

# **A prospective, randomized clinical trial comparing two hyperbaric treatment protocols for carbon monoxide poisoning.**

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Hampson N.B., Dunford R.G., Ross D.E., Wreford-Brown C.E. A prospective, randomized clinical trial comparing two hyperbaric treatment protocols for carbon monoxide poisoning. *Undersea Hyperb Med* 2006; 33(1): 27-32. Introduction: The optimal hyperbaric oxygen (HBO<sub>2</sub>) treatment protocol for acute carbon monoxide (CO) poisoning is unknown. This is indicated by one study that found 18 different protocols to treat CO poisoning by North American multiplace hyperbaric facilities. A pilot study was conducted to evaluate the feasibility of randomizing patients to different protocols and to determine whether any large differences in clinical outcome were present between the two most common protocols. Methods: Adult patients with accidental CO poisoning resulting in transient loss of consciousness, presentation to the emergency department within 12 hours, primary language English, high school education, and residence within 100 miles of the hyperbaric facility were recruited. Enrolled patients were randomized to one HBO<sub>2</sub> treatment at 2.4 atmospheres absolute (atm abs) pressure with 90 minutes of 100% oxygen breathing vs. treatment by the US Air Force CO protocol (3.0 atm abs maximum pressure). A neurocognitive screening test was performed immediately after hyperbaric treatment and repeated 14-21 days later. Results: From 1995 to 2002, 30 patients age 21 to 88 years were randomized, 18 to treatment at 2.4 atm abs and 12 to 3.0 atm abs. Average carboxyhemoglobin level for the population was  $24.8 \pm 8.8\%$  (mean  $\pm$  SD). Delay to hyperbaric treatment averaged  $313 \pm 129$  minutes. Neither variable was different between treatment groups. Six patients had abnormal neurocognitive testing immediately following hyperbaric treatment, 4 in the 2.4 atm abs group (22%) and 2 in the 3.0 atm abs group (17%) ( $P=0.71$ ). One patient in each group demonstrated abnormality on delayed testing ( $p=0.75$ ). One in each group did not return for follow-up. Conclusions: It is feasible to randomize CO-poisoned patients to different hyperbaric treatment protocols. Determination of differences in efficacy between treatment protocols will require a large multicenter trial with the use of detailed neurocognitive testing.

## **INTRODUCTION**

Carbon monoxide (CO) poisoning is common in the United States, resulting in an estimated 40,000 emergency department visits annually (1). CO poisoning is a common cause of accidental poisoning death. An estimated 3,800 individuals die from CO poisoning annually in the US, 1,100 from accidental exposure, 2,400 from intentional exposure and 300 from other or unknown intent (2).

Inhaled carbon monoxide causes toxicity via multiple mechanisms including

both hypoxic stress from binding to hemoglobin and intracellular sites, as well as non-hypoxic pathways including oxidative stress, endothelial leukocyte adhesion, and lipid peroxidation (3,4,5,6). Each of these has been implicated in the pathogenesis of brain injury resulting from CO poisoning and each has been demonstrated in animal models to be attenuated by hyperbaric oxygen (HBO<sub>2</sub>).

Six prospective clinical trials have been reported to date comparing hyperbaric and normobaric oxygen (NBO<sub>2</sub>) in the treatment of patients with acute CO poisoning

(7,8,9,10,11,12). Of the six trials, four have demonstrated statistically superior clinical outcomes among patients treated with hyperbaric oxygen (8,9,10,12), while two have claimed equivalent outcomes with NBO<sub>2</sub> and HBO<sub>2</sub> (7,11).

The preponderance of available evidence demonstrates that HBO<sub>2</sub> is effective therapy for CO poisoning. However, each of the published prospective trials has used a different hyperbaric treatment protocol. Furthermore, a survey of North American multiplace hyperbaric facilities found that 18 different protocols were used for treatment of CO poisoning (13). These issues led an expert panel on CO poisoning to conclude that an unanswered question in management of the disease is the most appropriate hyperbaric treatment protocol (14).

The current pilot study was conducted (1) to evaluate the feasibility of randomizing patients to different hyperbaric protocols, and (2) to determine effect size differences in clinical outcome between the two protocols most commonly used in North America to aid in planning future comparative trials.

## METHODS

Patients referred to Virginia Mason Medical Center in Seattle, Washington for hyperbaric oxygen treatment of CO poisoning and meeting all of the following criteria were recruited for study:

1. Acute, accidental carbon monoxide intoxication resulting in loss of consciousness
2. Emergency department presentation within 12 hours of CO exposure
3. Age 18 years or older
4. Minimum of high school education
5. Fully conscious upon evaluation in the Virginia Mason Emergency Department with normal screening neurological examination

6. Primary language English
7. Residence within 100 miles of Seattle
8. Willingness to sign informed consent for study participation

Enrolled patients were randomized to a protocol administering 90 minutes of 100% oxygen at 2.4 atmospheres absolute (atm abs) pressure, delivered in three 30-minute periods, or to a protocol delivering two 23-minute periods of oxygen at 3.0 atm abs, followed by two 25-minute periods at 2.0 atm abs (commonly known as the “US Air Force CO Table”) (15). These were the two protocols previously identified as most commonly utilized in North American multiplace hyperbaric facilities for treatment of CO poisoning (13). Randomization was intended to be 1:1 to the two protocols, through use of sealed envelopes kept in the hyperbaric facility and opened as each subject was enrolled. Patients were blinded to the protocol selected.

