REVIEW

Carbon monoxide poisoning: interpretation of randomized clinical trials and unresolved treatment issues

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Hampson NB, Mathieu D, Piantadosi CA, Thom SR, Weaver LK. Carbon monoxide poisoning: interpretation of randomized clinical trials and unresolved treatment issues. Undersea Hyper Med 2001; 28(3):157–164.— Since hyperbaric oxygen therapy (HBO_2) appeared as a treatment for CO poisoning in 1960, whether and when to use it for CO poisoning have often been debated. HBO_2 has been advocated to treat severe CO poisoning to limit delayed and permanent neurologic sequelae. Initially, inferences about efficacy were based on clinical experience and uncontrolled studies, but since 1989, six prospective clinical trials have been reported comparing HBO_2 and normobaric O_2 administration to treat patients with acute CO poisoning. Of the six trials, four found better clinical outcomes among patients receiving HBO_2 while two have shown no treatment effect. The most recent and best-designed randomized controlled clinical trial, performed in Salt Lake City, supports the efficacy of HBO_2 in severe acute CO poisoning in accordance with scientific rationale and clinical experience. However, a number of important issues remain for future investigation, which could be addressed in a large multi-center trial. Such a trial should attempt to determine the optimal number of HBO_2 treatments and the maximum treatment delay from CO poisoning for HBO_2 to provide efficacy in patients with specific risk factors for a poor outcome.

carbon monoxide, delayed neurologic syndrome, brain injury, hyperbaric oxygen, oxidative stress

The toxic effects of carbon monoxide (CO) poisoning on humans are initiated by the hypoxic stress of carboxyhemoglobin (COHb) formation, which decreases oxygen delivery to the tissues. However, the level of COHb does not predict the development of signs and symptoms of injury, particularly with respect to the brain (1–4). Non-hypoxic mechanisms including oxidative stress, related in part to cellular uptake of CO, have been implicated in the pathogenesis of brain injury (5–7). The cornerstone of treatment of CO poisoning is supplemental oxygen, which hastens dissociation of CO from hemoglobin and improves tissue oxygenation. Hyperbaric oxygen (HBO_2) causes COHb to dissociate at a rate greater than that achieved by breathing sea level (normobaric) O_2 (8,9). In experimental CO poisoning, treatment with HBO_2 but not normobaric O_2 (NBO_2) has other beneficial effects on the pathophysiology of central nervous system (CNS) injury. These include improved mitochondrial oxidative metabo-lism (10), inhibition of lipid peroxidation (11), and inhibition of leukocyte adherence to injured microvessels (12). Animals poisoned with CO and treated with HBO_2 also have more rapid improvement in cardiovascular function, fewer neurologic sequelae, and better survival (13,14).

Whether to use HBO_2 and, if so, when to use it for CO poisoning has been debated for many years. Since HBO_2 first appeared as a treatment for CO poisoning in 1960 (15), treatment guidelines have been developed on the basis of experience. HBO_2 has been advocated to treat severe CO poisoning to limit delayed and permanent neurologic sequelae. Most of the inferences about efficacy have been based on clinical experience and uncontrolled studies. In one study, the incidence of delayed neuropsychological syndrome (DNS) after CO poisoning was less in patients treated with HBO_2 compared to NBO_2, despite a greater number of severely poisoned patients in the former group (16). Lower morbidity and mortality in patients treated with HBO_2 also were suggested by comparing outcome in large cohorts of CO-poisoned patients treated at medical centers with chambers to those managed at centers without hyperbaric facilities (17,18). The benefit of HBO_2 also correlated with the timeliness of treatment, as severely poisoned patients reportedly fared better when HBO_2 was given within 6 h of the end of the CO exposure (19). Finally, benefit of multiple HBO_2 treatments was suggested by a study that found that CO-poisoned patients receiving two

or more treatments had fewer neuropsychological abnormalities than those treated only once (17).

