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JOURNAL TITLE:	Medical journal of Australia
USER JOURNAL TITLE:	Medical Journal of Australia
ARTICLE TITLE:	Hyperbaric or normobaric oxygen for acute carbon monoxide poisoning: a randomised controlled clinical trial
ARTICLE AUTHOR:	Carlos D Scheinkestel, Paul S Myles, D James Coope
VOLUME:	170
ISSUE:	5
MONTH:	3
YEAR:	1999
PAGES:	203-210
ISSN:	0025-729X
OCLC #:	

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Medical Journal of Australia 1914-2013
0025-729X
Hyperbaric or normobaric oxygen for acute carbon monoxide poisoning: a randomised controlled clinical trial
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volume 170 issue 5 year 1999
pages 203-210

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RESEARCH

Hyperbaric or normobaric oxygen for acute carbon monoxide poisoning: a randomised controlled clinical trial

Carlos D Scheinkestel, Michael Bailey, Paul S Myles, Kerry Jones, D James Cooper, Ian L Millar and David V Tuxen

Abstract

Objective: To assess neurological sequelae in patients with all grades of carbon monoxide (CO) poisoning after treatment with hyperbaric oxygen (HBO) and normobaric oxygen (NBO).

Design: Randomised controlled double-blind trial, including an extended series of neuropsychological tests and sham treatments in a multiplace hyperbaric chamber for patients treated with NBO.

Setting: The multiplace hyperbaric chamber at the Alfred Hospital, a university-attached quarternary referral centre in Melbourne providing the only hyperbaric service in the State of Victoria.

Patients: All patients referred with CO poisoning between 1 September 1993 and 30 December 1995, irrespective of severity of poisoning. Pregnant women, children, burns victims and those refusing consent were excluded.

Intervention: Daily 100-minute treatments with 100% oxygen in a hyperbaric chamber — 60 minutes at 2.8 atmospheres absolute for the HBO group and at 1.0 atmosphere absolute for the NBO group — for three days (or for six days for patients who were clinically abnormal or had poor neuropsychological outcome after three treatments). Both groups received continuous high flow oxygen between treatments.

Main outcome measures: Neuropsychological performance at completion of treatment, and at one month where possible.

Results: More patients in the HBO group required additional treatments (28% v. 15%, $P=0.01$ for all patients; 35% v. 13%, $P=0.001$ for severely poisoned patients). HBO patients had a worse outcome in the learning test at completion of treatment ($P=0.01$ for all patients; $P=0.005$ for severely poisoned patients) and a greater number of abnormal test results at completion of treatment ($P=0.02$ for all patients; $P=0.008$ for severely poisoned patients). A greater percentage of severely poisoned patients in the HBO group had a poor outcome at completion of treatment ($P=0.03$). Delayed neurological sequelae were restricted to HBO patients ($P=0.03$). No outcome measure was worse in the NBO group.

Conclusion: In this trial, in which both groups received high doses of oxygen, HBO therapy did not benefit, and may have worsened, the outcome. We cannot recommend its use in CO poisoning.

MJA 1999; 170: 203-210

For editorial comment, see page 197

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Carbon monoxide (CO) poisoning is one of the most common lethal poisonings,[1] with neurological or psychiatric sequelae occurring in up to 67% of survivors.[2]

Treatment with hyperbaric oxygen (HBO) is recommended because it reduces carboxyhaemoglobin (COHb) dissociation half-life from more than four hours at room air or 45 minutes on 100% oxygen to 23 minutes at 2.5 atmospheres absolute (ATA).[3] Carbon monoxide also inhibits cellular respiration by binding to cytochrome oxidase, a component of the mitochondrial electron transport chain.[4] Hyperbaric oxygen enhances the dissociation of CO from this enzyme.[5]

Despite these physiological effects, it has not been established in humans that HBO either improves survival or decreases neuropsychological deficits. Much of the evidence that HBO is more efficacious than normobaric oxygen (NBO) therapy in humans arises from isolated case reports,[6-8] uncontrolled clinical observations,[9-11] small,[12] non-randomised[13] and unblinded series[9,11,13-20] and incomplete assessment of outcome (no neuropsychological testing).[9,11,15-18]

All reported non-randomised studies have suggested benefit from HBO. Of the four published randomised studies, two report benefit from HBO[12,14] and two report no benefit[15,17] (Box 1). Three restricted entry to mildly poisoned patients, while the fourth[15] included severely poisoned patients, but did not allocate any to NBO treatment. None of the randomised studies blinded patients by using sham treatments for NBO, only one blinded outcome assessment[12] and only one used neuropsychological tests to assess outcome.[14]

Hence, the benefit of HBO in CO poisoning has been questioned[1,2,21-27] and remains unproven. We therefore performed a randomised double-blind

1: Published trials of carbon monoxide poisoning treated with hyperbaric oxygen (HBO) and normobaric oxygen (NBO)