Immediately after hyperbaric treatment, neurocognitive screening utilizing the Neurobehavioral Cognitive Status Examination (NCSE; Northern California Neurobehavioral Group, Inc., Fairfax, CA) was performed by a single tester experienced in the administration of the test and blinded to the treatment protocol utilized. Testing was performed in a quiet room in the building remote from the chamber area. The NCSE assesses eight cognitive domains. Impairment was defined for the purposes of this study as an abnormal score in any domain.

At the time of discharge from the facility, arrangements were made for the patient to return in 14 to 21 days for repeat neurocognitive testing. The time period selected for follow-up testing was based upon the delay to onset of neurocognitive sequelae and their duration reported in an earlier prospective study of CO poisoning (9).

When a patient demonstrated a persistent or delayed abnormality on NCSE testing, they

were asked to return monthly for repeat testing until the abnormality resolved or to a maximum follow-up of one year. Those patients who were found to have persistent or new abnormalities on follow-up testing were informed of the finding and offered referral to a neurologist for further evaluation and management.

Results in the two groups were compared with unpaired t-test with two-tailed P value (patient age, carboxyhemoglobin levels, and delay to hyperbaric treatment) or Chi square analysis (immediate and delayed NCSE test results).

## RESULTS

From 1995 to 2002, 30 patients ranging in age from 21 to 88 years were randomized, 18 to treatment at 2.4 atm abs and 12 to 3.0 atm abs. Results are summarized in Table 1. Average age for the entire study population was  $46 \pm 17$  years (mean  $\pm$  SD). Six patients were aged 60 years or older. Mean carboxyhemoglobin level for the total group was  $24.8 \pm 8.8\%$  (range 7.8 to 44.8%). Delay to hyperbaric treatment averaged  $313 \pm 129$  minutes (range 134 to 614

minutes). None of these variables was different between the treatment groups. Duration of CO exposure was roughly estimated from accompanying records and patient reports and ranged from 0.5 to 168 hours (median 2.0 hours).

Six patients had abnormal neurocognitive testing immediately following hyperbaric treatment, 4 in the 2.4 atm abs group (22%) and 2 in the 3.0 atm abs group (17%) ( $P=0.71$ ). Of those demonstrating an immediate test abnormality, one patient was over the age of 60 years.

One patient in each group did not return for follow-up NCSE testing. Both had been normal on immediate testing. The remaining 28 patients returned for delayed NCSE testing 13 to 36 days after hyperbaric treatment (mean  $22 \pm 6$  days; median 21 days). There was no significant difference between the groups with regard to day of repeat testing ( $p=0.83$ ). One patient in each group demonstrated abnormality on delayed testing, again not a significant difference ( $p=0.75$ ). Both abnormal test results were obtained on day 21 after treatment. One occurred in a patient in the 2.4 atm abs group

**Table 1. Patient data and results of neurocognitive screening (NCSE) following hyperbaric treatment.**

	Protocol A (2.4 atm abs)	Protocol B (3.0 atm abs)	
Number of patients randomized	18	12	
Patients lost to follow-up	1 (6%)	1 (8%)	$P=0.75$
Age (years)	$47.2 \pm 16.3$	$43.1 \pm 11.3$	$P=0.44$
Gender	10 M, 8 F	4 M, 8 F	$P=0.28$
Carboxyhemoglobin level	<b><math>22.4 \pm 8.5\%</math></b>	<b><math>24.3 \pm 13.2\%</math></b>	<b><math>P=0.65</math></b>
Delay to HBO <sub>2</sub> treatment	$300 \pm 133$ minutes	$331 \pm 128$ minutes	$P=0.53$
Abnormal immediate NCSE	4 of 18 (22%)	2 of 12 (17%)	$P=0.71$
Abnormal follow-up NCSE	1 of 17 (6%)	1 of 11 (9%)	$P=0.75$

who was also abnormal on immediate testing. The patient remained abnormal when repeat testing was performed on days 115 and 199, then was lost to follow-up. The other case with abnormal delayed testing occurred in a patient in the 3.0 atm abs group who was normal at the time of immediate testing. The patient remained abnormal on repeat testing on day 52 and then was normal on day 82. None of the patients over 60 years of age were abnormal on repeat testing.

## DISCUSSION

The question of an optimal hyperbaric treatment protocol for acute CO poisoning is significant for several reasons. Approximately 1,500 CO-poisoned patients are treated with HBO<sub>2</sub> in the US annually (16). If sequelae are less common following one protocol than another, morbidity might be avoided for a large number of individuals. Secondly, the incidence of CNS oxygen toxicity has been shown to be significantly greater in CO-poisoned patients treated at 2.8 or 3.0 atm abs, as compared to those treated at 2.5 atm abs (17). If there is no therapeutic gain from exposure to this increased risk, a protocol with lesser pressure should be utilized. Third, one must consider cost. Both institutional cost and patient billing for hyperbaric treatment are directly related to treatment duration. Among the 18 protocols utilized in North American multiplace hyperbaric chambers for treatment of CO poisoning, the shortest lasts 46 minutes while the longest lasts 3 hours (13). It may be possible to affect significant cost savings if hyperbaric treatment for CO poisoning were standardized and lengthy protocols abandoned.

