Hyperbaric oxygen should not be used routinely for carbon monoxide poisoning: CON

David Juurlink[1]

[1]Institute of Clinical and Evaluative Sciences

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David N. Juurlink, MD, PhD

Departments of Medicine, Pediatrics, and Health Policy, Management and Evaluation, University of Toronto, the Ontario Poison Centre, and Sunnybrook Research Institute

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Correspondence:

David Juurlink

Sunnybrook Health Science Centre G-106

2075 Bayview Avenue

Toronto Ontario

Canada M5N 1P6

T: 416 480 4835

E: david.juurlink@ices.on.ca

Disagreement about the role of hyperbaric oxygen (HBO) for carbon monoxide (CO) poisoning is nothing new, but there are several related points on which most everyone will agree. First, CO is an insidious and globally significant poison, killing upwards of 40,000 people and sickening perhaps a million others around the world each year.(1) This fact alone highlights why resolving disagreement about its treatment should be a priority. Second, absent a clear exposure history, the diagnosis of CO poisoning can be challenging because symptoms are nonspecific, ranging from headache, fatigue and nausea to chest pain, dyspnea, confusion and coma. Third, removal from exposure and administration of supplemental oxygen are the cornerstones of treatment, although it warrants mention that even oxygen itself has not been rigorously evaluated as a therapy.(2) Fourth—and this is an especially important point—the pathophysiology of CO poisoning is more complex than generally appreciated. While it is widely known that CO displaces oxygen from hemoglobin and shifts the oxygen-hemoglobin dissociation curve to the left, impairing peripheral oxygen delivery, it also generates reactive oxygen species,(3) inhibits cellular respiration by binding to mitochondrial heme, and directly peroxidates brain lipids, leading to neuroinflammation.(4)

Clinicians who treat CO poisoning know that supplemental oxygen hastens the elimination of carboxyhemoglobin, and that HBO hastens it further yet. The elimination half-life of carboxyhemoglobin while breathing room air averages about 6 hours, falling to around 75 minutes when breathing 100% oxygen ("normobaric oxygen", NBO) and about 22 minutes when breathing 100% oxygen at 3 atmospheres.(5)

But because clinicians tend to anchor their diagnostic and mechanistic thinking around carboxyhemoglobin, it can be tempting to infer that HBO *must* be beneficial simply because it promotes carboxyhemoglobin elimination. This reasoning oversimplifies CO poisoning, reducing it to a functional anemia akin to methemoglobinemia and discounting entirely its other mechanisms of toxicity.

Is hastening the elimination of carboxyhemoglobin intuitively appealing? Of course. But neither the carboxyhemoglobin concentration itself nor the rate of its disappearance is a clinical outcome. The carboxyhemoglobin concentration should be viewed in much the same way as an LDL-cholesterol concentration: a laboratory value that can be useful for diagnosis and lowered by medical intervention. In patients with CO poisoning, the goal of treatment is not simply lowering that number; the goal is the reduction of morbidity. And in the case of CO poisoning, morbidity is chiefly neurologic.

At issue, then, is whether HBO reduces the risk of neurologic sequelae compared to standard treatment with 100% oxygen. And it is on this point where champions and skeptics of HBO disagree.

As with any medical intervention, there is only one way to establish whether HBO does what is claimed of it: through well-designed randomized controlled trials (RCTs). The clinical utility of HBO simply cannot be divined from a collection of cases,(6) and certainly not from observational studies, which are easy to perform but hopelessly undermined by selection bias and information bias when the issue is one of treatment effects. The fact that observational studies cannot quantify the utility of HBO has not, however, stopped researchers from trying. Several such studies have been published using administrative data, generating conflicting results(7, 8) along with estimates of effect size that are frankly impossible. Simply put, database studies purporting to evaluate the effect of HBO are not to be taken seriously.

What then do the available RCTs tell us about the value of HBO in CO poisoning? Regrettably, not much. The strengths and weaknesses of the various trials have been reviewed in detail by Buckley and colleagues.(9, 10) But in a commentary advocating against the routine use of HBO, it's worth focusing specifically on the RCTs widely regarded as demonstrating its benefit.