Study	Patients included	No. HBO patients	No. NBO patients	Blinded	Neuropsychological tests	Number of treatments	Maximum ATA	Time at maximum ATA (min)	Entry criteria time to treatment (h)	Actual time to treatment (h)	HBO benefit reported
Non-randomised											
Roche et al[11]	All	20	20	No	No	1–10	2.5	60	?	?	Yes
Mathieu et al[16]	All	203	27	No	No	1–5	2.5	90	?	~4	Yes
Myers et al[20]	All	131	82	No	Yes	?	1.8–2.0	46	?	1–1.5	Yes
Willms et al[18]	All	72	46	No	No	3	2.5	?	?	?	Yes
Goulon et al[9]	All	273	29	No	No	2	2	90	?	?	Yes
Gorman et al[13]	All	92	8	No	Yes	1, 2, > 2	2.8	60	?	?	Yes
Ely et al[19]	All	4	26	No	No	1	2.5	120	?	?	Yes
Randomised											
Raphael et al[15]	Non-comatose	173	170	No	No	1	2	120	12	?	No
	Severely poisoned	145	141	No	No	1 v. 2	2	120	12	?	No
Thom et al[14]	Mildly poisoned	33	32	No	Yes	1	2.8	30			Yes
							2	90	< 6	~1	
Ducasse et al[12]	Non-comatose	13	13	Yes	No	1	?	?	?	~1	Yes
Mathieu et al[17]	Non-comatose	299	276	No	No	1	2.5	90	12	?	No
This study*	All	104	87	Yes	Yes	⩾3	2.8	60	< 24	7.1 (95% CI, 1.9–26.5)	No

ATA = atmospheres absolute; HBO = hyperbaric oxygen; NBO = normobaric oxygen; ? = not reported; ~ = approximately.
* Our study was the only one listed in which there were sham treatments for NBO patients.

trial in patients with all grades of CO poisoning, comparing HBO and NBO (with sham treatments for the NBO group), and using an extended series of neuropsychological tests to assess both persistent and delayed neurological sequelae (PNS and DNS).

Methods

The multiplace chamber at the Alfred Hospital, a university-attached quarternary referral centre, provides the only hyperbaric service in the State of Victoria (population, 4.5 million; area, 228 000 km^2). Between 1 September 1993 and 30 December 1995, most CO-poisoned and all severely poisoned patients were referred for treatment. We included all referred patients, irrespective of severity of poisoning. Patients were excluded if they were pregnant, children, burns victims or if they did not consent. Informed consent to enter the trial was requested from patients with a Mini-mental score > 24[28] and from the next of kin for those obtunded or with a score ⩽ 24.

The Alfred Hospital's Ethics Committee approved the trial, conditional on an independent blinded interim analysis after recruitment of 50 patients (using a stopping rule of $P < 0.001$); this allowed continuation of enrolment to completion.

Randomisation and blinding

Patients were randomly allocated to HBO or NBO treatment. To ensure a similar distribution of causes and severity of poisoning in both groups, patients were first stratified into four groups (suicide versus accidental, then mechanically ventilated versus non-ventilated). A hyperbaric technician then allocated patients to treatment groups by opening envelopes chosen from random blocks, each with equal numbers of HBO and NBO selections.

To minimise the impact of the trial on daily practice, we used cluster randomisation for patients who presented simultaneously from the same CO exposure, allocating them all to the same treatment group. Cluster randomisation accounted for the difference in numbers between HBO and NBO groups. As patients presenting simultaneously could be uniquely identified by having identical measurements for three continuous baseline severity measurements (exposure time, time to COHb measurement and time to treatment), any effects due to cluster randomisation could be controlled and adjusted for by including these variables in the generalised linear model.

The hyperbaric technicians and nursing staff had knowledge of the treatment group but patients and outcome assessor did not.

Interventions

Before arrival at Alfred Hospital, non-intubated patients received high flow oxygen by non-occlusive facemask and intubated patients received 100% oxygen. All patients were admitted to hospital, received three treatments on a once-daily basis and continuous oxygen by non-occlusive facemask at 14 L/min (100% oxygen for ventilated patients) between treatments.

Patients randomised to NBO therapy were treated for 100 minutes in the multiplace chamber with 100% oxygen at 1.0 atmosphere absolute (ATA). Non-ventilated patients used an occlusive facemask attached via a non-rebreathing valve to a Laerdal adult ventilation bag (1.6 L) with an oxygen reservoir (2.6 L; Armund S Laerdal, Stavanger, Norway). The chamber door was closed and the chamber flushed with air regularly to simulate pressurisation, but the chamber was not pressurised (sham treatment).

HBO patients received 100% oxygen by hood, occlusive facemask or mechanical ventilator in the hyperbaric chamber for 100 minutes (60 minutes at 2.8 ATA).

After the third treatment, patients were reassessed medically and underwent full neuropsychological assessment. Patients who were clinically abnormal or had poor neuropsychological outcome received three further treatments and received high flow oxygen between treatments.

