ASSESSING EFFICACY OF LIPID IN UNSTABLE, NON-LAST OVERDOSE PATIENTS

To the editor: I applaud the efforts of Mithani et al.[1] in "A cohort study of unstable overdose patients treated with intravenous lipid emulsion therapy" for addressing the effects of infusing lipid emulsion (ILE) in very ill overdose patients. I agree with their conclusion that further studies are needed to assess efficacy and determine the best ILE treatment regimes. However, two specific and related weaknesses undermine the clinical relevance of their work and its conclusions.

Firstly, the lack of matched controls precludes any determination of efficacy in what is essentially an outcomes-oriented case series. I encourage the authors to identify historical controls in the same dataset. The degree of clinical heterogeneity among patients, overdose drugs, and treatments dictates that stratification and propensity matching of control patients to those receiving ILE are necessary to allow meaningful between-group comparisons for key outcomes.

Secondly, the authors' statistical analysis raises further significant concerns. In particular, their use of $p > 0.05$ in a "cherry-picked" group leads to a conclusion that is at odds with the data. They used change in mean arterial pressure (MAP) as their key metric but excluded an ILE-treated patient with a greater-than-expected response, while including a patient who received a lipid infusion without the loading bolus – a substandard treatment that would substantially prolong the need to reach therapeutic blood triglyceride levels. In all, a third of their patients received non-standard or unspecified lipid doses. What information beyond a description of widely varying practice patterns is gained by keeping these patients in the analysis? Does combining data from heterogeneous treatment groups teach us anything about efficacy?

Nevertheless, the authors report an estimated MAP increase of 13.79 mm Hg (95% confidence interval 1.43 – 26.15), and when the "last available single MAP value carried forward to 1 hour, the mean change in MAP was 17.22 mm Hg ($n = 23$; median 13.33; $p = 0.044$)." Further, more than half of the latter group had at least a 10-mm Hg increase following ILE, the authors' threshold for ascribing an effect. Removing the one extreme value resulted in a mean MAP change of 14.52 mm Hg with $p = 0.085$, which the authors described as indicating a loss of statistical significance. Isn't "underpowered" a more accurate description? Most problematic is the ambiguity around the statistical comparisons. It is not valid to use a t-test with a single group. However, the statement, "… a one-sided t-test assessed if the change was at least 10 mm Hg" does not specify the comparison being made. It is never clear, for any MAP change, exactly what the reported *p*-values refer to since the comparators are not specified. Thus, although each analysis indicates a change in MAP > 10 mm Hg, the authors use an unspecified group (without reporting statistics) to claim no effect. This leads to the appearance of reporting a desired outcome instead of the actual outcome.

It is encouraging that Mithani et al. found ILE associated with 69% survival in a group of patients who had already failed standard resuscitation. Moreover, 88% of survivors returned to baseline neurological status at discharge. This is not a trivial finding, and I agree with the authors that it warrants future study given the concern over neurological outcome following pressor therapy during resuscitation.[2] Interestingly, this adds to evidence of a reliable clinical benefit for ILE because both the change in MAP and the improved neurological status comport with previous studies of ILE in non-local anesthetic systemic toxicity (LAST) overdose. For instance, Cave et al.[3] reported from a registry that ILE improved median systolic blood pressure (from 70 to 90 mm Hg) and that, among patients with cardiovascular collapse who failed standard resuscitative efforts, 63% survived after ILE. They also found a median improvement in the Glasgow Coma Scale of two points for patients presenting with altered mental status, a finding supported by two randomized controlled trials[4,5] that found accelerated neurological recovery after ILE versus control treatment.

It is important to know whether ILE improves outcomes in severely ill patients with xenobiotic poisoning and what timing and dose regimen of lipid most improve the likelihood of neurologically intact survival, clearly a more important outcome than a 10-mm Hg change in MAP. This is

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a tractable undertaking, and Mithani et al. have taken early steps in this direction. Adding matched controls and using proper statistical methods to assess changes in relevant metrics will take them a big step closer to this goal.

Conflicts of interest:

GW is a director, officer, shareholder and paid consultant for ResQ Pharma, Inc.

Guy Weinberg, MD

Department of Anesthesiology Physician, University of Illinois at Chicago College of Medicine and Jesse Brown VA Medical Center, Chicago, IL.

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