**Online Supplement B: Non-RCT study designs meeting eligibility criteria**

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| **Reference** | **Population Description****(# of participants)** | **Intervention** | **Outcomes** | **Adverse Events** | **Results** |
| **Pre-post Longitudinal Studies** |
| Churchill, 201337 | Stroke; Anoxia; Trauma (63) | HBO2: 60 sessions of 100% O2 at 1.5 ATM for 60 minutes | Neuropsychological measures, questionnaires, neurologic exams, physical functioning measures | Myopia (n=3); middle-ear barotrauma (n=3); otitis externa (n=1); fatigue/nausea (n=1). | While participants reported improvements in symptoms, such as memory and balance/ coordination, no standardized testing showed clinically important improvement. There were also improvements in a small subset of participants undergoing neuroimaging, such as auditory functional MRI and magnetic resonance spectroscopy (MRS), but the clinical relevance of neuroimaging changes is unclear.  |
| Gossett, 201039 | Severe TBI (27) | HBO2: 75 sessions at 1.5 ATM within a monoplace chamber | Cardiovascular and ventilatory parameters, intracranial pressure, brain tissue oxygen levels, brain temperature, and cerebral microdialysis | Significant drop in PbtO2 accompanied by an increased swelling in the neck (n=1); increased peak inspiratory pressure due to pre-existing basilar pleural disease (n=1). | Focus of paper was on logistics of administering HBO2 sessions. No clinical results reported. |
| Harch, 201240 | Mild to moderate TBI / Post-concussion Syndrome (PCS) / Post-traumatic Stress Disorder (PTSD) (16) | HBO2: 40 sessions of 1.5 ATA | Changes in PCS and PTSD symptoms, physical and neurological exams, SPECT, quality of life measures, and neuropsychological and psychological testing | Reversible middle ear barotrauma (n=5); transient deterioration in symptoms (n=4); reversible bronchospasm (n=1) | There were significant improvements in these outcome measures at post-treatment testing.  |
| Hayakawa, 197142 | Acute cerebral damage (13) | HBO2 | Cerebrospinal fluid pressure (CSFP), carotid blood flow, arterial blood pressure, central venous pressure and superior sagittal sinus pressure | ND | Three patterns for CSFP and HBO2 emerged: 9 cases CSFP decreased at the beginning and rose again at the end of HBO2; 2 cases CSFP fell with HBO2 and remained significantly lower than pretreatment level; and 2 cases CSFP showed little change with HBO2.  |
| Holbach, 197043 | Severe head injuries; cerebrovascular disease (44) | HBO2: Between 2 and 3 ATA for 30-60 minutes | Blood gases, pH, lactatepyruvate concentration, electrocardiogram, and electroencephalography. | ND | While there was an increase in aPO2, the levels of PCO2 and pH remained within normal limits. There was also a decrease in lactate and pyruvate concentrations as well as varying degrees of cerebral vasoconstriction under hyperbaric oxygen exposure.  |
| Holbach, 197244 | Marked cerebral injuries (10) | HBO2: Between 1 and 3 ATA | Cerebral glucose metabolism,concentrations of glucose, lactate and pyruvate. arterio-cerebral venous difference, and glucose oxidation quotients (GOQ) | ND | At 1.5 ATA, there was a well-balanced cerebral glucose metabolism, as indicated by normal GOQ level, but at 2.0 ATA, there was an excessively increased amount of glucose in comparison to significantly decreased O2 uptake.  |
| Mogami, 196941 | Severe acute cerebral damage (66) | HBO2: 1-2 daily sessions at 2.0 ATA for 60 minutes, plus 6 sessions of 3ATA for 30minutes | Electroencephalography (EEG), Cerebrospinal fluid pressure (CSFP), and lactate and pyruvate levels. | Worsening after sessions including one death soon after the end of the treatment (n=4), slightly increased convulsive seizures during HBO2 when carbon dioxide-mixed gas inhalations (98% O2, 2% CO2) (n=1) | After treatment, neurological improvements were observed in half of the patients, and reduction of EEG abnormalities was noted in one-third of the patients. While there were individual variations in the change of CSFP, the pressure generally decreased at the beginning of the treatment, was maintained at a low level during the treatment, and rebounded at the end of the treatment. HBO2 was also associated with a slight decrease in the lactate pyruvate ratio in the cerebrospinal fluid.  |
