The Effect of Residual Confounding on Mortality in Metformin-Associated Lactic Acidosis

Josh J. Wang¹ · Robert S. Hoffman¹

Received: 3 March 2020 / Revised: 3 March 2020 / Accepted: 13 March 2020 / Published online: 26 March 2020
© American College of Medical Toxicology 2020

We read with interest the recent systematic review of metformin-associated lactic acidosis (MALA) [1]. While the prognostic utility of nadir pH and peak serum lactate concentration for death appeared poor, we agree with the authors' statements that these results were likely affected by "misidentification of MALA for another disease process and vice versa, confounding by selection and reporting bias, and treatment intensity." As such, we were surprised by the authors' definitive conclusion that there are *no* data to support the role of pH or lactate in prognosticating MALA. We suspect that this seeming paradox is due to a failure to control for the aforementioned methodologic limitations rather than a true effect.

MALA is defined by acidemia, hyperlactatemia, and metformin exposure [2, 3]. Given the ubiquity of all three conditions, mild cases are likely missed while severe cases may not survive to receive the diagnosis. Indeed, mild cases were missing from this report (37% case fatality rate, median pH 7.02, median serum lactate 14.5 mmol/L). This likely biases any subsequent association between pH, lactate, and mortality towards the null. Furthermore, it was unclear how many of the included patients had plasma metformin measurements to confirm exposure. Finally, the authors do not include the confounder of treatment. If there is a belief that hemodialysis alters prognosis [3], then some of the sickest patients were treated further biasing towards the null.

While the receiver operating characteristic (ROC) curves for both pH and lactate suggest little prognostic value, we question the validity of these findings and kindly ask the authors to clarify the following: What proportion of patients had

acute, acute on chronic, and chronic metformin overdose? What proportion of patients had extreme pH and serum lactate concentrations outside of assays' analytical range and how did the authors deal with such values in subsequent calculations? What was the presenting kidney function of survivors and decedents? What proportion of patients experienced their nadir pH and peak serum lactate concentration before treatment versus after? Lastly, how many patients were treated with bicarbonate, hemodialysis, hemoperfusion, and mechanical circulatory support, and why were treated and untreated patients analyzed as one?

We look forward to the authors' reply and thank the journal for the opportunity to discuss this important topic.

Sources of Funding None

Compliance with Ethical Standards

Conflicts of Interest None

References

1. Blumenberg A, Benabbas R, Sinert R, Jeng A, Wiener SW. Do patients die with or from metformin-associated lactic acidosis (MALA)? Systematic review and meta-analysis of pH and lactate as predictors of mortality in MALA. *J Med Toxicol.* 2020;16(2): 222–229.
2. Luft D, Deichsel G, Schmülling RM, et al. Definition of clinically relevant lactic acidosis in patients with internal diseases. *Am J Clin Pathol.* 1983;80:484–9.
3. Calello DP, Liu KD, Wiegand TJ, Roberts DM, Laverne V, Gosselin S, et al. Extracorporeal treatment for metformin poisoning: systematic review and recommendations from the Extracorporeal Treatments in Poisoning Workgroup. *Crit Care Med.* 2015;43(8): 1716–30.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Supervising Editor: Lewis S. Nelson, MD

✉ Josh J. Wang
joshwang.md@gmail.com

¹ NYU Langone Health, Ronald O. Perelman Department of Emergency Medicine, Division of Medical Toxicology, New York, NY, USA