Point of view

Let's leave behind dogma!

We are on the edge of the new millennium and the medical profession can look forward to an exciting era of technological advancements, medical breakthroughs and improved patient outcomes. With this comes a responsibility: to determine which practices and beliefs we will take with us and which ones we will leave behind. What better way of making our choice than on the basis of 'evidence based medicine'. Unfortunately, few of our practices are based on Level 1 evidence. Sometimes it is frightening to learn just how little of our day to day practice is in fact evidence-based. This has been highlighted in the recent attempt to establish 'guidelines for the management of severe head injury'.[1]

The treatment of carbon monoxide (CO) poisoning is another such area. Since 1976, the Hyperbaric Oxygen Therapy Committee of the Underwater and Hyperbaric Medicine Society has recommended that CO Poisoning be treated with hyperbaric oxygen (HBO) claiming that this is clearly supported by prevailing scientific information. Much of this considerable scientific evidence arises from isolated case reports, uncontrolled clinical observations, small, non-randomised and unblinded series with incomplete assessment of outcome (e.g. no neuro-psychological testing) being the norm. It is clear however, that recovery from even severe CO poisoning can occur without HBO.[2] It is also important to note that while the hyperbaric 'true believers' insist that HBO therapy for CO poisoning is the 'gold standard', this does not appear to be the case in practice. Hampson's review of Carbon Monoxide poisoning in the Pacific Northwest[3] found that only 6.9% of CO poisoned patients received HBO.

The gold standard of clinical trials is a prospective randomised controlled trial; only these result in Level 1 evidence. Whilst all the reported non-randomised studies have suggested benefit from HBO, there have been only 5 published randomised studies;[4,5,6,7,8] two of which report some degree of benefit[4,7] and three which report no benefit.[5,6,8]

Ducasse *et al*,[4] had a series of 26 non-comatose patients with a Glasgow Coma Score of 15 on admission; 13 patients were randomised to each group. The mean time from rescue to treatment was 53 minutes. The HBO group received hyperbaric treatment for 120 minutes at 2.5 atmospheres absolute (ATA) followed by 100% normobaric oxygen (NBO) for four hours and a further six hours of 50% NBO. The NBO group received oxygen through a facemask at 100% for 6 hours, then at 50% for 6 hours. Patients were assessed on clinical signs and symptoms, EEG and cerebral blood flow response to acetazolamide. No neuro-psychological assessments were performed. The reported incidence of both persistent neurological sequelae (PNS) and delayed neurological sequelae (DNS) were zero. Clinical assessment at 2 and 12 hours favoured the HBO group. Two patients in the NBO group were changed to HBO at 12 hours and were asymptomatic at completion of treatment. All 26 patients were discharged home well, an average of 28 hours after presentation. There was no difference in the EEG at 24 hours between HBO and NBO groups. Eight of 26 patients (31%) were lost to follow-up. Follow-up EEG in the remainder was worse in the NBO group, but all patients were clinically normal, making the relevance of this unclear. Ducasse *et al*, concluded that HBO reduced the time to initial recovery and the number of delayed functional abnormalities in non-comatose patients with acute CO poisoning, attributing some of their success to the rapidity of treatment.

Thom *et al*[7] also included only patients with mild poisoning and no history of loss of consciousness. Patients presented within 6 hours of exposure and usually commenced treatment in about one hour. Thirty-two patients were allocated to NBO and thirty-three to HBO. Neither the patients nor the investigators were blinded to treatment. HBO patients were treated once for 30 minutes at 2.8 ATA followed by 90 minutes at 2.0 ATA. NBO patients received 100% oxygen through a non-rebreathing facemask until all symptoms resolved (4.2 ± 3 hours). The presence or absence of 5 signs and symptoms together with a carboxyhaemoglobin (COHb) level were used to assume the two groups were of similar severity of poisoning but delay taken in measurement of COHb is not mentioned and no baseline neuropsychometric testing was performed. Thom *et al*, used a carbon monoxide neuropsychological screening battery (CONSB) designed by Myers *et al*,[9] after completion of treatment, but not in a uniform manner. Some were performed immediately on completion of treatment, but if patients were 'fatigued', the tests were performed in the patients' homes within the next twelve hours. The paper does not state the number of clinicians involved in performing the neuropsychometric testing. The CONSB is said not to adequately measure memory. Formal neuropsychological testing was performed at one month, but the three-month review consisted of a telephone interview only. Twelve of 65 patients (18%) were lost to follow-up. Thom *et al*, reported no DNS in the HBO group, whilst 7 out of 30 in the NBO group developed problems ($p < 0.05$). No specific treatment was given to those who developed DNS. Three of these

patients refused follow-up. In the remaining four, neuropsychometric testing was repeated at intervals of 2-3 weeks until scores returned to baseline. It would appear that all DNS resolved. They concluded that HBO treatment decreased the incidence of DNS after CO poisoning.