In the late 1980s, hyperbaric medicine came under criticism for lack of prospective controlled studies supporting use of HBO_2 to treat human disease, including CO poisoning (20). Partly in response to such criticism, prospective studies have been undertaken comparing HBO_2 and NBO_2 for treatment of acute CO poisoning. As of this year, the results of six prospective clinical trials have been reported comparing these two routes of O_2 administration to treat patients with acute CO poisoning. Four of these have been published in peer-reviewed journals (21–24) and two in abstract form (25,26). Of the six trials, four have demonstrated better clinical outcomes among patients receiving HBO_2 (22,23,25,26), while two have shown no treatment effect (21,24).

SUMMARY OF RANDOMIZED CONTROLLED TRIALS (RCT) IN CO POISONING

The first prospective study of CO-poisoning by Raphael et al. from Paris in 1989 (21) randomized 343 patients without loss of consciousness (LOC) to receive either 6 h of NBO_2 or 2 h of HBO_2 (2.0 atm abs) plus 4 h of NBO_2. In a second arm of the study, 286 patients with LOC were randomized to one HBO_2 treatment session or two sessions at 2 atm abs. No difference in outcome was detected between the randomized treatment groups in either arm of the study however residual neuropsychological effects were high in all four groups (32–34% without LOC and 46–48% with LOC). The study was criticized for using overly broad inclusion criteria, an inadequate regimen for HBO_2, long treatment delays, and weak outcome measures (27,28). Although the Raphael study (21) was heavily criticized on multiple points of design, it was a catalyst for the HBO_2 community to launch better-designed RCT of treatment of CO poisoning.

The second prospective trial was also performed in France (22). It randomized 26 non-comatose patients with acute CO poisoning to receive NBO_2 (100% O_2 for 6 h, followed by 50% O_2 for 6 h) or HBO_2 (2 h at 2.5 atm abs, followed by 4 h of 100% NBO_2, followed by 6 h of 50% NBO_2). Poisoning was accompanied by LOC in a majority (65%) of the patients. Outcome measures included symptoms, electroencephalogram, and cerebral blood flow responses to acetazolamide administration. A significant benefit at 3 wk was seen in the HBO_2 treatment group ($P \leq 0.02$). Limitations of this trial included small size, inadequate allocation concealment and the use of surrogate outcome measures.

The third trial was performed in the United States at the University of Pennsylvania (23). It randomized 60 patients with mild CO poisoning, excluding those with history of unconsciousness or cardiac compromise, to treatment with HBO_2 (30 min of O_2 breathing at 2.8 atm abs, followed by 90 min at 2.0 atm abs) vs. NBO_2 administration until relief of symptoms. Patients were followed with serial neuropsychological testing in an attempt to detect development of delayed neuropsychological sequelae. DNS developed in 7 of 30 patients (23%) treated with NBO_2 and in no patients treated with HBO_2 ($P < 0.05$). Among those developing DNS, impairment persisted for an average of 6 wk and often interfered with normal daily activities. The trial was stopped early due to a treatment advantage in the HBO_2 group.

A fourth randomized trial performed in Australia by Scheinkestel et al. (25) randomized 191 CO-poisoned patients of different severity to daily HBO_2 (3.0 atm abs for 60 min) with intervening high flow O_2 for 3 or 6 days vs. high flow NBO_2 for 3 or 6 days. The outcome measure was neuropsychological testing after treatment and 1 mo later. Of seven tests performed, only one was significantly different between the groups at the end of treatment (Rey auditory learning verbal test), in favor of NBO_2 treatment. No differences between the groups were seen 1 mo later. Flaws in the design and execution of this study, however, make it impossible to draw meaningful conclusions from the data (29,30). For example, the CO poisonings were suicide attempts in 69% of the cases, and half of the patients had also ingested alcohol or other drugs. The presence of depression and psychoactive substances in many of the patients may have confounded the results of neuropsychological testing. Neither the HBO_2 nor the NBO_2 protocol followed standard treatment recommendations and both regimens were potentially toxic. The total dose of O_2 over the unusually prolonged period of treatment differed by only 7% between the two arms of the study. Finally, less than half (46%) of the patients completed the follow-up examination at 1 mo.