Outcome measures

Patient assessment at entry included length of CO exposure, COHb level, time from end of exposure to COHb measurement and to treatment, Mini-mental score and clinical effects of poisoning (Box 2).

We then assessed patients at completion of treatment (three or six treatments), and, wherever possible, at one month.

We attempted to quantify deficits known to occur in CO poisoning by assessing attention, information processing, memory and learning. A clinical psychologist trained in neuropsychological assessment of brain-injured patients performed all tests at completion of treatment and at follow-up. Computerised testing was used to standardise administration and data-recording procedures and increase objectivity.

The tests used were the digit span subtest of the Wechsler Adult Intelligence Scale — Revised,[29] comprising (i) *Digit span forward* and (ii) *Digit span backwards* (in which patients are asked to repeat a series of numbers read to them), which measures immediate auditory–verbal memory span, working memory and attention; computerised reaction-time tests,[30] consisting of (iii) *Simple reaction time* (in which subjects are requested to press the space bar on a computer keyboard as soon as they see anything appear on the screen) to give a basal measure of alertness or arousal, and (iv) *Choice reaction time* (which requires subjects to ignore stimuli in a centre box and to respond selectively to the word "SEVEN" as it appears around the periphery of the computer screen) to test selective attention (reaction time was tested because it can show diffuse cerebral dysfunction, and because processing speed is considered to underlie attention deficits[31]); (v) a score on the *Rey auditory verbal learning test*, in which a 15-word list (List A) is presented over five learning trials, followed by an interference trial (List B), after which (vi) *Short term free recall* is tested without any further presentation of the word list, and (vii) *Long term free recall* is tested 20 minutes later (this provides a measure of learning across trials, and retention of information following short and long delay periods[32]).

Raw scores of these seven neuropsychological tests were converted to z scores ([score − mean in normal population] / standard deviation), and then t scores (McCall's T; an adjusted z score so that the mean is 50 and the standard deviation is 10).[33] Age-based and education-based norms were used where available to calculate t scores.

A t score more than one standard deviation below the mean was considered abnormal, and two or more abnormal scores constituted a poor outcome.

Patients with poor outcome at hospital discharge were considered to have persistent neurological sequelae (PNS). Delayed neurological sequelae (DNS) were defined as morbidity found at follow-up that was not obvious at hospital discharge, or deterioration of neuropsychological subtest scores by more than one standard deviation.

2: Patient characteristics and description of severity of carbon monoxide poisoning for patients treated with hyperbaric oxygen (HBO) and normobaric oxygen (NBO)

	HBO (n=104)	NBO (n=87)	P
Demographic characteristics			
Age	37.8 (35.1–40.5)	34.8 (32.0–37.6)	0.13†
Male	89 (86%)	67 (77%)	0.13‡
Suicide attempt	68 (65%)	63 (72%)	0.3‡
Baseline severity			
Ventilated	20 (19%)	16 (18%)	0.88‡
Exposure time (h)	2.6 (2.0–3.2)	2.5 (1.9–3.1)	0.87†
Time to carboxyhaemoglobin level (h)*	3.2 (2.6–3.8)	2.6 (2.1–3.1)	0.11†
Carboxyhaemoglobin level (%)	20.5 (18.0–23.0)	22.0 (19.6–24.4)	0.39†
Time to treatment (h)*	7.5 (6.6–8.6)	6.6 (5.7–7.5)	0.16†
Mini-mental score	27.0 (26.1–27.9)	26.4 (25.4–27.4)	0.27†
No. with criteria for severe poisoning	72 (69%)	67 (77%)	0.23‡
Signs			
Coma	53 (51%)	49 (56%)	
Acidosis	11 (11%)	13 (15%)	
Focal neurological deficits	9 (9%)	6 (7%)	
Electroencephalogram changes	7 (7%)	9 (10%)	
Hypotension	3 (3%)	2 (2%)	
Arrhythmias	2 (2%)	7 (8%)	
Pulmonary oedema	2 (2%)	1 (1%)	
Convulsions	1 (1%)	3 (3%)	
Cardiac arrest	1 (1%)	1 (1%)	
Symptoms			
Headache	55 (53%)	38 (44%)	
Fatigue	47 (45%)	38 (44%)	
Difficulty in thinking	46 (44%)	37 (43%)	
Dizziness	38 (37%)	21 (24%)	
Nausea	38 (37%)	25 (29%)	
Acute confusional state	20 (19%)	10 (11%)	
Paraesthesiae	11 (11%)	6 (7%)	
Visual disturbance	9 (9%)	4 (5%)	
Palpitations	8 (8%)	3 (3%)	
Chest pain	7 (7%)	3 (3%)	
Tinnitus	4 (4%)	2 (2%)	
Abdominal pain	3 (3%)	0	
Diarrhoea	2 (2%)	2 (2%)	

Figures are number (%) or mean (95% CI). HBO = hyperbaric oxygen; NOB = normobaric oxygen. * Geometric mean; † t test; ‡ χ^2 test.