Unfortunately, few data are available to help guide clinicians in the choice of a protocol. No comparative studies have been reported to date. As mentioned previously, each of the six prospective, randomized, controlled clinical

trials comparing normobaric and hyperbaric oxygen in CO poisoning have utilized a different treatment protocol. It is unknown whether this played any role in the outcomes observed. The lack of clinical information available to guide selection of a hyperbaric protocol for CO poisoning is mirrored by data in animals. Some studies using animal models of CO poisoning have applied different treatment pressures but none have compared the range of pressures utilized in clinical hyperbaric practice. It should therefore not be surprising that a multiplicity of treatment protocols is used in clinical HBO<sub>2</sub> practice for CO poisoning (13).

The present study demonstrates that it is feasible to randomize CO-poisoned patients to different hyperbaric treatment protocols. With regard to feasibility, however, a number of lessons were learned from this study that may be useful when planning a future larger trial. When the study began in 1995, it was anticipated that 50 patients could be recruited over four years. In fact, only 30 patients were studied over seven years. The entry criteria were established to study a group of CO-poisoned patients that the majority of hyperbaric practitioners would treat with HBO<sub>2</sub> (loss of consciousness and delay less than 12 hours) (18), would be appropriate for neurocognitive screening (primary language English, age 18 years or older, high school education, accidental exposure), and would be likely to return for follow-up testing (residence within 100 miles of Seattle). In retrospect, it is apparent that these criteria were stringent and that a longer accrual period should have been anticipated.

A second issue was the difficulty in coordinating patient return for repeat NCSE testing within the narrow time frame established when the study was designed (14-21 days after HBO<sub>2</sub> treatment). This window was selected because of the prospective trial by Thom, published the year the present study was designed (9). In it, the onset and duration

of delayed sequelae after CO poisoning were quite variable, but all affected individuals were impaired on days 10 through 25. Of the 28 patients who returned for follow-up testing in the present study, 8 were tested beyond the planned 21 days post-treatment window. In a future study, a wider time frame (e.g.  $21 \pm 14$  days) might be considered.

The third feasibility issue was the fact that new information became available during the prolonged conduct of the study. When the study by Weaver and colleagues demonstrated a therapeutic effect of HBO<sub>2</sub> using three treatments per patient in 2002 (12), it seemed appropriate to consider repetitive treatment, at least for those patients still symptomatic or impaired after their first treatment. As such, our standard practice for treatment of CO poisoning was changed. We felt that it was not possible for us to continue accrual of subjects, as a lesser level of care (one HBO<sub>2</sub> treatment maximum) would be provided to patients enrolled in the trial.

Another lesson learned had to do with the method of randomization. A different number of patients were accrued to each study arm (18 vs. 12). The randomization process involved the selection of a sealed envelope containing the study treatment protocol. Because all 50 envelopes for the planned study were available, it offered the opportunity for unequal randomization, as occurred. This would not have occurred if the planned accrual had been achieved, but early termination of the study was not anticipated. Unequal randomization could have been avoided by using smaller batches of envelopes, each with an equal number of the two protocols inside. For example, if batches of 10 envelopes were used for randomization, assignment to the two arms would have been equal at 10, 20 and 30 patients enrolled.

Six of the 30 patients (20%) in the present study demonstrated cognitive

abnormality on NCSE testing immediately after the first HBO<sub>2</sub> treatment and 2 of 28 (7%) demonstrated an abnormality on delayed testing at  $22 \pm 6$  days. In the study by Weaver and colleagues, 25% of HBO<sub>2</sub> treated patients were abnormal on more extensive neurocognitive testing at 6 weeks (12). Their patient population was much more heterogeneous than that of the present study. When data from hyperbaric-treated patients in their study that met the entry criteria of the present trial are analyzed separately, 58% demonstrated cognitive impairment immediately following the first hyperbaric treatment and 25% were abnormal at 6 weeks (Lin Weaver, personal communication, August 2004). This suggests that the NCSE screening test was not as sensitive to CO-induced cognitive abnormalities as the more comprehensive testing used by Weaver et al., which should be considered in planning future trials.

With regard to outcome with the two protocols tested in this study, 22% of patients were impaired on neurocognitive screening in one arm and 17% in the other. A much larger study would be needed to prove whether a difference of this magnitude is real.

In summary, this pilot study demonstrated that it is feasible to randomize CO-poisoned patients to different hyperbaric treatment protocols and found no significant difference in outcome between two tested protocols. The value of the present investigation is the information it provides for the planning of a future larger trial examining the efficacy of different hyperbaric protocols. Power calculations should use small expected differences to estimate the number of patients required in such a study, and the need for the trial to be multicentered in order to achieve a reasonable accrual rate is clearly demonstrated.



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