Two randomized trials have been reported only in abstract form at the time of this writing. The study of Mathieu performed in France is the only multi-center study of treatment of CO poisoning (25). At an interim analysis, 575 patients had been randomized to one HBO_2 treatment (90 min of O_2 at 2.5 atm abs) vs. 12 h of NBO_2 administration. All patients were followed serially for 1 yr. At 3 mo, neurologic sequelae were significantly less in the HBO_2 treatment group (8.7%) than in the NBO_2 group (15.2%, $P = 0.016$). This difference lessened by 6 mo (6.4 vs. 9.5%; $P = 0.09$) and disappeared by 12 mo. Although benefit of HBO_2 treatment was demonstrated, the study was continued to try to identify subgroups of patients with features of CO poisoning most likely to benefit from the treatment.

Table 1: Summary of Weaver Inclusion and Exclusion Criteria

Inclusion criteria

1. Exposure to excess CO
   a. COHb ≥ 10%
   b. Documented ambient CO > 30 ppm
   c. Compelling history

AND

2. Any symptoms/signs of CO poisoning
   a. Loss of consciousness
   b. Confusion
   c. Headache
   d. Malaise
   e. Fatigue
   f. Forgetfulness
   g. Dizziness
   h. Visual disturbances
   i. Nausea
   j. Vomiting
   k. Cardiac ischemia
   l. Metabolic acidosis (base excess < −2 mol · liter^{-1} or lactate > 2.5 mol · liter^{-1})

Exclusion criteria

1. > 24 h from CO exposure to study enrollment
2. Age < 16 yr
3. No informed consent
4. Death believed to be imminent

A recent double blind, randomized trial from Salt Lake City by Weaver et al. (26). has demonstrated efficacy for HBO_2 therapy in acute CO poisoning by providing evidence that the treatment reduces cognitive sequelae after acute CO poisoning. In this study patients with acute CO poisoning were enrolled using the inclusion and exclusion criteria listed in Table 1. Patients were stratified by age < or ≥ 40 yr, time to end of CO exposure and treatment of < or ≥ 6 h, and history of LOC. All patients were treated 3 times at 6- to 12-h intervals in a monoplace chamber with HBO_2 or NBO_2. A neuropsychological test battery, consisting of general orientation, digit span, trail making test (parts A and B), digit symbol, block design, and story recall, was administered immediately after treatments 1 and 3. CO poisoning questionnaires, functional outcome evaluations, and the neuropsychological test battery were given at 2 and 6 wk after CO poisoning. Cognitive sequelae were considered present if any 6-wk neuropsychological subtest score was >2 SD below the mean (or if at least two subtest scores were each more than 1 SD below the mean) of demographically corrected standardized scores (31,32). Cognitive sequelae were present if a neuropsychological subtest score was >1 SD below the mean or if two subtest scores each were >0.5 SD below the mean and the patient complained of memory, attention, and/or concentration difficulties. A normal neuropsychological test battery was present when each subtest score of the CO screening battery was ≥ (mean − 1 SD).

The pre-treatment characteristics of the 152 patients enrolled in the trial were similar except that cerebellar dysfunction was more frequent in the NBO_2 group (P = 0.047). The mean COHb was 25%, and 49% of the patients had LOC. The trial used a group sequential design with early termination criteria (33). Interim analysis was conducted at 50, 100, and 150 patients, with a goal of 200 patients. The trial was stopped after the third interim analysis at 150 patients because HBO_2 was found to be efficacious (P = 0.007 for the difference in cognitive sequelae between groups; P value for stopping boundary, 0.01) (33,34). The group treated with HBO_2 had a lower incidence of cognitive sequelae than the group treated with NBO_2 after adjustment for pre-chamber cerebellar dysfunction and stratification (odds ratio = 0.45; 95% confidence interval = 0.219–0.919, P = 0.029). In patients who had complete neuropsychological data at all follow-up time points (n = 144), 24% of the group treated with HBO_2 had cognitive sequelae compared to 43.1% of the NBO_2-treated group (P = 0.014).Cerebellar dysfunction was associated with cognitive sequelae (odds ratio = 5.71, P = 0.004). A post hoc subgroup analysis incorporating risk factors for which HBO_2 therapy is often recommended (14,35–39), although limited by small group size, suggested HBO_2 was most effective in patients with LOC, COHb ≥25%, age ≥50 yr, a base excess < −2 mEq · liter^{-1}.