Statistical analyses

Statistical analyses were made using mixed linear models to adjust for all baseline covariants (age, sex, suicide attempt, COHb level, time to COHb level, duration of exposure, time to treatment, and presence of other drugs). Data were presented as mean and SD, median and interquartile range (IQR) or number and per cent. Continuous data were first assessed for normality and then analysed by unpaired two-tailed Student's t-test, or Wilcoxon rank sum test. Proportions were compared with χ^2 tests (with Yates' correction), or Fisher's exact test, as appropriate, with multiple logistic regression being used to adjust for confounding factors. We calculated odds ratios and 95% confidence intervals (95% CI) for the difference between proportions. The 95% CI for the difference between means and P values were calculated after adjustment for baseline covariants. All statistical analyses were performed using SAS.[34]

3: Neuropsychological outcome for all patients treated with hyperbaric oxygen (HBO) and normobaric oxygen (NBO)

	HBO (n=104)	NBO (n=87)	Difference (95% CI) in favour of HBO*	P*
At end of treatment				
No. requiring > 3 treatments	29 (28%)	13 (15%)	OR 2.8 (1.3–6.2)‡	0.01‡
Deaths	3 (3%)	3 (3.4%)		0.96‡
Average neuropsychological test results†				
Simple reaction time (s)	385	375	-10 (-50 to 30)	0.63§
Choice reaction time (s)	10.4	11.1	-0.7 (-1.9 to 0.5)	0.25§
Digit span forward (no. digits recalled)	8.2	8.1	0.1 (-9 to 1.1)	0.87§
Digit span backwards (no. digits recalled)	5.3	5.6	-0.3 (-1.1 to 0.5)	0.55§
Rey auditory verbal learning test (score)	42.2	47.7	-5.5 (-9.8 to -1.2)	0.01§
Short term free recall (no. objects)	3.2	3	-0.2 (-1.1 to 0.7)	0.54§
Long term free recall (no. objects)	4.4	4.2	-0.2 (-1.5 to 1.1)	0.76§
Improvement in Mini-mental score	0	0.7	-0.7 (-2.7 to 1.3)	0.53§
Average number of abnormal tests	3.4	2.7	-0.7 (-1.3 to -0.1)	0.02§
Poor outcome (PNS)	0.74	0.68	OR 1.7 (0.8–4.0)‡	0.19‡
Relapse (DNS)	5 (4.8%)	0		0.03¶

Figures are number (%) or mean (95% CI). HBO = hyperbaric oxygen; NBO = normobaric oxygen; OR = odds ratio; PNS = persistent neurological sequelae (> 2 abnormal test results); DNS = delayed neurological sequelae. * After adjustment for age, sex, suicide attempt, carboxyhaemoglobin (COHb) level, time to measurement of COHb level, duration of exposure, time to treatment, presence of other drugs; † See Methods section for description of neuropsychological tests; ‡ χ^2 test; § F-test; ¶ Fisher's exact test.

4: Characteristics of 139 patients with severe carbon monoxide poisoning, and the neurophysiological outcome for this subgroup

	HBO (n=72)	NBO (n=67)	Difference (95% CI) in favour of HBO*	P*
Demographic characteristics				
Age	38.6 (35.2–42.0)	36.7 (33.5–39.9)		0.42¶
Male	60 (83%)	55 (82%)		0.99§
Suicide	55 (76%)	54 (81%)		0.69§
Baseline severity				
Ventilated	20 (28%)	16 (24%)		0.74§
Exposure time (h)	2.5 (1.9–3.1)	2.2 (1.6–2.8)		0.45¶
Time to carboxyhaemoglobin level (h)†	2.9 (2.3–3.7)	2.2 (1.9–2.7)		0.07¶
Carboxyhaemoglobin level (%)†	23.0 (19.8–26.2)	22.9 (22.0–25.8)		0.94¶
Time to treatment (hours)	7.3 (6.3–8.5)	6.1 (5.4–6.9)		0.08¶
Mini-mental score	25.6 (24.3–26.9)	25.8 (24.5–27.1)		0.8¶
At end of treatment				
No. requiring > 3 treatments	25 (35%)	9 (13%)	OR 5.4 (2.0–14.8)	0.001§
Deaths	3 (4.2%)	3 (4.5%)	OR 1.0 (0.2–6.0)	0.97§
Average neuropsychological test results†				
Simple reaction time (s)	410	377	-33 (-72 to 6.0)	0.1 **
Choice reaction time (s)	9.9	10.7	-0.8 (-2.4 to 0.8)	0.32**
Digit span forward (no. digits recalled)	7.9	8	-0.1 (-1.3 to 1.1)	0.91**
Digit span backwards (no. digits recalled)	5	5.5	-0.5 (-1.6 to 0.6)	0.35**
Rey auditory verbal learning test (score)	42	49.2	-7.2 (-12.2 to -2.2)	0.005**
Short term free recall (no. objects)	4	3.5	-0.5 (-1.7 to 0.7)	0.43**
Long term free recall (no. objects)	4.6	5.2	0.6 (-1.1 to 2.3)	0.47**
Improvement in Mini-mental score	2	1.6	0.4 (-0.2 to 2.8)	0.71**
Average number of abnormal tests	3.7	2.6	-1.1 (-1.9 to -0.3)	0.008**
Poor outcome (PNS)	0.85	0.65	OR 3.6 (1.1–11.9)	0.03§