Raphael *et al*[6] patients were poisoned in the 12 hours prior to hospital admission. A total of 343 patients with mild CO poisoning (no impairment of consciousness) were randomised to receive either NBO or HBO and 286 severely poisoned patients were randomised to either one or two sessions of HBO 12 hours apart. Critically ill patients were excluded. Patients refusing the allocated treatment after randomisation (n = 19), were still retained in the study and analysed according to treatment intended. NBO therapy consisted of 6 hours of 100% inspired oxygen by facemask or endotracheal tube. HBO therapy consisted of 2 hours of HBO in a monoplace chamber (0.5 hours for compression, 1 hour at 2.0 ATA and 0.5 hours for decompression) plus 4 hours of NBO. Eleven percent of patients were lost to follow-up. They reported 32% - 34% incidence of PNS in patients without loss of consciousness and 46% - 48% PNS in those with loss of consciousness based on gross signs and symptoms, as neuropsychological testing was not performed. Patient assessment at one month consisted of a self-assessment questionnaire and a physical examination by their own doctor. If there was no response to the questionnaire, patients were telephoned. Thus DNS was diagnosed on a mail or telephone questionnaire. The physical examination was performed by the patient's own doctor.

However, inexperienced physicians not used to assessing these patients may miss subtle signs and symptoms and the use of multiple doctors precludes consistency. NBO was given by facemask only making the exact percentage of inspired oxygen unclear and the HBO regimes used are considered by some to be ineffective (2.0 ATA instead of 2.8 ATA). Raphael *et al*, concluded that in patients without loss of consciousness, HBO had no advantage over NBO. At the one-month review, recovery occurred in 66% of 170 NBO patients and 68% of 173 HBO patients. Ninety-seven percent of patients resumed their usual occupation and social activities irrespective of treatment. In patients with transient loss of consciousness, they found no difference in outcome between those patients having one or two treatments at 1 month follow up (54% versus 52% recovery, p=0.42).

Mathieu *et al*,[5] report an interim analysis after 3 years of a five-year multi-centre study. Only patients non-comatose on hospital admission and poisoned in the preceding 12 hours were enrolled. Delay to treatment is not specified. Treatment was either one HBO session of 90 minutes at 2.5 ATA (299 patients), or 12 hours of normobaric 100% oxygen (276 patients). Patients were neurologically normal at the time of hospital discharge, but at one month approximately one quarter had sequelae, with no difference between HBO and NBO (23% v.s. 26%). At three months, the incidence fell and there was a statistically significant difference between HBO and NBO (9.5% v.s. 15%; p = 0.016) but this was no longer evident at 6 (6.4% v.s. 9.5%; p = 0.09) or 12 months (4.3% v.s. 5%). They refer to the neurological manifestations as PNS, but given that the patients were neurologically normal at the time of hospital discharge, it is not clear whether they are PNS or DNS. Mathieu *et al*, provide no details of attendance at follow-up. Neuropsychological assessments were not performed either pre or post treatment or at follow-up.

Our study design which is "amongst the most rigorous yet published",[10] has received a Level 1 Evidence rating[11] and has been abstracted in Evidence-Based Medicine,[12] attempted to address the shortcomings of the previous trials.

We randomised patients with all grades of CO poisoning, used sham treatments in the multiplace chamber for the NBO group, used an HBO treatment protocol based on best available data, delivered 100% oxygen to the NBO group during their treatment sessions using either an occlusive face-mask or a hood, gave longer duration oxygen therapy to the NBO group than previous studies, used a pre-treatment baseline minimental examination, used an extended series of neuropsychological tests to assess both persistent and delayed neuropsychological deficits, used a clinical psychologist trained in neuropsychological assessment of brain injured patients to perform all the tests (at completion of treatment and at follow-up), and used computerised testing to standardise administration and increase objectivity.

Following consent, patients were stratified into four groups: suicide versus accidental, then mechanically ventilated versus non-ventilated. Randomisation (HBO or NBO) was then performed using sealed, opaque envelopes. Both patients and outcome assessor were blinded to treatment group. Patients had an initial minimental examination followed by full neuropsychological testing on completion of three treatments. Patients with poor neuropsychological outcome received three further treatments (as originally allocated) before neuropsychometric re-assessment.

