POST-ANOXIC ENCEPHALOPATHY

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Background

Post anoxic encephalopathy is a frequent pathology in intensive care especially after cardiac arrest. Despite the progress that has been made, prognosis remains severe. Cardiac arrest is indeed responsible for a very high mortality rate (over 90%), but also a significant morbidity rate including severe neurological sequelae.
Although no double-blind randomized study has been performed, hyperbaric oxygen therapy (HBOT) has been proposed and used as an adjunctive treatment for post-anoxic encephalopathy for more than 30 years. In recent years, both cell and animal studies have supported this proposal.

Clinical presentation

Anoxia causes various neurological conditions : from brain death to a normal state of consciousness with or without neurological sequelae. Between these two states, different stages are possible, including a vegetative state. After cardiac arrest, obviously it is the extent of neurological lesions which will influence the prognosis.

Standard management and outcome (1)

Nowadays the management of post-anoxic encephalopathy mainly involves non-specific procedures specifically geared at preventing a worsening of the patient's condition :

- maintaining a stable hemodynamic and respiratory condition & avoiding sudden blood pressure
- avoiding excessive oxygen consumption by preventing and treating hyperthermia and hypertension access
- correcting any metabolic disorder, acute renal failure, hyper catabolic state
- ensuring normoglycemia
- treating possible seizures (benzodiazepines, antiepileptics, propofol).
- preventing cerebral oedema: moderate hypocapnia and raised position (35 to 45°) of the head - Mannitol may be used.
- decreasing cerebral oxygen consumption by central hypothermia (32-34° during 12-24 hours)

Rationale for the use of HBOT

Among the various forms of post-anoxic encephalopathies, two have been studied with regard to the use of HBOT : Post-Cardiac Arrest Encephalopathy (PCAE), mainly in peri-operative situations, and post-hanging or strangulation encephalopathy.

Pathophysiology

When the blood flow is stopped in the brain, either during cardiac arrest or by an occlusion of the cervical vessels, a shortage in brain cell adenosine triphosphate (ATP) soon occurs, causing brain damage if continued. The collapse in ATP reserves causes an alteration of Na/K pumps resulting in a massive efflux of potassium, an entry of sodium and water, and membrane depolarization, inducing astrocyte swelling. This leads to calcium channel opening, an uncontrolled influx of calcium, activating phospholipase, hydrolyzing phospholipids of the membrane. All of which combine to destroy the mitochondrial and cell membranes, releasing free fatty acids (2).
This energy debt is geared at an anaerobic metabolism with increased tissue lactate concentration. When lactate concentration reaches a peak, it causes swelling and bursting of the astrocytes as well as endothelial cell necrosis (2).

The use of HBOT in post-anoxic encephalopathy is based on the significant increase of oxygen levels in blood, tissue and cells (3–5). HBOT puts the energy debt right, restores glucose metabolism with oxidative metabolism, thus suppressing lactate production in the brain (5–9). This has been shown in humans by measuring arterio-venous differences in the brain (10). One or more 90-minute sessions of HBOT at 2 ata increase arterio-venous differences in oxygen content, decrease arterio-venous differences in glucose content and increase the oxygen glucose index. This would improve the prognosis of patients (10). All of which combine to increase the oxidative metabolism with quiescence of the glycolytic pathway (10–13). In injured rats, these changes when HBOT was provided remained even after the animals were removed from the hyperbaric chamber (14).

When the blood flow is restored in the brain, two phases occur : first, a transient global hyperemia (15-30 minutes) followed by microcirculatory alterations and arrest responsible for the death of the brain cells that survived the initial ischemia. This ischemia-reperfusion phenomenon is explained by :

- Energy debt inducing cell depletion in antioxidant systems, particularly in reduced glutathione. During the reperfusion phase, the oxygen flow cannot be supported by the respiratory chain because of mitochondrial damage. This leads to an increase in the development of reactive oxygen species, which attack the membrane lipids and cause cell death (15). Furthermore, Fujita and Kitani reported a decrease of the intracellular concentration of potassium in red blood cells of patients with hypoxic encephalopathy (16). As HBO improves the function of membrane ion pumps in ischemic cells, HBOT can prevent the production of reactive oxygen species and contribute to repairing the damaged cells (5,17).
- Hypoxia causes microthromboses and alterations of erythrocyte deformability. At the cellular level, the endothelial oedema and swelling of pericapillary astrocytes combined with the decreased activity of their membrane pumps alter the local blood flow (there is no reflow) (18). HBOT induces tissue partial pressures of oxygen compatible with life and cell repair. Moreover HBOT has a favorable effect on the deformability of red blood cells, improving their contribution to tissue exchanges (19,20).
- Brain oedema (9) : if its occurrence is somewhat delayed in post-anoxic encephalopathy due to cardiac arrest, it occurs in an especially early and severe form in cases of hanging or strangulation, causing acute intracranial hypertension. In the case of hanging, brain oedema is due to three components : occlusion of return blood flow in the brain which induces significant plasma exudation responsible for the early vasogenic component ; alteration of the blood-brain barrier causes fluid transudation from intravascular areas to cerebral interstitial spaces and cell swelling due to cell ATP depletion. HBOT has been shown by many studies to provide an anti-oedematous effect by reducing intracranial pressure due to the hyperoxic vasoconstriction induced (5,21–26).