Figures are number (%) or mean (95% CI). HBO = hyperbaric oxygen; NBO = normobaric oxygen; OR = odds ratio; PNS = persistent neurological sequelae (> 2 abnormal test results); DNS = delayed neurological sequelae. * After adjustment for age, sex, suicide attempt, carboxyhaemoglobin (COHb) level, time to measurement of COHb level, duration of exposure, time to treatment, presence of other drugs; † Geometric mean (95% CI); ‡ See Methods section for description of neuropsychological tests; § χ^2 test; ¶ t-test; ** F-test.

Results

Two hundred and thirty patients with CO poisoning were referred for treatment. Thirty-nine were excluded (one child, eight burns victims, and 30 who refused consent) and treated with HBO. Thus, 191 patients entered the trial (Box 2). Based on the most sensitive neuropsychological test (*Short reaction time*), with 191 patients and a significance level of 0.05, we had greater than 99% power to detect a 10% difference between groups (ie, 408 seconds v. 450 seconds; SD, 63 seconds) (Clinical Trials Design Program, Biosoft, Cambridge, UK).

The groups (104 HBO patients, 87 NBO patients) were comparable in age, sex, incidence of suicide attempt, mechanical ventilation, Mini-mental score, and other markers of severity, including loss of consciousness (coma). Forty-four per cent of patients who had attempted suicide (44% HBO and 44% NBO) also had evidence of self-administration of drugs or alcohol.

Most of our patients (73%) had severe CO poisoning, defined by any of the following before or on arrival at Alfred Hospital: a Mini-mental score ≤24, COHb level >30%, confusion, focal neurological deficits, loss of consciousness, electrocardiogram abnormalities, arrhythmias, pulmonary oedema, metabolic acidosis, hypotension, convulsions, and cardiac arrest. All mechanically ventilated patients met the criteria of severe poisoning.

Overall mortality was 3%, and the incidence of PNS was 71% at hospital discharge and 62% at follow-up, with no significant differences between the HBO and NBO groups (Box 3).

A smaller proportion of NBO patients than HBO patients were considered to be medically or neuropsychologically impaired after three treatments and thus received additional treatments (all patients, 15% v. 28%, P=0.01; severely poisoned patients, 13% v. 35%, P=0.001).

The only statistically significant difference between groups in neuropsychological performance was in the learning test at completion of treatment (Boxes 3 and 4); this was in favour of the NBO group for both all patients (P=0.01) and severely poisoned patients (P=0.005).

NBO patients had a significantly lower number of abnormal test results at completion of treatment (all patients, 3.4 v. 2.7, $P=0.02$; severely poisoned patients, 3.7 v. 2.6, $P=0.008$) and, for those severely poisoned, there were fewer NBO patients with a poor outcome (85% v. 65%; $P=0.03$).

All five relapses (DNS) occurred in HBO patients ($P=0.03$) at a median of 40 days (IQR, 29–81 days) after initial treatment; these patients then received a mean 4.5 (SD, 2.5) additional treatments. Although three of these patients improved with further treatments, all DNS patients had a poor outcome after re-treatment, with a mean 6.3 (SD, 1.2) abnormal test results.

The evaluation at completion of treatment showed no difference in outcome between the HBO and NBO groups for patients:

- treated within four hours of exposure;
- with severe poisoning and treated within four hours of exposure;
- who required ventilation; and
- who were accidentally poisoned (as opposed to those who attempted suicide).

Only 46% of patients attended the one-month follow-up. Thus, the numbers in subgroups of interest at one month were small, but showed no difference in any test between HBO and NBO groups.

Ten patients had chamber-related complications; seven HBO patients experienced ear barotrauma, one HBO patient developed oxygen toxicity (convulsions) and two patients (one HBO and one NBO) developed severe claustrophobia. The incidence of such complications was thus 9% for HBO and 1% for NBO treatment.

Discussion

In patients with acute CO poisoning, we found no benefit and possible adverse effects of HBO therapy compared with three days of high-flow NBO. Our multiple comparisons between groups may have produced type 1 errors, and some differences may be spurious. However, differences were consistent and all suggested a more detrimental outcome in the HBO group. Despite multiple comparisons, we found no evidence to support HBO therapy. Our findings thus contrast with those of all other published studies, which have suggested benefit or lack of benefit, but never detriment, from HBO therapy (Box 1). To explain this, careful comparison with previous studies is required.