This trial by Weaver and colleagues (26) has several notable strengths lacking in some of the previous studies. It was double blind, which was preserved, the randomization was 1:1 and the patients had severe poisoning. It included an explicit a priori definition of cognitive sequelae, and neuropsychological tests were used as outcome measures and were corrected for age, gender, and education. The patients were treated soon after CO poisoning, the overall follow-up rate was high (94%), and the analysis was by intent to treat.

UNRESOLVED ISSUES IN THE TREATMENT OF ACUTE CO POISONING

The basis for use of HBO_2 in severe acute CO poisoning rests on a solid scientific rationale, good basic science research, and now on randomized controlled clinical trials, strengthened by the results of the latest study by Weaver et al. (26). However, a number of very important issues remain for future investigations. There remains a strong need for an objective test or criteria to determine which patients are "high risk" for delayed and/or permanent neurologic sequelae of CO poisoning. The

etiology and risk factors for delayed neurologic syndrome remain unknown although animal evidence indicates that CO can cause delayed pro-grammed cell death in the brain (40). The optimal dose of HBO_2, e.g., treatment number and treatment pressure, and the time after which it is no longer effective therapy are not yet clearly defined. Most RCTs have treated patients as soon as possible after CO poisoning based on papers by Goulon and associates (19) and others, which implied a 6-h window of greatest opportunity. Yet it is possible that the time of potential benefit goes beyond what has been investigated for some patients. Asked differently, are three treatments in 24 h as used in the Weaver study necessary? In those patients, most of the benefit of HBO_2 occurred after the first treatment. Is O_2 toxicity (41) or barotrauma significantly greater with three treatments than one treatment? The precise mechan-isms of action of HBO_2, apart from the first principles of hastening the clearance of the toxic substance from blood and tissues, also remain unclear.

The difficulties in addressing these issues are numerous and occur at multiple levels of inquiry. RCTs provide suitable tools for comparing HBO_2-based modalities, but the comparisons must be based on a strong scientific and practical rationale. RCT should be directed at solving clinical decision problems for they cannot address pathophysiological mechanisms. However they will raise pathophysiological questions, which are best addressed by laboratory research.

In planning RCT of CO poisoning in the future, four major points should be considered. First, validated definitions of severity of CO poisoning, which have been lacking in the past, should be incorporated into the study design. This is an important issue since assessment of heterogeneity among patient populations is needed to understand the effects of treatment on the factors that truly influence long-term outcome. For example, the patients enrolled in the study by Weaver et al. (26) appear to be representative of severely CO-poisoned patients encountered frequently in emergency departments. Although slightly more eligible patients declined participation than were enrolled for reasons of convenience, cost of transport, physicians declining referral, and chamber or study-related concerns, the clinical characteristics of the patients enrolled in the trial were similar to those declining trial participation, lessening the possibility that selection bias influenced the conclusions drawn from the data.

The second point is that the treatment modalities compared in RCTs must be clinically relevant and commonly available. Thus, comparison of a treatment modality that is costly or has limited accessibility, such as HBO_2, is appropriate to a control modality, which may be either no treatment (placebo) or the commonly accepted treatment at that time, such as 6–12 h of NBO_2 delivered by face mask. For CO poisoning, this means comparing a commonly accepted (e.g., safe) HBO_2 protocol to a commonly accepted NBO_2 protocol. Failure to follow this concept leads to one of the problems caused by the Scheinkestel study (24), which compared an unconventional HBO_2 protocol to an unconventional NBO_2 protocol and reached a conclusion that is not easily transferred to clinical practice.