The first of these, published in 1995 by Thom and colleagues,(11) involved 65 patients with mild to moderate CO poisoning presenting within 6 hours. Patients received either 100% oxygen at ambient pressure until asymptomatic (n=32) or HBO for two hours (n=33), by which time symptoms had resolved in all patients. The primary outcome was delayed neuropsychologic sequelae (DNS), defined as new symptoms developing after oxygen therapy *plus* deterioration from baseline in one or more neuropsychologic subtests. (The concept of delayed neurologic sequelae—symptoms developing after a period of normalcy—will become especially relevant later in this commentary). After excluding five patients lost to follow-up, Thom and colleagues identified DNS in 7 of 30 patients treated with NBO and 0 of 30 patients treated with HBO ($P<0.05$).

Setting aside the small size of the trial, three aspects warrant special emphasis. First, treatment allocation was not concealed; patients and investigators alike knew who had spent time in a chamber and who had not. Second, as Buckley has observed, outcomes were assessed by "clinicians who had been on the record for many years in support of HBO for CO poisoning."(9) Third, in 1992 the investigators presented an interim analysis of the study, reporting DNS in 4 of 29 subjects treated with NBO and 0 of 29 subjects treated with HBO (along with a P value of <0.005, a clear statistical impossibility.)(12) Thereafter, the trial was terminated after recruitment of just seven additional patients, with all three subjects newly recruited to the NBO arm developing DNS. Termination at this stage is remarkable if not curious. While this pattern of outcomes in the NBO arm before and after the interim analysis could conceivably represent the play of chance ($P=0.007$; Fisher's exact test), termination at this stage greatly exaggerated the apparent treatment effect. Moreover, the investigators did not adjust for multiple comparisons. Had they done so, the trial's overall result would not have been statistically significant.

The second positive trial—indeed, the one typically cited as definitive by proponents of HBO for CO poisoning—was published by Weaver and colleagues in 2002.(13) At first blush, the appeal of this study is evident: it was a multicentre randomized trial published in the New England Journal of Medicine, it enrolled 152 patients with a range of poisoning severity, it employed "sham dives" in which subjects in the

control (NBO) arm received 100% oxygen in a hyperbaric chamber, and outcome assessors were blind to treatment allocation. The study also suggested an impressive effect of HBO: at six weeks, cognitive sequelae were identified in 25% of those treated with HBO compared with 46% of those treated with NBO.

But scratch beneath the surface and several problems with the study quickly become evident. A detailed exposition of these is given by Buckley and colleagues,(9) with the key elements being baseline imbalance between treatment groups, a high likelihood of unblinding, biased handling of missing data, and repeated alterations of the primary outcome.

In the study by Weaver and colleagues, important differences between treatment groups were evident at baseline, with those in the NBO arm having far longer average exposure to CO (22 vs. 13 hours) and nearly four times the prevalence of cerebellar dysfunction (15% vs. 4%) than those in the HBO arm. The latter observation is especially relevant because two of the six neuropsychological tests defining the primary outcome involved "trail-making", which might be sensitive to clinically evident cerebellar signs. This apparent failure of randomization is compounded by the virtual certainty of unblinding: in the first interim analysis, the investigators reported that one group of patients was four times more likely than the other to be intolerant of the hyperbaric chamber.(14) There can only be one interpretation of this. Indeed, in the final publication, failure to complete the chamber sessions was much more common in the HBO group (18.4%) than the NBO group (3.9%).

Biased handling of missing data is apparent in the imputation of neurologic sequelae to patients with no outcome data at 6 weeks, including 4 of 76 patients (5.3%) in the NBO group and 1 of 76 patients (1.3%) in the HBO group. The wellbeing of these five patients was by definition unknown, and imputing the presence of neurologic sequelae necessarily inflated the apparent effect of treatment.

But arguably the most serious problem with the Weaver study is the evolution of the primary outcome over time, from one seemingly destined to show no benefit from HBO to one that did. The investigators' own writings from make this clear. Their original intent, reported in the first interim analysis presented in 1995, was to evaluate the effect of HBO on the incidence of *delayed* neurologic sequelae, defined exclusively by neuropsychiatric testing.(14) They reaffirmed this that same year, writing "Our major question is, does HBO reduce the incidence of delayed neurologic sequelae (DNS)?"(15) Yet nowhere in the final publication were rates of DNS reported. Instead, the eventual primary outcome consisted simply of "cognitive sequelae," defined using less stringent neuropsychiatric test cutoffs than originally planned, and newly incorporating nonspecific symptoms in its definition. In essence, a secondary outcome was elevated to primary, while the original primary outcome was simply discarded.