Baseline severity

No previous study has compared HBO with NBO in severely poisoned patients. Unlike the non-randomised studies (Box 1) which used HBO for all severely poisoned patients and NBO only for mildly poisoned patients,[9,13,16,18-20] all patients in our study were randomised. Of the randomised studies (Box 1), three included patients with mild CO poisoning only[12,14,17] (two showing benefit and one no benefit from HBO),[17] while the fourth compared one versus two HBO treatments for severely poisoned patients.[15]

Whereas most CO poisoning in the northern hemisphere occurs as a result of heating accidents, in Australia most results from suicide attempts. Not only had a high proportion of our patients (69%) attempted suicide, but, as in other studies,[9,35] many (44%) had ingested other drugs. Stratified randomisation equalised this factor between groups and hence could not account for lack of benefit in the HBO group.

Further, the six potential factors thought to influence baseline severity (listed in the Methods) were subsequently adjusted for in the generalised linear modelling process. This adjustment also accounted for the small imbalances in the data resulting from cluster randomisation.

Carboxyhaemoglobin level

Although COHb level is often used as an indicator of the severity of CO poisoning and to determine need for HBO,[12-16,20] our findings and other reviews[9,14,18,24,36-40] have shown no relationship between COHb level and outcome.

COHb level depends on CO exposure, time elapsed to measurement and whether or not oxygen has been given. The low COHb levels in our study (HBO 20.5%; NBO 22%) reflect the delay to the measurement and use of high flow oxygen before measurement. Most previous studies did not report time to measurement and used isolated COHb levels to compare severity of poisoning between groups.[12-16,20] Our multivariate analysis showed no correlation between outcome and COHb level even when taking the time to measurement into account. The low COHb levels do not explain the lack of benefit of HBO.

Treatment delay

Animal studies[5] reporting beneficial effects of HBO given immediately after CO exposure cannot readily be extrapolated to clinical practice because treatment delay is to be expected in all clinical scenarios. Our study had a geometric mean treatment delay of 7.1 hours (95% CI, 1.9–26.5 hours), which is longer than in others,[14,16,20] but well within entry criteria limits of most studies that report treatment delay[15,17,39] (Box 1).

Some authors have suggested that the benefits of HBO diminish with treatment delay,[12,41] that more than six hours' delay increases DNS and mortality,[9] and that treatment delay is associated with increased neuropsychological sequelae.[13]

Other studies have found treatment delay to be unimportant,[42] while some case studies[43] and small case series[7] report HBO benefit regardless of treatment delays ranging from days to months. Most North American hyperbaric facilities surveyed in 1995 treated CO-poisoned patients who had neurological deficits despite presentation delays ranging from six hours to 56 days,[44] and HBO has been advocated for DNS occurring weeks after initial exposure.[20,44]

In our study, analysis of patients commencing treatment within four hours (all patients or severely poisoned only) showed no differences in outcome between HBO and NBO. We also analysed time to treatment in quartiles (<3, 3–6, 6–12 and >12 hours) and found no difference in outcome between HBO and NBO. Further, multivariate regression analysis did not identify delay in treatment as a predictor of poor outcome. Thus, there was no evidence that delay to treatment might explain the lack of benefit from HBO.

Oxygen dose

There are no universally accepted recommendations for depth of pressurisa-

tion or duration of hyperbaric treatment for CO poisoning (Box 1). The only studies of the benefit of multiple treatments reached contradictory conclusions.[13,15,38] Raphael et al[15] found no difference in recovery at one month among 286 patients with transient loss of consciousness who received either one or two HBO treatments 12 hours apart. Gorman and Runciman reviewed 13 case series involving 3441 patients and concluded that HBO at 2–3 ATA for 1–2 hours on three or more occasions achieved the lowest mortality, PNS and DNS.[38]

Based on the conclusions of Gorman and Runciman, our study was designed to provide maximum advantage for HBO, with a daily 60-minute treatment at 2.8 ATA on three consecutive days. Because the required dose of NBO for treating CO poisoning is unknown, to ensure we did not undertreat patients, and to maximise similarity of treatment in HBO and NBO groups, all our patients received a treatment on at least three consecutive days and continuous oxygen by non-occlusive facemask at 14 L/min between treatments.

Compared with most previous studies, we performed more treatments, of longer duration, at higher ATA and in conjunction with prolonged high flow oxygen therapy between treatments (Box 1). Our HBO group received oxygen therapy equating to approximately 35.7 COHb-dissociation half-lives, while the NBO group received the equivalent of 28.5 COHb-dissociation half-lives.

Most other studies have used total oxygen doses of less than 7.0 COHb-dissociation half-lives,[9,12,14,15,17] with two series using up to 18 COHb-dissociation half-lives.[13,16]

It is possible that some of the reported beneficial effects of HBO are purely oxygen-dose related, and that adequate NBO, as given in our study, may achieve the same result. This is supported by an uncontrolled study in which a single HBO treatment had no benefit over NBO, but two or more HBO treatments of 60 minutes at 2.8 ATA resulted in significantly less PNS at hospital discharge and DNS at one month ($P < 0.005$).[13]

The apparent worse outcome in our HBO group may also be oxygen-dose related, with higher doses of oxygen adding no further benefit and possibly causing adverse effects. Hampson et al[45] (discussing seizures rather than neuropsychological sequelae) have suggested that CO-poisoned patients are at greater risk of brain injury because of the higher ATA used in treatment, concomitant use of other drugs and toxins (particularly in patients who have attempted suicide), as well as the underlying CO poisoning.

