Better Studies Are Needed to Guide Treatment of Carbon Monoxide Poisoning

To the Editor:

In their discussion of the treatment of carbon monoxide (CO) poisoning, Rose and colleagues state that "... hyperbaric oxygen significantly reduces the permanent neurological and affective effects of CO poisoning" (1). In support of this, they cite a randomized trial by Weaver and colleagues (2), which they characterize as the best available evidence because it fulfills all Consolidated Standards of Reporting Trials criteria. This characterization, however, overlooks multiple limitations we and others have detailed previously (3, 4).

Arguably the most serious of these is the evolution of the primary outcome from the study's inception to its final publication. As the investigators themselves made clear in early descriptions of the trial (5, 6), the original primary outcome was delayed neurologic sequelae defined by stringent criteria. In contrast, the eventual publication (2) evaluated all neurologic sequelae, using less stringent cutoffs and incorporating nonspecific symptoms in their definition. We subsequently demonstrated that the study by Weaver and colleagues (2) would have found no statistically significant benefit of hyperbaric oxygen had the original primary outcome been retained, and that further assumptions applied during the analysis phase conferred unwarranted statistical significance to outcomes at 6 and 12 months (3, 4).

We have raised these concerns previously, including in this *Journal* (7), only to have leaders in the field of hyperbaric medicine sidestep rather than acknowledge them (8). This is not a pedantic matter. Carbon monoxide poisoning remains a major cause of poisoning-related morbidity and mortality, and the available evidence does not make clear whether hyperbaric oxygen improves clinically meaningful outcomes and, if so, which patients are most likely to benefit. A properly designed randomized trial is needed to answer these questions. Until the limitations of the study by Weaver and colleagues (2) and the resulting clinical equipoise are openly acknowledged, such a trial is unlikely. In the meantime, the treatment of CO poisoning will remain guided by opinion rather than by sound evidence. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Reply

From the Authors:

We appreciate the comments of Dr. Juurlink and colleagues, who summarize the limitations of the currently available clinical trials data supporting the efficacy of hyperbaric oxygen therapy (HBO₂). Although there are several clinical trials testing the efficacy of HBO₂, pooled analysis is difficult owing to heterogeneity among the different trials (1, 2). The Weaver and colleagues study is the best designed trial and most resembles clinical practice (3).

Although we do not provide an in-depth critical review of the Weaver and colleagues trial (3), we certainly recognize the urgent need for new therapies for carbon monoxide (CO) poisoning (4).

Even if HBO₂ is as effective in general clinical practice as in the Weaver and colleagues trial—a number needed to treat of five to prevent one case of delayed neurologic sequelae—there would still be thousands of survivors of CO poisoning suffering from significant long-term morbidity every year (1, 3). We thus have focused much of our discussion on new therapies being developed that can be used at the point of care (1). One of the limitations of HBO₂ is treatment delay due to the transportation of a patient to a facility capable of emergent therapy. The development of antidotal agents, such as CO scavengers or hydroxocobalamin, that could be delivered on site or en route to a hospital would drastically cut time to treatment, if proven successful in further studies (1, 4, 5).

Our research team has recently published studies evaluating a potential antidote, based on a mutationally engineered recombinant neuroglobin molecule that binds CO with approximately 500 times higher affinity than hemoglobin binds CO (4). This molecule clears

CO *in vitro* from human red blood cells and *in vivo* from mouse blood with a half-life of only 25 seconds, compared with even the shortest half-life using HBO₂ of 20 minutes (1, 4). The antidote improved cardiovascular function, lactic acid clearance, and survival in a lethal CO poisoning mouse model (4). We are hopeful there may one day be improved strategies to address the important public health issue of CO poisoning. Overall, we strongly agree that further research in this area is necessary. ■

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