LETTER IN RESPONSE TO: "ASSESSING EFFICACY OF LIPID IN UNSTABLE, NON-LAST OVERDOSE PATIENTS"

We thank Dr. Weinberg for his comments and the opportunity to clarify the important issues that he has raised.

While a comparison to a historical cohort would have been helpful, there were several factors that led us to publish a case series. First, given the heterogeneity of our study population and the rarity with which life-threatening overdoses present, we felt it would be difficult to find appropriately matched historical controls. Moreover, our intent was for it to serve as both an addition to the existing case-based literature on intravenous lipid emulsion (ILE) and a catalyst for further investigation into the efficacy of ILE.

We disagree with Dr. Weinberg's comment regarding a "cherry-picked" group. Our primary analysis was a mixed-effects model using all data. At one hour, the estimated increase in mean arterial pressure (MAP) was 13.79 mm Hg (95% CI 1.43–26.15). This analysis did not provide evidence that the MAP had increased by at least 10 mm Hg during the first hour. The estimated increase using only values at one hour was 17.22 mm Hg, which was significantly larger than 10 mm Hg because of an extreme value. As tests of means are more easily understood by many readers than mixed-effects models are, we wanted to provide both summaries and explain how they might differ from the primary analysis. In particular, one extreme value does have considerable influence on the one-sided *t*-test results, but we are not suggesting that the patient be removed from the primary analysis.

We wanted to provide a full analysis by showing the effect of an extreme value and reported a loss of statistical significance if the value was removed. This loss of statistical significance was in relation to our 0.05 threshold, a commonly used value. Some authors would report a *p*-value between 0.05 and 0.1 as "some evidence of statistical significance." We could have stated this change as some evidence of statistical significance, but larger than the 0.05 threshold. We do not feel underpowered is a more accurate description. We did not conduct power calculations, and we do not know the size of the effect that either the full sample or the full sample without the extreme value would be able to detect.

The statement "It is not valid to use a *t*-test with a single group" is incorrect. A one sample *t*-test assesses if a sample mean is different from a particular value. That assessment is exactly the assessment we conducted (i.e., the particular value of interest was 10 mm Hg). The test was one-sided because we wanted to test "at least" 10 mm Hg. Hence, the change in MAP was not being compared to a group but rather to the particular value, 10 mm Hg. Further, the sample mean change in MAP is an estimate, and a hypothesis test determines whether the sample data would lead to the rejection of the null hypothesis. While the sample mean MAP change may be >10 mm Hg, the sample data may not lead to a statistically significant *p*-value from a one-sided *t*-test that assessed if the change in the MAP was at least 10 mm Hg. Statistical tests are required to draw conclusions beyond a sample. We have drawn conclusions based on appropriate statistical methods and reported the actual outcomes.

Finally, regarding the inclusion of non-standard doses of ILE, we felt it was important to keep these patients in our analysis because of its applicability to how ILE is used in reality. This reality is illustrated in our data. Despite an educational campaign regarding dosing and the indications for ILE, there was still significant variability in dosing. We felt that it was important to include this variability in our analysis to account for how ILE is currently applied in clinical practice by physicians.

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