The third point relates to timing the final evaluation, which is of great importance. Most of the studies have fixed the evaluation within a short period after treatment (e.g., at hospital discharge or 1 mo). It is important to keep in mind that neurological manifestations persisting after CO poisoning are not fixed and may vary with time. Mathieu's group has shown a progressive decrease in the number of CO-poisoned patients complaining of persistent neurologic manifestations after treatment, which reaches a plateau after 1 yr. This illustrates why the term "sequelae" should be reserved for permanent neurologic manifestations and should not be applied earlier than 1 yr after the poisoning episode. The Weaver study used a 6-wk end-point, which is relatively short but reasonable considering that new delayed neuropsychological effects usually appear within 1 mo after acute CO poisoning and the chances of obtaining a high follow-up evaluation in this time frame are very good. The follow-up rate (94%) was remarkably high for a clinical trial of this type, and in this patient population.

An important problem raised by short-term evaluation end-points is that true persistent post-CO neurologic manifestations are mingled with the so-called "post-stress reaction", which occurs frequently in the setting of CO poisoning. This reaction is related to the unexpected circumstances, emergency evacuation, extensive medical evaluations, and hospital environments. The post-stress reaction occurs in the weeks following CO poisoning, interferes with evaluation of CO-induced neurologic manifestations, and makes it more difficult to show significant difference between study groups. An optimal long-term follow-up period is probably 3–12 mo and should include more than one time point. On the other hand, an extended follow up raises the problem of the major end points upon which the study will be evaluated. After the interim analysis in the Mathieu study (25) showed the HBO_2-treated group has a lower rate of persisting neurologic manifestations at 3 and 6 mo compared to the NBO_2-treated groups but that this difference had disappeared at 1 yr, the investigators were faced with two types of reactions. Some people considered the study

positive for HBO_2 benefit because of the shorter time during which the patient was impaired, whereas some considered the study negative because there was no difference detected between the groups after 1 yr.

This observation introduces the fourth point. Depending on the clinical goal considered important to achieve for the patient, the application of the RCT in clinical practice may vary. For CO poisoning, it is highly unlikely that HBO_2 treatment for any type or severity of CO poisoning will give an indisputable advantage over NBO_2 treatment. That is the meaning of the conclusion of the recent Cochrane Library review on this topic stating "unselected" use of HBO_2 has not been validated (42).This conclusion agrees with experienced clinicians who recommend HBO_2 treatment according to a set of reference criteria such coma, loss of consciousness, extreme exposure, or pregnancy. Thus, future RCTs of CO poisoning should incorporate into their design phase a clinically relevant stratification of subgroups of patients. The results of such studies will help clinicians face the daily challenge of making decisions for individual patients.

IS THERE A CONSENSUS ON THE TREATMENT OF ACUTE CO POISONING WITH HBO_2?

The current recommendations of the Hyperbaric Oxygen Committee of the Undersea and Hyperbaric Medical Society for treatment of acute CO poisoning with HBO_2 (14) are not highly detailed for many of the reasons outlined above. However, patients who manifest transient or prolonged unconsciousness, neurologic signs, cardiovascular dysfunction, or severe acidosis are recommended for at least one HBO_2 session regardless of COHb level. Many hyperbaric physicians recommend HBO_2 to treat patients with less severe symptoms when neuropsychological tests are abnormal or when the COHb levels are elevated to the range of 25%. The actual treatment pressure and time vary, but treatment pressure should be between 2.5 and 3.0 atm abs. In patients with persistent neurologic dysfunction after the initial treatment, subsequent treatments are recommended at 6- to 8-h intervals and continued once or twice daily until there is no further improvement in cognitive function. Utilization review is mandatory after the fifth treatment. The Weaver study used 3.0 atm abs (26), and two other RCTs that found benefit for HBO_2 (22,23) used 2.5 and 2.8 atm abs, whereas Raphael et al used 2.0 atm abs (21). Hence, our consensus is that treatment at lower pressures (e.g., 2.0 atm abs) is probably insufficient. The final word on adequacy of the O_2 dose, however, is pulmonary gas exchange, which requires measurements of arterial blood gas tensions (43).

