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Oxygen therapy for CO poisoning: rationale and recommendations

Tlenoterapia w leczeniu zatruć CO: racjonalne przesłanki i zalecenia

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CO poisoning remains a serious public health problem. Oxygen is the basis of its treatment and HBO has been proven more effective to prevent cognitive sequelae than NBO. Most commonly accepted criteria for HBO treatment are: comatose patient, loss of consciousness, neuropsychological and cardiac symptoms and pregnancy. However, patients not requiring HBO, have to be treated by a correct NBO regimen.

Zatrucia CO są ciągle poważnym problemem zdrowia publicznego. Podstawą leczenia jest tlenoterapia, a leczenie tlenem hiperbarycznym (HBO) okazało się bardziej skuteczne w zapobieganiu odległym zaburzeniom funkcji poznawczych niż podawanie tlenu w normobarii. Najpowszechniej zaakceptowanymi wskazaniami do stosowania HBO są: śpiączka, utrata przytomności, zaburzenia neuropsychologiczne, objawy ze strony układu krążenia i ciąża. Pacjenci, którzy nie wymagają HBO powinni być leczeni tlenem normobarycznym zgodnie z przyjętymi zasadami postępowania.

Introduction

Carbon monoxide (CO) poisoning remains a leading cause of death and neurological disability. Since the experimental studies of Haldane [8,9], oxygen has been recognised as the main treatment of CO poisoning and, following *Smith's* study in 1960 [22], Hyperbaric Oxygen (HBO) has been commonly used in clinical practice.

I. Pathophysiological rationale for HBO in CO poisoning

Toxic effects of CO on humans have long been considered as due to the hypoxic stress of carboxyhemoglobin (COHb) formation, which decreases oxygen delivery to tissues. However, the level of COHb does not predict the development of signs and symptoms of injury, particularly with respect to the brain [2,5,17,30]. Non-hypoxic mechanisms including oxidative stress related in part to cellular uptake of CO, also participate to brain injury [24,25,31]. Oxygen breathing hastens dissociation of CO from hemoglobin and improves tissue oxygenation. Hyperbaric Oxygen causes carboxyhemoglobin to dissociate at a rate higher than that achieved by breathing normobaric oxygen (NBO) [4,19]. In experimental CO poisoning, HBO but not NBO has other beneficial effects: improvement of mitochondrial oxidative metabolism [1], inhibition of lipid peroxidation [23] and inhibition of leukocyte adherence to injured microvessels [26]. Animal poisoned with CO and treated with HBO have more rapid improvement in cardiovascular function, fewer neurological sequelae and better survival.

II. Clinical studies

Since HBO was first used as a treatment in CO poisoning in 1960 [22], treatment guidelines have been developed on the basis of clinical experience. Numerous uncontrolled studies reported lower mortality and morbidity in patients treated by HBO [6,7,11,18]. In the late 1980s, HBO treatment came under criticism due to the lack of prospective controlled studies supporting its use in CO poisoning.

This last 15 years, 6 prospective randomised trials have been reported comparing HBO and NBO for CO poisoning [3,15,20,21,27,29]. Of the 6 trials, 4 demonstrated better clinical outcome among patients receiving HBO while 2 showed no effect.

The first randomised study by *Raphael* et al. [20] included 343 patients without loss of consciousness and treated either by HBO (2 ata, 60 minutes) or NBO (6 hours). No significant difference in neurological manifestations present at one month after poisoning was found. Same negative conclusion was drawn from 286 patients with loss of consciousness treated either by one or two HBO sessions. This study was criticised for using overly broad inclusion criteria, inadequate HBO regimen, time of evaluation and weak outcome measure.

A second prospective trial was performed by *Ducasse* et al. [3] and included 26 non-comatose patients treated by HBO or NBO. Evaluation was done by clinical examination, electroencephalogram and cerebral blood flow response to acetazolamide. A significant benefit at 3 weeks was found in the HBO treated group. Limitation of this study included small size of the studied sample and use of surrogate outcome measures.

A third study by *Thom* et al. [27] included 60 patients with mild CO poisoning, excluding those with history of unconsciousness

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or cardiac disturbances. After randomisation, patients were treated by HBO (2.8 ata during 30 minutes, followed by 2 ata, 90 minutes) or NBO (until symptom relief). Patients were followed with neurological testing. Persistent neurological manifestations were found in 7 of 30 (23%) patients treated by NBO and in no patients treated by HBO ($p<0.05$). Neurological manifestations persisted for an average of 6 weeks and often interfered with normal daily activities. The trial was stopped early due to the treatment advantage but has revealed limitations: small sample size, lack of double blinding and number of patients lost for follow-up.