Assessment of outcome

Abnormalities of the basal ganglia, subcortical white matter and hippocampus are the most consistent neuropathological findings in victims of CO poisoning[42,46] and are associated with deficits of attention, information processing and memory.[47] These deficits can be easily missed on casual assessment or simple neurological examination unless specifically targeted. Studies that did not use neuropsychological assessments[9,12,15] reported a lower incidence of PNS than those that did,[48] including our study.

Appropriately targeted neuropsychological assessment provides the most objective, reliable and sensitive evaluation of outcome after CO poisoning,[24,49,50] and in studies that did not report these data[9,12,15-17] it is possible that significant adverse effects were missed, making resulting conclusions unreliable.

The *Carbon monoxide neuropsychological screening battery* (CONSB)[50] does not adequately measure memory, which may be impaired following CO poisoning.[47] The neuropsychological tests we used were therefore more comprehensive than the CONSB, very sensitive to the deficits known to occur in CO poisoning and were computerised (thus increasing objectivity). Further, as one clinical psychologist performed all our testing, interviewer bias was eliminated.

Because a full pretreatment neuropsychological assessment was not practical, a Mini-mental examination was used as our baseline neuropsychological assessment, as it gives a global assessment of severity of cerebral injury. Although not ideal, it had the advantages that (i) it could readily be performed by the assessing doctor and quantified, (ii) it enabled us to determine which patients were capable of giving informed consent, and (iii) as it was tested on presentation, completion of treatment and at follow-up, patients served as their own "controls".

Our definition of an abnormal test result (> 1 SD below the mean) would have included 16% of normal patients. This definition was deliberately chosen to be sensitive to small group differences. We defined a poor outcome as at least two test scores more than one standard deviation below the mean, which would have included less than 2.6% of normal patients. While it is possible that the true incidence of poor outcome or PNS may therefore be slightly lower than we report, the important analyses in making the group comparisons were based on the raw data.

Non-randomised studies (Box 1) suggest beneficial effects of HBO, but only two[13,20] used neuropsychological tests. One used extensive neuropsychometric evaluation at the one-month review,[13] but no evaluation before or at completion of treatment. The other used the CONSB before treatment whenever possible,[20] but not after treatment.

Of the randomised studies (Box 1), one supplemented clinical assessments with electroencephalogram and cerebral blood flow reactivity to acetazolamide,[12] but the clinical relevance of these is uncertain, as the abnormal results were found in patients who were clinically normal. Another used the CONSB, but only after completion of treatment and if patients were "fatigued", the tests were performed in the patients' homes within 12 hours, and a three-month review was only a telephone interview. The lack of baseline assessment, the variable circumstances of immediate outcome assessment and the restricted assessment of delayed outcome greatly limit the interpretation of the findings.

Insensitive assessments and lack of blinding may also have missed important differences and created bias in these randomised studies.

Study outcomes

Our high rate of PNS (compared with previous studies) is probably attributable to our high proportion of severe poisonings (73%) and suicide attempts (69%, likely to be associated with depression and possibly a poor outcome on neuropsychological testing), as well as the comprehensive neuropsychological testing we employed. A type 1 error

resulting from multiple testing may have contributed, as well as our cautious definition of PNS (≥2 test scores < 1 SD below the mean). The rate of DNS in our study (2.6%) is lower than in most previous reports[9,13,16,17,51] (especially given our higher proportion of severe poisonings) and possibly the result of effective treatment with higher doses of oxygen.

Our findings differ from those of most published series (Box 1).

Although all the non-randomised studies[9,11,13,16,18-20] have reported benefit from HBO, none had a control group of matching severity, most had no neuropsychological assessment, and all had low doses of oxygen (brief treatment times) in the NBO groups. With these significant limitations, it is not possible to rely on the conclusions of these studies nor to compare them with adequately conducted randomised trials.

None of the four randomised trials included pretreatment or follow-up neuropsychological assessments or sham treatment of the NBO group (our study is unique in doing this). Three did not have blinded outcome assessments. Both randomised trials that concluded there was benefit from HBO[12,14] studied only patients with mild CO poisoning, thereby excluding the patients in whom the effects of HBO might be most important. The other two found no benefit in HBO and support our findings.[15,17] Mathieu et al found a significantly different incidence of neurological sequelae between HBO and NBO at three-month review (9.5% v. 15%; $P = 0.016$), but not at completion of treatment, one month, six months or 12 months.[17] Raphael et al randomised only mildly poisoned patients,[15] and both treatment regimens used (HBO and NBO) have been criticised.[38]

Interim results (61 patients) of a United States randomised controlled trial enrolling all patients, irrespective of severity of poisoning and also using sham normobaric treatments, found no difference in PNS between NBO and HBO.[52] Of the four published randomised studies, the two small ones[12,14] reported a benefit from HBO, whereas the two larger studies[15,17] did not. If our study is included, three studies involving 1395 patients have now shown no benefit for HBO, compared with two studies involving 91 patients which showed a benefit. Thus, it appears that much of the evidence supporting HBO for CO poisoning is flawed.