Most HBO_2 practitioners treat CO poisoning with one treatment, but occasionally offer additional HBO_2 treatments for patients exhibiting persistent abnormalities following the first HBO_2 treatment (14,17,38). Weaver et al. (26) administered three HBO_2 treatments in 24 h because retrospective observations of Gorman et al. (17) suggested the cognitive sequelae relapse rate was lower in patients treated two times or more compared to once. The HBO_2 protocol of Weaver et al. for initial treatment was similar to that used by the U.S. Air Force (44), with the exception of 25-min O_2 breathing periods at 3.0 atm abs instead of 23 min and two 30-min O_2 breathing periods at 2.0 atm abs instead of two 25-min O_2 breathing periods (Fig. 1). After discussion, the consensus was that there is probably no need to automatically treat all patients 2 or 3 times with HBO_2, despite the treatment plan of Weaver. The general thought was that all patients at high risk deserved a single treatment, and multiple treatments should be used in those who fail to demonstrate full recovery (normalization of mental status) upon completion of the first treatment.

The window of opportunity for treatment with HBO_2 remains unclear. Providing HBO_2 as rapidly as possible is the goal, but the maximum time after which HBO_2 is no longer effective is not clear. Inasmuch as Weaver used 24 h as an outside parameter for inclusion in the study, that is probably a legitimate end-point. However, the benefits of HBO_2 in Weaver's study were most pronounced after the first treatment, suggesting there is still a need to take into account observations indicating a 6-h window of maximum opportunity.

Great concern persists over the definition of "high risk" CO poisoning that renders the patient at greater risk for neurologic sequelae. Neurologic abnormalities and a history of LOC remain the major risk parameters identified. Of note, the Weaver study identified abnormalities of the cerebellar examination as a risk factor. The predictive value of objective laboratory tests remains unclear, but Weaver's preliminary post hoc analysis appears to support continuing to recommend HBO_2 therapy for patients with a COHb > 25%. There is also concern regarding the risk posed by extremes of age on CO-mediated neurologic sequelae; however, firm recommendations cannot yet be made except that infants, children, and the elderly require special consideration.

A final issue is the determination of optimal treatment of CO poisoning for patients who are not recommended for HBO_2 therapy. The majority of practitioners recommend 6–12 h of 100% NBO_2 delivered by a tight-fitting face mask, although there are insufficient clinical data to firmly support this recommendation. A major concern of