A fourth randomised trial performed by *Scheinkestel* et al. [21] enrolled 191 CO poisoned patients of different severity. Patients were treated either by HBO (1 session a day, 3 ata, 60 minutes with intervening NBO for 3 to 6 days) or NBO for 3 to 6 days. Outcome measures were clinical evaluation and neuropsychological testing after treatment and one month after. No beneficial effect was found. Flaws were numerous. First, most of the CO poisoning were suicidal and associated to ingestion of alcohol and drugs that may have interfered with the results of psychoneurological testing. Second, neither HBO nor NBO protocol were commonly used regimen and the HBO group received only 7% more oxygen than the NBO. Such a small difference could hardly make a significant difference. Finally, less than a half of the patients completed the follow-up at one month.

These conflicting results have fed the controversy. But, a recent randomised prospective double-blinded study by *Weaver* et al. [29] has reported unequivocal beneficial results of HBO treated patients. 152 patients were included and randomised to receive either HBO (3 sessions in 24 hours) or NBO. An extensive neuropsychological test battery was performed at 6 weeks and one year. Cognitive sequelae were significantly lower at 6 weeks in the HBO treated patients than in NBO treated patients (25% versus 46%, $p<0.07$). The beneficial effect persisted at one year (4% vs. 15%, $p<0.04$).

A post hoc analysis of the results of this study [28] showed the beneficial effect of HBO was present in patients with: age over 50 years, having presented loss of consciousness during exposure, carboxyhemoglobin level over 25%, metabolic acidosis (BE lower than -2mEq/l). HBO has no advantage on NBO in patients without these criteria.

An other prospective randomised trial has been published but only in abstract [15]. It concerned an interim analysis of a prospective multicentre study. 575 non-comatose patients were randomised to receive either HBO (1 session, 2.5 ata, 90 minutes) or NBO (12 hours). Follow-up was done at 1, 3, 6, 9 and 12 months. A significant difference in favour of HBO existed at 3 months (8.7% vs. 15.2%, $p<0.016$), lessened at 6 months and disappeared at 1 year.

III. HBO for CO poisoning: which patients ?

Treatment of CO poisoning by HBO has demonstrated its superiority on treatment by NBO, regarding neurological sequelae. However, treatment by HBO of all forms of CO poisoning is probably not indicated [10]. HBO should be used for patients at high risk of neurological sequelae. Presently, those high-risk patients are not sufficiently well defined and studies have to be done to precise those high-risk patients.

From the published studies [14,28] comatose patients, loss of consciousness, neurological abnormality, especially cerebellar impairment, carboxyhemoglobin over 25%, metabolic acidosis are the most probable criteria. Neuropsychological testing could perhaps be an important tool in the future.

There is no randomised study for the CO poisoned children. It seems acceptable to follow the same decision tree than in adults even if impairment in cognitive function is more difficult to assess in a young child than in an adult. Thus, HBO indications are often broader in children.

Finally, due to the severity for the foetus of CO poisoning in the mother [12], despite the lack of randomised prospective study, CO poisoned pregnant woman has to be treated with HBO [13].

IV. HBO in CO poisoning: what protocol?

Results of recent randomised studies strengthen the basis to use HBO in acute CO poisoning. However, a number of very important issues remain not answered. The optimal doses of HBO, e.g. number of sessions, treatment pressure and duration are not yet clearly defined. Most of the protocols used between 1 and 3 HBO sessions. In the *Weaver's* study, most of the benefit appeared after the first treatment. In clinical practice, it is usual to repeat the HBO session when the clinical state has not normalized after the first session.

Time after which it is no longer useful to treat is also an unanswered question. In a study performed by *Goulon* [7], the best results were obtained when the patients were treated within six hours. In clinical practice, it is usual not to treat after 24 hours from exposure if the patient is symptom-free.

Conclusion

CO poisoning remains a serious public health problem. Oxygen remains the basis of its treatment and HbCO has been proven more effective to prevent cognitive sequelae than NBO. Most commonly accepted criteria for HBO treatment are: comatose patient, loss of consciousness, psychoneurological and cardiac symptoms and pregnancy. However, if it is necessary to select high-risk patients to be treated by HBO, other patients have to be treated by a correct NBO regimen. A recent survey in our region showed that 50% of CO poisoning patients requiring NBO were treated with an insufficient NBO regimen [16]. This also may lead to severe consequences in morbidity and socioeconomic costs.

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