Animal study

Experimental work on cats (27), dogs (28,29) and rats (30) evidenced the interest of HBOT in post-anoxic encephalopathy with respectively : slower electroencephalographic recoveries and changes in cerebrospinal fluid lactate (27), faster neurologic recoveries (28,29), reduced ischemic neuronal injuries and brain oedemae (26,30). On the other hand, Ruiz et al. reported no significant effects (survival duration, cardiac function and neurologic scoring) of HBOT and hemodilution in dogs who underwent circulatory arrest for 12 minutes due to ventricular fibrillation (31).

To conclude, pathophysiological as well as animal studies form a firm basis in favor of the use of HBO in clinical practice.

Evidence–based review of the use of HBO

There is no randomized controlled clinical study comparing patients with post-anoxic encephalopathy provided or not with HBOT.

In patients with post-hanging anoxic encephalopathy, a small study published as an abstract found a beneficial effect of HBOT compared to conventional treatment in terms of mortality and sequelae

(32). In a larger series of 170 patients, 132 out of 170 patients (77.5%) recovered without sequelae, 30 (17.5%) died and 2 (5%) suffered neurological sequelae (33). Complete recovery is the rule for patients arriving in a coma with an initial Glasgow coma score of over 6. Neurologic recovery most often occurs within 24 hours after admission, during or just after the first HBOT session. Complete recovery is achieved less frequently in patients in deeper states of coma, but remains possible without sequelae. In this study, a series of 5 HBOT sessions was provided over a period of 48 hours. After these 5 sessions, if the Glasgow coma score was still under 5, cerebral prognosis was seriously compromised.

Current protocol

90-minute sessions of HBOT at 2.5 ata are provided. 3 sessions are provided over the first 24 hours, then 2 over the next 24 hours. Since no other studies are available, experts agree that HBOT should be discontinued after 5 sessions.

Recommendations

The level of evidence for the use of HBOT in post cardiac arrest anoxic encephalopathy is very low. So, we recommend using HBOT for the purpose of clinical studies only. Patients with chronic post-anoxic encephalopathy should not be transferred to a hyperbaric facility unless they are to be included in a clinical trial.

For patients with post-anoxic encephalopathy following hanging or strangulation, we consider reasonable to propose HBOT as an optional adjunctive treatment (Type 3 recommendation, Level C evidence).

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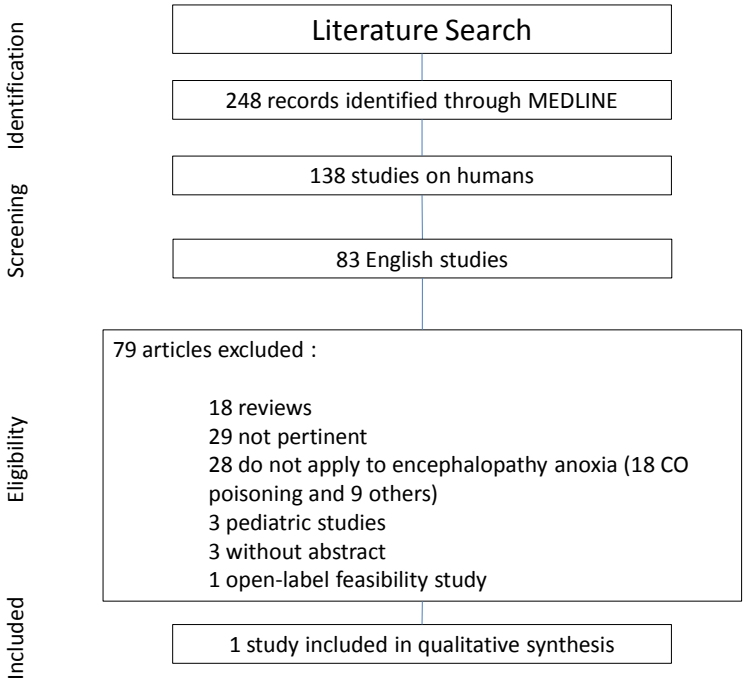
Identification
Screening
Eligibility
Included
Literature Search
248 records identified through MEDLINE
138 studies on humans
83 English studies
79 articles excluded :
18 reviews
29 not pertinent
28 do not apply to encephalopathy anoxia (18 CO poisoning and 9 others)
3 pediatric studies
3 without abstract
1 open-label feasibility study
1 study included in qualitative synthesis

Study (author, year)	**Type**	**Nb of patients**	**Aim(s) / Evaluation criteria**	**Inclusion / Exclusion Criteria**	**HBOT protocol** (pressure, duration, nb of sessions)	**Results**	**Conclusion / comment**
Mathieu, 1987	Cohort study	170	Neurologic recovery	All post-hanging patients admitted between 1971 and 1981	2.5 ata 90 mn 1-5 sessions	132 out of the 170 patients (77.5%) healed without sequelae, 30 (17.5%) died 2 (5%) suffered neurological sequelae	HBOT proves useful in dealing with post-hanging patients