The investigators' decision to change the primary outcome has never been publicly acknowledged, let alone justified. Confronted on this point years later, leaders in the field of hyperbaric medicine have repeatedly chosen to sidestep the issue rather than address it.(16, 17)

Notwithstanding its shortcomings, the study by Weaver et. al continues to be portrayed as definitive evidence of the benefit of HBO in CO poisoning.(18) For a moment, set aside the various concerns—the baseline differences between groups, the early unblinding, the dubious handling of missing data, and alteration of the primary outcome—and consider the following question: Despite these limitations, all of which favour the active treatment arm, what do the study's findings suggest about the objective effects of HBO in patients with CO poisoning? The figure below, reproduced from Buckley et al.(9), give us some idea.

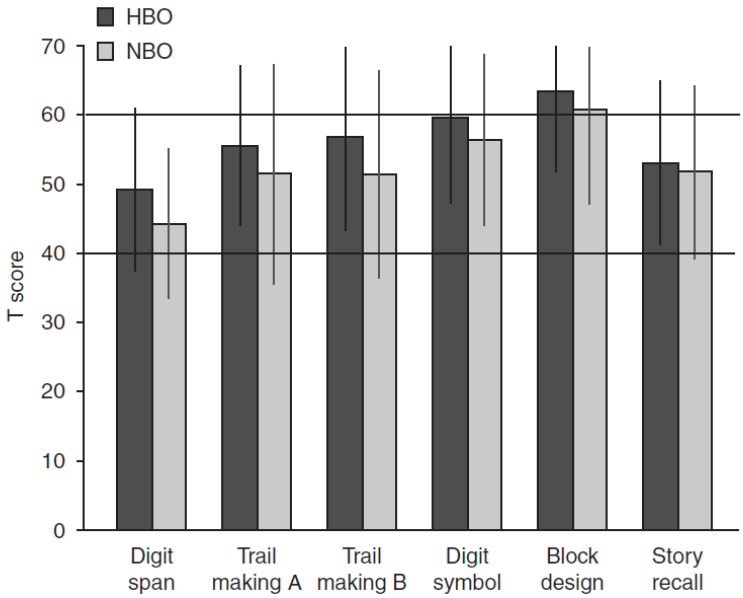

Fig. 2. Neuropsychological test T scores (population norm is 50, normal range shown by horizontal lines) and standard deviations at 6 weeks (time of primary outcome) in the study by Weaver et al.[9] **HBO** = hyperbaric oxygen; **NBO** = normobaric oxygen.

Not only were the average subtest scores no different in patients treated with HBO and NBO, the average performance of patients who received NBO was normal or above normal in every domain. Recalling that the original primary outcome was DNS defined solely by neuropsychological testing, the figure makes clear that the study would have been resoundingly negative had the original outcome been retained.

In short, despite their positive framing, the studies of both Thom and Weaver could, for different reasons, be legitimately interpreted as negative. But even when viewed as positive, they do not provide compelling evidence of benefit from HBO.

Where does this leave us? It should not lead us to conclude that HBO has no role in the management of CO poisoning. There are clearly grounds to speculate that it might. If so, the effect is likely to be small.(2) The available data do not tell us which patients are most likely to benefit, how much real benefit they might reasonably expect from treatment, what the optimal HBO regimen might be, or whether the benefits of therapy justify the potential harms and costs, since treatment sometimes entails the transport of patients over long distances to a hyperbaric chamber.

Every day, thousands of patients around the world are poisoned by carbon monoxide. Some die in the prehospital setting, but many more present in need of treatment. Clinicians who elect to treat them with HBO do so in the hope that it might help, not because they know it will—operating, as Seger puts it, on nothing more than informed guesswork.(19) This same phenomenon plagues much of clinical toxicology, but in this instance the problem is hardly an insoluble one. There is ample justification for a large, multicentre RCT of HBO in CO poisoning to answer, once and for all, the important questions that remain unanswered.

Such a trial is not only justified, it is exigent. Yet we face a formidable barrier to its implementation—one that was articulated more than 15 years ago(9) and must be articulated yet again. For such a trial to come to fruition, we must help those who hold the keys to the hyperbaric chambers understand that the evidence for HBO in CO poisoning is not as compelling as they would believe.

If, another 15 years from now, we find ourselves no further ahead on this issue, it will represent not only a

missed opportunity to properly evaluate a potentially useful treatment relevant to countless patients around the world each year, it will constitute nothing less than a monumental failure of the field of hyperbaric medicine.

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