Patients received daily treatments in a hyperbaric chamber for a minimum of 3 days: HBO patients (n = 104) for 60 minutes at 2.8 ATA; NBO patients (n = 87) with 100% oxygen at 1.0 ATA. Between treatments, both groups received high flow oxygen.

In this prospective randomised controlled trial of 191 patients, in which both groups received high doses of oxygen, the addition of HBO therapy did not benefit

patients and may have worsened their outcome.

Our study has however, attracted a number of criticisms. In the accompanying editorial, Moon and DeLong[10] expressed concern about cluster randomisation. Weaver[13] expressed similar concern in his editorial in the BMJ.

To minimise the impact of the trial on daily practice, cluster randomisation was used for simultaneously presenting patients from the same exposure: the treatment group assigned to the first patient was allocated to the other simultaneously presenting patient(s). Randomisation took place only after the group was assembled. Cluster randomisation accounted for the difference in numbers in HBO and NBO groups. We used cluster randomisation, allocating more than one person simultaneously to the same treatment on 22 occasions, (2 on 12 occasions, 3 on 5 occasions and 4 on 5 occasions). Overall 14 clusters (i.e. 40 patients) were allocated to HBO and 8 clusters (i.e. 19 patients) to NBO. 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 randomization could be statistically controlled and adjusted for by including these variables in the generalised linear model. Continuous outcome variables were also analysed by the mixed procedures in SAS (2) which allows a repeated measures analysis of variance, with the variable cluster being treated as a random repeated measurement, thus 'adjusting for' within cluster variation. We also repeated the analysis excluding all patients who were allocated as part of a cluster. These analyses indicate that our results were not biased by cluster randomization.

Both Moon and DeLong and Weaver also express concern about the delay to treatment (geometric mean of 7.1 hours). Although this is not dissimilar from three of the above studies, we also performed subgroup analysis of patients treated within 4 hours (all patients and just severely poisoned patients). There were 44 patients treated within four hours (22 HBO and 22 NBO), 33 of which were severely poisoned (15 HBO and 18 NBO) with no outcome measure favouring the use of HBO. We further analysed time to treatment in quartiles (e.g. < 3, 3-6, 6-12, >12 hours) and found no difference in outcome between HBO and NBO. Further multivariable analysis did not identify delay in treatment as a predictor of poor outcome. Thus there was no evidence that delay to treatment might have explained the lack of benefit of HBO.

Weaver expresses concern that concomitant depression and use of psychoactive drugs might have influenced the results given the large percentage of suicide attempts in our patient cohort. Whilst it is true that depression and the use of medication may have resulted in a higher incidence of poor outcome overall, this would not in any way have biased the comparison between normobaric and hyperbaric groups as patients were specifically stratified for suicide attempt prior to randomization to therapy. Both Moon and DeLong and Denson and Hay[14] raise the issue that we performed a multitude of tests and that only one showed a statistically significant result (in favour of NBO). Although we performed a multitude of tests, not one showed a benefit in favour of HBO.

The comprehensive assessment of all patients at completion of treatment showed no benefit for HBO. Patients were then requested to attend for review at one month. The review appointment was confirmed by mail and if required, patients were actively pursued by telephone. Despite repeated efforts, only 46% of patients attended follow-up. This low rate of attendance at follow up is indeed a major problem. Our patient population, with its high incidence of suicide attempts and depression, many referrals from distant locations, and lack of incentive, probably contributed to the low follow-up rate, which was however, equal in both groups, and evenly distributed across subgroups.

For those attending follow-up, our assessment was rigorous (much more so than a telephone survey) and failed to show any benefit for HBO. Previously published randomised studies have experienced lower but significant non-attendance rates at delayed review of 11-31% with Mathieu *et al*, study not quoting the 'drop-out' rate.

We believe there are two major limitations to our study. We would have clearly liked the follow-up rate to be higher, but this was not within our control. We set out to demonstrate an advantage for HBO and selected what appeared to be the optimum treatment regime to achieve this. In the absence of any evidence as to the best NBO treatment protocol, we tried to give both groups identical treatment (minus the hyperbaric component). We have demonstrated that there is no advantage in outcome for HBO over 3 days of high flow oxygen therapy. Our study cannot answer whether the same outcomes can be achieved with shorter duration of high flow normobaric oxygen therapy.

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