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The Reply

We thank Drs. Safiri and Ashrafi-Asgarabad for their interest in our study on outcomes in severe hyponatremia with desmopressin (DDAVP) usage.[1] They raise 3 issues about the methodology.

First, they suggest performing a regression analysis of outcomes in severe hyponatremia based on DDAVP usage to reduce confounding. We agree that our results may be affected by confounding and acknowledged this in our paper; however, we disagree that regression is an appropriate solution. Contrary to the authors' assertion that "many confounders could be controlled" in our study, we were unable to measure important clinical variables that could lead to residual confounding. For example, differences in rates of hypovolemia between groups could confound the results, because hypovolemia is associated with more rapid sodium correction.[2] Unfortunately, hypovolemia is challenging to abstract reliably from chart review[1] and impractical for such a large study. Although urine electrolytes can be helpful, they were not available in 36% of subjects. Importantly, multivariate models that omit relevant variables can generate biased results.[3]

Second, the authors suggest using the Mann-Whitney *U* test to compare nonnormally distributed independent samples. We agree; in fact, the Mann-Whitney *U* was what we used. The Mann-Whitney *U* test is also known as the Wilcoxon rank-sum test, which may be the source of the confusion.[4]

Third, regarding the multivariable logistic regression for the outcome of death in the hospital, the authors suggest a threshold of 10% change in odds ratio (OR) to select variables for inclusion in the model. However, several methods for variable selection exist, and there is considerable controversy about which is the most appropriate.[5] Furthermore, variables can be included in a model if they are clinically important despite not being statistically significant, so as to ensure that known predictors of the outcome of interest are included,[6] emphasizing the importance of subject-matter expertise when designing and conducting analyses.

The model in our paper was an exploratory analysis to determine whether the association of DDAVP administration with death was modified by 6 variables (age, sex, number of comorbidities, and initial levels of plasma sodium, potassium, and creatinine). We chose to present the full model with all potentially relevant variables. The adjusted OR for in-hospital death was 0.39 in the DDAVP group (95% confidence interval, 0.18-0.75). However, the unadjusted OR (which we did not report) was similar at 0.41 (95% confidence interval, 0.20-0.75), suggesting that the 6 variables do not contribute to the effect. Because we do not believe that DDAVP has a protective effect on mortality (based on detailed chart review of the deaths), there must be other unmeasured confounders driving this result. For example, it is possible that DDAVP is given more often to healthier patients and less often to unhealthy patients such as palliative patients.

While we agree that it is sometimes desirable to eliminate variables from a model, we do not believe that this applies to all cases. Our model had poor explanatory power due to residual confounding; using variable selection to make the model more parsimonious would not make it any more useful.

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