| Nakamura, 200845 | Disturbances in consciousness after head injury in the sub-acute phase (7) | HBO2: 5 daily sessions of 100% O2 at 2.7 ATA for 60 minutes | Cerebral circulation by mean flow velocity (mFV), pulsatility index at horizontal portion of middle cerebral artery by transcranial Doppler (PI), cerebral metabolism by arterio-jugular venous difference of oxygen (AJDO2) and jugular venous lactate (lac-JV). | ND | While both PI and lac-JV were significantly decreased after HBO2 treatment, there were no significant changes in mFV and AJDO2.  |
| Rockswold, 200146 | Severely brain injured patients (37) | HBO2: 7 or fewer sessions of 100% O2 at 1.5 ATA for 60 minutes | Cerebral blood flow (CBF),arteriovenous oxygen difference (AVDO2),cerebral metabolic rate of oxygen (CMRO2), ventricular cerebrospinal fluid (CSF) lactate andintracranial pressure. | ND | HBO2 treatment increased CMRO2 and decreased CSF lactate levels and had a prolonged effect on CBF and cerebral metabolism at 6-hour post measurement, but the effects of each HBO2 treatment did not last until the next HBO session. Based on these findings, authors asserted that shorter, more frequent exposure to HBO2 may optimize treatment.  |
| Shi, 200647  | Neuropsychiatric disorders arising from traumatic brain injury (310) | HBO2: 2 sessions | SPECT, CT  | ND | Following HBO treatment, significant improvements were detected by SPECT.  |
| **Clinical Controlled Trials** |
| Barrett, 200436 | Chronic stable TBI patients at least 3 years post injury (10); healthy subjects (5); data bank to compare SPECT scans (68) | HBO2: 120 sessions with an interval five-month break after the first 80 sessions.  | Neurologic, neuropsychometric, and exercise testing, MRIs, or CT scans, SPECT. | issues equalizing pressure (n=ND) | There were no significant objective changes in neurologic, neuropsychometric, exercise testing, MRIs, or regional CBF. In this small pilot study, HBO2 did not effect clinical or regional cerebral blood flow improvement in TBI subjects. |
| Holbach, 197748 | Head injury or ischemic brain lesion (30) | HBO2: Either 2.0 ATA or 1.5 ATA. | Cerebral arteriovenous difference (AVDO2),levels of glucose, pyruvate, and lactate, blood gas pressures, pH, and cerebral glucose metabolism. | ND | At 1.5 ATA, there was an improved balanced cerebral glucose metabolism or the appearance of a Pasteur effect, indicating an adequate cerebral oxygenation and energy formation of the affected brain. However, at 2.0 ATA, there was a considerable increase in cerebral glycolysis and disturbed oxidative energy formation. Thus, the results showed HBO2 exposure at 1.5 ATA is well tolerated by an injured brain and has a favorable effect on the glucose or energy metabolism, while exposure at 2.0 ATA is not well tolerated. |
| **Chart Reviews** |
| Giebfried, 198638 | Head and neck diseases (ND) | HBO2 |  | The review found serious complications associated with hyperbaric oxygen treatment, including seizure, stroke, and myocardial infarction.  | Only adverse events reported. Please see adverse events report. |
| Sahni, 201249 | TBI patients who received HBO (20) vs “standard care” (20) | HBO2 or “standard care” | Disability Rating Scale (DRS), Glasgow Coma Scale (GCS), and Rancho Los Amigos Scale (RLAS).  | ND | According to the analysis, a significantly higher proportion of patients receiving HBO2 showed improvements compared to patients receiving only standard care.  |
| **Survey** |
| Myers, 198250 | Use of HBO2 at 83 North American HBO2 centers |  |  | ND | According to the 57 centers that responded to the survey, a total of 10,942 patients were treated during the eight-year survey period and 8,408 patients (76%) had category I or II conditions, as defined by the Undersea Medical Society. |
| **Case Studies** |