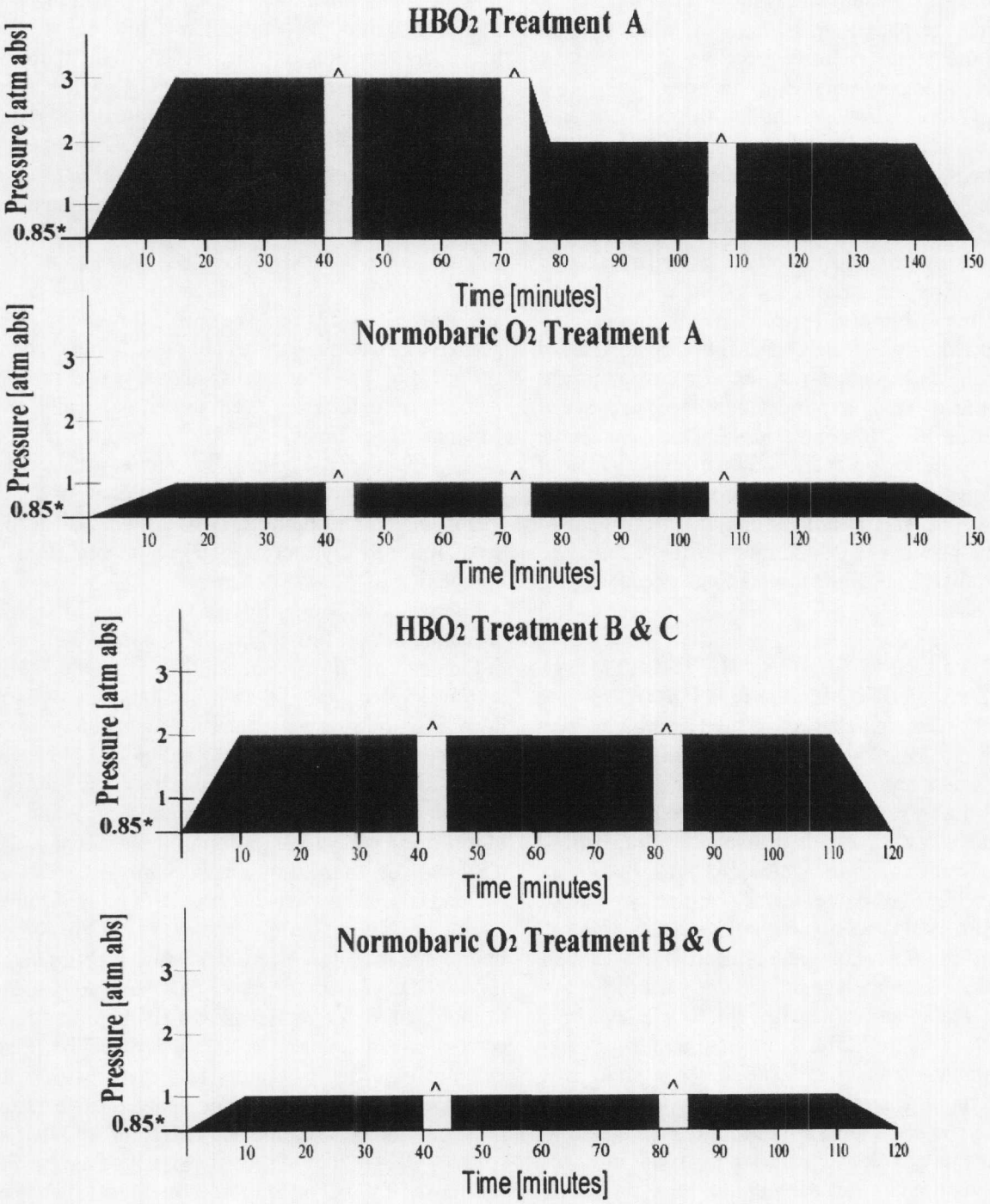

FIG. 1—Treatment schedule for patients randomized to HBO_2 or NBO_2. *Open area* = air; *shaded area* = 100% O_2. * = Atmospheric pressure in Salt Lake City, Utah; ^ = air breathing for 5 min (except for NBO_2 treatment A as below). For patients treated with HBO_2, the chamber was compressed with 100% O_2. For patients treated with NBO_2, the chamber was compressed with air to 1 atm abs. During HBO_2 treatment A, patients breathed O_2 by non-rebreathing face masks (or endotracheal tubes). In the NBO_2 treatment A, 100% O_2 was provided for the 5-min "Air" breathing periods. For NBO_2 treatments B and C, patients were compressed to 1 atm abs and breathed air, or supplemental O_2 if clinically necessary, to maintain arterial O_2 saturations >0.90.

not recommending HBO_2 is to avoid the implication that specific NBO_2 therapy is unnecessary.

CONCLUSIONS

The findings of a great deal of research, including the most recent clinical study from Salt Lake City, provide a basis for use of HBO_2 in severe acute CO poisoning. This treatment now rests on a solid scientific rationale, good basic science studies, and well-designed randomized controlled clinical trials. However, a number of very important issues remain for future investigations. Based on the results of Weaver et al. (26) and earlier RCTs, a large multi-center trial would be a logical next step to investigate the optimal number of HBO_2 treatments and the maximum treatment delay from CO poisoning to HBO_2 that provide efficacy in patients with well-defined risk factors for a poor outcome. It must be emphasized that neither HBO_2 nor any other therapy can be expected to prevent cognitive sequelae of CO poisoning due to cell death sustained during the exposure. Therefore, prevention of CO poisoning remains an important public health concern. Optimal follow up of CO poisoned patients is important to recognize and deal appropriately with residual neurologic sequelae. Patients with persistent CO-related complaints should be referred to clinical neuropsychologists with specific training and experience in cognitive evaluation.

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