysate using examples from the literature as support. We hope that our minireview of the literature serves as an impetus for future studies to incorporate a larger sample sizes, longer follow-up intervals, and evaluation of more variables, e.g. a direct comparison of sodium modeling and cooled dialysate and its effect on clinical measures such as interdialytic weight gain, interdialytic blood pressure control, cardiovascular and cerebrovascular events, memory, cognitive function, etc. Additionally, if largescale studies demonstrate a significant increase in quality of life measures or a significant decrease in economic burden (as evinced by decreased admissions for hypotension or by reduced frequency of nursing intervention on dialysis), this would potentially serve as a springboard to change the way intradialytic hypotension is managed by nephrologists around the world.

"A similar study by Rezki, *et al*^[22] evaluated 16 patients in a two-phase protocol. The first phase consisted of three standard HD sessions with a sodium concentration of 140 mEq/L with dialysate temperature at 37°C and served as the control for each patient. During the second phase, patients were dialyzed successively under the following conditions: fixed sodium dialysate concentration at 144 mEq/L, sodium modeling from 152 to 138 mEq/L, one hour of ultrafiltration alone followed by three hours of standard dialysis, dialysis with cooled dialysate ($T < 37^{\circ}\text{C}$), and a combination of sodium modeling with cooled dialysate. When compared to the control protocol, there was a statistically significant decrease in the signs and symptoms of hypotension and in the incidence of IDH when patients were dialyzed with sodium modeling, cooled dialysate, or the combination protocol. When compared to the control protocol, fewer medical staff interventions were required when patients were dialyzed with the combination protocol or cooled dialysate. There was no increase in subjective thirst or in interdialytic weight gain when a protocol employing sodium modeling was performed. In this study, four of the 16 patients noted shivering when dialyzed with cooled dialysate.

Both of these studies suggest that cooling dialysate temperature is as effective a method as sodium modeling when it comes to mitigating IDH. They also suggest that cooling dialysate may be poorly tolerated and associated with patient discomfort on HD. However, sodium modeling has been associated with a number of side effects including worse hypertension and increased interdialytic weight gain due to increased thirst^[23]. Whether one method is superior at reducing IDH or is better tolerated than the other remains to be seen in a larger trial with longer follow-up periods."

Reviewer 2:

Conclusion should promote and emphasize your idea, and that, conceptually, sublimates all that in one unit. It is not necessary that, in conclusion, enter further dilemmas, i.e., at this place are not necessary your comments.

Thank you for pointing this out. We have removed the following from our conclusion:

Although this has not been studied, if patients who are more satisfied with their dialysis experience with cooled dialysate, it is plausible to infer that they would in turn have improved compliance with dialysis and hence higher quality of dialysis than those patients with poorer compliance.