| Brown, 198851 | 1) Diffuse cerebral swelling after blunt trauma 2) Gun shot wound (2) | HBO2: 4 sessions of 100% O2 at 2.0 ATA  | Intracranial pressure (ICP) | ND | During pressurization the mean ICP dropped from 13 to 8 Torr, rising to 14 Torr during HBO2 at 2 ATA, and to 16 Torr during depressurization to 1 atmosphere, then returning to 12 Torr after HBO2. |
| Hardy, 200752 | 54, m, traumatic injuries resulting in neurological symptoms (1) | HBO2: 2.0 ATA | Electrophysiological, metabolic and behavioral measurements. | ND | Following the initial treatment series of 20 exposures, the patient showed improvements, especially in sensorimotor functions, but these gains were no longer observed one year after treatment. However, after an additional treatment series of 60 exposures, the improvements were reinstated.  |
| Lee, 200933 | 40, m, subdural hemorrhage, skull bone fractures, facial bone fractures, sinus fractures, and cerebrospinal fluid (CSF) leakage after a one-story fall (1) | HBO2 |  | Tension pneumocephalus (n=1) | This case report advises that pneumocephalus, untreated skull base fracture, and CSF leakage should be considered contraindications to HBOT. |
| Lee, 201234 | 25, m, left occipital bone fracture and subarachnoid and subdural hemorrhage after being hit by a car (1) | HBO2 |  | Tension pneumocephalus (n=1) | This case report suggests that patients with unrepaired skull base fracture and cerebrospinal fluid diversion be carefully evaluated before receiving hyperbaric oxygen therapy.  |
| Neubauer, 199453 | 40, m, closed head injury after a car accident (1) | HBO2: 1.5 & 1.75 ATA within a monoplace chamber  | SPECT | ND | There was a significant improvement with recoverable brain tissue.  |
| Woolley, 199954 | 17, m, severe TBI (1) | HBO2: 1.5 ATA | Postural stability and gait | ND | Although some improvements in postural stability and walking abilities were observed immediately following HBO2, these improvements were not evident at six weeks measurement.  |
| **Case Series** |
| Wright, 200955 | US Air Force Airmen with mTBI and accompanying symptoms, such as irritability, sleep disturbances, and headaches (2) | HBO2: 1.5 ATA | Automated Neuropsychological Assessment Metrics (ANAM) testing. | ND | There was a significant improvement in all measured areas of ANAM as well as improvements in most symptoms, including headache and sleep disturbances.  |
| Artru, 197656  | Head-injured patients, in coma (ND) | HBO2: 2.5 ATA | Cerebral blood flow (CBF), cerebral metabolic rates of oxygen (CMRO2), glucose (CMRGL), lactate (CMRL act), and various cerebrospinal fluid (CSF) parameters. | ND | Changes to CBF following HBO2 were inconsistent, increasing in some patients and decreasing in others. Changes in cerebral metabolic rates were also inconsistent. A correlation, however, was found between the variations of CMRGL and those of arterial blood and CSF glucose content. |
| Hollin, 196857 | Severe head injuries; chronic neurological residua following subarachnoid hemorrhage and craniotomy for an aneurysm (5) | HBO2: up to 3 ATA | Cerebrospinal fluid pO2, pCO2 and pH of cerebrospinal fluid and blood.  | ND | After HBO2, there was an increase in cisternal cerebrospinal fluid oxygen tension. |
| Lv, 201158 | Paroxysmal sympathetic hyperactivity (PSH) following extremely severe TBI (6) | HBO2 | ND | ND | After limited success with conventional medication regimens, HBO2 was successfully used in these patients to control paroxysmal autonomic changes and posturing in the early sub-acute phase.  |
| Mitani, 200459 | Acute subdural hematoma (ASH) or diffuse axonal injury (DAI) following traumatic head injuries (ND) | HBO2 | Glasgow Outcome Scale (GOS). | ND | Although improvements were observed in some ASH patients, the overall outcome was poor for ASH. Mild to moderate DAI patients recovered well, but outcomes were poor for those classified with severe DAI. |
| Sukoff, 198235 | Acute traumatic cerebral edema (5) | HBO2: 2.0 ATA | Intracranial pressure (ICP),cerebral blood flow. | Transient generalized motor seizure (n=1); major motor seizure (n=1); barotrauma (n=4). | HBO2 reduced ICP and cerebral blood flow while increasing cerebral oxygenation. |