Although our multiple tests increased the likelihood of a type 1 error, as the main outcome measures (the number of abnormal tests and a "poor outcome") were based on combining all tests we have minimised the chance of a spurious result.

Delayed review

Despite repeated efforts, only 46% of patients attended for follow-up. This low rate was probably affected by many of our patients having characteristics associated with suicide attempts and depression, many being referred from distant locations, and lack of incentive. However, the follow-up rate was equal in both groups, and evenly distributed across subgroups.

Our follow-up assessment was more comprehensive than in all but one other study,[13] but failed to show benefit for HBO.

Others studies have had significant non-attendance rates at delayed review of 11%–47%.[12-15,19,48] Most studies do not quote the "drop-out" rate.[9,16-18,20]

Conclusion

Our prospective, randomised controlled trial of CO-poisoned patients of all severities attempted to address the shortcomings of previous studies by incorporating sham treatments for the NBO group, blinded outcome assessment and extensive neuropsychological assessment. Our HBO protocol was designed to provide the maximum potential advantage for HBO therapy based on currently available knowledge. When compared with three days of normobaric oxygen, we could find no evidence that treatment with HBO was beneficial to outcome and therefore do not recommend its use.

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(Received 25 Mar, accepted 1 Dec, 1998)

Book Reviews

To give or not to give?

Organ and tissue donation for transplantation. Jeremy Chapman, Mark Deierhoi, Celia Wright, editors. London: Arnold 1997 (xiii + 280 pp., $195.00). ISBN: 0 340 61394 7.

This book is edited by an Australian renal physician, an American renal transplant surgeon and a British transplant coordinator. Their stated aim is to "understand what the real barriers [to tissue donation] are, and how they may be overcome." To encompass this wide brief, the book is organised in three main sections: religion, ethics and society; the actual process of organ and tissue donation (this section includes a marvellous chapter on the problems affecting donor families); and methods of increasing organ and tissue donation.

The international contributors cover these fields in great detail. Some sections, such as that on tissue banking and procurement, are easily readable; however, other chapters, such as the one on allocation of donor organs, are difficult to follow and would have benefited from further editing. The (sometimes contentious) issue of brain death is very well covered in an elegant, definitive and complete discussion, but unfortunately the section entitled "organ and tissue donation in society", with its brief and incomplete look at the attitudes of religious groups to organ donation, is rather thin.

The chapter on paid organ donation offers an intellectual discussion of the subject, with some attempt to justify what, to most, is unjustifiable, and is well worth reading. I would have liked to have seen greater discussion of the Australian attitude to ethical and legal aspects of organ donation. As most Australian models of organ donation are heading towards giving the intensivist primacy in recognising potential donors and requesting permission for donation, the section "Approaching the family", which refers to the organ donation program in Spain, is essential reading.

Overall, this is a good book. Certainly, it fulfils the authors' goal, and with larger print and better paragraphing it would be a very good book.

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Peer review

Problem doctors. A conspiracy of silence. Peter Lens, Gerrit Van Der Wal (editors). Amsterdam: IOS Press 1997 (ix + 274 pp., $106.00). ISBN: 90 5199 287 4.

The medical profession has a proud history of international sharing of both clinical and research knowledge. Unfortunately, there has been far less international sharing of ideas on medical registration, discipline, impairment and incompetence. *Problem doctors* aims to redress the imbalance and is long overdue. The book's subtitle, *A conspiracy of silence*, emphasises that the medical profession needs to face, openly and energetically, the risks posed to the community by members whose performance falls, for whatever reason, below acceptable levels. In this respect, the opening chapter on self-regulation of the medical profession by Marilyn Rosenthal, a sociologist who has empathetically studied this subject, deserves special mention.

Edited by two Dutch physicians with experience in the field, the book draws together general themes relating to problem doctors. It not only covers areas such as doctors' incompetence, impairment, drug dependence and sexual misconduct, but includes reports on how problem doctors are handled in European, North American and Australian jurisdictions and four chapters which offer suggestions for prevention and treatment.

The international perspective of the book is at once a strength and a weakness. Despite the clear guidelines laid down by the editors, some contributors have not directly addressed the topic of problem doctors or have redefined the topic to suit local purposes. Nevertheless, the strengths of the book far outweigh its weaknesses.

Problem doctors should particularly interest those involved in identifying, supporting, counselling and monitoring doctors who are impaired or functioning poorly. It also contains ideas on preventing the occurrence of problem doctors by changing the process of selecting medical students. Well laid-out and well referenced, although unfortunately not indexed, it represents reasonable value for money.

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